

Accelerating the End of TB:

Field Research from Management Sciences for Health: 2008–2024

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Management Sciences for Health (MSH)

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November 04, 2024

Dear Colleagues,

The Global tuberculosis report 2024 recently released by the World Health Organization (WHO) shows mixed progress in the fight against the disease. In 2023, nearly 8.2 million people were newly diagnosed with tuberculosis (TB), marking the highest number since 1995. Access to TB diagnosis and treatment has improved, but challenges remain. Additionally, limited access to rapid molecular diagnostic tests is an important barrier globally.

Although the number of TB-related deaths decreased in 2023, the estimated total of people falling ill with TB rose slightly, meaning the TB incidence and deaths are far from the UN's Sustainable Development Goals (SDGs) and End TB targets.

Despite some progress, TB remains one of the deadliest infectious diseases in the world, ranking among the top ten causes of death (replacing COVID-19).

TB Preventive Treatment (TPT) has achieved a record of 4.2 million people receiving TPT. Despite this progress, TPT coverage among contacts is still very low, at just 21% globally. In addition, drug-resistant strain TB (DR-TB) indicators are similar to previous years, with only 44% of people with RR/multidrug-resistant TB (MDR-TB) receiving treatment out of the estimated 400,000 who were sick. Chronic lack of resources for TB prevention and control worldwide contributes to the problem, with current funding reaching only 26% of the global target set by last year's UN High-level Meeting. Additionally, nearly 50% of people affected by TB and their families incur catastrophic costs related to TB care. The situation is even more dire for those with DR-TB, where an estimated 82% face catastrophic costs.

As a global community, we have the knowledge, tools, technologies, and treatments to end the TB epidemic. However the chronic lack of funding; huge catastrophic costs for people affected by TB and families; the combined threats of HIV and AIDS, diabetes, and other chronic diseases; the emergence of MDR-TB; increasing social conflicts and war with migration and displaced people; climate change; and pandemics have all affected the capacity of national health systems to offer basic TB services to the most vulnerable populations.

To address these phenomenal challenges and accelerate an end to TB, we must unify global and country level efforts and rethink current health systems. It is crucial that we reinforce primary health care; integrate health services such as diagnostic and laboratory platforms; and increase engagement of both public and private sectors, those affected by TB, local communities, and civil society organizations.

Bold policies—such as universal health coverage, political commitment at all levels of a health system (from health workers to national leadership), increased domestic and international financing support, strong social protection for patients and families, and research—are critical to stop TB.

For more than 22 years, Management Sciences for Health (MSH) has managed complex global TB projects in numerous countries. Our donors include the US Agency for International Development (USAID), US Centers

for Disease Control and Prevention (CDC), the Bill & Melinda Gates Foundation, the Global Fund, and numerous other organizations. Through our work, we have developed trusted partnerships with donors, government agencies (including ministries of health and national TB programs [NTPs] in Africa, Asia, Europe, and Latin America and the Caribbean), multilateral institutions, international partners, and the private sector.

Using a people-centered approach, we collaborate with local partners to develop health system solutions that address the needs of people affected by TB in several countries. We focus on strengthening national, regional, district, and local health managers and their institutions to provide high-quality health services, which is essential for enhancing the resilience and sustainability of health systems. Additionally, we have documented effective technical strategies, research findings, results, and lessons learned from our TB projects. We are committed to sharing these experiences, evidence, and insights with other stakeholders and implementers to support the ongoing efforts to end the TB epidemic.

With this publication, we celebrate 17 years of TB research from MSH staff and local and international partners, as well as our donors, through the publication of more than 120 peer-reviewed articles in noted global public health and clinical scientific journals.

Our research and publications highlight MSH's technical approaches in the following technical areas:

- Quality directly observed treatment, short course (DOTS) implementation
- TB and COVID-19
- MDR-TB care and treatment
- TB contact investigation and TB preventive treatment
- e-TB Manager
- TB drug management and pharmacovigilance
- Capacity building and surveillance systems
- TB elimination
- TB in fragile states and volatile environments
- Urban DOTS and CB DOTS
- TB epidemiology, monitoring, and evaluation
- TB diagnostics, including GeneXpert implementation and digital X-ray
- Patient-centered care for vulnerable and special populations, including those with HIV and other diseases (e.g. Diabetes Mellitus)
- TB financing
- Stigma and discrimination
- Private sector engagement

I hope these collected articles will continue to provide insight to other partners and implementers and incentivize new generations of public health workers and experts to be involved in TB research on the frontline of the global fight against TB.

We are thankful for the deep collaboration of our respected colleagues: numerous MSH staff, international and national partners (ministries of health, NTPs, local nongovernmental organizations, and universities), and particularly the generous support provided by USAID.



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January 2008–July 2024

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Scaling up TB DOTS in a fragile state: post-conflict Afghanistan

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SUMMARY

SETTING: Afghanistan.

OBJECTIVE: To describe the results of rapid expansion of the DOTS strategy in a post-conflict environment, with a focus on the experience of the Rural Expansion of Afghanistan's Community-based Healthcare (REACH) Program.

RESULTS: Despite the destruction of the National Tuberculosis Program (NTP) and basic health services by war and an uncertain security situation, the NTP, with assistance from many partners and REACH, increased the number of patients receiving DOTS by 136% in 4 years (from 9261 cases in 2001 to 21 851 in 2005), with an 86% treatment success rate. By focusing on rapidly expanding the number of facilities capable of providing tuberculosis (TB) diagnostic and treatment services and involving community health workers in case detection, referrals and home-based DOTS, REACH showed a 10-fold rise in the number of facilities providing TB services and a 380% increase in the number of sputum smear-positive pulmonary TB cases detected in 2 years (from 251/month in 2004 to 818/month in 2006) in 13 provinces.

CONCLUSION: At the current rate of expansion, case detection and successful treatment of TB cases in Afghanistan will continue to expand rapidly. The NTP and REACH have demonstrated that expansion of TB services in Afghanistan is possible despite the challenges.

KEY WORDS: tuberculosis; community health services; Afghanistan

THIS STUDY describes the rapid expansion of high-quality DOTS in Afghanistan, which has one of the lowest standards of living and some of the worst health indices in the world after decades of conflict. The maternal mortality ratio of 1600 per 100 000 population is the second highest in the world, and translates into a lifetime risk that one in seven women will die of complications of pregnancy and childbirth.[1] Twenty-five per cent of children will die before their fifth birthdays.[2]

For 23 years, the Afghanistan National Tuberculosis Program (NTP) was in a state of crisis. Since 2002, however, the new Afghanistan government, the Ministry of Public Health (MoPH) and international stakeholders such as the World Health Organization (WHO), the US Agency for International Development (USAID), the World Bank, the European Commission, the Asian Development Bank, Japan International Cooperation Agency, the Canadian International Development Agency, the Italian Cooperation, non-governmental organizations (NGOs) and other donors have made tuberculosis (TB) control a national priority. The US$139 million Rural Expansion of Afghanistan's Community-based Healthcare (REACH) Program, funded by the USAID, established rapid expansion of TB diagnosis and treatment services as a priority and served as an operations research project to discover what was possible in this setting. This article reports the results of DOTS expansion through both the NTP and REACH, which provided basic health services to 7.5 million people in 13 provinces.

Among the world's 22 high-burden TB countries, Afghanistan has the sixth highest mortality rate due to TB. The estimated incidence of sputum smear-positive pulmonary TB is 150 patients/100 000/year, and incidence (all forms) is estimated at 333/100 000/year. Prevalence (all forms) is estimated at 661 patients/100 000/year. Sixty-six per cent of the cases detected are women, an unusual finding. The WHO estimates that 79 500 new TB cases occur annually, of which 36 000 are TB sputum smear-positive.[3] An estimated 20 000 individuals die from TB each year and the TB mortality rate (all cases) is estimated at 93 cases/100 000/year.[3] The prevalence of human immunodeficiency virus (HIV) infection is low (<0.1% in adults)[4] and does not play a significant role in the epidemiology of TB in Afghanistan.

In 2000, a tuberculin skin test survey conducted in Kabul found an estimated prevalence of TB of 4.3% and an annual risk of infection (ARI) of 0.6%.[5] These findings indicate a marked decrease from the ARI of 3% based on a 1978 national prevalence survey. The

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WHO estimated the incidence of TB based on an ARI of 3%.[3] These discrepancies indicate a need for a TB prevalence survey to establish reliable baseline data.

In this context, REACH collaborated with the WHO, the Global Fund for AIDS, TB and Malaria (GFATM), other partners and the MoPH to gain political and technical support for DOTS expansion in Afghanistan. The NTP was reorganized under one director, with the National TB Institute and regional and provincial coordinating units reporting to a central unit that includes about 18 persons. An Interagency Coordinating Committee on TB was formed, and the Country Coordinating Mechanism provided a coordinating function for GFATM awards. The partners worked together to produce a strategic plan and annual operational plans for rapid expansion of TB services.

With the NTP and partners, REACH worked to:

- train doctors, nurses, community health workers and community health supervisors in TB diagnosis and DOTS
- support laboratory improvements
- help provide anti-tuberculosis medications
- provide supervision and quality assurance for laboratories and DOTS
- and develop a community-based DOTS model.

STUDY POPULATON AND METHODS

Setting

Afghanistan is bisected by high mountains that make transportation and access to services difficult. Afghanistan's estimated population was 23.6 million in 2006. However, deaths as a result of war and the migration of 6 million people make accurate population estimates difficult to obtain. The country has faced dramatic declines in human and socio-economic indicators; the annual gross domestic product per capita in 2002 was US$190, and illiteracy was high.[6]

In 2002, the new MoPH established the Basic Package of Health Services (BPHS) as the policy for implementing health services nationwide.[7] The BPHS forms the core of service delivery in all health care facilities and promotes redistribution of health services, especially in underserved areas and to women and children. The BPHS provides a comprehensive list of services offered in health posts, basic health centers, comprehensive health centers and district hospitals. September 2006 data showed 1266 active health facilities (132 hospitals, 412 comprehensive health centers, 379 basic health centers and 343 others) with 359 laboratories capable of performing TB diagnosis.

The DOTS strategy

The main challenges to scaling up TB diagnostic and treatment services through DOTS in Afghanistan are increasing case detection by training providers, strengthening the laboratory system and expanding DOTS to the community level. Although TB services are integrated into the BPHS, in 2002 only provincial and some district hospitals offered TB services. Although the BPHS was a significant change from the previous 23 years when TB services were offered only at provincial TB centers, most health care providers in the country had little training and experience in TB diagnosis and treatment.

The MoPH has adopted the WHO Stop TB strategy, with the vision of a TB-free Afghanistan by 2050. In 2004, the NTP revised the TB guidelines for Afghanistan, following the WHO DOTS strategy.[8] These guidelines outlined policies and procedures for the components essential for TB control.

In 2005, the NTP developed an operational plan to expand DOTS coverage over 2 years.[9] This plan aimed to expand DOTS into all comprehensive health centers, implement DOTS in nine provincial hospitals of eight high-prevalence regions, expand DOTS into 20% of basic health centers, improve the case detection rate from 23% to 40% and implement a community DOTS program in 10% of comprehensive health centers by involving community health workers. REACH agreed to take the lead in implementing these activities in its provinces.

Main TB control activities

The principles of TB control under the revised NTP guidelines are early case detection, accurate diagnosis and appropriate treatment and follow-up in line with the DOTS strategy for all TB patients. All services are free and are available in DOTS health facilities. Health facilities first identify persons with respiratory symptoms (productive cough for 2 weeks) that meet the definition of suspected TB and need to be assessed by sputum smear examination. Sputum smears are examined only in hospitals and comprehensive health centers. However, nurses in basic health centers and trained community health workers in health posts can identify suspected TB patients and refer them for TB screening and sputum microscopy. Patients with negative smears and persistent respiratory symptoms receive a medical examination and X-rays (if available). Repeat sputum smears may also be done, although the new guidelines indicate that suspect cases of active TB with negative sputum smears can be treated empirically if they meet the case definition for TB.

Directly observed treatment (DOT) is provided by community health workers and by nursing staff in health facilities in areas reserved for this purpose. As 53% of the community health workers are women, this approach ensures that women, who bear a disproportionate share of the TB burden, are reached. Patients are encouraged to attend for treatment by the offer of food packages provided by the World Food Program. The community health workers are instructed in the administration and follow-up of TB treatment. They are supervised by community health supervisors at each

facility and receive non-financial incentives, such as training and certificates.

Data

Because the NTP ceased its activities during the war, the number of TB cases detected in that period is unknown, and we cannot establish the trend of TB notification in the country for this period. Using the WHO epidemiological model and the current TB notification patterns, however, data suggest that the TB epidemiological situation now is similar to that between 1970 and 1980.

The data used in our analysis come from routine reports of the NTP and the Afghanistan National Health Management Information System (HMIS). One weakness of this analysis is reliance on service reports, which are always incomplete. However, more recent data are significantly more accurate than earlier service reports, as strengthening the HMIS and improving the reporting system were emphasized nationwide. By 2006, more than 90% of health care facilities were submitting monthly service reports. The present study used these two data sets and the following standard indicators: total DOTS health facilities and TB cases reported by the NTP and REACH during April 2004–March 2006; treatment outcomes collected as part of routine data for the same period, including numbers of patients treated successfully (cure or treatment completed); the number in whom treatment failed (sputum smear-positive at 5 months or at the end of treatment); and those who defaulted (treatment missed for ⩾60 consecutive days) or died during treatment.

As this was not original research involving human subjects, but a report on program activities, no ethical review board approval was needed.

RESULTS

Over the past 3 years, Afghanistan has made slow and steady progress in increasing the percentage of cases detected, with more rapid expansion of coverage in the last 2 years.

DOTS coverage in the country

By 2005, DOTS had been implemented in 65% of districts and 81% of the entire population of Afghanistan. The number of districts implementing DOTS increased from 36 in 2001 to 253 in 2005. This change represents a 600% increase in the number of districts applying DOTS over 4 years (Table 1).[10]

Table 1 DOTS status in districts, Afghanistan, 2001–2005

Year	Districts	Districts applying DOTS *n* (%)
2001	330	36 (11)
2002	330	70 (21)
2003	330	126 (38)
2004	398	178 (45)
2005	398	253 (64)

Source: WHO/NTP/REACH/ANHRA, 2004.[10]

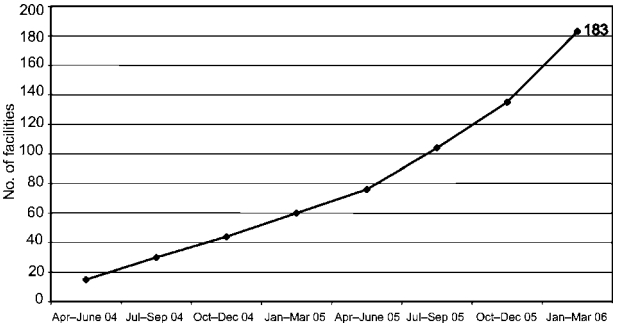

Figure 1 Number of REACH facilities (including basic health centers) that reported providing DOTS. REACH = Rural Expansion of Afghanistan's Community-based Healthcare.

Figure 1 shows the growth in the number of REACH facilities providing TB services over the past 2 years, a 12-fold rise. Figure 2 shows that this growth has all occurred in basic and comprehensive health centers. The number of health facilities applying DOTS increased from 36 in 2001 to 466 in 2005, reflecting a slightly higher than 10-fold increase in 4 years (Table 2).

By 2005, of the 6300 community health workers working in the REACH provinces, 10% were trained in TB case detection, referral to the nearest facility offering TB services, and home-based DOT. The use of community health workers contributed to a rapid rise in case detection rates and low default rates.

Case detection and treatment

In public and NGO health facilities, TB case notification increased from 9261 cases in 2001 to 21 851 in 2005—a 136% increase over 5 years (Table 3). The case detection rate in 2005 represents only 27% of the expected number of new TB cases, which means

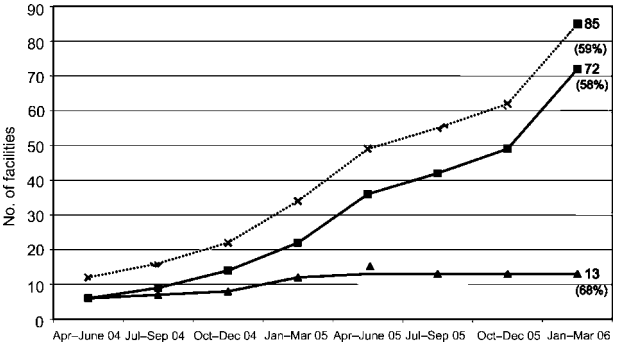

Figure 2 REACH-supported hospitals and comprehensive health centers offering active diagnosis and treatment of tuberculosis. Dotted line = total; line with squares = comprehensive health centers with active diagnosis and treatment services; line with triangles = district hospitals with active diagnosis and treatment services. REACH = Rural Expansion of Afghanistan's Community-based Healthcare.

Table 2 DOTS status in health facilities, Afghanistan, 2001–2005

Year	Health facilities	Health facilities applying DOTS *n* (%)
2001	1013	36 (3.5)
2002	1013	79 (7.7)
2003	1013	131 (12.9)
2004	1013	202 (20.0)
2005	1115	466 (41.8)

Source: NTP/REACH/ANHRA, 2004.[10]

Table 3 Number of new tuberculosis (TB) cases, Afghanistan, 2001–2005

Year	All new TB cases	TB sputum smear-positive cases	Case detection rate
2001	9 261	4 465	14
2002	12 305	6 035	18
2003	13 204	6 510	17
2004	18 402	9 976	23
2005	21 851	10 805	27

Source: NTP, 2005.[11]

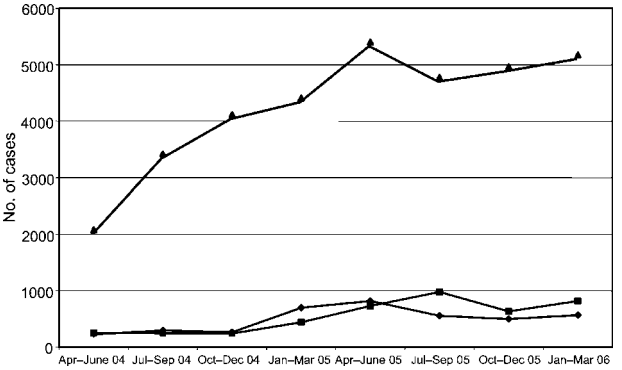

Figure 3 Suspected and newly diagnosed TB cases and treatment completion in REACH facilities (including provincial hospitals). Line with triangles = number of suspected TB cases; line with diamonds = number of new smear-positive TB cases; line with squares = number of TB cases who completed treatment and were smear-negative. REACH = Rural Expansion of Afghanistan's Community-based Healthcare; TB = tuberculosis.

that 73% of TB cases went undetected. However, there was a 53% rise in sputum smear-positive cases between 2003 and 2004.

The treatment success rate for new TB sputum smear-positive cases has increased continually. In 2002, successful treatment of a new TB sputum smear-positive case in the DOTS health facilities was only 59% (Table 4). In 2005, the NTP reported an 87% cure rate for the first three quarters of the year.[11]

Available data from 2000 to 2003 show important inconsistencies. For example, in 2001 and 2002, the numbers of TB sputum smear-positive cases analyzed in the study cohort were respectively 41% and 20% more than the actual number of TB sputum smear-positive cases notified. This reflects the poorly developed NTP management information system before 2004. Data from 2004 onward are considered to be reliable.

Figure 3 shows the dramatic improvement in the number of sputum smears and active cases detected. Over 2 years, the number of REACH facilities providing DOTS increased 10-fold, and the number of patients diagnosed and treated for TB increased by 380% (from 251/month in 2004 to 818/month in 2006) in the provinces covered by REACH, which represent about 35% of the population of Afghanistan.

DISCUSSION

Although rapid expansion of DOTS coverage in the TB high-burden countries has posed many challenges, Afghanistan has achieved progress in a complex emergency environment. Similarly, since 1979, Cambodia has rebuilt its NTP. Recent studies have shown that the prescribing practices of TB service providers were acceptable and the knowledge of new TB sputum smear-positive patients about the disease and their treatment was high. Locating DOTS in primary care centers instead of separate TB centers markedly reduced delays in starting TB treatment in Cambodia.[12,13] East Timor had a well-developed NTP using both the

Table 4 Tuberculosis treatment outcomes in new sputum smear-positive cases, Afghanistan, 2001–2004

	TB sputum smear-positive cases			Outcomes, *n* (%)					
Year	Notified *n*	Analyzed in study cohort *n*	Notified cases analyzed in study cohort %	Cured	Completed treatment	Failure	Death	Defaulted	Transferred
2000	4639	2918	63	2334 (80)	175 (6)	88 (3)	88 (3)	175 (6)	58 (2)
2001	4465	6292	141	3272 (52)	2013 (32)	126 (2)	251 (4)	440 (7)	189 (3)
2002	6035	7780	120	4582 (59)	2139 (27)	148 (2)	303 (4)	381 (5)	225 (3)
2003	6510	6793	104	5505 (81)	340 (5)	349 (5)	117 (2)	253 (4)	229 (3)
2004	9976	NA	NA	7705 (77)	992 (10)	177 (2)	297 (3)	266 (3)	339 (3)

Source: WHO Global Reports 2003, 2004, 2005, and NTP Afghanistan. 2005 data are incomplete, but for the first three quarters of the year showed an 87% cure rate. The WHO Global Report 2007 was unavailable when this article was written.
TB = tuberculosis; NA = not available.

private and public sectors that was disrupted in the conflict of 1999. In 2000, the NTP was rebuilt with a local NGO as the lead agency and the TB case notification rate rose to 108/100 000, the highest in the region, although the cure rate was only 81%. Coordination and collaboration among partners were identified as major contributors to the success of the program.[14,15] These three experiences show that DOTS can be implemented in challenging environments but requires international support and good coordination.

Analyses of the results of global TB control, with emphasis on high-incidence countries, have concluded that despite great progress in treatment, targets for case detection are not being met.[16–18] Four actions are seen as being important to speed progress toward achieving targets: 1) equipping NTPs to engage all health providers in the country to implement DOTS; 2) establishing national certification and quality assurance programs for DOTS; 3) promotion of community involvement in detecting cases, contributing to DOTS and advocating the expansion of TB services; and 4) increase in support to high-burden countries to rapidly expand DOTS.

By adopting this four-pronged approach, Afghanistan's NTP has made steady progress since 2002 in the number of facilities providing DOTS (from 36 in 2001 to 466 in 2005) and the number of new TB cases detected. The 53% rise in case detection between 2003 and 2004 seems to reflect the intensive efforts to improve laboratory services for TB. Low case detection remains a significant problem, however, as only 27% of estimated new cases were detected in 2005. Expansion of DOTS was hampered by the destruction of the health infrastructure, limited capacity of human resources, climatic and geographical difficulties and an unstable security situation. Although faced with similar challenges, REACH showed a dramatic rise in facilities providing DOTS (from 15 in 2004 to 183 in 2006) and in TB patients treated (from 251/month in 2004 to 818/month in 2006) in just 2 years, indicating the success of focusing on improving service delivery points.

CONCLUSIONS

Even in a difficult environment, an NTP can be rebuilt and DOTS services expanded rapidly. This success was possible due to the collaboration and support of many partners.

Managing and coordinating this partnership requires time and resources that detract from service delivery. Now that the coordination mechanisms, national plans and BPHS integration procedures are well developed, however, this partnership should produce a rapid expansion of case detection and treatment that is sustainable.

REACH was able to mobilize resources quickly and focus attention on the expansion of TB diagnostic and treatment services in 2 years in a large population. REACH demonstrated that an approach focused on improving service delivery points, training health facility staff, and incorporating community health workers into TB case detection and treatment can significantly increase DOTS coverage.

The lessons learned by the Afghanistan NTP and the REACH Program about the rapid expansion of TB diagnostic and treatment services will apply to other countries recovering from complex emergencies, be they conflicts or natural disasters.

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RÉSUMÉ

CONTEXTE : Afghanistan.
OBJECTIF : Décrire les résultats de l'expansion rapide du DOTS dans un environnement post-conflit en se focalisant sur l'expérience du Programme d'Expansion Rurale des Soins de Santé basés sur la Collectivité en Afghanistan (REACH).
RÉSULTATS : Malgré la destruction par la guerre du Programme National de la Tuberculose (PNT) et des services de santé de base et malgré une situation précaire de sécurité, le PNT, aidé par beaucoup de partenaires et par REACH, a augmenté le nombre de patients bénéficiant du DOTS de 136% en 4 ans (de 9261 cas en 2001 à 21 851 cas en 2005), avec un taux de succès du traitement de 86%. En se focalisant sur l'expansion rapide du nombre d'installations capables de fournir des services de diagnostic et de traitement de la tuberculose (TB) et en impliquant les travailleurs de santé de la collectivité dans la détection, la référence et le DOTS basé sur le domicile, le REACH a démontré une multiplication par dix du nombre d'installations assurant les services de TB et une augmentation de 380% du nombre de cas de TB pulmonaire à bacilloscopie positive détectés sur 2 ans (de 251 par mois en 2004 à 818 par mois en 2006) dans 13 provinces.
CONCLUSION : Le taux actuel d'expansion signifie que la détection des cas et les traitements couronnés de succès des cas de TB en Afghanistan vont continuer à augmenter rapidement. Le PNT et le REACH ont démontré que l'expansion des services de TB en Afghanistan est possible malgré les défis rencontrés.

RESUMEN

MARCO DE REFERENCIA : Afganistán.
OBJETIVO : Describir los resultados de la rápida ampliación de la estrategia DOTS en situaciones posconflicto, con énfasis particular en la experiencia del Programa de la ampliación rural de la atención comunitaria de salud en Afganistán (REACH).
RESULTADOS : Pese a la destrucción del Programa Nacional de Tuberculosis (PNT) y de los servicios básicos de salud a causa de la guerra y una situación de seguridad inestable, con la ayuda de múltiples colaboradores y del programa REACH, se ha logrado en 4 años aumentar en 136% el número de pacientes que reciben DOTS en el PNT (de 9261 casos en 2001 a 21 851 en 2005) y se ha alcanzado una tasa de éxito terapéutico del 86%. Con prioridades como la rápida expansión de los centros que ofrecen servicios de diagnóstico y tratamiento de la TB y la incorporación de trabajadores de salud de la comunidad a las actividades de detección, referencia y DOTS domiciliario, con el programa REACH se ha logrado aumentar en 10 veces el número de centros con servicios de TB y en 380% el número de casos de TB pulmonar bacilífera detectados en 2 años (de 251 por mes en 2004 a 818 por mes en 2006) en 13 provincias.
CONCLUSIÓN : El ritmo actual de ampliación de servicios indica que la detección y el tratamiento exitoso de los casos de TB en Afganistán continuarán aumentando rápidamente. El PNT y el REACH demostraron la factibilidad de expansión de los servicios de TB en Afganistán, pese a los múltiples obstáculos.

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Delay in Tuberculosis case detection in Pwani region, Tanzania. a cross sectional study

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Abstract

Background: Delay in Tuberculosis (TB) case detection may worsen the disease and increase TB transmission. It is also a challenge to the National TB and Leprosy control Program (NTLP).

Methods: We conducted a cross sectional study in four out of six districts in Pwani region to estimate the extent and factors responsible for delay in TB case detection in Pwani region. Delays were divided into patient, health facility and total delay.

Results: We enrolled a total of 226 smear positive TB patients. Out of 226 patient's results were available for 206. The majority (66.5%) of the patients were males. Mean age for males and females were 37.3 and 33.7 years respectively. Mean (SD) total delay was 125.5 (98.5) days (median 90). Out of 206 patients, 79 (38.35%) delayed to seek TB health care. Health facility delay was observed among 121 (58.7%) patients.

Risk factors for delay was poor knowledge that chest pain may be a TB symptom (OR = 2.9; 95%CI 1.20- 7.03) and the belief that TB is always associated with HIV/AIDS (OR = 2.7; 95%CI 1.39-5.23). Risk for delay was low among patients who first presented to a government health facility (OR = 0.3; 95%CI 0.12- 0.71) and those presenting with chest pain (OR = 0.2; 95%CI 0.10-0.61).

Conclusion: There is a considerable delay in TB case detection in Pwani mainly contributed by patients. Risk factors for delay include misconception about TB/HIV and poor knowledge of TB symptoms.

Background

Annually, about 2600 Tanzanians die from TB, which continues to be one of the major public health problems. The increased burden of TB in Tanzania is being fueled by HIV/AIDS [1].

A case of untreated smear positive tuberculosis can infect up to 15 people annually and over 20 during the natural course of untreated disease [2,3]. Early case detection and prompt treatment of infectious TB cases is the basis for achieving the millennium development goals, which aim to have halted and begun to reverse the incidence of TB by year 2015 [4].

TB case detection in Tanzania is mainly through passive case finding where patients present themselves to the health facility to seek care. However passive case finding depends much on the patient motivation and knowledge, financial capability, degree of suspiciousness of health workers, and the accuracy and effectiveness of diagnostic services [5]. Studies in Nigeria showed that 83% of patients presented in health facilities after a month or more from the onset of their symptoms [6]. In Ethiopia, the median patient and health facility delay were 60 and 6 days, respectively [7]. WHO estimates show that Tanzanian case detection rate is less than 50% [8]. Studies conducted in Tanzania and Botswana showed that patient from rural areas, patients with low education level, site of first visit, lack of TB information and female gender were associated with TB delay [9-12].

Except for the study conducted in two high TB burden cities of Mwanza and Dar es Salaam [8,9,11], the magnitude and factors responsible for delay in low TB burden regions of Tanzania is unknown.

This study was therefore, conducted to estimate the extent and factors responsible for delay in TB case detection in Pwani.

Methods

Setting

We conducted the study in Pwani region which is located in the eastern part of Tanzania Mainland (Coordinates 7°00'S, 39°00'E). The total population of Pwani in 2002 was 889,154 with 440,161 males and 448,993 females [13]. The study was conducted in four out of six districts located in Pwani region (Bagamoyo, Kibaha, Kisarawe and Mkuranga). Almost 73% of the population stays in the four districts studied (Bagamoyo 230,164; Kibaha132, 045; Kisarawe 95,614 and Mkuranga187, 428) [13]. Like in other parts of the country, TB services are free in all government facilities and health facilities are fairly well distributed with 90% of the population being within 10 kilometers from a health facility [8,14].

Study design and data collection

We conducted a cross sectional hospital based study between April and October 2007. Four districts were randomly selected out of six districts in Pwani region. All four district hospitals were included into the study plus a random sample of 10% of all health facilities which offer TB services. In total we included the four hospitals, four health centers and eight dispensaries. All smear positive TB patients aged 15 years and above who were diagnosed within three months prior to the day of interview were enrolled and interviewed using a structured questionnaire which included open and close-ended questions. To ensure that all smear positive patients are enrolled, we identified all smear positive patients who have been diagnosed three months prior to the day of interview using registers before commencing data collection activities. We also enrolled smear positive patients who have just been diagnosed when the interview was going on. A maximum of two weeks was used to collect information in one facility depending on the number of smear positive patients available in the facility as well as patients drugs collecting schedule. We collected the following information: socio-demographic characteristics, knowledge about TB, place of first consultation and time spent to go to the nearest health facility. Other information collected were date of onset of pulmonary symptoms, date of first visit to a health facility, dates of collection of all three sputum samples, and date of starting treatment. If a patient did not remember the exact dates, he/she was asked if it was at the beginning of the month, at mid month or at end of the month. The beginning of the month was labeled as 5th, mid month was labeled as 15th and end of the month was labeled as 25th of the respective month. Patient TB treatment cards were also used to look at the date treatment was started.

We were granted ethical clearance to conduct this study by the Tanzania Medical Research Coordinating Committee which is the ethics coordinating body. We obtained informed verbal consent from each interviewee before enrolment. Data collectors were trained and questionnaires translated in Swahili and pre tested.

Standard procedure for the diagnosis of pulmonary tuberculosis in Tanzania is that all patients with cough of two or more weeks should collect three sputum samples in the form of "spot-morning-spot". Spot specimens are collected on the day the patient is suspected to have tuberculosis, morning samples are collected early in the morning of the second day and the third specimen is collected on submission of the morning specimen. Results of the sputum sample examinations should be communicated to the patient and treatment initiated on the same day after submission of the morning and spot specimens [1].

We calculated the sample size using Epi info version 6 on the assumption that the previous estimate of patient delay of more than 30 days for smear positive patients was 85% [9], total population of Pwani to be 900,000 and worst acceptable margin of 80% [15].

Analysis

Data were double entered and cleaned using Epi data and analyzed using SPSS 11.5 for windows (SPSS Inc, Chicago, IL, USA). Description of each variable by delay was done. Risk factors for delay were estimated by bivariate logistic regression using cross tabulation with 95% confidence intervals (CI) given for odds ratios (OR) indicating statistically significant relationship if both values were above or below 1. Mean and median days of delay were calculated. We used the following time intervals:

Patient delay: the time interval between the day of experiencing for the first time one of the current pulmonary symptoms to the day the patient sought medical advice for the first time. Interval that exceeded 30 days was considered as patient delay [9,11]. **Health facility delay**: the time interval between first consultation at a health facility to the day the treatment was initiated. We considered a time interval of 5 days as health facility delay [11]. **Total delay**: the sum of the patient and health facility delay.

Patients who knew that TB can be spread from one person to another by coughing/sneezing were defined as having 'good' knowledge on TB transmission. Patients who mentioned prolonged cough plus two other symptoms from the following: fever, night sweat, chest pain, difficult in breathing, weight loss and coughing blood were defined as having good knowledge of TB symptoms [11].

Results

General patient's characteristics

We enrolled a total of 226 smear positive TB patients. The majority (66.5%) of the patients were males. Their mean (SD) and median age was 37.3 (14.5) and 35 years respectively. Mean (SD) and median age for females was 33.7 (12.8) and 31 years. Seventy nine patients (38.35%) delayed to seek TB health care for more than 30 days. Mean (SD) and median (range) time interval between onset of symptoms to first consultation at any health facility was 10.9 (9) and 9 (30) days respectively among patients who did not delayed to seek TB health care. Mean (SD) and median (range) patient delay among delayed patients was 75.8 (43.5) and 62 (181) days. Only 92 (44.7%) of the patients were suspected in their first visit. Fifty two (24.9%) patients were not started on treatment until more than three months from the onset of their illness. General patients' characteristics as risk factors for TB patient's diagnosis delay are shown in table 1. Patients who first presented to a government health facility had 0.3 (95%CI 0.12- 0.71) times the odds of delay compared to those who attended private health facilities.

Presenting symptoms

The majority of the patients presented with a combination of symptoms. However, the most frequently reported symptoms were prolonged cough 78.6% (95%CI 73.00-84.2), evening fever 53.3% (95%CI 46.49-60.11), chest tightness (30.1%) (95%CI 23.84-36.36), weight loss 19.4% (95%CI 14.00-24.8), chest pain 18.5% (95%CI 13.20-23.80) and hemoptysis 13.1% (95%CI 8.49-17.71).

Patient's knowledge on TB

Generally, 67 (32.5%) (95%CI 26.1-38.9) and 185 (89.8%) (95%CI 85.67-93.93) of patients had good knowledge on TB symptoms and possible ways of TB transmission, respectively. One hundred and seventy three patients (84.0%) (95%CI 78.99-89.01) were aware that prolonged cough is a TB symptom. Almost all patients (98.1%) (95%CI 96.24-99.96) were aware that TB is curable. Other symptoms mentioned were; evening fever (60.2%) (95%CI 53.53-66.88), difficulty in breathing (29.1%) (95%CI 22.9-35.3), loss of weight (20.9%) (95%CI 15.35-26.45), coughing blood (19.4%) (95%CI 14-24.8) and chest pain (17.0%) (95%CI 11.87-22.13).

Risk factors for TB patients delay

Table 2 illustrates risk factors for patients delay. Patients who presented with chest pain were 0.2 times (95%CI 0.10-0.61) less likely to delay compared to those with no chest pain. Other risk factors associated with patients delay was a belief that TB is always associated with HIV/AIDS (OR = 2.7; 95%CI 1.39-5.23) and having poor knowledge that chest pain may be a TB symptom (OR = 2.9; 95%CI 1.20- 7.03).

Factors related to Patients and health facility delay among smear positive patients

Table 3 summarizes factors related to patients and health facility delay. There was no statistically significant difference when comparing factors associated with patients as well as health facility delay across gender, education level, presenting symptoms and knowledge of TB symptoms. This could mean that both patient and facility delays are impacting on TB problem equally.

Health facility delay

Health facility delay was observed among 121 (58.7%; 95%CI 51.98-65.42) patients. Of these, 78 (64.5%; 95%CI 57.97-71.03) were males and 43 (35.5%: 95%CI 28.97-42.03) were females. Mean (SD) and median (range) health facility delay was 49.7 (56.0) and 28.0 (262) days. Seventy three (61.3%; 95%CI 54.65-67.95) were between 18-40 years. The majority 65 (53.7%; 95%CI 46.89-60.51) completed primary school (table 4). Mean (SD) and median (range) time interval between first consultation to any health facility and initiation of treatment was 2.3 (1.4) and 2.0 (5.0) days respectively among patients with no health facility delay.

Table 1: Socio-demographic characteristics as risk factors for patients delay.

	Patient delay n (%)	No patient delay n (%)	Odds ratio and 95%CI
Gender			
Male	58/79(73.42)	79/127 (62.20)	OR = 0.6 (95%CI 0.32-1.10)
Female	21/79(26.58)	48/127 (37.80)	
Marital Status			
Single	33/79 (41.77)	60/127 (47.24)	OR = 0.8(95%CI 0.45-1.41)
Couple	46/79 (58.23)	67/127 (52.76)	
Age group *			
< 18 Years	2/79(2.53)	6/124 (4.84)	
18-40	49/79(62.03)	80/124 (64.52)	OR = 0.5 (95%CI 0.10-2.80)
> 40	28/79(35.44)	38/124 (30.65)	OR = 05 (95%CI 0.08-2.41)
Education Level			
No formal education	33/79 (41.77)	60/127 (47.24)	OR = 0.8(95%CI 0.45-1.41)
Completed primary school and above	46/79 (58.23)	67/127 (52.76)	
Place of first presentation**			
Government Facility	47/78(60.26)	97/126 (76.98)	**OR = 0.3; (95%CI 0.12- 0.71)‡**
Private facility	16/78(20.51)	20/126 (15.87)	OR = 0.5; (95%CI 0.17- 1.38)
Traditional Healers	15/78(19.23)	9/126 (7.14)	
Time spent to go to the nearest Health facility***			
30 minutes or less	37/79 (46.8)	58/125 (46.4)	OR = 1.0 (95%CI 0.56-1.73)
More than 30 minutes	42/79 (53.2)	67/125 (53.6)	
HIV self reported****			
HIV positive	14/65 (21.5)	36/103 (35.0)	OR = 2.0 (95%CI 0.96- 4.01)
HIV negative	51/65 (78.5)	67/103 (65.0)	

*n = 3 were missing age,
** n = 2 were missing place of first consultation
***n = 2 missing time spent to go to the nearest facility
**** n = 38 were missing HIV status

Total delay

Mean (SD) and median time interval between onset of symptoms to initiation of treatment was 125.5 (98.5) and 90.0 days respectively among patients who delayed to seek TB health care.

Discussion

Our study indicates that 79 (38.4%) patients delayed to seek TB health care. Thirty days was considered as a cut off point for patient delay, taking into account the local situation of these communities and other studies conducted in Tanzania [9,11]. Cut off point for health facility delay was set at 5 days. The mean time interval between onset of symptoms to first consultation at any health facility was 75.8 days among patients who delayed to seek TB health care, and these patients may serve as potential reservoirs for infection.

The proportion of patients who delayed was not as high as what has been found in other studies [9,15], and is smaller than what was found in Mwanza [9]. However, it is almost the same as previously reported from Dar es Salaam [11]. Though not investigated in this study, the differences in delay could probably be explained by the study site, cultural factors and increased awareness of TB among communities since 2000 when the study in Mwanza was conducted.

Almost a quarter of patients were not started on treatment until more than three months from the onset of their illness. This is similar to what has been found in Ethiopia [7]. The major contributor to the total delay observed in this study was the delay of patients (63%) but this was lower than what was found in Mwanza where patient contributed to the total delay by more than 90% [9]. Studies in Ethiopia and Nigeria also show dominance of patients delay in the total delay [6,7]. Patients take long time before diagnosis when considering both patient and health system delay of more than 35 days. This has implication on delayed case detection hence increased trans-

Table 2: Risk factors for patients delay.

	Delay n (%)	No delay N (%)	Odds ratio and 95%CI
Presenting symptoms			
Cough > 2 weeks	64/79(81.0)	98/127(77.2)	OR = 0.8(95%CI 0.39-1.59)
Cough with blood	12/79(15.2)	15/127(11.8)	OR = 0.7(95%CI 0.33-1.69)
Difficult in breathing	23/79(29.1)	39/127(30.7)	OR = 1.1(95%CI 0.58-2.00)
Chest Pain	6/79 (7.6)	32/127(25.2)	**OR = 0.2(95%CI 0.10-0.61)‡**
Fever	44/79(55.7)	70/127(55.1)	OR = 1.0 (95%CI 0.56-1.72)
Loss of weight	20/79(25.3)	20/127(15.8)	OR = 0.6(95%CI 0.27-1.11)
Poor knowledge of TB symptoms			
Cough > 2 weeks	16/79(20.3)	17/127(13.4)	OR = 1.64(95%CI 0.78-3.48)
Cough with blood	58/79(73.4)	108/127(85.0)	OR = 0.5(95%CI 0.24-0.98)
Difficult in breathing	56/79(70.9)	90/127(70.9)	OR = 1.0(95%CI 0.54-1.86)
Chest Pain	72/79(91.1)	99/127(78.0)	**OR = 2.9(95%CI 1.20- 7.03)‡**
Fever	33/79(41.8)	49/127(38.6)	OR = 1.1(95%CI 0.64-2.02)
Loss of weight	60/79(75.9)	103/127(81.1)	OR = 0.7(95%CI 0.37-1.45)
Poor knowledge of transmission			
Cough/Sneezing	10/79(12.7)	11/127(8.7)	OR = 1.5(95%CI 0.62-3.78)
Sharing eating utensils	71/79(89.9)	109/127(85.8)	OR = 1.5(95%CI 0.60-3.55)
Shaking hands	31/79(39.2)	46/127(36.2)	OR = 1.1(95%CI 0.64-2.03)
Mosquito bite	47/78 (60.3)	64/127(50.4)	OR = 1.5(95%CI 0.84-2.64)
Mother to child transmission during pregnancy	66/79(83.5)	103/127(81.1)	OR = 1.2(95%CI 0.56-2.49)
Believe that TB is always associated with HIV/AIDS*	52/69 (75.4)	59/111 (53.2)	**OR = 2.7(95%CI 1.39- 5.23)‡**
Poor knowledge of TB curable	1/79(1.3)	3/127(2.4)	OR = 0.5(95%CI 0.05-5.19)

*n = 26 were missing

mission in communities since TB patients would have stayed longer in the community before diagnosis and treatment. Public interventions are therefore inevitable if we are to reduce TB transmission in the community and increase case detection rate. Interventions targeting change of health seeking behavior, ways of increasing diagnostic suspicion index of health personnel and improving laboratory methods would reverse the transmission trends.

Patients with symptom of chest pain and those who first presented to government health facilities were less likely to delay to seek TB health care. This may be partly related to TB services which are mostly offered in government compared to private facilities because TB services are free of charge. Interventions to improve early case detection and treatment should also target TB service in private facilities, and we thus recommend to put more effort to improve public private partnership in TB control in the country.

In addition, patients with poor knowledge that chest pain was one of the TB symptoms and those who believe that TB is always associated with HIV/AIDS delayed to seek TB health care. This finding is similar to a study conducted in Dar es Salaam [11]. Though not investigated in this study, similarities of some of TB symptoms with that of HIV/AIDS and stigma associated with HIV/AIDS could offer an explanation.

Level of education attained and gender had no significant effect on delay of seeking TB health care, similar to findings in Uganda [15]. However, this is in contrary to studies conducted in Dar es Salaam and Mwanza [9,11]. Furthermore, patients delay was not significantly associated with self reported HIV/AIDS status. Though we did not investigate whether these patients were tested before or after TB diagnosis, it is well known among TB health workers that every TB patient should be HIV tested [1]. Therefore, if they had HIV test following TB diagnosis, their HIV/AIDS status would not affect their health seeking behavior.

Likewise, health care seeking observed in this study differs from other studies. More patients in our study first sought help for their pulmonary symptoms in government hospitals, in contrast to a study in India, which showed a high proportion of TB patients first seeking health care in private facilities [16]. However, despite that more patients in our study first sought health care for their pulmonary

Table 3: Factors related to events of patients and health facility delay among smear positive patients.

	Patient delay n (%)	Health facility delay n (%)	No patient delay n (%)	No health facility delay n (%)
Gender				
Male	58/79(73.42)	78/121 (64.5)	79/127(62.20)	59/85 (69.4)
Female	21/79(26.58)	43/121 (35.5)	48/127(37.80)	26/85 (30.6)
Marital Status				
Single	33/79(41.77)	58/121 (47.9)	60/127(47.24)	35/85 (41.2)
Couple	46/79(58.23)	63/121 (52.1)	67/127(52.76)	50/85 (58.8)
Age group				
< 18 Years	2/79(2.53)	6/119 (5.0)	6/124 (4.84)	1/84 (1.2)
18-40	49/79(62.03)	73/119 (61.3)	80/124(64.52)	57/84 (67.8)
> 40	28/79(35.44)	40/119 (33.6)	38/124(30.65)	26/84 (31.0)
Education Level				
No formal education	33/79(41.77)	56/121 (46.3)	60/127(47.24)	37/85 (43.5)
Completed primary school and above	46/79(58.23)	65/121 (53.7)	67/127(52.76)	48/85 (56.4)
HIV self reported				
HIV positive	14/65(21.5)	29/101 (28.7)	36/103 (35.0)	21/68 (30.9)
HIV negative	51/65(78.5)	72/101 (71.3)	67/103 (65.0)	47/68 (69.1)
Presenting symptoms				
Cough > 2 weeks	64/79(81.0)	93/121 (76.9)	98/127(77.2)	68/85 (80.0)
Cough with blood	12/79(15.2)	14/121 (11.6)	15/127(11.8)	13/85 (15.9)
Difficult in breathing	23/79(29.1)	36/121(29.8)	39/127(30.7)	27/85(31.8)
Chest Pain	6/79(7.6)	29/121(24.0)	32/127(25.2)	10/85(11.8)
Fever	44/79(55.7)	65/121(53.7)	70/127(55.1)	50/85(58.8)
Loss of weight	20/79(25.3)	19/121(15.7)	20/127(15.8)	21/85(24.7)
Poor knowledge of TB symptoms				
Cough > 2 weeks	16/79(20.3)	19/121(15.7)	17/127(13.4)	14/85(16.5)
Cough with blood	58/79(73.4)	102/121(84.3)	108/127(85.0)	64/85(75.3)
Difficult in breathing	56/79(70.9)	83/121(68.6)	90/127(70.9)	63/85(74.1)
Chest Pain	72/79(91.1)	98/121(81.0)	99/127(78.0)	73/85(85.9)
Fever	33/79(41.8)	47/121(38.8)	49/127(38.6)	34/85(40.0)
Loss of weight	60/79(75.9)	97/121(80.2)	103/127(81.1)	65/85(76.5)

symptoms in government facilities, yet more than 55% delayed to be suspected at their first visit, even if many of them (78.6%) had prolonged cough of more than two weeks prior to their first consultation. Although our study did not assess the availability of TB diagnostic services in the facilities where patients visited for their first consultation but the NTLP guidelines requires clinicians working in facilities with no TB diagnostic services to refer patients or send patient's sputum early to a facility with TB diagnosis services for TB investigation [1]. Unfortunately, in most cases the guidelines are not always well known and are even less well followed by health care providers. How much the guidelines are known and followed is an area which needs further studies.

Other limitations of the study include recall bias on estimation of delay. Our data analysis did not use random effect model to adjust for possible individual or practice variations. The data was not sufficient enough to use the model. This could have some effect in the 95% Confidence Interval. However, in longitudinal and cluster trial studies involving repeated measure of parameter estimates this bias can lead to invalid inferences regarding measures of effect such as risk ratios (RR) or OR [17].

Conclusion

There is a considerable delay in TB case detection in Pwani mainly contributed by patients. Risk factors for delay include misconception about TB/HIV and poor knowledge of TB symptoms. Interventions are required to change public health seeking behavior so as to reduce patient delay, and to equip and train health personnel at facility level so as to eliminate health system delay.

Competing interests

The authors declare that they have no competing interests.

Table 4: Risk factors for health facility delay

	Health facility delay n (%)	No health facility delay n (%)	Odds ratio and 95%CI
Gender			
Male	78/121 (64.5)	59/85 (69.4)	OR = 0.8(95%CI 0.44-1.44)
Female	43/121 (35.5)	26/85 (30.6)	
Marital status			
Single	58/121 (47.9)	35/85 (41.2)	OR = 0.8(95%CI 0.43-1.33)
Couple	63/121 (52.1)	50/85 (58.8)	
Age group *			
< 18 Years	6/119 (5.0)	1/84 (1.2)	
18-40	73/119 (61.3)	57/84 (67.8)	OR = 0.3(95%CI 0.03-2.25)
> 40	40/119 (33.6)	26/84 (31.0)	OR = 0.2(95%CI 0.02-1.82)
Education level			
No formal education	56/121 (46.3)	37/85 (43.5)	OR = 0.9(95%CI 0.51-1.56)
Completed primary school and above	65/121 (53.7)	48/85 (56.4)	
HIV self reported**			
HIV positive	29/101 (28.7)	21/68 (30.9)	OR = 0.9(95%CI 0.46-1.76)
HIV negative	72/101 (71.3)	47/68 (69.1)	
Presenting symptoms			
Cough > 2 weeks	93/121 (76.9)	68/85 (80.0)	OR = 0.8(95%CI 0.42-1.64)
Cough with blood	14/121 (11.6)	13/85 (15.9)	OR = 0.7(95%CI 0.32-1.63)
Difficult in breathing	36/121(29.8)	27/85(31.8)	OR = 0.9(95%CI 0.50-1.66)
Chest Pain	29/121(24.0)	10/85(11.8)	OR = 2.4(95%CI 1.08-5.16)
Fever	65/121(53.7)	50/85(58.8)	OR = 1.2(95%CI 0.70-2.16)
Loss of weight	19/121(15.7)	21/85(24.7)	OR = 1.2(95%CI 0.64-2.43)
Poor knowledge of TB symptoms			
Cough > 2 weeks	19/121(15.7)	14/85(16.5)	OR = 0.9(95%CI 0.44-2.00)
Cough with blood	102/121(84.3)	64/85(75.3)	OR = 1.8(95%CI 0.88-3.53)
Difficult in breathing	83/121(68.6)	63/85(74.1)	OR = 1.0(95%CI 0.62-1.58)
Chest Pain	98/121(81.0)	73/85(85.9)	OR = 1.3(95%CI 0.90-1.95)
Fever	47/121(38.8)	34/85(40.0)	OR = 1.0(95%CI 0.54-1.68)
Loss of weight	97/121(80.2)	65/85(76.5)	OR = 1.2(95%CI 0.64-2.43)

*n = 3 were missing age
** n = 37 were missing HIV status

Authors' contributions

ESN is the primary author who was responsible for conceiving of the research idea, designing of the study, collection of data, analysis and interpretation of the results and writing of the draft and final manuscript. She is also the corresponding author. GSM, ERW and OM participated in proposal write up, data analysis and interpretation of the results, and writing of the draft and final manuscript.

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Pulmonary tuberculosis among women with cough attending clinics for family planning and maternal and child health in Dar Es Salaam, Tanzania

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Abstract

Background: Tuberculosis (TB) case detection in women has remained low in developing world. This study was conducted to determine the proportion of smear positive TB among women with cough regardless of the duration attending family Planning (FP) and Maternal and child health (MCH) clinics in Dar es Salaam.

Methods: We conducted a cross sectional study in all three municipal hospitals of Dar es Salaam, between October 2007 and June 2008. All women with cough attending FP and MCH clinics were screened for TB by smear microscopy. Pearson chi-square was used to compare group difference for categorical variables. Risk factors for smear positive were estimated by logistics regression with 95% confidence intervals (CI) given for odds ratios indicating statistically significant relationship if the CI did not include one.

Results: We enrolled a total of 749 TB suspects. Five hundred and twenty nine patients (70.6%) were from MCH clinics. Mean (SD) age was 27.6 (5.2) years. A total of 616 (82.2%) patients were coughing for less than two weeks as compared to 133 (17.8%), who coughed for two or more weeks. Among 616 TB suspects, 14 (2.3%) were smear positive TB patients, and of the 133 who had coughed for two or more weeks, 13 (9.8%) were smear positive TB patients. Risk factors associated with smear positive results were having attended more than one visit to any facility prior to diagnosis (OR = 6.8; 95%CI 2.57–18.0) and having HIV/AIDS (OR = 4.4; 95%CI 1.65–11.96). Long duration of cough was not a risk factor for being smear positive (OR = 1.6; 95%CI 0.59–4.49).

Conclusion: The proportion of smear positive TB patients among women with cough attending MCH and FP was 3.8%. Visits to any health facility prior to Diagnosis and HIV infection were risk for having a smear positive TB.

Background

TB is a problem especially in developing countries. More men than women are diagnosed with TB, whereas more women than men die from TB [1,2].

Since 1983 the annual increase of TB cases in Tanzania has been 2–5% and this is attributed to the increase in HIV/AIDS [3]. Women have been a highly vulnerable group for HIV compared to males, but TB case notification is higher in males as compared to females. Case detection of TB has remained low and it is even lower in women than in men. In 2005, only 37.2% of all smear positive TB patients detected in Tanzania were females [3].

TB case detection in Tanzania is mainly through passive case finding. Passive as oppose to active TB case finding is when symptomatic patients present themselves to the out-patients department (OPD) with cough of two or more weeks with or without accompanying symptoms, are screened for TB [4].

Low TB case detection in women has been associated with socio-cultural factors, low socio-economic status of women and women's tendency of regarding family matters as more important than their own health [5,6]. As shown in a study from India [7], women were found to visit heath facilities for immunization and their children's wellbeing rather than for their own health.

Interventions aimed at integrating passive TB case finding in other clinics like antenatal clinics has proven to be acceptable and has also been recommended in Malawi and South Africa [8,9]. Active case finding for TB revealed a significant number of undiagnosed TB cases among women attending PMTCT clinics in South Africa [9]. However, little is known about the extent of smear positive TB among women with cough attending FP and MCH clinics. This study was therefore, conducted to determine the proportion of smear positive TB among women with cough regardless of their cough duration, attending FP and MCH clinics in Dar es Salaam [3].

Methods

Setting

We conducted the study in three health facilities in Dar es Salaam. Dar es Salaam is located in the eastern part of the country, and is administratively divided into three districts namely Kinondoni, Temeke and Ilala, with respective populations of 1,083,913, 768,451 and 634,924 [10]. For operational reasons each district is regarded by the National Tuberculosis and Leprosy Control Program (NTLP) as a region [4]. The facilities included the municipal hospitals of Mwananyamala, Amana and Temeke. We selected Dar es Salaam purposefully because of its high TB burden.

Study design and data collection

We conducted a cross sectional hospital based study between October 2007 and June 2008. We enrolled all women with cough, attending family planning clinics and those who escorted their children for MCH services. To ensure that all women with cough were enrolled into the study, some of the data collectors were placed at the MCH and FP registration area, in such a way that every woman was asked if she had cough. Those with cough were directed to a study clinician. Those who reported cough, regardless of the duration, were regarded as TB suspects and therefore screened for TB by smear microscopy.

We trained study clinicians and other data collectors from FP and MCH clinics from the selected hospitals. We requested them to register all patients with cough in a study register and asked the patients to submit three sputum samples as per national guidelines[11]. Study registers contained information on patients' socio-demographic characteristics, cough duration in days or weeks and sputum results. Other information included other clinics of consultation for the current respiratory symptoms and number of visits made.

The standard procedure recommended by NTLP in the diagnosis of pulmonary tuberculosis is to examine by smear microscopy all sputum samples from self presenting symptomatic patients [4]. None of the TB case detection activities are routinely conducted at MCH and/or FP clinics. This study was carried out at a time when the Central Tuberculosis Reference Laboratory (CTRL) was conducting quality assurance using Lot Quality Assurance System (LQAS). The results of all laboratories under the study were satisfactory. The quality check for the submitted samples was done according to routine NTLP guidelines [4].

We calculated the minimum sample size of 567 using Epi info version 6.4, statcalc computer software, with the assumption that total population of women aged 15–44 years in Dar es Salaam is 710,486 [10] and we wished to determine with 95% confidence interval (α error of 0.05) a prevalence range of 0.3% to 0.75% of pulmonary tuberculosis (PTB) among women aged 15 to 44 years in Dar es Salaam in 2005 [3].

Operational definitions

TB suspect: Any woman of reproductive age group with cough, regardless of the duration, who attended FP and MCH clinics.

Smear positive patient: a patient where at least two sputum samples were positive for acid fast bacilli [4].

Smear negative patient: a patient where all three sputum samples were negative for acid fast bacilli [4].

Ethical considerations

We were granted ethical clearance by the Tanzania Medical Research Coordinating Committee. We obtained informed verbal consent from each interviewee before enrolment into the study. Patients with one smear positive sputum sample were excluded from the analysis but they were referred to the district tuberculosis and leprosy coordinator (DTLC) for treatment and follow up using NTLP procedures. All patients with PTB were also referred to the DTLC for treatment. Non TB patients were treated according to their respective diagnosis.

Analysis

Data collected were double entered, cleaned and coded using Epi-info version 6 (Centre for Diseased Control and Prevention, Atlanta, GA, USA). We analyzed the data using SPSS version 14 for windows (SPSS Inc, Chicago, IL, USA). The outcome variable was diagnosis of smear positive TB. We calculated the proportion of patients with smear positive TB. We explored possible associations between cough duration and smear results, clinic of diagnosis, place of first presentation and number of visits made prior to diagnosis. We used Pearson chi-Square to compare group difference for categorical variables. Differences were considered statistically significant if $p \leq 5\%$. Finally, we estimated risk factors for smear positive by logistic regression with 95% (CI) given for odds ratios indicating statistically significant relationship if both values were above or below 1.

Results

Baseline profile of the study participants

We enrolled a total of 749 TB suspects. Five hundred and twenty nine patients (70.6%) were from MCH clinics. Table 1 shows the baseline profiles of the 749 study participants according to their smear results. Mean (SD) age was 27.6 (5.2) years (95% CI 27.2–28.0) and median (range) age was 27 (16–50) years. The majority (90.2%) were between 15 to 34 years.

Comparison of smear positive PTB patients by cough duration

A total of 616 (82.2%) patients were coughing for less than two weeks as compared to 133 (17.8%) who coughed for two or more weeks. Among patients who coughed for less that two weeks, 425 (69.0%) were from MCH as compared to only 191 (31.0%) from FP. Among 133 patients who coughed for two or more weeks, 104 (78.2%) were from MCH clinics as compared to 29 (21.8%) from FP. A significantly higher proportion (78.2%) of patients who coughed for two or more weeks attended MCH clinics ($X^2 = 4.5$, $p = 0.035$). As summarized in figure 1 and table 1, among 616 TB suspects who had coughed for less than two weeks 14 (2.3%) were smear positive TB patients, and of the 133 who had coughed for two or more weeks 13 (9.8%) were smear positive TB patients.

Comparison between smear positive TB patients and place of first consultation

Among the 749 TB suspects, 430 (57.4%) had visited health facilities for care prior to their diagnosis. Out of these, 124 (28.8%) had coughed for two or more weeks. The most visited facilities were medical stores by 227 (52.4%), government hospitals by 110 (25.6%), private hospitals by 84 (19.5%) and traditional healers by 9 (2.2%) as shown in Table 1. A high proportion (81.5%) of smear positive patients had visited a health facility for care prior to their diagnosis ($X^2 = 6.6$, $p = 0.010$). It was more common for smear positive patients to have used hospitals as their first point of visit than smear negative patients ($X^2 = 4.4$, $p = 0.035$). Moreover, a higher proportion of smear positive patients (42.9%) made more than two visits prior to diagnosis as compared to smear negative patients (11.4%) ($X^2 = 17.5$, $p = 0.001$).

Comparison of smear positive PTB patients by clinic

Out of 749 TB suspects, 27 (3.8%) were smear positive TB patients. Among the 27 smear positive patients, 22 (84.6%) were from MCH clinics and 5 (15.4%) were from FP clinics. There was no statistically significant difference when comparing the distribution of proportions of smear positive TB patients among TB suspects from MCH and those from FP clinics ($X^2 = 0.2$; $p = 0.686$).

Risk factors associated with smear positive results

Risk factors associated with smear positive results were having attended more than one visit to any facility prior to diagnosis (OR = 6.8; 95%CI 2.57–18.0) and having HIV/AIDS (OR = 4.4; 95%CI 1.65–11.96). Long duration of cough, clinic of diagnosis and social demographic characteristics investigated were not risk factors for smear positive TB as shown in Table 1.

Discussion

The key finding of this study is that the proportion of women with active pulmonary tuberculosis among coughers attending MCH and FP clinics was 3.8%.

According to the existing NTLP guidelines, none of the TB screening activities are done in MCH and FP clinics. Our study indicates that a significant proportion of women with cough attending MCH and FP clinics have pulmonary TB. Taking into consideration the low case detection

Table 1: Risk factors associated with pulmonary TB among women with cough attending FP and MCH clinics.

Patient characteristics	Smear positive TB patients n (%)	Smear negative patients n (%)	Total n (%)	Odds ratio (95%CI)
Age distribution				
15 to 34 yrs	23/27 (85.2)	619/684 (90.5)	642/711 (90.3)	1.66 (0.56–4.94)
> 34 years	4/27 (14.8)	65/684 (9.5)	69/711 (9.7)	
Marital status				
Married or cohabiting	17/27 (63.0)	481/686 (70.1)	498/713 (69.8)	1.4 (0.62–3.07)
Single, divorced, or widow	10/27 (37.0)	205/686 (29.9)	215/713 (30.2)	
Education Level				
Primary school	24/27 (88.9)	636/686 (92.7)	660/713 (92.6)	1.6 (0.46–5.46)
> primary school	3/27 (11.1)	50/686 (7.3)	45/713 (6.3)	
Occupation				
House wife	19/26 (73.1)	374/685 (54.6)	393/711 (55.3)	1.9 (0.85–4.25)
Employed	1/26 (3.8)	19/685 (2.8)	20/711 (2.8)	
Self employed	6/26 (23.1)	292/685 (42.6)	298/711 (41.9)	
Cough duration*				
Two weeks or more	13/27 (48.1)	114. 686 (16.6)	127/713 (17.8)	1.6 (0.59–4.49)
Less than 2 weeks	14/27 (51.9)	572/686 (83.4)	586/713 (82.2)	
Clinic of attendance				
MCH	22/27 (81.5)	487/686 (71.0)	509/713 (71.4)	1.8 (0.67–4.81)
FP	5/27 (18.5)	199/686 (29.0)	204/713 (28.6)	
Place of 1st consultation				
Government facility	6/22 (27.3)	75/388 (19.3)	81/410 (19.8)	
Private facility	9/22 (40.9)	96/388 (24.7)	105/410 (25.6)	
Pharmacy	7/22 (31.8)	208/388 (53.6)	215/410 (52.4)	
Traditional healer	0	9/388 (2.3)	9/410 (2.2)	
No of visit to any facility				
More than one visit	15/21 (71.4)	104/387 (26.9)	119/408 (29.2)	6.8 (95%CI 2.57–18.0)
Only one visit	6/21 (28.6)	283/387 (73.1)	289/408 (70.8)	

Table 1: Risk factors associated with pulmonary TB among women with cough attending FP and MCH clinics. *(Continued)*

HIV/AIDS self reported				
HIV/AIDS positive	10/18 (55.6)	43/196 (21.9)	53/214 (24.8)	4.4 (1.65–11.96)
HIV/AIDS negative	8/18 (44.4)	153/196 (78.1)	161/214 (75.2)	

*Cough duration unadjusted for HIV/AIDS: OR 4.7 (95%CI 2.13–10.18)
*Cough duration adjusted for HIV/AIDS: OR = 1.6 (95%CI 0.59–4.49)
Some total do not add up to 749 owing to some missing information.

in women coupled with increase in TB/HIV co-infection, it may be necessary to expand TB diagnostic services to MCH and FP clinics. However, there is a need to conduct more studies to look at the cost-effectiveness and feasibility of expanding TB diagnosis services to the MCH and FP clinics.

Moreover, the majority of the smear positive women were more likely to have visited government hospitals prior to their diagnosis without being recognized as TB suspects. In fact, the majority of them had visited health facilities prior to their diagnosis and made more than one visit but was yet not suspected. Our finding of failure to suspect women is consistent with other studies conducted in Vietnam and Tanzania, where factors like poor knowledge of recognizing and reporting TB symptoms and ignorance among health care workers were associated with delay in TB case detection [11,12].

The majority of women had visited health facilities prior to their diagnosis and made more than one visit but was yet not suspected. This might be explained, though not investigated in this study, by patients' inability to explain well the symptoms and duration of their illness. They could also have first visited health care posts where they were not properly taken care of, e.g. medical stores and traditional healers. Lack of awareness by health personnel and lack of TB diagnostic services could also offer an explanation [6,11,13]. Like in other studies conducted in Brazil and Dar es Salaam, where the probability of having TB did not depend on cough duration [14,15], risk factor for being smear positive TB patient in our study did not depend on the duration of cough. Other risk factors associated with smear positive results were having HIV/AIDS. This is in contrary to other studies where HIV/AIDS positive patients were more likely to be smear negative [16,17]. Though not investigated in this study, but as shown in other studies, possibly the level of immune suppression of our study patients was not so severe to the extent of affecting their TB presentation [18].

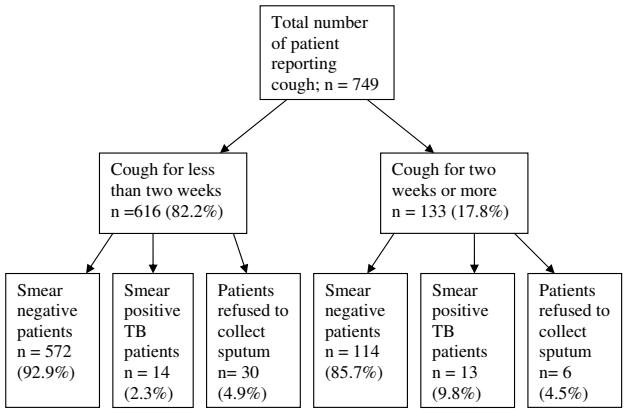

Figure 1
Comparison of smear results by cough duration.

Worthy of note also is the fact that women who had a long duration of cough were more likely to be attending MCH than FP clinics. MCH clinics in the study areas were not only the clinics for checking under-fives wellbeing but also acted as referral clinics for the sick children. Studies have indicated that women place the needs of their children and other family activities above their own health. A study in India demonstrated that women tended to visit heath facilities for immunization and their children's wellbeing rather than for their own health [7].

However, it should be kept in mind that the observations from our study are limited to municipal hospitals. A more comprehensive knowledge base could be provided by a multi-site study, with a mixture of governmental and private health facilities, including both urban and rural areas. Another limitation of the study is the potential possibility of imprecise estimates of cough duration, type of facility and number of visits made prior to diagnosis due to recall bias.

Conclusion

Proportion of smear positive TB patients among women with cough attending MCH and FP is 3.8%. Visits to any facility prior to diagnosis and HIV Co-infection were risk for having a smear positive TB.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

ESN is the primary author who was responsible for conceiving of the research idea, designing of the study, collection of data, analysis and interpretation of the results and writing of the draft and final manuscript. She is also the corresponding author. GSM, ERW and OM participated in proposal write up and were consulted during data collection. Also, they participated during, data analysis and interpretation of the results, writing of the draft and final manuscript. All authors read and approved the final version of the manuscript.

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Tuberculosis regimen change in high-burden countries

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SUMMARY

BACKGROUND: Experience with past tuberculosis (TB) regimen changes can guide future regimen changes.

METHODS: To explore the process, major players and procedural success factors for recent public sector TB regimen changes, we conducted 166 interviews of country stakeholders in 21 of the 22 TB high-burden countries (HBCs).

RESULTS: Stakeholders described 40 distinct regimen changes for drug-susceptible TB. Once countries committed to considering a change, the average timing was ~1 year for decision-making and ~2 years for rollout. Stakeholders more often cited concerns that were program-based (e.g., logistics and cost) rather than patient-focused (e.g., side effects), and patient representatives were seldom part of decision making. Decision-making bodies in higher-income HBCs had more formalized procedures and fewer international participants. Pilot studies focused on logistics were more common than effectiveness studies, and the evidence base was often felt to be insufficient. Once implementation started, weaknesses in drug management were often exposed, with additional complications if local manufacturing was required. Best practices for regimen change included early engagement of budgeting staff, procurement staff, regulators and manufacturers.

CONCLUSIONS: Future decision makers will benefit from strengthened decision-making bodies, patient input, early and comprehensive planning, and regimens and evidence that address local, practical implementation issues.

KEY WORDS: regimen change; tuberculosis drugs; high-burden countries

THE DEVELOPMENT of new drugs for tuberculosis (TB) is an identified global priority,[1,2] but adoption will undoubtedly bring challenges.[3] For TB regimen change, existing examples can provide guidance for future efforts. In the present study, we examine recent experiences with regimen change in 21 of the 22 high TB burden countries.*

Regimens for drug-susceptible TB have been shortened based on clinical trials[4] and altered due to widespread human immunodeficiency virus (HIV) infection,[5] leaving the two main variants as 2HRZE/6HE and 2HRZE/4RH.†[6] The World Health Organization (WHO) initially recommended both,[5] but then favored the 6-month regimen for high HIV settings (starting in 2003), and then for all settings[7,8] (starting in 2004). The latter change was based on the trial of the International Union Against Tuberculosis and Lung Disease (The Union) demonstrating increased efficacy of 2HRZE/4HR over 2HRZE/6HE.[9]

Some of the resulting changes from 8 to 6 month regimens are documented in this study, as is the adoption of various fixed-dose combinations (FDCs) of TB drugs. FDCs prevent monotherapy,[10] and can simplify regimens for patients, physicians, and procurement and distribution systems, thus potentially helping to reduce medication errors and stock-outs.[11–13] FDC use may increase adherence, although supporting evidence for this is scarce.[14,15] Adoption of FDCs has sometimes been delayed by the lack of access to FDCs with proven bioequivalence to single drug formulations.[16]

Decision making during regimen change requires the balancing of evidence. For future changes, the competition posed by the existing regimen for drug-susceptible disease is considerable. The existing Category I regimen works with ~95% efficacy under trial conditions (so efficacy improvements are impractical and unlikely), and costs US$20–30 for the entire multidrug, multi-month regimen (therefore, drug costs are likely to increase). It can be delivered using only two types of pills (one four-drug FDC and one two-drug FDC; so drug management may be more complex with a new regimen), and uses drugs with few or no other indications (so controlling TB drug use may

*Interviews in Myanmar were not possible due to the intervention of Cyclone Nargis.

†That is, 2 months of isoniazid (H), rifampin (R), pyrazinamide (Z) and ethambutol (E), followed by 6 months of H and E or 4 months of H and R.

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become more challenging). However, shorter regimens for drug-susceptible TB may increase adherence, reduce default, attract more TB patients, and bring higher effective cure rates and fewer new cases of multidrug-resistant TB (MDR-TB). Therefore, the identification of lengthy regimens as a problem and treatment shortening as a global goal have been formalized by the Stop TB Partnership in the Global Plan 2006–2015.[1]

Treatment-shortening research is furthest advanced for 4-month multidrug regimens that include either gatifloxacin or moxifloxacin. Both of these fluoroquinolone antibiotics are in Phase III trials to test the non-inferiority of the fluoroquinolone-containing regimen compared to the standard 2HRZE/4HR regimen.[17]

Regimen change requires active effort[18] by many actors,[3,12] including an agent—often outside the national programs—that is specifically responsible for promoting and facilitating the change.[19,20] Here, we present an analysis of the processes of adoption, introduction and implementation of past TB regimens for drug-susceptible TB. These experiences provide a rationale for prioritizing future actions that will maximize uptake of new TB regimens.

METHODS

Included in this study are the 22 high-burden countries (HBCs) for TB, representing 80% of the worldwide burden of TB. As in our previous study,[21] our primary focus was on public sector decision making, given the importance of the public sector in TB control, and on drug-susceptible TB specifically, as MDR-TB raises very different cost and complexity issues.

Interview topics were based on results from our previous study[21] and the stepwise process of regimen change outlined by the Stop TB Partnership's Retooling Taskforce.[3] A core interview guide about regimen change and the health system, an abbreviated guide for interviewees with experience across TB programs in multiple countries, and a regulatory guide for staff with regulatory expertise were administered during respectively 116, 88 and 46 interviews.

Each interviewer (one per country) was trained by phone using a standardized information packet and training presentation. Interviewees were identified by a combination of purposive sampling and snowball sampling, as in previous studies of public sector regimen change.[20,21] Each interviewer identified, in collaboration with the central study team, an initial set of three key interviewees—one each from the National TB Program (NTP), the WHO country office, and the regulatory authority. The initial NTP and WHO interviewees were asked to identify other individuals and organizations involved in TB regimen decision making.

From April to August 2008, 166 interviews were conducted in 21 countries (4–12 interviews per country, Table 1). Interviews were conducted in person in all countries but Pakistan, where phone interviews

Table 1 Country stakeholders interviewed

Country	NTP	Regulatory authority	WHO	MoH	NGO/TA provider	TB/chest hospital physician	Researcher/ academic/ associate professor	Donor	Other	Interviews *n**	Respondents *n**
Afghanistan	—	1 (2)	1 (3)		2					4	7
Bangladesh	1	2	2		1	1 (3)	2			9	11
Brazil	1 (3)	1 (2)	1 (2)	1	1		1			6	10
Cambodia	1	2	2		3					8	8
China	1 (2)	2	2			3 (15)				8	21
Democratic Republic of Congo	1	1	1		1		3	1		8	8
Ethiopia	1	1	1		2					5	5
India	1	2	2 (3)	1	1	1 (2)	3 (5)			11	15
Indonesia	1	2 (3)	2 (3)		1		1			7	9
Kenya	1	3	1		5		1	1		12	12
Mozambique	1		2		2			1		6	6
Nigeria	1	1	1		5		1			9	9
Pakistan	1	1	1		1					4	4
Philippines	1	2	1	1	2 (3)		3 (5)			10	13
Russian Federation	NA	1	1	1	1		3		1	8	8
South Africa	1	3			2		4			10	10
Thailand	NA	1	1	2		1	2		1	8	8
Uganda	2	1	1		3	2	2			11	11
United Republic of Tanzania	1	1	1		1		2			6	6
Viet Nam	1 (5)	1 (3)	2	1	2		1		1	9	15
Zimbabwe	1	1	1	1			1		2	7	7
Total										166	203

*Some interviews included multiple respondents. In the columns to the left, the number of distinct interviews is listed, and the number of people interviewed (if different) is listed in parentheses.

NTP = National TB Program; WHO = World Health Organization; MoH = Ministry of Health; NGO = non-governmental organization; TA = technical assistance; TB = tuberculosis.

were used. Informed consent was obtained verbally using a standard script. No ethics committee was involved, as the unit of inquiry was held to be institutions (and their behavior) rather than individuals. Cyclone Nargis prevented interviews in Myanmar; information was therefore gathered from publicly available sources and by e-mail from two expert reviewers.

Responses were collated into country reports, which were reviewed by the interviewers and one or more external reviewers. The reports referenced the source of every response, allowing quantitation of the qualitative responses. Repeated observations by an individual were counted only once. Positive and negative factors for past regimen change were volunteered by stakeholders without the use of any probes (i.e., based on general accounts of past regimen change), thus reducing potential bias. Similarly, expectations about future changes were derived from general questions about the ease and speed of adoption.

RESULTS

Types and lengths of regimen changes

Stakeholders in 21 HBCs were asked about the most recent regimen changes for drug-susceptible TB in their country. They described 40 regimen change events, including 16 FDC adoptions, seven considerations of the change from the 8- to the 6-month Category I regimen, and four deletions of Category III (Table 2). Multiple changes were often introduced at once (Brazil, Cambodia, Indonesia, Mozambique, Uganda, see Table 2). Older adoption events, such as the adoption of the 6-month regimen in many Asian countries, were not mentioned and therefore not included in the analysis.

Timing estimates for decision-making and roll-out were available for 28 of the regimen changes. After excluding four regimen changes that took longer than average due to the size of the country, complexity of the change, or political instability, and three simpler and shorter Category III deletions, the 21 remaining changes took 0.91 ± 0.54 years for decision-making and 1.93 years ± 0.99 years for roll-out (mean ± standard deviation).

In Ethiopia and Nigeria, the change from the 8- to the 6-month regimen was indefinitely postponed after an initial, positive decision, and Afghanistan considered but rejected the same change. Indeed, of the 10 HBCs using the 8-month regimen at the time of the 2003 and 2004 WHO recommendations, only half had changed to the 6-month regimen; these five decisions were reached an average of 2 years after the locally relevant WHO recommendation. Stakeholders reported that the reticence to change regimens was primarily due to a perceived lack of directly observed therapy (DOT) and thus concern about increasing rifampicin (RMP) resistance.

Table 2 Past regimen changes described by stakeholders

Country	Regimen changes	Date of decision
Afghanistan	Introduce Category III regimen (including HRZ 3-drug FDC)	2003
Bangladesh	Intermittent to daily dosing in continuation phase	2008
	Adoption of FDCs	2002
Brazil	12 to 6 months (4RHZ/2HR); addition of RH FDC	1979–1980
	Add E to intensive phase; alter H and Z doses, new RH FDC (plus new MDR-TB regimens)	2008
Cambodia	8 to 6 months; introduce (RHZ) and (RH) FDCs	2005
	Introduction of 4-FDC	2008
	Adoption of WHO's pediatric TB guidelines	2008
China	FDC adoption	Ongoing
	Delete Category III regimen	2007
	Option of daily treatment	2007–8
Democratic Republic of Congo	4-FDC adoption	2001
	8 to 6 months; change from intermittent to daily continuation phase	2004
Ethiopia	4-drug FDCs for Category I and II, replacing (RHZ)S	2004–2005
	4-drug FDCs for Category III regimen	2007
	8 to 6 months (stalled for fear of poor adherence)	2007
India	Daily to intermittent regimen	1997
	Combipack and pediatric formulations	2005–2006
Indonesia	FDC adoption (included dosage and frequency changes)	2002 (partial); 2005
	Deletion of Category III	2006
Kenya	8 to 6 months	2006
Mozambique	8 to 6 months, including new FDC	2005
Myanmar	FDCs daily (replaced intermittent loose drugs)	2004
Nigeria	Introduced 4-FDC for Category I and II	2007
	8 to 6 months (not completed)	2008
Pakistan	Adoption of FDCs	2000
	Deletion of Category III	End 2002
Philippines	Single agents to FDCs	2002
Russian Federation	Introduction of Categories I, II, III	2003
	Introduction of Regimen IIb	
South Africa	Change from 5 to 7 days per week dosing	2007
	FDC adoption	1996
Thailand	Deletion of Category III (plus change in MDR-TB regimens)	2008
	FDC adoption	2005–2006
	Change to short-course regimen	1983
Uganda	10 to 8 months, and introduction of FDCs	1995–1996
United Republic of Tanzania	8 to 6 months	2006
Viet Nam	FDC adoption (3-drug and 2-drug)	1997
	9 to 8 months	1999
Zimbabwe	FDC adoption	2007

H = isoniazid; R = rifampin; Z = pyrazinamide; FDC = fixed-dose combination; E = ethambutol; MDR-TB = multidrug-resistant tuberculosis; WHO = World Health Organization; S = streptomycin.

Role of decision-making procedures and bodies at country level

Capacity to consider TB regimen change varies among the 21 HBCs. Nine of the HBCs have specific bodies and clear procedures to consider regimen changes; six have specific bodies but somewhat unclear procedures; two have bodies that could potentially fulfill such a function; and four do not have such bodies.

Membership of decision-making bodies was exclusively or almost exclusively national in 10 HBCs, a mixture of nationals and internationals in six HBCs, and led by the NTP but with large numbers of international organizations represented in four HBCs. Higher-income countries had more predominantly national representation in these decision-making structures.

The decision to adopt was most often reached by consensus-driven committees, but decisions in at least three HBCs were reportedly made by a single individual. Although the latter approach led to rapid decision making, in one HBC this decision was later overturned.

The TB decision-making bodies were described as having a public health orientation, with the notable exception of Bangladesh, whose committee included more physicians and was reported to take a more medically oriented view. Patient input was rarely mentioned in accounts of past regimen changes (Kenya only) and descriptions of future regimen change procedures (Brazil, Kenya and Nigeria only), and patient advocates were listed as members in few of the decision-making bodies (Bangladesh, Brazil and Indonesia only).

Types of evidence used to justify past regimen changes

Factors cited most commonly as supporting past regimen changes (Table 3) were WHO recommendations (both globally and from local country offices), and results from in-country studies (clinical trials, effectiveness studies or pilots—see below).

The supply of free drugs from the Global Drug Facility (GDF, available only as FDCs) was cited as a major reason for regimen change in 8 of the 16 FDC adoptions described. FDCs were also adopted based on the potential for improved adherence and easier logistics (four and five of the FDC adoptions, respectively).

There was a noticeable predominance of programmatic considerations in decision making, with less mention of issues that would directly affect individual patient acceptability. For example, major stakeholders in countries such as China and the Philippines stated that FDCs were adopted due to ease of drug management, but they did not mention patient benefits such as reduced pill burden. Across all HBCs, certain concerns closer to patient care (side effects from thioacetazone, and lower pill burden) were mentioned only once.

In general, awareness of WHO recommendations (Table 3) penetrated to the country level more successfully than did the global evidence base (e.g., peer reviewed, clinical trial results). Improved efficacy was noted as a reason for changing from 8 to 6 months only in the Democratic Republic of Congo and Kenya (and for making other changes in three other HBCs). One stakeholder in each of these two HBCs cited the evidence from the Union trial that demonstrated the clinical superiority of the 6-month regimen.[9]

There was a perception of insufficient evidence to support decision-making, contributing to a difficulty reaching consensus (13 stakeholders each, Table 4). Exacerbating these conditions, local studies were started but were either not completed or not sufficient to inform decision-making (five HBCs), and there was a lack of effectiveness data and lack of local studies (two to three HBCs each). Some stakeholders noted that some past regimen changes were based less on direct evidence and more on a push (from global technical organizations) for global standardization.

The most frequently cited factor hindering a decision to change was cost (Table 4). In China, it was a

Table 3 Positive factors affecting decision-making during past regimen changes

Decision factor during regimen change	Total respondents *n*	Countries *n*
WHO recommendation (global)	52	19
Results from in-country study (randomized controlled trial, effectiveness or pilot study)	20	10
WHO recommendation (country office)	17	13
Free drugs from GDF	9	8
Increased efficacy	7	5
Improved adherence	7	6
Easier logistics (delivery, procurement, distribution)	7	5
Lower cost (of delivery, etc)	4	2
Union recommendation	4	4
Public sector following private sector example	4	3
Adoption by neighboring countries as positive influence	3	3
Results from Union trial	2	2
Introduction of other systemic changes	2	1
Reduction in side effects	2	2
Pressure from civil society	1	1
Lower pill burden	1	1
KNCV recommendation	1	1
Stop TB Partnership recommendation	1	1
ISTC as guidance	1	1
Cost-effectiveness data	1	1
Physicians outside NTP led the way	1	1
Treatment alignment with private sector	1	1
Manufacturers promoted the change to NTP	1	1
Easier to do DOT 3×/week	1	1
Change easier due to pattern of previous changes	1	1
Total responses	151	
Total respondents in this section	100	

WHO = World Health Organization; GDF = Global Drug Facility; Union = International Union Against Tuberculosis and Lung Disease; TB = tuberculosis; ISTC = International Standards of Tuberculosis Care; NTP = National TB Program; DOT = directly observed therapy.

Table 4 Negative factors during past regimen changes

Delay or difficulty during decision making or roll-out	Total respondents *n*	Countries *n*
Cost as significant determinant	20	8
Insufficient evidence	13	10
Lack of consensus slowed decision making	13	8
Problems with drug logistics after change	12	10
Local study started but not completed or insufficient for decision making	6	5
Better DOT needed in continuation phase/ fear loss of R to resistance	5	4
Lack of acceptance by physicians	4	2
For 6 months: must delay HIV/AIDS drugs by 6 months or use efavirenz	3	1
New drugs failed QA tests	3	1
Lack of local study slowed decision	3	3
Delay due to phase-out of old drugs	3	2
Insufficient effectiveness data	2	2
Delay due to raising new budget	1	2
Adherence benefit less important	1	1
Changed who had power in system	1	1
Concern about side effects	1	1
Concern about stability of drugs	1	1
No written procedures for regimen change	1	1
Resistance from local WHO officer	1	1
Regimen change was slowed because it was packaged with other interventions	1	1
Delay due to resistance from local manufacturers	1	1
Total responses	95	

DOT = directly observed therapy; R = rifampin; HIV = human immunodeficiency virus; AIDS = acquired immune-deficiency syndrome; QA = quality assurance; WHO = World Health Organization.

Table 5 Evidence required for future regimen change

Requirement*	Total respondents *n*	Countries *n*
Safety and efficacy		All
Price information/depends on price	37	15
Assessment of logistics prior to implementing	28	10
Cost-effectiveness data	20	9
Implementation evidence from other countries	13	6
Drug resistance data	11	7
Funding for training	10	7
Greater efficacy	7	4
Reduction in relapse rate	5	3
Proof of improved adherence	4	3
Intermittent regimen	4	1
Evidence of patient acceptance	4	2
Second-line regimen that has an alternative to fluoroquinolones	3	2
Sputum conversion rate	3	1
Evidence of provider acceptance	3	2
List of adverse effects	3	3
Fewer side effects	3	2
Adoption in high-income countries	2	1
Better DOT as prerequisite	2	2
Pill burden that is the same or less	2	2
New mechanism of action	2	2
Delay for drug manufacturer's contract to expire or for the disposal of current stocks	2	2
Education that shortening of the regimen is not due to corruption	2	2
Equal or lower cost for program	1	1
Local manufacturing	1	1
Improved drug management as prerequisite	1	1
WHO African Region recommendation	1	1
Data from TB-HIV co-infected individuals	1	1
Involvement of HIV program and no ARV interactions	1	1
Involvement of drug manufacturers	1	1
Safeguards against non-TB use of new drugs	1	1
Total	178	

*A question in this section asked about 'data required from local clinical trials', so mentions of 'local trials' were not scored here (but see Table 6).
DOT = directly observed therapy; WHO = World Health Organization; TB = tuberculosis; HIV = human immunodeficiency virus; ARV = antiretroviral.

'primary determinant' slowing FDC adoption; in Thailand, cost alone delayed FDC adoption, and then resulted in a 2-year hiatus in the roll-out. The need to raise additional funds in TB budgets also delayed regimen changes in Afghanistan and Kenya.

Evidence needed to support future regimen changes

Price was the evidence that most stakeholders would request for future changes (Table 5). Cost-effectiveness data were also requested (20 respondents, Table 5), although only one stakeholder had mentioned it as playing a part in past regimen change (Table 3), and several stakeholders mentioned that absolute cost was more influential than more formal cost-effectiveness analyses.

Cost was also the main reason why a 4-month regimen might not be favored (17 respondents in five HBCs). The most cited reason for favoring a 4-month regimen—improved adherence (22 respondents in 11 HBCs)—was volunteered over 5-fold more often than the main patient-centered reason (reduction of side effects, four respondents in two HBCs).

Contribution of and requirements for local research

The distinction between clinical studies, effectiveness studies and pilots was not clear to all respondents. However, descriptions of past regimen changes included the following accounts of local research: four HBCs did no local studies; nine HBCs did only pilot studies; Bangladesh, China, Indonesia and the Russian Federation did effectiveness studies; and Brazil, India, South Africa and Uganda did randomized controlled trials (RCTs) plus pilot studies (Table 6). Of the nine HBCs that did only pilot studies, only two indicated that these pilot studies were part of the decision-making process. The remaining seven were described as part of a phased roll-out, with the adoption decision already having been made, and the pilot contributing only to the refinement of operational aspects before full implementation.

For adoption of a future regimen by the NTP, stakeholders stated that local clinical research would be: required in-country by Brazil, China, and possibly India; required only at a regional level by 11–12 HBCs; and not required by seven HBCs. They believed that local effectiveness studies would be required in-country by 12 HBCs (although in half of these the

Table 6 Requirement for local effectiveness studies*

Country	May require local effectiveness studies for future NTP adoption	Did research by a local institution contribute to any past regimen change?	Were in-country trials mentioned in the specific accounts of regimen change in this study?	Were the resulting data (from previous column) used in decision making?
Afghanistan	No	No	None	No
Bangladesh	Yes, limited	Yes	Effectiveness studies and pilot studies	Yes
Brazil	Yes	Yes	RCTs and pilot studies	Yes
Cambodia	Yes, limited	No (pilot by donors)	Pilot studies	Yes
China	Yes	Yes	Effectiveness studies	Yes
Democratic Republic of Congo	No	No	None	No
Ethiopia	No	No	None	No
India	Yes	Yes	RCTs and pilot studies	Yes
Indonesia	Yes, limited	No (trial conducted by KNCV)	Effectiveness studies and pilot studies	Yes
Kenya	Regional	Yes	Pilot studies	No†
Mozambique	No	No	Pilot studies	No
Myanmar	Unknown	NA	NA	NA
Nigeria	Yes, limited	No	Pilot studies	No
Pakistan	Yes, limited	No	None	No
Philippines	Yes, limited	Yes	Pilot studies	No‡
Russian Federation	Yes	Yes	Effectiveness studies and pilot studies	Yes
South Africa	Yes, but regional OK	Yes	Yes, non-specifically. RCTs and pilot studies mentioned elsewhere in report	Yes
Thailand	Yes	No	Pilot studies	No
Uganda	Mixed opinion	Yes	RCTs and pilot studies	Yes
United Republic of Tanzania	Mixed opinion	Yes	Pilot studies	No§
Viet Nam	Yes	Yes	Pilot studies	Yes
Zimbabwe	Mixed opinion	Yes	Pilot studies	No

*Responses are color coded, with unknown responses in white, negative responses in red, partially positive responses in yellow, and positive responses in green. Thus, countries with multiple green entries have been and will be strongly reliant on local evidence for change.
†The Kenya Medical Research Institute (KEMRI) provided data for other regimen changes not described in detail in this study.
‡Local evidence showed that compliance was low, but not that FDCs would improve this.
§The National Institute of Medical Research (NIMR) may have contributed evidence for other regimen changes not described in detail in this study.
NTP = National TB Program; RCT = randomized controlled trial; NA = not available; FDC = fixed-dose combination.

studies should be limited in scope to operational issues and/or pilot studies).

Stakeholders stated that studies by local researchers could serve multiple functions, including bridging the gap between clinical trial and field conditions, empowering local advocates to support a change, and speeding adoption.

Local manufacturing and quality assurance

Some governments favor locally manufactured drugs (to support nascent industries), whereas donors may insist on internationally sourced drugs (if local drugs are not proven to meet international standards of quality assurance). During a regimen change, uncertainties about funding source may lead to uncertainties in new drug procurement. For example, during an FDC regimen change in Indonesia, the funding source for the new drug was reportedly changed from government to the Global Fund to Fight AIDS, TB and Malaria (Global Fund), thus requiring a switch from local manufacturers to Global Drug Facility (GDF) drugs. This left local manufacturers with excess supply, and was a disincentive to their future participation in the TB drug market. This problem is more likely for HBCs that are developed enough to have local manufacturing, but still reliant on outside

funding for a substantial portion of their TB drug procurement.

First-line anti-tuberculosis drugs were reported as being produced by local (in-country) manufacturers in significant quantities in 13 of the 22 HBCs.* Procurement from local manufacturers was described as being absolutely required only in Brazil, but encouraged (sometimes strongly, if government funds are being used, e.g., in Indonesia) in 12 additional HBCs.

Procedural delays, difficulties and best practices

Prior to roll-out, several procedures were mentioned as potentially causing major, local adoption delays—up to a year or more for each. These include getting sufficient funds into long-range budget plans (for training and drug costs for a new regimen); addition of a drug to the National Essential Medicines List (NEML); negotiating and doing technology transfer between global and local manufacturers; procurement processes; and using up old drug stocks before rolling out (as countries stockpile 12 months or more of current drugs).

The biggest problems identified during roll-outs were related to drug logistics. Regimen changes put additional stress on drug procurement and distribution systems. Phase-out plans were reportedly lacking in Cambodia and Pakistan; large-scale expiries and drug destruction occurred during regimen changes in Cambodia, Democratic Republic of Congo, Kenya and Zimbabwe; there were overlapping orders of new and old drugs and substandard drugs in Indonesia; and a regimen change led to a drug shortage in Nigeria. Finally, the quantity of drugs in stock drove the speed of roll-out in Kenya (first delay, then acceleration) and the Philippines (immediate roll-out prior to completing a pilot).

Training was mentioned frequently. One stakeholder in the Philippines noted that training costs would delay the implementation of serial regimen changes, and a stakeholder in Mozambique noted that community-based DOTS is becoming more widespread, and that this may make retraining for a new regimen more challenging. Finally, a stakeholder in Nigeria noted that, during a treatment-shortening regimen change, patients received insufficient information and believed they were being shortchanged by government staff.

Successful practices in past regimen changes included early identification of sufficient funding (Philippines), redistributing old drug regimens from early adopting districts to late adopting districts (Tanzania), timing a change to coincide with a drug tender, and early engagement of regulators on regulatory requirements and manufacturers on product specifications (South Africa).

* Bangladesh, Brazil, China, India, Indonesia, Kenya, Myanmar, Pakistan, Philippines, Russian Federation, South Africa, Thailand and Viet Nam.

DISCUSSION

The first step required for regimen change is the identification of a problem that is felt to need a solution.[20] Attainment of WHO targets for case detection and treatment success may lead NTPs to become complacent, and indeed a number of stakeholders stated that they would be unlikely to approve a future regimen change because the current program is working well. The recent adoption of universal treatment targets[22] should refocus programs on how innovations, including a new TB regimen, could improve program outcomes.

Factors promoting TB regimen change, as noted by stakeholders in this study, included WHO recommendation, evidence from local pilot projects, free drugs supplied by the GDF, increased efficacy (for the 6-month regimen) and simplified logistics (for FDC adoption). Barriers to regimen change included cost, lack of sufficient evidence and lack of capacity for changes in drug logistics. Best practices included early identification of funding sources and early engagement of procurement staff, manufacturers and regulators.

Regimen change involves both a global and a local consideration of evidence. The interviewers and some respondents in this study were international technical assistants, which may have introduced some bias toward international viewpoints, but in general we examined the characteristics of regimen change from a local perspective. This revealed the importance of issues that most directly confront national-level stakeholders, such as cost and logistics, with less frequent mentions of patient-related issues and benefits.

Even with the restriction of the study to recent events, the description of those events may have included inaccuracies due to recall error or personal bias. We tried to minimize such problems by collecting accounts from multiple sources, and assuring those sources that their opinions would remain confidential. Notably, the large number of countries covered, and the relative concentration of decision-making power among a small number of individuals per country, did not allow for significant cross-country analysis.

Planning for regimen change

As all HBCs have been through at least one regimen change in recent memory, the idea of a regimen change in the future will not be entirely unfamiliar. However, introduction of novel TB drugs (rather than a reassortment of the current drugs, as in many past TB regimen changes) may present additional challenges, so sufficient preparation will be particularly important.

Structures and processes for TB regimen change vary (Figure). For public sector regimen changes, there is a gradient of country capacity—in the decision-making apparatus, manufacturing ability, piloting capability and expectations of in-country trials—and these factors often track together (i.e., if one factor is high in a given country, so are the remaining factors).

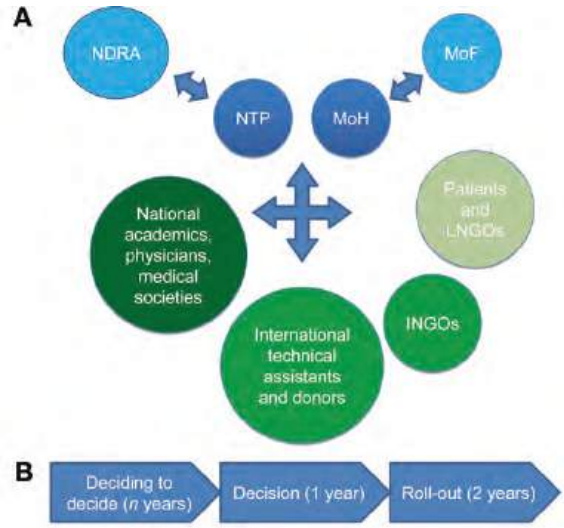

Figure Influence diagram for regimen decision making. **A.** The NTP and MoH are central to decision making, with the NTP providing guidance on priorities to the NDRA, and the MoF requiring a cost justification from the NTP and MoH. In an advisory capacity, national academics, physicians and medical societies are dominant in richer countries, whereas donors, international technical assistants and INGOs can be more influential in lower-income countries. In most countries studied, patients and LNGOs have little or no influence. **B.** Together, this group must decide to discuss a topic, then reach a decision, leading finally to implementation. NDRA = National Drug Regulatory Authority; NTP = National TB Program; MoH = Ministry of Health; MoF = Ministry of Finance; INGOs = international non-governmental organizations; LNGOs = local NGOs. This image can be viewed online in color at http://www.ingentaconnect.com/content/iuatld/ijtld/2010/00000014/00000012/art00010

Introduction plans for the two extremes of this gradient may look quite different: from coordination of multiple national stakeholders and technical partners driven by global consensus (e.g., Cambodia) to working with a perhaps more integrated and research-focused government sector (e.g., Brazil).

Costs, risks and benefits

Based on the evidence from past regimen changes documented here, stakeholders evaluate possible TB regimen changes on both negative (cost and risk) and positive (benefit) grounds.

Cost concerns focused on the direct costs of retraining, adjusting drug management, and recurring drug procurement, rather than on formal cost-effectiveness analyses. Changes in health outcomes are generally considered not in cost terms but as 'risks' and 'benefits' at the level of epidemiology. As past examples made it clear that regimen change decisions may be based on budget alone, financing solutions need to be in place at the same time that medical evidence is presented. Compared to current regimens, some future regimens (e.g., including gatifloxacin) may have similar direct drug costs; others (e.g., including moxifloxacin), although shorter and provided at cost, may be significantly more expensive.

The adopter's perception of risk has been described as 'the fundamental obstacle to the spread of change'.[18] A perception of risk arises because evidence on regimen change is almost always equivocal —there is inevitably some opposing evidence or lack of critical positive evidence. For the introduction of FDCs, the specific risk was that providers might struggle with side-effect management, resulting in poorer adherence and greater relapse;[23] there was also a concern that substandard manufacturing would be more likely for the more complex FDCs.[16]

For introduction of the 6-month regimen, the most prominent risk was an increase in resistance to RMP —seen as the most valuable sterilizing drug—due to the use of RMP for the entire regimen.[24] Thus, the initial recommendation was to implement the 6-month regimen only where DOT could be ensured during the entire regimen.[6]

Benefits of new regimens may also be incompletely defined. For FDCs, prior to introduction there was no calculation of predicted epidemiological benefits, and little evidence was provided to decision makers regarding potential changes in adherence or effectiveness.[11,14] However, the theoretical benefits of FDCs included simplification of drug logistics.[11] Such simplification is, as this study found, central to the practical concerns of local stakeholders. In addition, the promise of reduced resistance development, even if not fully documented, was appealing given the public health orientation of global stakeholders. Although the introduction of FDCs also reduced pill burden, this was rarely noted as having influenced decision makers.

The pressure for adoption of the 6-month regimen increased once it was shown to be clinically superior to the 8-month regimen.[9] However, with the efficacy of the first-line regimen now at 95% or above in a clinical trial setting, the adoption of future, shorter regimen changes must rely on benefits other than increased efficacy. Treatment shortening is expected to increase adherence and thus increase effective cure rates and reduce the emergence of MDR-TB (a possible benefit not promoted widely for the 8- to 6-month change). Furthermore, shorter regimens will increase patient tolerance (and thus potentially increase patient recruitment), reduce the time of exposure to potential side effects, and be consistent with the historical, global trend in the TB field of treatment shortening.

Highlighting any patient benefits during future decision making about regimen change will not be easy. The current study revealed that patient perspectives were not incorporated in most previous TB regimen change decisions. Rather, the emphasis has been on system-based incentives (e.g., free drugs and simplification of procedures for providers, such as through use of FDCs). Given the increased role of advocates and civil society, future decision making may also

need to highlight issues, such as side effects, that are of interest to patients.

Local data requirements

The current Phase III trials are designed to show that the efficacy of 4-month regimens is 'non-inferior' to that of 6-month regimens. Many stakeholders in the current study stated, however, that treatment shortening will likely improve adherence and thus regimen effectiveness in real-world settings. A large effectiveness trial or demonstration project, which was requested by many stakeholders, could potentially prove that this logic holds.

The conduct of such a project would be consistent with the need for effectiveness data in other therapeutic areas, such as malaria,[20] although, due to the longer treatment duration for TB, such a project could add several years to the timelines for regimen change. A demonstration project could provide the three key inputs requested by stakeholders: data on adherence (Table 3); logistics assessment; and implementation evidence from other countries (Table 5). It would overcome past misgivings that local data were insufficient and that regimen change was driven by standardization rather than evidence.

CONCLUSION

The focus of many stakeholder comments was on practical considerations for regimen change. This is a reminder that any new TB regimen must be adapted to local practice and delivery systems. Furthermore, the evidence base for new regimens should address not only the public health and patient considerations but also practical issues. With this comprehensive approach, and continued strengthening of local decision-making structures, the impact of new TB regimens can be maximized.

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RÉSUMÉ

CONTEXTE : Les expériences concernant les modifications antérieures de régime pour la tuberculose (TB) peuvent servir de guide pour les modifications futures de ces régimes.

MÉTHODES : Nous avons mené 166 interviews de responsables nationaux dans 21 des 22 pays à haut fardeau de TB afin d'explorer le processus, les acteurs principaux et les facteurs de succès des procédures des modifications récentes du régime TB dans le secteur public.

RÉSULTATS : Les responsables ont décrit 40 modifications distinctes de régime pour la TB à germes sensibles aux médicaments. Une fois que les pays sont soucieux d'envisager une modification, la durée moyenne est d'environ 1 an avant la prise de décision et d'environ 2 ans avant l'exécution. Les responsables ont cité plus souvent des préoccupations basées sur le programme (par exemple la logistique et le coût) plutôt que focalisées sur le patient (par exemple, les effets collatéraux) ; les représentants des patients ont rarement pris part à la décision. Les organes de prise de décisions dans les pays à haute prévalence et à revenus plus élevés disposent de procédures plus formalisées et d'un plus petit nombre de participants internationaux. Les études-pilote orientées sur la logistique ont été plus courantes que les études d'efficience, et les résultats sont souvent perçus comme insuffisantes. Une fois la mise en route démarrée, les déficiences dans la prise en charge des médicaments sont fréquemment avancées, avec des complications supplémentaires lorsqu'une fabrication locale est nécessaire. Les meilleures pratiques pour une modification de régime ont compris un engagement précoce du personnel pour la budgétisation, du personnel pour l'achat, des décideurs et des fabricants.

CONCLUSION : A l'avenir, les preneurs de décisions pourront bénéficier d'organes renforcés de prise de décision, de l'apport des patients, d'un planning précoce et complet et de régimes et de preuves permettant de faire face aux problèmes de mise en œuvre pratique au niveau local.

RESUMEN

MARCO DE REFERENCIAS: La experiencia previa con las modificaciones del régimen antituberculoso puede orientar los cambios en el futuro.

MÉTODOS: Con el propósito de investigar el mecanismo, los principales actores y los factores de éxito del procedimiento en las recientes modificaciones de las pautas del tratamiento antituberculoso en el sector público, se llevaron a cabo 166 entrevistas a interesados directos del país en 21 de los 22 países con alta carga de morbilidad por tuberculosis (TB).

RESULTADOS: Los interesados directos describieron 40 modificaciones precisas de las pautas del tratamiento de la TB sensible a los medicamentos. Una vez que los países se habían comprometido a considerar la introducción de un cambio, el tiempo promedio hasta tomar la decisión fue de 1 año y el lapso hasta la introducción de las modificaciones fue 2 años. Los interesados citaron con mayor frecuencia cuestiones relacionadas con el programa (como los aspectos organizativos y los costos) y no centradas en los pacientes (como las reacciones adversas) y los representantes de los pacientes rara vez participaron en la toma de decisiones. Los organismos decisorios en los países con mayores ingresos y alta morbilidad contaban con procedimientos más formalizados y menos participantes internacionales. Los estudios preliminares que se centraban en los aspectos organizativos fueron más frecuentes que los estudios de eficacia y en muchas ocasiones se consideró que la base científica era insuficiente. Una vez comenzada la ejecución, se expusieron con frecuencia fallas en la gestión de los medicamentos y las complicaciones fueron mayores cuando se precisaba fabricarlos localmente. Entre las prácticas óptimas de modificación del régimen se encontraron un compromiso temprano el personal encargado del financiamiento, del personal de servicios de adquisiciones, las instancias normativas y los fabricantes.

CONCLUSIÓN: Las personas encargadas de tomar las decisiones en el futuro encontrarán muy útil la existencia de organismos decisorios fortalecidos, las sugerencias de los pacientes, el planeamiento precoz y exhaustivo y el régimen terapéutico que hayan dado prueba de responder a las necesidades prácticas de ejecución local.

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WHO GUIDELINES

WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update

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ABSTRACT: The production of guidelines for the management of drug-resistant tuberculosis (TB) fits the mandate of the World Health Organization (WHO) to support countries in the reinforcement of patient care.

WHO commissioned external reviews to summarise evidence on priority questions regarding case-finding, treatment regimens for multidrug-resistant TB (MDR-TB), monitoring the response to MDR-TB treatment, and models of care. A multidisciplinary expert panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to develop recommendations.

The recommendations support the wider use of rapid drug susceptibility testing for isoniazid and rifampicin or rifampicin alone using molecular techniques. Monitoring by sputum culture is important for early detection of failure during treatment. Regimens lasting $\geqslant$20 months and containing pyrazinamide, a fluoroquinolone, a second-line injectable drug, ethionamide (or prothionamide), and either cycloserine or *p*-aminosalicylic acid are recommended. The guidelines promote the early use of antiretroviral agents for TB patients with HIV on second-line drug regimens. Systems that primarily employ ambulatory models of care are recommended over others based mainly on hospitalisation.

Scientific and medical associations should promote the recommendations among practitioners and public health decision makers involved in MDR-TB care. Controlled trials are needed to improve the quality of existing evidence, particularly on the optimal composition and duration of MDR-TB treatment regimens.

KEYWORDS: Ambulatory care facilities, diagnosis, drug therapy, guideline, multidrug-resistant tuberculosis

This article reproduces the recommendations of the update of the World Health Organization (WHO) *Guidelines for the programmatic management of drug-resistant tuberculosis* [1] released in June 2011. The guidelines were developed in compliance with the requirements of the WHO Guidelines Review Committee for evidence gathering, assessment and formulation of recommendations. Some of the text and the tables presented in this article are reproduced from the guidelines [1] and are presented with the permission of WHO.

Tuberculosis (TB) control in the world today must face the challenge posed by the global spread of *Mycobacterium tuberculosis* strains that are resistant to standard anti-TB drugs [2, 3]. It is estimated that ~3% of incident new TB cases in the world have

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multidrug-resistant TB (MDR-TB), defined as resistance to at least isoniazid and rifampicin, the two most effective anti-TB drugs [4]. Around 440,000 MDR-TB cases (95% CI 390,000–510,000) are estimated to emerge annually among new and retreated TB patients. The frequency of MDR-TB varies according to region and is much higher among previously treated patients. Amongst the vast majority of MDR-TB patients, very little is known about their access to quality care. Treatment of MDR-TB is complex and uses toxic drugs that must be administered for a longer duration than for drug-susceptible TB patients, with a lower likelihood of treatment success [5].

In 2009, in recognition of the threat posed by drug-resistant TB to global public health security, the World Health Assembly urged Member States to achieve universal access to diagnosis and treatment of patients with this form of disease [6]. The WHO was mandated to provide technical support to countries for the development and implementation of national frameworks of care for drug-resistant TB patients. The production of guidelines for the programmatic management of drug-resistant TB is part of this role. WHO has previously developed guidelines on this subject, which were based on an assessment of available evidence and best practice by a large group of TB specialists [7, 8]. In 2008, an Emergency Update of the guidelines was published, which expired in 2010. Here, we report on the 2011 update of the guidelines [1], which was developed through a coordinated process that began in 2009. The guidelines target priority areas in drug-resistant TB care. They followed a careful process of systematic retrieval and synthesis of evidence in preparation for the formulation of recommendations by a multidisciplinary expert panel (Guideline Development Group, see Acknowledgements). The panel included TB practitioners, public health professionals, representatives of professional societies, National TB Control Programme staff and guideline methodologists, as well as members of civil society and nongovernmental organisations who provided technical support, and WHO staff. A second group composed of National TB Control Programme staff, WHO regional advisers, clinicians and public health experts was appointed to serve in a peer-review capacity as an External Review Group (see Acknowledgements).

MATERIAL AND METHODS

Defining the scope of the updated guidelines ("scoping")

The 2008 Emergency Update [8] of the guidelines identified areas of controversy in which guidance in policy and practice was to be prioritised in future editions of the guidelines. In early 2009, an evaluation of the first two versions of the guidelines was conducted *via* a user questionnaire [9]. The members of the Guideline Development Group discussed the findings of these two versions and decided to limit the scope of the guidelines to: 1) case-finding (rapid molecular tests for drug resistance, and the investigation of contacts and other high-risk groups); 2) MDR-TB treatment regimens and duration in HIV-positive and HIV-negative patients; 3) monitoring during treatment; and 4) models of care.

This process was translated into the following seven specific questions, which were formulated using PICO (Population, Intervention, Comparator to the intervention, and Outcome) [10] or a similar format.

1) At what prevalence of MDR-TB in any group of TB patients is rapid drug susceptibility testing warranted to detect resistance to rifampicin and isoniazid or rifampicin alone on all patients in the group at the time of TB diagnosis, in order to prescribe appropriate treatment at the outset?

2) Among patients with MDR-TB receiving appropriate treatment in settings with reliable direct microscopy, is monitoring using sputum smear microscopy alone, rather than sputum smear and culture, more or less likely to lead to the relevant outcomes listed in table 1?

3) When designing regimens for patients with MDR-TB, is the inclusion of specific drugs (with or without documented susceptibility) more or less likely to lead to the relevant outcomes listed in table 1?

4) When designing regimens for patients with MDR-TB, is the inclusion of fewer drugs in the regimen (depending on the drug used, the patient's history of using the drug and isolate susceptibility) more or less likely to lead to the relevant outcomes listed in table 1?

5) In patients with MDR-TB, is shorter treatment, compared with the duration currently recommended by WHO, more or less likely to lead to the relevant outcomes listed in table 1?

6) In patients with HIV infection and drug-resistant TB who are receiving antiretroviral therapy (ART), is the use of drugs with overlapping and potentially additive toxicities, compared with their avoidance, more or less likely to lead to the relevant outcomes listed in table 1?

7) Among patients with MDR-TB, is ambulatory therapy compared with in-patient treatment more or less likely to lead to the relevant outcomes listed in table 1?

The External Review Group also provided input into the design and content of the questions. The Guideline Development Group then selected and scored outcomes to determine those which were critical or important for making decisions on recommendations and on which data were to be sought during evidence retrieval and synthesis (table 1).

Reviewing the evidence

Data sources

Between October 2009 and May 2010, WHO commissioned teams from leading academic centres (see Acknowledgements) to review and compile evidence for each of the questions through a series of systematic reviews of the literature using methods suggested by the Cochrane Collaboration [11]. The teams screened the titles, abstracts and full text of potentially relevant papers using key subject words and text words. The search was not limited by study type or by a time period. In addition, the teams contacted article authors and consulted the Guideline Development Group members to identify studies that were missing or in progress. Individual patient data were collected from authors of published studies to address questions dealing with bacteriology and treatment regimen (questions 2–6). Modelling methods were used for questions 1 and 2. The question on models of care (question 7) was addressed by a review of published and unpublished studies with economic evaluation of MDR-TB patients on treatment.

Analysis

Where possible, relative effects (hazard ratios, relative risks or odds ratios of an event) were calculated using pooled data

TABLE 1 What are the most important outcomes to consider when making decisions on testing and treatment strategies for drug-resistant tuberculosis (TB)?

Outcomes (bracketed outcomes rephrased as the negative)	Mean score	Relative importance
1) Cure (treatment failure)	8.7	Critical
2) Prompt initiation of appropriate treatment	8.3	Critical
3) Avoiding the acquisition or amplification of drug resistance	8.1	Critical
4) Survival (death)	7.9	Critical
5) Staying disease-free after treatment; sustaining a cure (relapse)	7.6	Critical
6) Case holding so the TB patient remains adherent to treatment (default or treatment interruption due to non-adherence)	7.6	Critical
7) Population coverage or access to appropriate treatment of drug-resistant TB	7.5	Critical
8) Smear or culture conversion during treatment	7.4	Critical
9) Accelerated detection of drug resistance	7.4	Critical
10) Avoid unnecessary treatment for MDR-TB	7.2	Critical
11) Population coverage or access to diagnosis of drug-resistant TB	7.1	Critical
12) Prevention or interruption of transmission of drug-resistant TB to other people, including other patients and healthcare workers	6.9	Important but not critical
13) Shortest possible duration of treatment	6.7	Important but not critical
14) Avoiding toxicity and adverse reactions from TB drugs	6.5	Important but not critical
15) Cost to patient, including direct medical costs as well as others, such as transportation and lost wages due to disability	6.4	Important but not critical
16) Resolution of TB signs and symptoms; ability to resume usual life activities	6.3	Important but not critical
17) Interaction of TB drugs with non-TB medications	5.6	Important but not critical
18) Cost to the TB programme	5.4	Important but not critical

Members of the Guideline Development Group submitted scores for TB outcomes which they considered to be the most critical when making decisions on drug-resistant TB management. Members were asked to take a societal perspective in rating the outcomes. Rating by relative importance was on an incremental scale, as follows. 1–3 points: not important for making recommendations on choice of testing and treatment strategies for drug-resistant TB (none of the outcomes was scored in this category); 4–6 points: important but not critical for making recommendations on choice of testing and treatment strategies; 7–9 points: critical for making recommendations on choice of testing and treatment strategies. MDR-TB: multidrug-resistant TB.

from the studies included. In two of the analyses, outcome was expressed as the cost per disability-adjusted life year (DALY) averted. The DALY is a summary indicator that expresses the burden of mortality and morbidity in a single value, with perfect health valued at 1 and death at 0 (a year with TB disease is valued at 0.729) [12]. To model drug-susceptibility testing (DST), the cost outcomes estimated included total costs for each DST strategy, incremental cost per MDR-TB case prevented, cost per TB-related death avoided and cost per DALY averted. For the analysis of models of care (question 7), any of the following costs were included: cost from the health service provider's perspective, cost from the patient's perspective (including direct medical costs and indirect costs related to transportation) and total societal cost. Whenever possible, the following outcomes were included: proportion of treatment success, default or long-term deaths (including secondary, default and relapse cases) and case reproduction rate (transmission from primary cases).

Developing the recommendations

Summaries of evidence and GRADE (Grading of Recommendations Assessment, Development and Evaluation) profiles based on the results of the systematic reviews were prepared for each question using a standard approach [13]. These summaries presented the effect of the intervention on each outcome and the quality of the evidence for each effect, categorised into four

TABLE 2 Quality of evidence and definitions

Quality of evidence	Definition
High (⊕⊕⊕⊕)	Further research is very unlikely to change our confidence in the estimate of effect
Moderate (⊕⊕⊕○)	Further research is likely to have an important impact on our confidence in the effect and may change the estimate
Low (⊕⊕○○)	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low (⊕○○○)	Any estimate of effect is very uncertain

levels (table 2) [14]. The review teams assessed the quality of evidence using the following criteria: study design, limitations in the study (risk of bias), inconsistency, indirectness (whether the evidence directly answers the question being addressed; see [13] for an explanation of the two types of indirectness), imprecision, publication bias, magnitude of effect, dose–effect relationship, and the effect of residual confounding.

On 25–27 October, 2010, the members of the Guideline Development Group met to develop the recommendations at WHO's Headquarters in Geneva, Switzerland. The teams conducting the reviews presented their findings and the GRADE profiles to the Group. The GRADE profiles allowed the Group members to base their judgments on uniformly summarised evidence. In their deliberations, the Group members judged the strength of the recommendations from the perspective of different users (table 3). The higher the quality of evidence, the more likely it was that it led to a strong recommendation. However, a strong recommendation was possible in the presence of very low-quality evidence, as consideration was given to values and preferences that experts attribute to the target population, the balance between desirable and undesirable consequences of an intervention, and resource implications [14]. The Group reached agreement on the recommendations following discussion.

Throughout the guideline revision, the Guideline Development Group considered that the proper management of drug-resistant TB requires a concerted effort from various components of the National TB Control Programme on all activities of care, including case detection, treatment, prevention, surveillance, monitoring and evaluation of programme performance. In the development of the recommendations, the Group attached importance to the following guiding principles: 1) promotion of universal access to care in low-resource settings; 2) prevention of death and transmission of MDR-TB through early diagnosis; 3) avoidance of harm; and 4) provision of care in a setting acceptable to the patient and which optimises the use of resources.

RECOMMENDATIONS

11 recommendations were made by the Guideline Development Group regarding diagnosis, treatment, monitoring and models of care.

Recommendation 1. Rapid DST of isoniazid and rifampicin or of rifampicin alone is recommended over conventional testing or no testing at the time of diagnosis of TB, subject to available resources (conditional recommendation, ⊕○○○/very low-quality evidence)

Remarks

The effect of different DST strategies was simulated using decision-analysis modelling [15]. This method can only generate very low-quality evidence. Despite limitations, sensitivity analyses showed that the results were fairly consistent under different conditions.

A DST for isoniazid and rifampicin or rifampicin alone that provides a diagnosis within a day or two of testing was considered rapid for this recommendation. Currently, only molecular tests can detect resistance so quickly, of which two technologies, line probe assay and Xpert MTB/RIF, are recommended for use by WHO. (Xpert MTB/RIF refers to the currently available methodology that employs an automated real-time nucleic acid amplification technology for rapid and simultaneous detection of TB and rifampicin resistance.) The basic assumption is that rapid DST will reduce the delay to the start of appropriate second-line therapy, and thus provide benefit to the patient by increasing cure, decreasing mortality, reducing development of additional drug resistance, and reducing the likelihood of failure and relapse.

Rapid DST performed on all patients before the start of treatment was the most cost-effective strategy for averting deaths and preventing the acquisition of additional resistance. Rapid testing for both isoniazid and rifampicin at diagnosis, rather than later during treatment, was the most cost-effective testing strategy available, starting from a MDR-TB prevalence of >1% and an isoniazid resistance (other than MDR-TB) of >2%. Rapid DST for rifampicin alone could also avert many deaths but might not prevent the acquisition of additional resistance in patients resistant to isoniazid alone.

The influence of resistant strains on secondary transmission was not included in the model and therefore, estimations of reductions in mortality and morbidity from early detection and treatment are likely to be conservative. The increased costs of using the diagnostic test may be offset by a reduction in the amount of conventional laboratory capacity needed.

TABLE 3 Implications of the strength of a recommendation for different users

Perspective	Strong recommendation	Conditional recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences	The majority of individuals in this situation would want the suggested course of action, but many would not
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guidelines could be used as a quality criterion or performance indicator	It should be recognised that different choices will be appropriate for individual patients, and that patients must be helped to arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences
For policy makers	The recommendation can be adapted as policy in most situations	Policy making will require substantial debate and the involvement of various stakeholders

The Group considered costs to the TB programme to be important but not critical. The recommendation is conditional, in part because of the resources required for implementation. Programmes that cannot adhere to the recommendation for all patients may still apply it to groups at higher risk of MDR-TB or unfavourable outcomes, particularly patients treated for TB in the past or with HIV-associated TB, as has been recommended previously [16].

Detection of rifampicin resistance by Xpert MTB/RIF usually suffices to start a patient on a second-line TB regimen [17]. However, the positive predictive value of Xpert MTB/RIF is low in patient groups in which rifampicin resistance is rare. Therefore, to reduce the possible harms of false-positive results for drug resistance, which include wasted resources and avoidable toxicity from the administration of unnecessary second-line medications, results need to be confirmed by phenotypic DST or line probe assay in these patient groups. This is an important consideration given that access to Xpert MTB/RIF is expected to expand substantially in low-resource countries [18].

Recommendation 2. The use of sputum smear microscopy and culture rather than sputum smear microscopy alone is recommended for the monitoring of patients with MDR-TB during treatment (conditional recommendation, ⊕○○○/very low-quality evidence)

Remarks

The evidence used to assess how best to monitor treatment in MDR-TB patients with the use of sputum smear microscopy and culture in settings with reliable direct microscopy was based on data pooled from 10 published observational studies [19–26] included in two recent reviews [5, 27]. Monthly culture monitoring was used as the reference in all of the analyses. Random-effects Cox proportional hazards models were used to estimate the hazard ratio of failure, comparing monthly culture to alternative monitoring strategies.

The use of monthly sputum smear microscopy and culture performed best at identifying failures earlier. Sputum smear microscopy alone resulted in delayed detection of failure; when performed at monthly rather than two-monthly intervals, it increased the detection of failure slightly (not significant). In patients who were smear-negative at the start of treatment, monthly smear monitoring (compared with culture) resulted in a statistically significantly greater risk of delayed detection of failure compared with smear-positive patients. Stratified estimates by HIV serostatus, body mass index, and extent of disease on chest radiograph were not significantly different ($p>0.05$).

The related end-points of drug resistance, initiation of appropriate treatment and the acquisition of resistance were not measured. There was no information about reversion or re-infection and no data were available to assess the quality of culture and smear testing. Other methods of evaluating response to treatment, such as clinical indicators or chest radiograph, were not evaluated.

Concomitant use of sputum smear microscopy and culture test results helps identify patients whose bacteriology remains positive or reverts back to positive following initial conversion to negative. This is of use to the clinician in identifying patients likely to fail their treatment as well as to institute infection control measures in a timely manner. There was overall certainty in the Group about the risk of missing or delaying the detection of failure if smear microscopy alone was used instead of culture. Additional benefits would be expected from reducing transmission and development of resistance as well as appropriate changes to the treatment regimens, but these were not explicitly addressed by the analysis.

Delayed detection of failure is expected to increase transmission and increase the probability of acquisition of resistance. The 2008 Emergency Update of the guidelines recommended that MDR-TB patients be monitored through monthly sputum smear microscopy and culture examination prior to culture conversion to negative (defined as two consecutive sets of negative results of sputum smear microscopy and culture from samples collected $\geqslant$30 days apart) and quarterly culture with monthly smear examination after conversion [8]. Even if monthly culture throughout treatment showed the highest benefit of detecting failures, resource implications are important. The cost of sputum smear testing alone is much lower than for culture and ranged between one fourth to one half of the combined cost of culture and smear testing in studies across different settings reviewed for the guidelines [28–34]. It is likely that this difference may be higher where culture diagnosis is not readily available. More laboratory resources (staff, equipment, utilities) are required to perform culture, and fewer culture laboratories exist in the low-resource conditions of most high-burden countries. In settings where the risk of failure is low, selected patients can be prioritised for monthly culture.

The user should be aware of differences in the quality of culture performance. A false-positive result of culture or direct microscopy of sputum smear could lead to unnecessary continuation or modification of a regimen with increased risk of toxicity. A false-negative culture result may change a treatment decision that was based on suggestive clinical findings and a positive sputum smear microscopy result.

A high value was placed on outcomes such as preventing death, decreasing the transmission of MDR-TB that could result from its delayed diagnosis, and avoiding increased use of resources. The recommendation is conditional in part because of the resources required for its implementation. As direct microscopy of sputum smear can identify the most infectious cases within a very short time, it has added value alongside culture for infection control purposes.

Recommendation 3. In the treatment of patients with MDR-TB, a fluoroquinolone should be used (strong recommendation, ⊕○○○/very low-quality evidence)

Recommendation 4. In the treatment of patients with MDR-TB, a later-generation fluoroquinolone rather than an earlier-generation fluoroquinolone should be used (conditional recommendation, ⊕○○○/very low-quality evidence)

Recommendation 5. In the treatment of patients with MDR-TB, ethionamide (or prothionamide) should be used (strong recommendation, ⊕○○○/very low-quality evidence)

Recommendation 6. In the treatment of patients with MDR-TB, four second-line anti-TB drugs likely to be effective (including a parenteral agent from among the second-line injectables kanamycin, amikacin or capreomycin), as well

as pyrazinamide, should be included in the intensive phase (the initial part of a course of treatment during which a parenteral agent is used) (conditional recommendation, ⊕○○○/very low-quality evidence)

Recommendation 7. In the treatment of patients with MDR-TB, regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent (kanamycin, amikacin or capreomycin), ethionamide (or prothionamide), and either cycloserine or p-aminosalicylic acid (PAS) if cycloserine cannot be used (conditional recommendation, ⊕○○○/very low-quality evidence)

Remarks

The evidence used to address the questions on which drugs to include and the number of drugs to be used in regimens for MDR-TB patients was based primarily on studies included in three systematic reviews [5, 27, 35]. Studies published before 1970 and those reporting only extensively drug-resistant TB (XDR-TB) were excluded. The reviewers of these questions pooled individual patient data for a meta-analysis from 32 studies with >9,000 treatment episodes for which the authors could be contacted and were willing to share their data (study in preparation by the Collaborative Group for Meta-analysis of Individual Patient Data in MDR-TB). Cohorts included had to have a minimum of 25 subjects treated for MDR-TB, with one or more of the treatment outcomes meeting the standard definitions [36]. Patients with XDR-TB (n=410) were excluded from the analysis as their treatment regimens were not considered to be comparable with those of other MDR-TB patients. None of the cohorts was part of a randomised controlled trial and bias was very likely to be substantial (certain drugs may have only been used for sicker patients). The quality of evidence was judged to be low or very low. While the odds ratios in the analysis were adjusted for age, sex, HIV serostatus, past TB treatment, past MDR-TB treatment and extent of disease, residual confounding was certainly to be expected. Other limitations included incomplete ascertainment of relapse, the under-representation of certain geographical regions, and missing data for some of the variables examined. In many of the studies included, drug regimens were adjusted based on DST results. Findings from this analysis may not necessarily be generalisable to all populations in settings with a high or low prevalence of drug resistance or different levels of resources. Nonetheless, the results of this analysis represented the best available evidence to date for the Group to make recommendations on the composition of treatment regimens.

Use of drugs to which the strain was reportedly susceptible showed some added benefit when compared with their use regardless of susceptibility patterns. Choice of drug would thus depend on the DST of the strain isolated from the patient or close contact with MDR-TB, previous use of the drug in the patient, and frequency of use of the drug or documented background drug resistance in the setting. In applying this observation to clinical practice, it is important to underline the uncertainties around the reproducibility and reliability of DST for pyrazinamide (and ethambutol) [37], as well as the second-line anti-TB drugs other than the parenteral agents and the fluoroquinolones [38].

The analysis showed that in the intensive phase, a regimen with at least four drugs likely to be effective, when adjusted for clinical covariates, all other drugs used concomitantly as well as the total number of susceptible drugs used throughout treatment, was associated with a statistically significant peak in cure with a plateau thereafter.

Data from this analysis did not reveal any second-line parenteral agent (kanamycin, amikacin or capreomycin) to be superior in effect to any other. Given its lower cost, kanamycin would be preferable. Amikacin can be used instead of kanamycin. In an analysis comparing patients who were cured or completed treatment with those who failed or relapsed, capreomycin was shown to be effective in the case of resistance to kanamycin. The use of streptomycin in MDR-TB patients is not recommended given the greater likelihood of ototoxicity and the frequent occurrence of resistance to it among MDR-TB patients.

Fluoroquinolones should always be used unless there is a contraindication. They showed a significant association with cure and this effect was more pronounced in later-generation fluoroquinolones (in this analysis, this refers to levofloxacin ($\geqslant$750 mg·day^{-1}), moxifloxacin, gatifloxacin and sparfloxacin), and was highest when used against strains known to be susceptible. Estimates of effects of fluoroquinolones were probably conservative given that patients treated with ciprofloxacin were included in the control group. Ciprofloxacin, even if it may have some anti-TB activity, should not be used [39].

Among the oral bacteriostatic drugs, the association with cure was higher with ethionamide than with cycloserine, which was higher than with PAS. Ethionamide or prothionamide should therefore be included in a regimen unless there is a particular contraindication. Ethionamide showed little effect in patients who were treated previously for MDR-TB. PAS performed the worst in the main analysis. Its use would thus be recommended only if an additional drug is needed to have at least four effective second-line drugs in the regimen, and if ethionamide or cycloserine cannot be used or are unlikely to be effective. Studies of the *inhA* promoter region mutation (not assessed in the review) may, at an additional cost, guide treatment by identifying strains that are resistant to ethionamide [40]. The data did not allow comparison of outcomes between once daily PAS and divided doses, or the formulation of PAS. Decisions on how to administer PAS should thus rely on a balance between its tolerance in the patient and the resources available to observe doses.

Patients who were treated with Group 5 drugs (including clofazimine, linezolid, amoxicillin/clavulanate, thioacetazone, clarithromycin and imipenem; in the analysis for the guidelines, azithromycin, roxithromycin, high-dose isoniazid and thioridazine were also included under Group 5 when used) were observed to have generally worse outcomes, an effect largely attributed to confounding by indication. When the individual effect of amoxicillin/clavulanate, azithromycin, clarithromycin, clofazimine, roxithromycin and thioacetazone was analysed, no significant association with cure could be discerned. No separate analysis was possible for linezolid and high-dose isoniazid given the small number of cases treated with these agents.

Pyrazinamide showed a slightly added benefit in one of the analyses in which adjustment was made for other medication used concomitantly. Ethambutol was associated with a marginal but statistically significant reduction in the likelihood of cure among patients not previously treated for MDR-TB. As

in the case of Group 5 drugs, this effect was attributed to confounding rather than a detrimental effect of ethambutol.

The main changes from the 2008 Emergency Update [8] of the guidelines are shown in table 4. The meta-analysis performed for the 2011 update indicated that a minimum of four drugs was associated with a greater likelihood of success. The decision to recommend an additional drug to the regimen during the intensive phase of treatment was based on expert opinion. The intention is to safeguard against the acquisition of additional resistance, particularly in the case of undetected primary resistance to the four drugs considered to be effective given the unreliable nature of DST for drugs other than parenteral agents and fluoroquinolones. If ethambutol and

TABLE 4 Main changes to the recommendations in the 2008 Emergency Update [8] following the 2011 update of the guidelines

	2008 emergency update	2011 update
Monitoring response to MDR-TB treatment	Monitoring of MDR-TB patients by monthly sputum smear microscopy and culture examination prior to culture conversion to negative and quarterly culture, with monthly smear examination after conversion	Monthly sputum smear and culture throughout treatment is recommended, subject to resource implications, given that it has the highest benefit to detect failure
Regimen composition	Include at least four anti-TB drugs with either certain, or almost certain, effectiveness during the intensive phase of treatment	Include at least four second-line anti-TB drugs likely to be effective, as well as pyrazinamide during the intensive phase of treatment
	Consider adding more drugs in patients with extensive disease or uncertain effectiveness	No evidence found to support the use of more than four second-line anti-TB drugs in patients with extensive disease. Increasing the number of second-line drugs in a regimen is permissible if the effectiveness of some of the drugs is uncertain
	The regimen should include pyrazinamide and/or ethambutol, one fluoroquinolone, one parenteral agent and second-line oral bacteriostatic anti-TB drugs (no preference of oral bacteriostatic second-line anti-TB drug was made)	The regimen should include pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide) and cycloserine, or else PAS if cycloserine cannot be used
	Ethambutol may be considered effective and included in the regimen if DST shows susceptibility	Ethambutol may be used but is not included among the drugs making up the standard regimen
	Treatment with Group 5 drugs is recommended only if additional drugs are needed to bring the total to four	Group 5 drugs may be used but are not included among the drugs making up the standard regimen
Duration of treatment	Use of a parenteral agent for a minimum of 6 months and $\geqslant$4 months after culture conversion	An intensive phase of 8 months' duration is recommended. The duration may be modified depending on bacteriological status and other indicators of progress on treatment
	A minimum total length of treatment of 18 months after culture conversion	A total treatment duration of $\geqslant$20 months is recommended in patients without any previous history of MDR-TB treatment. Patients who have had previous treatment for MDR-TB may need longer treatment. The duration may be modified depending on bacteriological status and other indicators of progress on treatment
Use of ART in drug-resistant TB patients with HIV	The timing of the start of ART was in part determined by CD4 cell count	ART is recommended for all patients with HIV and drug-resistant TB requiring second-line anti-TB drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of anti-TB treatment
Models of care for managing MDR-TB	Programmes are encouraged to incorporate community-based care and support into their national plans	Patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalisation

MDR-TB: multidrug-resistant tuberculosis; TB: tuberculosis; PAS: *p*-aminosalicylic acid; DST: drug-susceptibility testing; ART: antiretroviral therapy.

Group 5 drugs are used to treat MDR-TB patients, they should not be counted among the main drugs making up the MDR-TB regimen, given the inconclusive evidence on their effectiveness. The principle of using additional drugs for extensive disease could not be supported by the data used for the review.

A slight incremental trend in serious adverse events (SAEs) was discerned as the number of drugs in the continuation phase increased from two to five. This association was not observed during the intensive phase. Data were incomplete but SAEs were more often attributed to oral bacteriostatic drugs (14%) than to the other drugs evaluated (1–6%). The long-term potential for SAEs, particularly in children and for the later-generation fluoroquinolones, remains unknown. However, a Cochrane review assessing fluoroquinolones as additional or substitute drugs in regimens for patients with drug-susceptible and drug-resistant strains found that substituting or adding fluoroquinolones to a regimen had no demonstrable effect on the occurrence of SAEs [39].

As patients with XDR-TB were excluded from the analysis, the recommendations do not necessarily apply to this subgroup of patients. Until better evidence is available to optimise regimens for the treatment of these patients, the same principles used to design MDR-TB regimens should be used, based where possible on the DST pattern of strains from the individual patient, particularly for later-generation fluoroquinolones and second-line parenteral agents. All MDR-TB patients should thus be tested for susceptibility to these two classes of drugs.

The aim of the recommendations contained in this section is to increase the likelihood of cure and reduce the risk of failure, relapse and death. A high value was placed on preventing death and transmission of MDR-TB and a lower value on the potential for SAEs resulting from long-term treatment. As a result, the long-term use of fluoroquinolones was considered to outweigh the higher cost and any possible long-term SAEs. The recommendation was therefore strong. While the use of later-generation fluoroquinolones is generally preferred, a separate recommendation on their use was classified as conditional rather than strong because of uncertainty about the risk of SAEs from the long-term use of these agents.

Recommendation 8. In the treatment of patients with MDR-TB, an intensive phase of ⩾8 months' duration is recommended (conditional recommendation, ⊕○○○/very low-quality evidence)

Recommendation 9. In the treatment of patients with MDR-TB, a total treatment duration of ⩾20 months is recommended in patients without any previous MDR-TB treatment (conditional recommendation, ⊕○○○/very low-quality evidence)

Remarks

The evidence base used to derive these two recommendations was the same as that used for questions 2 to 4 on regimen composition (recommendations 3 to 7). All data were from observational studies and the quality of evidence was classified as very low. Patients with XDR-TB were also excluded from the analysis. Attempts to control for bias and confounding in the review were also unlikely to have adjusted for all important factors. In particular, patients receiving longer therapy may be those who are sicker. These findings may not be generalisable to all populations in settings with a high or low prevalence of drug resistance or with different levels of resources.

The analysis provided evidence for an association between treatment success and the total length of treatment and the length of the intensive phase. The trend in relative risk for cure over successive months of treatment was studied to determine the optimal minimum duration for both total treatment and the intensive phase. The adjusted relative risk for cure peaked at an intensive phase lasting 7.1–8.5 months. For total treatment duration, the peak occurred at 18.6–21.5 months for patients who had no previous MDR-TB treatment. While the peak occurred later in patients who had been treated for MDR-TB (27.6–30.5 months), no clear incremental trend in success was observed in this patient group and the number of observations was far fewer than for those who had no previous MDR-TB treatment. Most patients may be expected to receive this length of treatment but in some it may have to be modified depending on their bacteriological status and other indicators of progress on treatment.

The recommendations have thus changed from those contained in the 2008 Emergency Update [8], which recommended a treatment duration for MDR-TB patients based on the use of a parenteral agent for a minimum of 6 months and ⩾4 months past culture conversion, and a minimum total length of treatment of 18 months after culture conversion. The new recommended duration of the intensive phase is 2 months longer than the minimum previously recommended. There is, however, no substantial difference in the total length of treatment being recommended, given that conversion typically takes a few months to occur. The data used for this analysis could not inform whether a minimum duration of the intensive phase after conversion was a determinant of outcome.

The risk of SAEs was observed to increase beyond the first 12 months of treatment but was not correlated with the length of the intensive phase beyond the first 2 months. These trends should be interpreted with caution as they may be confounded by the number of drugs used (independently correlated with SAEs) as well as features of the illness process not accounted for in the measure of extent of disease used in the analysis.

A high value was placed on preventing death and transmission of MDR-TB as a result of failed treatment, as well as avoiding harms and minimising use of resources. The Group placed a lower value on reducing the duration of treatment, while acknowledging that many patients may place a higher value on avoiding a long treatment course due to burden and inconvenience. When selecting the duration of treatment, the analysis allowed a choice to be made within a narrow margin of a few consecutive months, thus reducing the likelihood of prolonging treatment unnecessarily. While shorter regimens would confer clear benefits and be preferred, evidence for the effectiveness of a 9-month regimen for MDR-TB patients has as yet been limited to data from one setting (included in the review) [23]. The Guideline Development Group supports further investigation of safety and effectiveness of shorter regimens using the randomised controlled trial design in order to get stronger evidence for their potential use for the treatment of drug-resistant TB.

Recommendation 10. ART is recommended for all patients with HIV and drug-resistant TB requiring second-line

anti-TB drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of anti-TB treatment (strong recommendation, ⊕○○○/very low-quality evidence)

Remarks

Evidence was reviewed from 10 studies [41–50] to assess patient treatment outcomes when ART and second-line anti-TB drugs were used together. None of the data were from randomised controlled trials. Individual patient data were available for 217 drug-resistant TB patients in total, of whom 127 received ART. The quality of evidence in individual observational studies varied from low to very low quality.

The pooled individual patient data showed a lower risk of death and a higher likelihood of cure and resolution of TB signs and symptoms in patients using ART compared with those not using ART (low-quality evidence). There was very low-quality evidence for other outcomes, which were considered critical or important for decision-making (for example, SAEs from second-line drugs for drug-resistant TB, occurrence of conversion of sputum smear or culture, interactions of ART with anti-TB drugs and default from treatment). Available data did not allow assessment of a number of other outcomes of interest, namely avoiding the acquisition of additional drug resistance, preventing TB transmission, sustaining relapse-free cure, establishing the optimal duration of MDR-TB treatment, avoiding unnecessary MDR-TB treatment, and reducing cost and improving population access to appropriate care.

The strong recommendation for use of ART is based in part on indirect evidence from its use in any patient with active TB that shows large beneficial effects and a very high mortality when ART is not employed [51], particularly in very immunocompromised patients (CD4 cell count <50 cells·mm^{-3}) [52, 53]. In the absence of other data specific to patients with drug-resistant TB receiving second-line anti-TB medication, the decision on when to start ART should be no different from the approach to the HIV-positive drug-susceptible TB patient. ART should thus be initiated regardless of CD4 cell count and as soon as anti-TB treatment is tolerated, ideally as early as 2 weeks and no later than 8 weeks after initiation of anti-TB treatment [51, 54].

A high value was placed on outcomes such as preventing early death and TB transmission, and a lower value was placed on the resources required to make ART available to all MDR-TB patients with HIV. The capacity to implement this recommendation will require that more providers be trained specifically in the care of HIV and drug-resistant TB and drug–drug interactions. A substantial increase in the availability of and patients' access to treatment and additional support for ensuring adherence is likely to be necessary. The need for increased integration of HIV and TB care for effective patient management, prompt evaluation of adverse events and case-holding throughout treatment will necessitate more resources. For the benefit of the user, a table of adverse events for which both an ART and an anti-TB drug have been implicated, and could conceivably interact, is presented (table 5).

Recommendation 11. Patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalisation (conditional recommendation, ⊕○○○/very low-quality evidence)

Remarks

Outcomes from models of MDR-TB care based mainly on clinic-based ambulatory treatment were compared with those using mainly hospital-based in-patient treatment. The data used came from published and unpublished cost-effectiveness studies in four countries (Estonia, Peru [24], the Philippines [25] and the Russian Federation (Tomsk Oblast)). The design of these observational studies did not allow direct comparison of

TABLE 5 Potentially overlapping toxicities of antiretroviral and anti-tuberculosis (TB) drugs (including first-line anti-TB drugs)

Potential toxicity	Antiretroviral drugs	Anti-TB drugs
Peripheral neuropathy	Stavudine, didanosine	Cycloserine, isoniazid, ethambutol, fluoroquinolones, streptomycin, kanamycin, amikacin, capreomycin, viomycin, ethionamide/prothionamide, linezolid
Psychiatric symptoms	Efavirenz	Cycloserine, isoniazid, fluoroquinolones, ethionamide/prothionamide,
Hepatitis	Nevirapine, ritonavir-boosted protease inhibitors, efavirenz, etravirine, maraviroc	Pyrazinamide, isoniazid, rifampin/rifabutin, PAS, ethionamide/prothionamide, fluoroquinolones
Gastro-intestinal intolerance	Zidovudine, protease inhibitors, didanosine	Ethionomide/prothionomide, PAS, pyrazinamide, isoniazid, rifampin, ethambutol, clofazimine
Renal toxicity	Tenofovir, indinavir	Streptomycin, kanamycin, capreomycin, amikacin, viomycin, rifampin
Bone marrow toxicity	Zidovudine	Linezolid, rifampin/rifabutin
Lactic acidosis	Stavudine, didanosine, zidovudine	Linezolid
Stevens–Johnson syndrome	Nevirapine, efavirenz, etravirine	Thioacetazone, cycloserine, linezolid, ethambutol, streptomycin
Arrhythmias/QT prolongation	Atazanavir/ritonavir, saquinavir/ritonavir, lopinavir/ritonavir	Fluoroquinolones
Rash/pruritus	Nevirapine, efavirenz, etravirine, abacavir	Rifampin/rifabutin, pyrazinamide

PAS: *p*-aminosalicylic acid.

effects between models of care. Given that none of the studies were randomised controlled trials, the evidence was considered to be of very low quality. Cost-effectiveness was modelled for all possible WHO Member States in a probabilistic analysis of the data from the four countries [55].

Cost varied widely across the modelled settings. The cost per DALY averted by an ambulatory model in one setting was sometimes higher than the cost per DALY averted by a hospitalisation model in another setting. However, cost per DALY averted was lower under outpatient-based care than under in-patient-based care in $\geqslant$90% of the settings for which cost-effectiveness was modelled. The variation in cost-effectiveness among settings correlated most strongly with the variation in the cost of general healthcare services and other non-drug costs. There was no evidence to show that treatment in a hospital-based model of care leads to a more favourable treatment outcome.

The overall cost-effectiveness of care for a patient receiving treatment for MDR-TB can be improved with an ambulatory model. The benefits, when compared with hospitalisation models, include reduced resource use and at least as many deaths avoided among primary and secondary cases. This result is based on clinic-based ambulatory treatment (patients attending a healthcare facility); in some settings, home-based ambulatory treatment (provided by a worker in the community) might improve cost-effectiveness even further. One of the studies of ambulatory care dated from a time when the regimen drug combinations were not yet optimised, so the success achieved was probably inferior to that which can be accomplished with the regimens in use today.

In addition to reducing or avoiding hospitalisation where possible and prioritising community-care approaches for TB management, exposure to people who are infectious can be minimised by reducing the number of outpatient visits and avoiding overcrowding in wards and waiting areas [56]. The benefit of reduced transmission with an ambulatory model can only be achieved if proper infection control measures are in place in both the home and the clinic.

There may be some important barriers to accessing clinic-based ambulatory care, including distance to travel and other costs to individual patients. Shifting costs from the service provider to the patient has to be avoided, and implementation may need to be accompanied by appropriate enablers. While placing patients on adequate therapy would be expected to decrease the bacterial load and transmission of drug-resistant TB, infection control measures for home- and clinic-based measures will need to be part of an ambulatory model of care to decrease the risk of transmission in households, the community and clinics. TB control programmes will have to consider whether they are capable of reallocating resources from hospital to ambulatory care support in order to undertake the necessary changes in patient management. The choice between these options will affect the feasibility of implementing the recommendation in a particular programme.

A high value was placed on conserving resources and on patient outcomes, such as preventing death and transmission of MDR-TB as a result of delayed diagnosis and in-patient treatment. Admission to hospitals for patients may have important social and psychological consequences that need to be taken into account. However, there should always be provision for a back-up facility to manage patients who need in-patient treatment. This may be necessary in certain patient groups at particular risk, such as children during the intensive phase, among whom close monitoring may be required for a period of time.

CONCLUSIONS

As MDR-TB treatment programmes scale up globally, it becomes critical for treating clinicians to base their practice on the best available evidence. The recommendations for MDR-TB care and control in the new guidelines have been developed following the systematic examination of available evidence on the most salient questions in this area. Although the recommendations on composition and duration of treatment are now based on a meta-analysis of a large set of observations, the quality of all evidence in these studies varied from low to very low. The paucity of costing data has limited the number of studies that could be included to assess the performance of different models of care.

Whilst there have been no drastic changes in the recommendations from the previous guidelines, some changes and the presentation of the evidence on which the recommendations are based will contribute to the dual goals of improving access to care and treatment success. Rapid molecular testing for isoniazid and rifampicin is advisable even in previously untreated patients if resources make it possible. Monthly culture for the monitoring of treatment response is preferred. An intensive phase of 8 months' duration is conditionally recommended instead of the previous minimum of 6 months. The addition of pyrazinamide to a minimum of four second-line anti-TB drugs that are likely to be effective is recommended. The use of fluoroquinolones and ethionamide is strongly recommended. Later-generation fluoroquinolones are preferred. The contribution of ethambutol and Group 5 drugs in MDR-TB treatment remains unclear. All patients with drug-resistant TB and HIV who are on second-line anti-TB medications should be placed on ART as soon as they can tolerate it. Systems that primarily employ ambulatory models of care are recommended over others based mainly on hospitalisation.

The process of developing these guidelines revealed some important gaps in the knowledge that should be addressed in future research, particularly in the context of large-scale expansion of treatment for patients with drug-resistant TB. These include a lack of high- or moderate-quality evidence from randomised controlled trials for the optimisation of treatment regimen in patients with drug-resistant TB, particularly for determining the best combination of drugs and treatment duration. In addition, evidence was lacking on: 1) the treatment of paediatric MDR-TB; 2) the best drug regimens for treatment of patients with isoniazid resistance, XDR-TB or non-MDR-TB poly-drug resistance; 3) effective chemoprophylaxis for contacts of MDR-TB cases; and 4) therapy for symptomatic relief from adverse reactions linked with second-line anti-TB drugs.

In anticipation of the availability of new anti-TB drugs in the near future, and the development of novel diagnostic tools, these recommendations require a strong commitment by national TB

programmes to ensure their implementation at all levels. WHO, in collaboration with its technical and implementing partners, will strive to communicate them through different means. As in the past, the support of the European Respiratory Society (ERS) [57] and other leading scientific groups in respiratory medicine, including the American Thoracic Society (ATS), the Pan African Thoracic Society (PATS), the International Union Against Tuberculosis and Lung Disease (The UNION), the American College of Chest Physicians (ACCP), the Asian Pacific Society of Respirology (APSR) and ALAT (Asociación Latinoamericana del Tórax), will be crucial to the effective spread of the key messages and to assist countries to adapt the recommendations and evaluate their implementation.

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STATEMENT OF INTEREST

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Operational research in malawi: making a difference with cotrimoxazole preventive therapy in patients with tuberculosis and HIV

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Abstract

Background: In Malawi, high case fatality rates in patients with tuberculosis, who were also co-infected with HIV, and high early death rates in people living with HIV during the initiation of antiretroviral treatment (ART) adversely impacted on treatment outcomes for the national tuberculosis and ART programmes respectively. This article i) discusses the operational research that was conducted in the country on cotrimoxazole preventive therapy, ii) outlines the steps that were taken to translate these findings into national policy and practice, iii) shows how the implementation of cotrimoxazole preventive therapy for both TB patients and HIV-infected patients starting ART was associated with reduced death rates, and iv) highlights lessons that can be learnt for other settings and interventions.

Discussion: District and facility-based operational research was undertaken between 1999 and 2005 to assess the effectiveness of cotrimoxazole preventive therapy in reducing death rates in TB patients and subsequently in patients starting ART under routine programme conditions. Studies demonstrated significant reductions in case fatality in HIV-infected TB patients receiving cotrimoxazole and in HIV-infected patients about to start ART. Following the completion of research, the findings were rapidly disseminated nationally at stakeholder meetings convened by the Ministry of Health and internationally through conferences and peer-reviewed scientific publications. The Ministry of Health made policy changes based on the available evidence, following which there was countrywide distribution of the updated policy and guidelines. Policy was rapidly moved to practice with the development of monitoring tools, drug procurement and training packages. National programme performance improved which showed a significant decrease in case fatality rates in TB patients as well as a reduction in early death in people with HIV starting ART.

Summary: Key lessons for moving this research endeavour through to policy and practice were the importance of placing operational research within the programme, defining relevant questions, obtaining "buy-in" from national programme staff at the beginning of projects and having key actors or "policy entrepreneurs" to push forward the policy-making process. Ultimately, any change in policy and practice has to benefit patients, and the ultimate judge of success is whether treatment outcomes improve or not.

Keywords: Operational research, cotrimoxazole preventive therapy, tuberculosis, HIV/AIDS, Malawi, Africa

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Background

Operational research may be defined as the search for knowledge on strategies, tools or interventions which leads to improved programme performance and/or health service delivery [1]. In 1996, the Malawi National Tuberculosis Control (NTP) Programme embraced the concept of operational research and started a research programme that translated directly into several improvements in policy and practice [2,3]. Before this year, TB control activities had not been going well, quarterly supervision had declined and funding was an issue. The Department for International Development, UK, (DFID) pledged support for TB programme activities, such as procurement of drug and consumable supplies and routine quarterly supervision, and for operational research with the latter activity being used within the programme to collect data on weaknesses and to implement interventions to solve the challenges that it faced. This support by a new donor at that time was welcomed by the Malawi Ministry of Health.

Between 1996 and 2004, other donors such as the Norwegian Agency for International Cooperation (NORAD) and the Royal Netherlands Tuberculosis Association (KNCV) came on board to support activities within the Malawi NTP that included operational research as an integral part of programme activities. For the research, a partnership was set up whereby research ideas from within the National TB Programme, from local institutions (such as the Malawi Medical School, non-governmental organizations such as Medecins sans Frontieres and the National AIDS Programme) and from international organizations (such as the World Health Organization, The International Union Against Tuberculosis and Lung Disease and the Liverpool School of Tropical Medicine) were discussed and endorsed at the six-weekly meetings of the Malawi TB Programme Management Group. After priorities were established, research activities were then implemented by the various stakeholders, although many were planned, initiated, completed and published within the Malawi TB Programme itself.

The guiding principles that under-pinned the research agenda included i) defining the programme objectives, ii) identifying constraints that prevented objectives being met, and iii) asking research questions around those constraints to try and find solutions that would allow programme objectives to be achieved. In 2004, when scale up of antiretroviral therapy (ART) started in Malawi, operational research based around the same guiding principles was also used to inform policy and practice around the delivery of ART.

As an example of how this can work at the national level for TB and ART programmes and how guiding principles of operational research are put into practice, we describe the operational research that was carried out in Malawi with cotrimoxazole preventive therapy (CPT), initially in HIV-infected tuberculosis (TB) patients and then all HIV-infected patients starting ART. We outline the steps that were taken to translate these findings into policy and practice, and for both TB patients and HIV-infected patients starting ART show how the implementation of CPT made a difference and reduced death rates. We finally draw on general lessons that can be learnt for other settings and interventions, and suggest that such outcome indictors of deaths prevented or lives saved are the true measure of whether operational research in programme settings is useful or not.

Discussion

Effect of HIV on increasing death rates and reducing cure rates in the Malawi TB Control Programme

Malawi is a small country in southern Africa with a current population of about 13 million. In the 1980s, the country had one of the first "model" TB control programmes, a harbinger of the "DOTS" strategy, with about 4,000 registered cases per annum and cure rates in new smear-positive pulmonary TB patients at or higher than 90% [2,3]. These excellent treatment success rates were not to last. In December 1985, the first AIDS case was reported in the country, and within ten years HIV-prevalence in the adult population had soared to 14% [4]. Despite a well functioning NTP, annual case notifications spiralled out of control to reach 25,000 by the mid-1990s, which were associated with HIV co-infection rates of 75% [2,3].

Accompanying the increase in case notifications was a rapid increase in case fatality, which was reported from the programme setting and as well as from carefully monitored cohorts of patients, the case fatality also being strongly associated with HIV [2,3,5,6]. This had a major impact on cure rates in new smear-positive PTB patients which plummeted to their nadir in 1996 at 63% [2,3]. It became apparent in the mid-1990s that "DOTS" on its own was insufficient to control the TB epidemic, and HIV-associated interventions would be required if death rates were to be reduced.

Need for operational research to assess interventions to reduce death rates in TB patients

Two randomised controlled trials in Cote d'Ivoire assessing the effect of cotrimoxazole in HIV-infected adults were published in 1999. The first showed a decrease in morbidity in HIV-infected adults [7], while the second conducted in HIV-infected patients with TB showed a significant reduction in mortality [8]. These studies

persuaded the Joint United Nations Programme on AIDS (UNAIDS) to issue provisional recommendations in 2000 that all people living with HIV (PLHIV) in Africa who were symptomatic should receive CPT as part of a standard package of care [9].

The Cote d'Ivoire trial and the UNAIDS recommendations had important implications. At the time, there were three randomised controlled trials on CPT taking place in Malawi, Senegal and Cape Town, and all of these were prematurely stopped due to ethical considerations that evidence of efficacy was now established. However, the Malawi Ministry of Health (MoH) was reluctant to embark on a national policy of CPT for all PLHIV because of concerns about differences in commonly occurring disease pathogens and cotrimoxazole resistance rates between West and Central Africa. Furthermore, there were fears that widespread use of CPT would encourage cross-resistance to sulphadoxine-pyrimethamine which, at the time, was the national first line anti-malarial treatment for *Plasmodium falciparum* [10]. The Malawi MoH therefore encouraged and endorsed district operational research to gather national evidence to support or refute the use of CPT.

Operational research on offering HIV testing and cotrimoxazole to TB patients in Malawi and the initial policy decision

Two district-based operational research studies were undertaken and completed in Thyolo, the southern region, and Karonga, the northern region of Malawi [11,12]. The aim of the two studies was similar, namely to evaluate the feasibility and effectiveness of a package of HIV testing and CPT offered to TB patients registered under routine programme conditions. Mortality during anti-TB treatment was documented in all TB patients offered this package and registered during a 12-month period, and compared with mortality in all TB patients not offered the package and registered during a 12-month period the year before - namely, "historical controls". Active household tracing of patients was undertaken in both districts to ensure that mortality data were reliable.

A total of 2,703 TB patients were studied in both groups and in the two districts. In Thyolo, overall case fatality significantly declined from 36% in the control group to 28% in the intervention group, and in Karonga overall case fatality was also significantly reduced from 37% to 29%. The number of TB patients needing HIV testing and CPT to prevent one death during the course of anti-TB treatment was calculated at 12.5 in each district. In Blantyre district, a further study was conducted in 579 HIV-infected TB patients comparing two different doses of CPT and comparing case fatality rates with those observed in the National TB cohort and a previous TB cohort in whom a large majority had been tested for HIV and carefully followed to the end of TB treatment [13]. Case fatality was significantly reduced in patients offered CPT, and there was no difference in outcomes between patients offered CPT 480 mg daily and those offered 960 mg daily.

The results of these district operational research studies were presented at a large stakeholders' meeting convened by the Malawi MoH in October 2002. This meeting was organised by certain key actors within the TB Programme - so called "policy entrepreneurs"(see Table 1) - who ensured that the policy-making process remained on the agenda and moved forward. Important policy decisions were made at the end of that meeting [14]. The package of HIV testing and CPT was to be continued in the three districts in TB patients, and the intervention was to be scaled up to all TB patients country wide in a phased approach over three years. This was to be accompanied by appropriate guidelines, a training package and responsibility for procurement and distribution of CPT staying in the hands of the Malawi NTP. The uptake of the intervention was to be carefully monitored along with treatment outcomes, and further operational research was to be conducted as necessary to answer relevant questions arising from the field. As there was no evidence to support the benefit of HIV testing and CPT in PLHIV who did not have TB, the intervention was to be used only for HIV-infected TB patients until such time as additional evidence of benefit in PLHIV without TB was available.

Table 1 "Policy entrepreneurs" in the context of the Malawi National TB Programme

These are senior people within the National TB Programme (TB Programme Director and National TB Advisor responsible for operational research), who are well connected with senior personnel in the Ministry of Health and other actors in the health sector (for example, the Medical School)
They are responsible for the overall TB operational research programme and provide direction to the research questions and research implementation in the field
They assess the outcomes of the research and decide how this may influence policy within the context of the TB Programme and the wider health sector: this is discussed within programme management group meetings
Once decisions are made about the way forward, they assume responsibility for initial discussions with senior people in the Ministry of Health (for example, director of preventive services, secretary for health)
They take responsibility for the forthcoming policy meetings, and act as the secretariat for the organization and chairmanship of the meetings and for writing the minutes
They take responsibility for drafting new policy, and once this is agreed for dissemination country wide

Scaling up HIV counselling and cotrimoxazole for TB patients, further operational research and impact on TB programme performance

As a result of the policy decision from the MoH, the Malawi NTP together with the National AIDS Commission developed a 3-year plan to expand HIV-TB activities [14]. Soon after this plan was approved in late 2002, a country-wide situational assessment was carried out to assess the state of HIV/AIDS and joint HIV/TB services in hospitals, health centres and clinics throughout the country and to identify facilities to be included in the first phase of HIV testing and CPT implementation. National guidelines were developed that included how the package was to be administered, contraindications to CPT, doses for adults and children, management of adverse effects, logistics of providing CPT and finally how to use the new HIV testing and CPT registers for monitoring and evaluation. These registers were prepared and printed, and were used alongside TB patient registers. A training package was developed and a structured plan put in place to brief and train all TB registration facilities over a three-year period

CPT scale up started in 2003 at 15 facilities. An early review of the first 3 months' activities was carried out and proved invaluable in identifying challenges and solving misunderstandings [14]. Further operational research was also undertaken to answer pertinent questions. A study in Thyolo district showed that adherence to CPT in rural areas was excellent based on verbal verification of drug intake, physical verification of pill count balance and urine trimethoprim detection by gas chromatography and mass spectrometry [15]. Despite good medication adherence, research also demonstrated a growing increase of faecal *Escherichia coli* resistance to cotrimoxazole in HIV-infected TB patients receiving the drug, which prompted some concerns about the long term protective benefits of such chemoprophylaxis [16]. During scale up, the Malawi NTP was responsible for the administration of CPT during anti-TB treatment, but once this was completed patients were referred back to general health services to receive medication. Operational research documented that the majority of patients continued receiving CPT from health centres, although drug stock-outs and transport costs to health centres to collect drugs lead to interruptions of prophylaxis [17].

Routine data from the Malawi NTP showed that between 2002 and 2008 there was a significant increase in HIV testing amongst TB patients with the majority of HIV-positive patients being started on CPT (Table 2a). Treatment outcomes in new smear-positive pulmonary TB patients gradually improved, and by 2008, the global cure rate target of 85% was reached for the first time in 20 years since the start of the HIV/AIDS epidemic (Table 2b).

Scale up of antiretroviral therapy and the problem of early death rates

In 2004, the country embarked on rapid scale up of antiretroviral therapy (ART), supported financially through the Global Fund to fight AIDS, TB and malaria (GFATM) and implemented through a public health approach based on TB-DOTS principles [18,19]. One of the major problems encountered in the first years of ART scale up was high early mortality- defined as deaths during the first 6 months of treatment. This

Table 2 National Tuberculosis case finding and treatment outcome data in Malawi between 2002 and 2008

2 (a): Case Notifications, HIV testing and Cotrimoxazole Preventive Therapy (CPT)

	2002	2003	2004	2005	2006	2007	2008
TB case notifications	27,531	28,234	27,000	27,610	27,105	25,966	25,688
Number HIV tested (%)	2130 (8%)	3983 (14%)	6681 (25%)	12243 (44%)	17,253 (64%)	21,551 (83%)	21557 (84%)
Number HIV-positive (%)	1,630 (77%)	2,734 (69%)	4,804 (72%)	8,453 (69%)	12,064 (70%)	15,491 (72%)	13,677 (63%)
Number started CPT (%)	Not known	2,349 (86%)	4,649 (97%)	8,073 (96%)	11,244 (93%)	13,779 (89%)	13,148 (96%)

2 (b): Treatment outcomes in new smear-positive PTB patients evaluated nationally for outcomes

	2002	2003	2004	2005	2006	2007	2008
New smear-positive PTB patients evaluated	7,693	7,603	8,021	7,965	7,955	8065	7632
Treatment success (%)	5,572 (72%)	5,650 (74%)	6,082 (76%)	6,178 (78%)	6,369 (80%)	6707 (83%)	6534 (86%)
Death (%)	1,500 (19%)	1,410 (19%)	1,387 (17%)	1,265 (16%)	1,018 (13%)	739 (9%)	574 (7.5%)
Other outcomes (%)	621 (9%)	543 (7%)	552 (7%)	522 (6%)	568 (7%)	619 (8%)	524 (6.5%)

Legend: other outcomes = default, transfer out, failure. *[the data were obtained from annual NTP reports]*

finding was similar to other countries all over sub-Saharan Africa [19,20]. In the quarterly reports produced by the HIV Department, a consistent finding was that two thirds of all patients known to have died on ART did so in the first three months of treatment. Measures to reduce early mortality were urgently needed.

Operational research on cotrimoxazole to reduce early death rates in HIV-infected persons starting antiretroviral therapy and policy decision

Anecdotal experience suggested that CPT given before or at the start of ART reduced early death rates, and operational research was carried out to provide more evidence for this intervention. Comparisons of 6-month mortality with data obtained from ART registers and medical records were made between 6 facilities providing ART without CPT and 5 facilities providing ART with CPT [21]. The 6-month mortality rate was significantly lower at ART-CPT sites (10.7%) compared with ART sites alone (18%) [6-month mortality risk reduction = 41%, p = 0.0013], with survival differences apparent as early as 40 days after the start of ART. These data were consistent with subsequent reports from other African countries demonstrating a synergistic effect of CPT with ART, especially in the early months of treatment [22,23]. The Malawi data prompted the HIV Department of the MoH, again through "policy entrepreneurs", to convene a national stakeholders meeting to re-examine the use of CPT in PLHIV.

At the national stakeholders meeting in 2005, new evidence on CPT was reviewed, particularly studies that had been carried out in other sub-Saharan African countries [24-27], which included the joint WHO/UNAIDS/UNICEF statement on use of cotrimoxazole as prophylaxis in HIV-exposed and HIV-infected children [28]. Evidence showed that CPT was associated with a 25%-46% reduction in mortality in PLHIV in sub-Saharan Africa, even in areas with high bacterial resistance to the antibiotic. CPT was also associated with fewer hospitalisations, weight gain, a rise in CD4-lymphocyte counts and a decrease in HIV viral loads. Efficacy was maintained over 1-2 years of follow-up. There were few adverse reactions and high levels of adherence were documented. In summary, CPT appeared to be a safe, cheap and readily available anti-microbial agent, which could extend and improve the quality of life of PLHIV. The earlier concerns about widespread use of CPT increasing resistance of *Plasmodium* falciparum to sulfadoxine-pyrimethamine were partially allayed by studies in children in Mali [29].

There was therefore unanimous agreement to modify the current national recommendations for CPT, and for Malawi to adopt a policy that CPT be provided free of charge to adults and children living with HIV/AIDS as part of a minimum package of care [30] (see Table 3). Malawi's policy and guidelines were in line with those subsequently released by WHO in 2006 [31].

From policy to practice: scaling up of cotrimoxazole preventive therapy for people living with HIV and impact on early deaths on antiretroviral therapy

Following the adoption of the policy, the HIV department of the MoH wrote a circular with guidelines on CPT drug regimens and individual patient supplies, contraindications, duration of therapy, recruitment, follow-up monitoring and evaluation and drug supply issues. This circular was distributed country-wide for immediate use, and national ART guidelines were eventually updated based on the new evidence [32]. ART treatment cards were modified to incorporate data on use of CPT. Pharmacy dispensing registers for CPT in PLHIV who were not eligible for ART were also developed and printed to track uptake and usage of CPT, and these were placed in pharmacies under the responsibility of pharmacy technicians. A training package was developed, and the CPT policy and guidelines were incorporated into the ARV-HIV related diseases management module that was taught to clinicians and nurses in the country. The policy was also incorporated into other

Table 3 Policy Guidelines for Cotrimoxazole Preventive Therapy in Malawi (2005)

In Adults:

Cotrimoxazole should be offered to the following HIV-positive adults (aged 15 years and above):

- All persons with symptomatic HIV disease (WHO Clinical Stage 2,3 and 4)
- All persons who have a CD4-lymphocyte count of 500/mm^3 or less, regardless of symptoms
- Pregnant women after the first trimester who are symptomatic or have a CD4-lymphocyte count < 500/mm^3

Note: In adults there is not enough evidence to recommend cotrimoxazole to HIV-positive adults who are asymptomatic (i.e., WHO Clinical Stage 1). However, if evidence is forthcoming in the future to support a change, then this recommendation will be re-examined. It is also felt that the threshold of CD4-count of 500 cells/mm^3 may be too high, but it is agreed to stay with this threshold as it is similar to that recommended by the World Health Organization. Again, if evidence is forthcoming in the future that this threshold is too high, the recommendation will be re-examined

In Children:

Cotrimoxazole should be offered to children in the following circumstances:

- Any child, aged 6 weeks or above, born to an HIV-positive woman irrespective of whether the woman received antiretroviral therapy in pregnancy
- Any child, 6 weeks or more, who is HIV-positive regardless of symptoms

Note: All HIV-positive children should be offered cotrimoxazole because they have higher viral loads than adults, progress faster to AIDS and to death compared with adults and at present do not have the same opportunities to access antiretroviral therapy as adults

Reference [30]

ongoing training courses such as Integrated Management of Childhood Illness (IMCI). Teachers at the various training institutions in Malawi for nurses, clinical officers and medical doctors were made aware of the policy revisions so that they could incorporate them into the curriculum for undergraduate teaching of the management of HIV-related illness. A non-governmental organization assisted the HIV Department in training clinical, nursing and pharmacy staff at all district and mission hospitals in the country, and especially pharmacy technicians on the use and monitoring of CPT.

National forecasting and procurement of CPT needs was integrated into the established practices for ARV drugs. Special packaging of 120 cotrimoxazole tablets per tin was ordered to facilitate 2-month adult dispensing, and thus removing the previous tiresome burden on nurses having to count tablets from 1000-tablet tins. The number of patients receiving CPT is now recorded every quarter as part of the HIV Department's quarterly reports for the country.

As of December 2010, 95% of the 250,987 patients on ART (including HIV-infected TB patients) were on CPT, and a cumulative total of 338,609 patients (pre-ART and ART) had been entered in CPT registers. However, this underestimates the use of CPT as the registers had not been used consistently by all sites [33]. Early mortality on ART has declined considerably. In quarter 2, 2006, 11% of new patients died within the first three months of ART initiation [33]. Early mortality has declined to less than 5% in quarter 4, 2010, according to the routine records [33]. This may be partly due to CPT and also due to the decline in the proportion of patients starting ART in WHO Clinical Stage 4 from 25% in quarter 2, 2005, to about 10% in quarter 4, 2010 [33].

Lessons learnt

The operational research conducted on HIV testing and CPT, first to HIV-infected TB patients and then to all PLHIV, provides some important lessons about how to successfully integrate operational research into a programme setting. The key stages for this were: initial placement of "operational research" within the programme setting and ensuring senior persons could act as "policy entrepreneurs"; developing relevant research questions; carrying out the research studies; disseminating and publishing the study findings; translating the study findings into action on the ground; and assessing the impact on programme performance. Some of the key lessons learnt, including generic lessons, are illustrated in Table 4, and are further discussed below.

Contextual placement of operational research within a programme setting

Right from the start, the operational research programme was placed within the Malawi NTP with the Programme Director strongly supporting and the National TB Advisor taking responsibility for coordinating the research programme. These two people were the "policy entrepreneurs" (see Table 1), well connected to senior people in the Ministry of Health and to other stakeholders in the health sector such as the Medical School and non-governmental organizations. A similar context prevailed in the HIV/AIDS programme. The small size of the country, the strong support from the Government Ministry of Health for this type of work and the close connections with other key stakeholders in the health sector were important determinants of the success of the operational research. Larger countries with different political and governance systems may find this more difficult.

Defining the research questions, getting "buy-in" and using "policy entrepreneurs"

The importance of defining relevant questions for programme and country staff, obtaining "buy-in" from national programme staff and other interested stakeholders at the beginning of a project and having the key actors or "policy entrepreneurs" [34] to push forward the policy-making process cannot be overemphasised, and these were probably the most important elements of the success of moving this research endeavour through to policy and practice. Without this structure, it is likely that the research would have been published, but without the impact for changing policy or practice. The research questions that were asked were priorities for the programme, and were not set by academic institutions which might have had a different agenda. Furthermore, the results of the various studies were of immense interest to the NTP and to the HIV/AIDS programme, and this ensured that strong linkages were made in getting the research findings to policy at the Ministry of Health and to practice at health facilities in the districts. Important lessons are that operational research should be embedded within a programme structure with a focal point identified, research questions asked from within the programme and a clear budget line set aside to support activities.

Disseminating and publishing results

It is important to disseminate and particularly publish results, as the latter lends credibility to the findings [35]. Operational research, if undertaken, is often not written up and submitted for scientific publication, and many of the lessons that could be learnt do not appear in the public domain [36,37]. At country level, it is crucial to have a clear roadmap for dissemination through MoH channels to allow policies to be adopted and the necessary practices that are needed for implementation to be driven forward on the ground.

Table 4 Generic lessons learnt from operational research with cotrimoxazole preventive therapy in Malawi

Malawi-based experience	General lessons learnt
There were high case fatality rates of TB patients on anti-TB treatment alone, and thus a need for HIV-specific interventions There were high early death rates of people living with HIV starting antiretroviral treatment	Research questions must be relevant to programme needs. Operational research leadership and coordination must be placed within the programme.
Research on cotrimoxazole was endorsed by MoH, and district studies were designed and implemented in conjunction with national programme staff	Research should be endorsed and designed with programme MoH staff in order to increase the probability of findings and recommendations from the study being accepted and implemented
Research was carried out at district or facility level using routine systems; data were collected using registers and treatment cards; all patients were included with no special inclusion and exclusion criteria	Research can and should be effectively carried out within programme settings and routine health services
Key actors or "policy entrepreneurs" in the programmes helped to move forward the process of policy making National meetings were held to engage all stakeholders, to obtain "buy-in" of the results and to get advice and direction as to how to move forward Publication of results in international-peer reviewed journals brought credibility to findings as a result of the peer-review process, and allowed dissemination of results internationally	Key actors or "policy entrepreneurs" must be identified and given the task of moving forward the policy process When research is completed, dissemination must occur nationally, and if judged of wider importance then internationally as well Publication of operational research in peer-reviewed journals adds credibility to the study findings
Clear policy decisions were obtained from MoH about the study findings, and directives given about how to implement the new interventions	Research should influence national policy and practice
Policy documents were prepared and widely distributed through circulars around the country National Guidelines were updated with new evidence and new policy Monitoring tools were prepared and disseminated; drug forecasting was integrated into established processes; training materials were developed and used at different levels; uptake of new interventions were reported in national quarterly reports	Programmes need to implement the new policy and practices Key actors and "policy entrepreneurs within programmes play an important role in this process International guidelines or a road-map need to be developed to better direct the national steps that logically help move research to policy and practice
There was a clear demonstration of impact in reducing case fatality and increasing treatment success in TB patients, and in reducing early death rates in people with HIV starting ART	The ultimate benefit is an impact on programme performance and treatment outcomes

MoH = Ministry of Health; ART = antiretroviral therapy

Translating research into policy and practice on the ground

At present, guidelines or a road-map for this process of moving research into policy and practice do not exist at national or international level, and the activities that happen tend to be ad hoc. This should change, and clear, practical steps for dissemination and influencing policy and practice need to be made, based on successful experiences such as those illustrated in this paper.

Assessing the impact on programme performance

Ultimately, any change in policy and practice has to benefit patients and the community, and hence the ultimate judge of success is whether treatment outcomes improve or not. It is sometimes difficult to ascribe direct causality in these situations, but that is of secondary concern to programmes where achievement of performance (be it through a direct effect or as an indirect effect of introducing new interventions) has to be the ultimate goal.

Summary

- In Malawi, high case fatality rates in patients with tuberculosis (TB), who were also co-infected with HIV, and high early death rates in people living with HIV during the initiation of antiretroviral treatment (ART) adversely impacted on treatment outcomes for the national TB and ART programmes respectively.
- District and facility-based operational research was undertaken to assess the effectiveness of cotrimoxazole preventive therapy (CPT) in reducing death rates in TB patients and subsequently patients starting ART under routine programme conditions. Studies showed the beneficial effects of CPT in HIV-infected TB patients and in HIV-infected patients about to start ART, following which the findings were rapidly disseminated nationally at stakeholder meetings convened by the Ministry of Health and internationally through conferences and peer-reviewed scientific publications.
- The Ministry of Health made policy changes based on the available evidence, following which there was countrywide distribution of the updated policy and guidelines. Policy was rapidly moved to practice with the development of monitoring tools, drug procurement and training packages. National programme performance improved, as was demonstrated from routine data, which showed a significant decrease in case fatality rates in TB patients as well as a

reduction in early death rates in people with HIV starting ART.

• Key lessons for moving this research endeavour through to policy and practice were the importance of placing operational research within the programme setting, defining relevant questions for programme and country staff, obtaining "buy-in" from national programme staff at the beginning of projects and having key actors or "policy entrepreneurs" to push forward the policy-making process.

Ethics Statement

An ethics statement was not required for this work.

List of abbreviations used

AIDS: acquired immune deficiency syndrome; ART: antiretroviral therapy; CPT: cotrimoxazole preventive therapy; DOTS: directly observed treatment, short course; GFATM: Global Fund to fight AIDS, TB and malaria; HIV: human immunodeficiency virus; IMCI: Integrated Management of Childhood Illness; MoH: Ministry of Health; NTP: national tuberculosis control programme; PLHIV: people living with HIV.

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Authors' contributions

ADH and RZ had the idea for the paper and wrote the first draft. All authors contributed to further drafts of the manuscript, and all read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Implications of the current tuberculosis treatment landscape for future regimen change

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SUMMARY

BACKGROUND: The current tuberculosis (TB) treatment landscape has been studied extensively, but researchers rarely consider how it creates challenges or opportunities for future regimen change.

METHODS: In 166 stakeholder interviews in the TB high-burden countries (HBCs), we investigated areas of first-line TB treatment and control that would affect, and be affected by, a future TB regimen change. Responses were compared with existing standardized data.

RESULTS: Public sector regimens are converging towards a single standard, which facilitates comparison with a single control arm from clinical trials. However, final product design is challenging if the goal is fixed-dose combinations and patient kits, whose current widespread use addresses continuing weaknesses in drug management. Any product must address broad groups, as relatively low levels of drug susceptibility testing (DST) do not allow for individualized therapy. Finally, the protection of new drugs from the development of resistance will be challenging, as the implementation of directly observed therapy and public-private mix programs is incomplete, and substantial private sectors have been identified as early adopters of these drugs.

CONCLUSIONS: Health systems for TB treatment and control must be improved not only to allow better implementation of current treatments but also to set the stage for implementation of new, improved TB regimens.

KEY WORDS: regimen change; tuberculosis drugs; high-burden countries

A NEW TUBERCULOSIS (TB) regimen must compete with current regimens[1] based on clinical trial evidence, but it must also fit into the existing health system.[2] Here, we quantify certain parameters of the existing TB treatment landscape and investigate how this landscape would impact the introduction of a new TB regimen.

Within the DOTS approach, a key variable is the choice of regimen by the National TB Program (NTP). These choices have at times been controversial;[3] conservative approaches with the current first-line drugs have been common due to the paucity of alternative drug options. More recently, an increase in the evidence base has helped to fine-tune World Health Organization (WHO) recommendations regarding regimen choice.[4–6] The limited capacity for drug susceptibility testing (DST) in the high-burden countries (HBCs)[7] has not allowed for individualized regimens.

Adherence to the regimen is maximized by delivering TB drugs with directly observed treatment (DOT).[8] Variants of this approach include facility-based or community-based DOT, with observation by health workers, community health workers, or family members.[9] As the optimal strategy depends on context, more recently the emphasis has been on taking a patient-centered approach.[10]

A new regimen would need to fit into TB drug delivery systems that have been simplified over the past two decades. Two leading approaches to minimize problems with weak drug management have been the use of fixed-dose combinations (FDCs)[11] and patient kits. A single patient kit holds an entire 6- or 8-month regimen for a patient; the kits ensure that drugs do not run out mid-regimen, simplify drug quantification, and help patients to understand that the regimen is lengthy, for a fixed term, and requires commitment.

Public-private mix (PPM) programs allow the public sector to monitor and influence the regimens used in the private sector, via activities such as supervision, referral and provision of standardized drugs; they were devised in recognition of the substantial private sector involvement in TB care.[12] Scaled-up PPM interventions are cost-effective,[13] but PPM programs have faced challenges.[14]

The new regimen that may enter this landscape in

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the near future is a 4-month multidrug regimen that includes either gatifloxacin or moxifloxacin. Both of these fluoroquinolone antibiotics are in Phase III trials to test the non-inferiority of the fluoroquinolone-containing regimen compared to the standard 6-month regimen (2HRZE/4HR, i.e., 2 months of isoniazid [H], rifampicin [R], pyrazinamide [Z] and ethambutol [E], followed by 4 months of HR).[15]

Planning for global regimen change requires greater knowledge about the extent of certain key practices that will affect, and be affected by, regimen change. This article provides such a quantitative overview, and identifies a number of action points that will strengthen delivery of both current and future regimens.

METHODS

While investigating past regimen changes,[11] we surveyed stakeholders about TB health system issues related to regimen change. The countries included in the study are the 22 defined by the WHO as HBCs for TB, and the majority of our questions were on public sector policies, given the importance of the public sector in TB control (although some questions on the private sector were included). The primary focus was on the delivery of treatment for drug-susceptible TB, as treatments for multidrug-resistant TB (MDR-TB) have very different financial and human resource requirements.

From April to August 2008, data were collected by conducting 166 stakeholder interviews in 21 countries, as described[11] (inquires were restricted to e-mail for Myanmar due to Cyclone Nargis). No ethics committee was involved, as the unit of inquiry was held to be institutions (and their behavior) rather than individuals. Informed consent was obtained verbally using a standard script; interviewees agreed that it was 'OK to summarize your comments, without specific attribution to you or your institution, for inclusion in a public report.' Any documents that associated an individual with a response were restricted to the study team, who had signed confidentiality agreements. Before public release of data, responses were combined and anonymized. The substantial number of respondents per country ensured continued anonymity.

Each interviewer (one per country, each a professional in the field of TB drug management) was trained by phone using a standardized information packet and training presentation. Interviewees were identified by a combination of purposive sampling and snowball sampling, as in previous studies of public sector regimen decision-making.[1,2] Each interviewer identified, in collaboration with the central study team, an initial set of three key interviewees—one each from the NTP, the WHO country office, and the regulatory authority. These and subsequent interviewees were asked to identify other key individuals and organizations involved in TB health systems and TB regimen decision making.

Interview topics were identified by considering all the regimen change steps outlined by the Stop TB Partnership's Retooling Taskforce[16] and the concerns previously raised by stakeholders regarding new TB regimens.[1] We considered the following as relevant to regimen change: which TB drugs are used (public sector regimens, FDC use, regimen choice in the private sector); how TB drugs are delivered (NTP performance, drug management performance, how DOT is practiced, size of TB private sector, extent of PPM programs); and how the continued efficacy of drugs is ensured (extent of DST, and FDC and DOT issues mentioned above). As there are two fluoroquinolones in Phase III trials for drug-susceptible TB, we asked about the availability of fluoroquinolones and of data on fluoroquinolone resistance.

Interviewees were asked to respond 'to the best of [their] knowledge'. Answers from different interviewees were cross-checked and, where possible, the data collected were compared to WHO data.[17] If stakeholders made a qualitative observation, the observation is noted in the text followed by the names of the stakeholders' countries in parentheses. These observations were elaborations from the questions originally asked, so were only detected in the countries noted.

RESULTS

Public sector regimens

In the public sector, the current regimen provides the baseline against which any new regimen will be judged. Although WHO guidelines have allowed for some variation in treatment regimens for drug-susceptible TB, we found that globally these regimens in HBCs (Table 1) have been moving (Table 2) towards a

Table 1 First-line regimens in the HBCs

Regimen	Dosing	*n*	HBCs
2HRZE/4HR	Daily	13	Bangladesh, Brazil, Cambodia, Democratic Republic of Congo, Indonesia,* Kenya,† Mozambique, Myanmar, Philippines, South Africa, Thailand, United Republic of Tanzania, Zimbabwe
2HRZE/4HR	Intermittent	2	China,‡ India
2HRZE/6HE	Daily	5	Afghanistan, Ethiopia, Nigeria, Pakistan, Uganda§
2HRZS/6HE	Daily	1	Viet Nam§
2HRZE/S/4HR	Daily	1	Russian Federation

*Intermittent in continuation phase.
†Transitioning from 8 months.
‡Daily for those with HIV/AIDS, and daily being phased in for other patients.
§Committed to daily 2HRZE/4HR after our interview period concluded.
HBC = high-burden country; H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol; S = streptomycin. Numbers before the letters indicate the duration in months of the phase of treatment; HIV = human immunodeficiency virus; AIDS = acquired immune-deficiency syndrome.

Table 2 Movement of HBC regimens towards a single standard

	HBC (year)
Changes bringing regimens closer to 2HRZE/4HR (7 days/week)	
Add E to intensive phase	Brazil (2008)
Continuation phase daily not intermittent	Bangladesh (2008)
From 8- to 6-month regimen	Cambodia (2005); Democratic Republic of Congo (2004); Kenya (2006); Mozambique (2005); Tanzania (2006)
'Daily' increased from 5–6 days to 7 days/week	South Africa (2007); Tanzania (2006)
Changes rejected or indefinitely postponed	
From 8- to 6-month regimen	Afghanistan (2007); Ethiopia (2007); Nigeria (2008)
Dosing frequency	
Intermittent (3 days/week)	China (daily as option), India, Indonesia (continuation phase only), Russian Federation (one option in continuation phase only)*
Daily (7 days/week)	14 HBCs [35% of global burden]
Daily (6 days/week)	2 HBCs [2% of global burden]
Daily (6–7 days/week)	1 HBC [1% of global burden]
Daily (5, 6 or 7 days not determined)	3 HBCs [6% of global burden]

*This accounts for 37% of global burden, based on stakeholder estimates that for public programs 90% of China, 66% of Indonesia (i.e., 100% of continuation phase), 10% of Russian Federation, and 100% of India use intermittent therapy.
HBC = high-burden country; H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol. Numbers before the letters indicate the duration in months of the phase of treatment.

Table 3 Weight bands used for adult Category I regimens

	Rifampicin dosages in treatment guidelines?				Weight bands
Country	300 mg	450 mg	600 mg	750 mg	*n*
Brazil	Yes	Yes	Yes	No	3
China (daily)	No	Yes	Yes	No	2
China (intermittent)	No	No	Yes	No	1
Democratic Republic of Congo	Yes	Yes	Yes	Yes	4
Ethiopia	Yes	Yes	Yes	Yes	4
India (intermittent)	No	Yes	Yes	No	2
Indonesia	Yes	Yes	Yes	Yes	4
Kenya	Yes	Yes	Yes	No	3
Nigeria	Yes	Yes	Yes	No	3
Pakistan	Yes	Yes	Yes	Yes	4
South Africa (IP)	Yes	Yes	Yes	Yes	4
Tanzania	No	Yes	Yes	No	2
Uganda	Yes	Yes	Yes	Yes	4
Total	9	12	12	6	

Light gray denotes weight bands that are not present in a country, and countries with only 3 weight bands. Dark grey denotes countries with only 1–2 weight bands
IP = intensive phase.

single standard of daily 2HRZE/4HR (true for 13/22 HBCs). These data are in agreement with WHO data,[17] with the exception of a recent regimen change by Bangladesh. After our interviews were completed, Uganda and Viet Nam also committed to the 6-month regimen.

Weight band information for adult (>30 kg) Category I patients (i.e., new smear-positive or serious smear-negative cases) was available for 12 HBCs (Table 3). Exact cut-offs for weight bands differ between countries but, more importantly, so do the number of weight bands. Of the 12 HBCs, only half used four weight bands. Thus, some HBCs do not dose entirely within the recommended range of 8–12 mg/kg of rifampicin.

Variants on the standard regimen

Stakeholders were asked if there were any variants on the standard Category I regimens. The two main categories of regimen variants mentioned were 'overtreatment' (the addition of extra drugs to 'ensure a cure') and the beginning of a regimen change (see private sector section below). Overtreatment reportedly arises because physicians are faced with rising drug resistance and inadequate DST capacity; distrust in drug quality was also mentioned by one stakeholder. Their solution is often the addition of a single drug, usually a fluoroquinolone, even though this may be the only new, active drug in an otherwise failing TB regimen (Indonesia, Philippines, and Thailand for Category I; China and Russian Federation for Category II).

Use of fixed-dose combinations

A critical component of the TB treatment landscape is the use of quality-assured FDCs. Current use of FDCs by NTPs was reported (Figure) as being more widespread than indicated by WHO data.[17] Stakeholders reported that NTPs in 20/22 HBCs use a two-drug FDC, usually for the continuation phase. The remaining two countries are China, which is piloting both two- and four-drug FDCs, and India, which is the only HBC NTP with no use or plans for use of FDCs. Both China and India use co-blistered drugs as an alternative to FDCs.

Stakeholders also stated that 18 of the 20 HBC NTPs that were using a two-drug FDC were also currently using a four-drug FDC. The two that were not were Brazil, which had firm plans to adopt a four-drug FDC in 2009, and Viet Nam, which reportedly

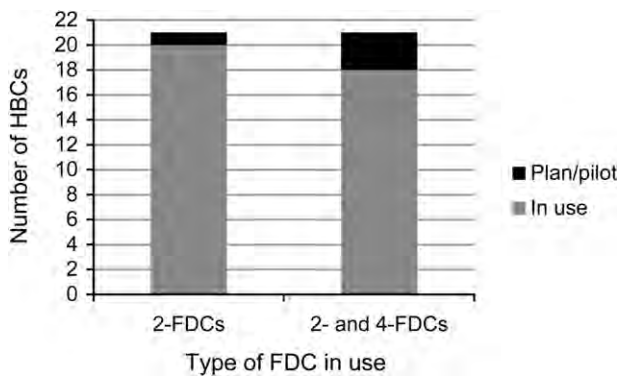

Figure Number of HBCs using 2- and 4-FDCs. HBC = high-burden country; FDC = fixed-dose combination.

remained open to a four-drug FDC if and when it drops streptomycin from its Category I regimen. Finally, three-drug FDCs were reportedly in use in the public sector in 15 HBCs, primarily for Category II (retreatment). We did not assess quality assurance mechanisms, such as tests of bioavailability, although these are a vital component of any FDC strategy.

In 12 HBCs it was clear that loose drugs were only available in very limited amounts (e.g., for side-effect management), suggesting that FDCs were the primary dosing formulation used by NTPs in these countries. Of the remaining countries, two (India and China) use few or no FDCs, and seven yielded responses that were unclear. Only in Thailand was it stated that providers could choose whether they used loose drugs or FDCs.

The Global Drug Facility (GDF) supplies eight different adult and pediatric FDCs. Five additional FDCs were available in at least one HBC other than the Russian Federation; the latter country had 14 additional, unique formulations.

Patient kits and drug management

Although we did not ask about packaging, the use or adoption of patient kits in the country was mentioned by stakeholders in Kenya, Myanmar, Nigeria (adoption initiated) and Viet Nam (adoption desired but not yet initiated). The GDF reported that, in at least one of the last 3 years, they have supplied patient kits to 23 countries (including 6 HBCs, namely Afghanistan, Indonesia, Kenya, Myanmar, Nigeria and the Philippines; T Moore, GDF, personal communication based on GDF database). In addition, India and South Africa supply their own kits. These 8 HBCs represent 42% of the worldwide burden of smear-positive TB.[17]

When asked about strengths and weaknesses of drug management, stakeholders mentioned significant issues with TB drug stock-outs in 7 HBCs (Cambodia, China, Democratic Republic [DR] of Congo, Kenya, Pakistan, South Africa and Uganda), TB drug expiries in 2 HBCs (Ethiopia and Tanzania) and both stock-outs and expiries in 4 HBCs (Indonesia, Mozambique, Nigeria and Zimbabwe). Seven of these HBCs figure amongst the 11 HBCs previously reporting stock-outs of first-line drugs at either central or peripheral locations.[17]

Extent of drug susceptibility testing

Stakeholders stated that eight HBCs conduct no testing for fluoroquinolone resistance in the public sector outside of a clinical trial setting. Another 8 HBCs test some MDR-TB patients and/or retreatment patients for fluoroquinolone resistance, but often at one or very few treatment centers. Widespread testing for fluoroquinolone resistance was claimed only in the Russian Federation and was planned for the future in Brazil (DST capacity not determined in four HBCs). The WHO reports that 9 HBCs have access to second-line DST either within or outside the country.[17]

This lack of fluoroquinolone DST contrasts with the widespread availability of fluoroquinolones, which are used for a number of non-TB indications. Stakeholders stated that fluoroquinolones require a prescription in 18 HBCs (none required in 2 HBCs; status unknown in 2 HBCs), and yet they are available over the counter in 15 HBCs (mixed opinion or unclear in 5 HBCs; not available over the counter in 2 HBCs). Many respondents made it clear that fluoroquinolones were freely and widely available in their country. Fluoroquinolones were believed to be used for first-line TB treatment in the public and private sectors in the Russian Federation and in the private sector in 5 HBCs in Asia; opinions on this topic for China were mixed.

Extent of directly observed treatment

Stakeholders were asked to describe the frequency of DOT in both treatment phases and to identify the personnel conducting DOT. Due to the variability of DOT within most HBCs, answers were not always simple to interpret. However, stakeholders did mention that encounters with health care centers are often restricted to weekly, biweekly or monthly visits (Table 4). In many HBCs, stakeholders noted that direct observation is primarily conducted by family (Indonesia, Kenya, Mozambique, Zimbabwe), self (Ethiopia, Nigeria, Russian Federation) or either family or self (China). The concept of self-DOT seems contradictory and was not an option in the interview guide; the answer is nevertheless reported because it was provided.

Private sector size and PPM coverage

The importance of the private sector in TB regimen change depends on how many TB patients access

Table 4 Frequency of patient contact with health care system in the HBCs

Phase	Frequency of encounters with health care system*	HBCs
Intensive	Weekly	Indonesia, Pakistan, South Africa, Zimbabwe
	Biweekly	Brazil, Kenya
	Monthly	China,† Mozambique
Continuation	Weekly	India
	Biweekly	Brazil
	Monthly	China,† Ethiopia, Indonesia, Kenya, Mozambique, Nigeria, Pakistan, Russian Federation, South Africa, Zimbabwe

* Listed only when responses were clear; may not be uniform through a given country.
† This is for collecting drugs from the county doctor. Some patients then do family DOT; others see the village doctor every other day.
HBC = high-burden country; DOT = directly observed treatment.

private treatment. Based on the mean of stakeholder estimates (and a recent prevalence survey in Viet Nam[18]), the private sector treats ~30–53% of the TB cases in 8 HBCs; ~8–17% in 5 HBCs; and ~4% or less in the rest (Table 5).

TB treatment in the private sector was reported as being prohibited in Brazil and the Russian Federation, prohibited but without enforcement in Cambodia and Zimbabwe, and not prohibited in the remaining 18 HBCs. Stakeholders added that TB drug sales in the private sector are prohibited at least in Brazil, DR Congo, Ethiopia, the Russian Federation, and Zimbabwe, and TB drugs in Tanzania are restricted to the public sector via importation controls.

The influence of PPM programs depends on their size. Stakeholders were asked about the number of patients and physicians in PPM programs. Up to 9 HBCs reported having minimal or no PPM programs (Table 5). For the remaining HBCs, the percentage of incident cases covered by PPM programs is often unclear.[17] Based on WHO and stakeholder estimates, we calculated that PPM programs involve over 500 physicians in only Cambodia, India, Indonesia, Pakistan and the Philippines, detect 22% or less of the private sector in all but Kenya, Myanmar, and the Philippines, and leave 29% or more of a country's total incident TB cases being treated in the private sector without the benefit of PPM in 6 or more HBCs (Table 5).

Early adoption by the private sector

Stakeholders noted that practices in the private sector, although much less uniform, have often preceded the process of public regimen change, especially if the NTP resists regimen change for a long time. (Non-recommended practices may also be adopted by the private sector, but this study focused on WHO and NTP guidelines.) Past examples mentioned by stakeholders included: adoption of FDCs in the Philippines

Table 5 Estimated size of private sector and PPM programs

Country	A Percentage of patients getting TB treatment from private sector, mean of estimates*	B Percentage of private sector covered by PPM (estimate)†	C Percentage of incident patients in the unregulated private sector, i.e., in private sector but NOT in PPM, C = A − (A × B)
Afghanistan	50%	0%	50%
Bangladesh	13%	14%	11%
Brazil	0%	No PPM	0%
Cambodia	40%	4%	38%
China	15% (non CDC hospitals)	Extensive PPM	Low
Democratic Republic of Congo	0%	Unknown	0%
Ethiopia	1%	13%	0.9%
India	45%	⩽13% (13% of the Indian population lives in districts with at least some PPM activity‡)	⩾39%
Indonesia	53%	5%‡ or 20%§ of private physicians are enrolled in PPM	43–50%
Kenya	3.5%	67%	1.2%
Mozambique	2.5%	No‡ or minimal (5 physicians§) PPM	2.5%
Myanmar	44%	34% (15% of all incident cases are covered by PPM‡)	29%
Nigeria	30%	Probably incomplete, as there are only 410 PPM physicians§ and ~65 000 private patients	Unknown
Pakistan	45%	5% of private physicians§ or 20% of notified cases.[19] (One third of districts have at least some PPM‡)	32–43%
Philippines	40%	68% (~27% of all incident cases are in PPM‡)	13–19%
Russian Federation	0%	No PPM	0%
South Africa	4%	Unknown	Unknown
Thailand	12%	22% of private physicians§	9.4%
Uganda	0%	No PPM	0%
United Republic of Tanzania	17%	Minimal PPM (12 physicians§)	~17%
Viet Nam	8%¶	No PPM	8%
Zimbabwe	0%	No PPM	0%

*Estimated percentages are coded as high (dark grey), medium (light grey) or low (white). Some cases may later transfer to public sector (e.g., Cambodia and Myanmar). The figures include hospitals in China that are government-funded but not aligned with the national TB program, but they exclude large faith-based organizations and NGO sectors in Cambodia, DR Congo and Nigeria.

†Where noted, this figure comes directly from stated survey information‡ or WHO data.§ In all other cases, this was calculated as (number of patients treated by PPM) / [(incident cases, all forms) × (% patients in private sector)]. The first and third terms in this equation were stakeholder estimates.

¶Based on the recent prevalence survey results.[18]

PPM = public-private mix; TB = tuberculosis; CDC = Centers for Disease Control and Prevention; NGO = non-governmental organization; WHO = World Health Organization.

and Viet Nam; the daily continuation phase in Bangladesh; and the changes from an 8- to a 6-month regimen in Kenya and Uganda. Certain private sector practices may also predict future changes, as they mimic the global consensus more than the current national guidelines (e.g., the RHZE intensive phase in Viet Nam, 6-month regimen in Pakistan and Viet Nam, and daily dosing in India, estimated by one stakeholder to be practiced by ~40% of private practitioners in India).

Stakeholders believed that regimen change 'should' occur first in the public sector (54/59 responses) due to the public sector's greater adherence to standard regimens. But they acknowledged that change may be more likely to occur first in the private sector. Private physicians reportedly want to offer new treatments to attract patients; this may lead them to seek out change (Indonesia, Philippines, and Viet Nam) and sometimes oppose a public sector regimen change so that the private sector retains its edge (China, Kenya). Early adoption in the private sector may be even more likely with a new, relatively expensive TB drug, as at least some private patients can pay (China, Indonesia, Philippines, and Viet Nam). Stakeholders in Indonesia and Pakistan noted that the private sector may also be a major audience for any new MDR-TB drugs as, according to them, currently the private sector bears most of the burden of this treatment.

Within the 17 HBCs responding to the relevant question, regimen choice in the private sector is most strongly influenced by medical associations (mentioned in 11 HBCs), drug companies and their representatives (10 HBCs), specialists (4 HBCs), and social marketing programs (2 HBCs). NTPs and PPM programs were often mentioned as playing a minor role.

DISCUSSION

Any new TB regimen will enter a complex treatment environment that includes various first-line regimens, retreatment regimens, MDR-TB regimens, pediatric regimens, extra-pulmonary regimens, fixed-dose combinations, patient kits, weight bands, and diagnostic and DST protocols. The potential impacts of a new regimen across all of these factors must be considered. To form a basis for this analysis, we outline here the current treatment landscape and the implications for future TB regimen change. Some of these data were verifiable (e.g., current regimens in guidelines), other questions elicited consistent answers (e.g., extent of DST), while private sector size was, in the absence of new data collection mechanisms, an estimate. In sum, however, we believe these data provide a valuable overview of the current treatment landscape.

Regimens and their use

The most basic component of the current treatment landscape is the first-line regimen. Convergence of HBC Category I regimens towards a single standard (2HRZE/4RH, with dosing 7 days a week) will make the assimilation of Phase III clinical trial results easier, as this regimen matches the control arm used in these trials. This convergence is consistent with movement in WHO guidelines from a list of equal options[20] to a clear preference for a single Category I regimen[5,6] based on an improved evidence base.[4] Where known, 'daily treatment' usually means 7 days a week. Thus, TB drug developers will probably not need to provide evidence of the efficacy of 5-day dosing to accommodate NTP demands.

Under WHO guidelines, all current first-line TB drugs are weight banded. This is thought to be necessary for at least some of the drugs to keep them within acceptable limits of efficacy and toxicity, and its uniform application eases the design of FDCs. We found, however, that the implementation of weight banding is variable. Of note, weight banding is not necessary for many of the new TB drugs currently being tested (i.e., the same dose can be given to all adult patients). Building on previous analyses,[21] stakeholders could ideally reach a consensus on how many adult weight bands are necessary for new regimens. Initially, new regimens may be a more complex mix of weight banded and non-weight banded drugs, but truly novel regimens may not require weight banding.

These analyses will have important implications for the development of new FDCs. With FDCs now widely adopted (in excess of previous reports[17]), their presence in new regimens is expected.[1] Development of new FDCs takes time and resources. Thus, the introduction of a completely novel first-line TB drug may result, at least initially, in the replacement of four- or even two-drug FDCs with loose pills, thus increasing the number of commodities to be handled and the chances that at least one will be subject to a stock-out.

Many countries in Asia have large private sectors for TB treatment. Based on Table 5, private sectors in the HBCs may treat ~21% of the global TB burden, but only ~5% of the global burden is covered by PPM. In a more recent analysis, drug usage data in 10 HBCs yielded a relative ranking of private market size similar to that estimated by stakeholders.[22] However, for the more significant private markets, their absolute size appears to be substantially greater than the stakeholder estimates, likely due to repeated treatments in the private and public sectors.

Stakeholders indicated that the private sector can act as an early adopter, although with the risk that providers will use treatment regimens of variable length and with low adherence,[23] resulting in a risk of increased drug resistance and poor treatment outcomes. The modest size of most PPM programs (documented previously[24] and in this study) suggests that, in most countries, the current PPM programs are unlikely to reduce this risk substantially. As new TB

drugs move through development, expansion of PPM efforts and increasing implementation of the International Standards for Tuberculosis Care (ISTC)[25] via professional associations will be essential.

The costs and benefits of DOT and adherence

The WHO has recommended DOT for any intensive phase and for continuation phases that include rifampicin.[5] In many settings, however, and especially in the continuation phase, DOT goes no further than family supervision and may require only one visit to a health care center per month, as noted in this study. Thus, a 4-month regimen may save just two visits and only modestly reduce the burden on the health care system.

However, a 4-month regimen would result in other epidemiological[26,27] and programmatic savings. It would reduce by one third the size of the caseload that must be monitored, followed for side-effects management, and traced for defaulters. Furthermore, many health care systems maintain other, more frequent forms of DOT (e.g., community-based DOT) and other adherence interventions (provider training, patient health education, reimbursement, peer support, defaulter tracing, attendance prompts, contracts, and removal of barriers at community and family levels). The expenses of providing these interventions in the final 2 months of treatment warrant further investigation. This is not, however, an area where it is possible to generalize. Adherence approaches, and the partner organizations who implement them, vary widely even within a single country.

DST coverage and prospects for its expansion

The possible emergence of drug resistance has been a prominent concern during past regimen changes, resulting in significant adoption delays.[11] This is of particular concern for a future fluoroquinolone-containing first-line TB drug regimen. Fluoroquinolones are a mainstay of second-line drug treatment; they are used for major non-TB indications, and are widely available over the counter. This would greatly increase the challenges of managing their rational use.

Ensuring sufficient use of DST for future determination of drug resistance, even for the existing first-line drugs, will not be easy. The baseline levels of DST use are low—only 4.7% of retreatment cases and 2% of new cases.[17] The current study confirmed that existing fluoroquinolone DST capacity is extremely limited and its use almost always restricted to cases of treatment failure or MDR-TB. Furthermore, insufficient DST in a background of rising MDR-TB was reportedly increasing the pressure for ad hoc addition of more drugs during first-line treatment.

DST has been recommended and used primarily as a tool for surveillance[28] and regimen design[29] rather than treatment; it has therefore been targeted only at retreatment cases, as this is where trends in resistance development are first seen.[30,31] However, the availability of line-probe assays and GeneXpert®, the formation of the Global Laboratory Initiative (GLI), the expanded populations being targeted for DST in new treatment guidelines,[6] and the aggressive plans for expansion of MDR-TB treatment have raised the prospect of a greatly increased level of DST for first-line drugs. Indeed, DST capacity is already expanding.[19]

Prior to introducing a fluoroquinolone-containing first-line regimen, decision makers would benefit from an assessment of fluoroquinolone resistance rates in treatment-naïve TB patients (which may require a dedicated initiative) and a realistic assessment of likely future DST coverage (for both first-line drugs and fluoroquinolones). To limit concerns about resistance, efforts to implement a fluoroquinolone-containing regimen and build DST capacity should be linked geographically. Quality assurance efforts,[32] which are not considered in depth here, will also remain crucial. In fact, for the introduction of new TB drugs in general, a broad consideration of measures to protect the drugs from resistance development (DST, DOT, FDCs, and strict controls over drug quality and distribution) will be an important part of the decision process.

CONCLUSION

By considering the current health systems used for TB treatment, TB drug developers can prioritize products that are more likely to meet the needs of TB programs, physicians, and patients. The same analysis can also highlight areas of health systems strengthening that can be undertaken now to facilitate future regimen changes. Improvement of drug management, and expansion of PPM, DOT (and other adherence mechanisms), FDC use, and DST are all initiatives that have been highlighted as benefiting the delivery of current treatment regimens.[19,33] The case for these actions is only strengthened by considering their impact on the introduction of new TB regimens.

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RÉSUMÉ

CONTEXTE : Le paysage actuel du traitement de la tuberculose (TB) a été largement étudié, mais les chercheurs ne considèrent que rarement la façon dont il crée des défis ou des occasions de modifications futures des régimes.

MÉTHODES : Lors de 166 interviews de responsables dans les pays à fardeau élevé de TB (HBC), nous avons examiné les zones du traitement de première ligne et de la lutte qui pourraient affecter ou être affectés par une modification ultérieure du régime antituberculeux. Les réponses ont été comparées avec des données standardisées existantes.

RÉSULTATS : Les régimes du secteur public convergent vers un seul régime standard, ce qui facilite la comparaison avec un seul bras contrôle provenant d'essais cliniques. Toutefois, le schéma du produit final représente un défi si le but visé est constitué de combinaisons à dose fixe et des kits pour les patients, dont l'utilisation répandue actuellement répond aux faiblesses persistantes de la prise en charge des médicaments. Tout produit doit s'appliquer à de larges groupes, puisque les niveaux relativement faibles des tests de sensibilité aux médicaments (DST) ne permettent pas un traitement individualisé. Finalement, la protection à l'égard du développement de la résistance pour de nouveaux médicaments constituera un défi puisque la mise en œuvre du traitement directement observé (DOT) et les programmes mixtes publics-privés (PPM) sont incomplets et que des secteurs privés substantiels ont été identifiés comme adoptant précocement les nouveaux médicaments.

CONCLUSIONS : Les systèmes de santé doivent s'améliorer pour le traitement et la lutte contre la TB, non seulement pour permettre une meilleure mise en œuvre des traitements actuels mais aussi pour se mettre en état de mettre en œuvre de nouveaux régimes antituberculeux améliorés.

RESUMEN

MARCO DE REFERENCIA: El panorama actual del tratamiento de la tuberculosis (TB) ha sido el centro de numerosos estudios, pero en pocas ocasiones los investigadores han examinado las dificultades y las oportunidades que esta situación ofrece a las futuras modificaciones del protocolo terapéutico.

MÉTODOS: Mediante entrevistas a 166 interesados directos se investigaron los aspectos del tratamiento antituberculoso de primera línea y del control de la enfermedad que serían pertinentes en una futura modificación de la pauta terapéutica y que se verían afectados por la misma. Las respuestas se compararon con los datos normalizados existentes en la Organización Mundial de la Salud.

RESULTADOS: Los tratamientos suministrados por los sectores públicos convergen hacia una pauta única, lo cual facilitaría la comparación con un solo grupo de referencia en los estudios clínicos. Sin embargo, el diseño del producto final es problemático cuando las metas son las asociaciones de dosis fijas o los estuches para pacientes, cuyo uso generalizado revela en la actualidad continuas deficiencias en materia de gestión de los medicamentos. Todo nuevo producto se debe dirigir a amplios grupos de personas, pues la baja cobertura con las pruebas de sensibilidad a los medicamentos no permite los tratamientos individualizados. Por último, un aspecto difícil será la protección contra la aparición de resistencia a los nuevos medicamentos, pues la ejecución del tratamiento directamente observado es incompleta, la instauración de programas sanitarios mixtos del sector público y privado no está generalizada y además, se observó que una proporción importante del sector privado adopta en forma temprana las nuevas pautas.

CONCLUSIÓN: Es importante perfeccionar los sistemas sanitarios dedicados al tratamiento y el control de la TB, no solo con el fin de optimizar la ejecución de los tratamientos actuales, sino con el objeto de preparar el terreno para la introducción de nuevas pautas mejoradas de tratamiento antituberculoso.

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RESEARCH ARTICLE Open Access

A first insight into the genotypic diversity of *Mycobacterium tuberculosis* from Rwanda

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Abstract

Background: *Mycobacterium tuberculosis* complex (MTC) is the causative agent of tuberculosis (TB). Globally, increasing evidence shows that in *M. tuberculosis,* transmission varies from strain to strain and that different strains exhibit a range of geographical and host specificities, pathogenicity, and drug susceptibility. Therefore rapid and accurate differentiation of the members of MTC is critical in guiding treatment and public health decisions. We carried out a study at different health units and the National Reference Laboratory in Rwanda identify *Mycobacterium tuberculosis* complex species prevalent in TB patients in Rwanda. We further characterized the isolates using spoligotyping in order to gain an insight into the strain diversity of drug resistant and susceptible isolates of *M. tuberculosis* in this setting.

Methods: A total of 151 isolates from culture positive sputum samples were harvested, heat killed at 80°C for two hours, and then shipped to Makerere University College of Health Sciences, Uganda, for speciation and typing. Species identification was achieved by regions of difference (RD) analysis, while Spoligotyping was done to identify strain types.

Results: Region of difference analysis identified all the 151 isolates as *M. tuberculosis*. Spoligotyping revealed predominance of the T2 family (58.3%, 88/151), with SIT 52 being the most prevalent strain (31.8%, 48/151). Among the 151 isolates, 64 (42.4%) were multidrug resistant (MDR) with 3 cases on mono-resistance. Of 94 retreatment cases, 48 (51.1%) were MDR and of 46 newly presenting cases 14 (30.4%) were MDR. There was a significant difference (p=0.01) in anti-TB drug resistance between new and retreatment cases in the sample. However, there was no significant relationship between HIV serostatus and the two major strain types SIT 52 (p =0.15and SIT 152 (p = 0.41).

Conclusion: *Mycobacterium tuberculosis* is the most prevalent species of *Mycobacterium tuberculosis* complex in Rwanda, and SIT 52 (T2) the predominant strain. There is significantly more MDR in the retreatment cases but no significant difference was observed by HIV status in relation to any spoligotypes.

Background

Together with other highly related bacteria, *Mycobacterium tuberculosis*, the major causative agent of tuberculosis (TB), forms a complex, the *Mycobacterium tuberculosis* complex (MTC), a single species as defined by DNA/DNA hybridization studies [1]. Other major members of the complex include *M. bovis,* which is mainly responsible for bovine TB, and *M. africanum,* the main causative agent of human TB in West Africa [2,3]. World over, many studies have shown that the propensity of spread of *M. tuberculosis* is dependent on strains types, and that these strains will not only be predominate in different settings but are also host specific [3-7]. DNA fingerprinting techniques in *M. tuberculosis* have made strain typing for epidemiology possible, thus it is now practical to predict transmission rates as well as identify and track strains associated with outbreaks [8], severe disease [9-11], and drug resistance [12].

In Rwanda, TB is one of the leading causes of mortality. Recent (2010) WHO data show a burden of 106 per 100,000 population [13]. Currently, the only data available on MTC in Rwanda focuses on drug resistance studies [14-16], and less is known about the prevalent species and strains, and how these relate with host demographic

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characteristics as well as drug resistance of the strains. Local studies on circulating MTC strains are important for comparison with the global *M. tuberculosis* population archived in various databases. Such knowledge enables a better understand the global traffic of common *M. tuberculosis* clades.

In the current study, genomic deletions also called regions of difference (RDs) were used to determine the predominant species of the MTC in TB patients in Rwanda. We analyzed samples brought in at the national tuberculosis reference laboratory (NRL) (located in Kigali) between March and September 2009. According to the National TB algorithm, NRL receives samples from all parts of the country, mainly: new cases with contact of known MDR patients; cases that had been on treatment for three months and remained sputum smear positive; and retreatment cases. Furthermore, we characterized our strain collection using spoligotyping, a robust and easy to perform technique that has found use in tracking TB epidemics, detecting new outbreaks, and better defining high-risk populations [17], so as to determine the genetic diversity of the strains from this locale. Following previous reports elsewhere of significant numbers of TB cases also co-infected with HIV [6,18], we investigated associations between the predominant spoligotypes and HIV sero-status of the patients as well as resistance to two key anti-tuberculosis drugs in this setting.

Methods

Ethical considerations

This study was approved by the Institutional Research and Ethics Committee of Kigali Health Institute, and Rwanda National Ethics Committee. Informed consent to participate in the study as well as permission to use isolates from samples provided were obtained from all enrolled participants. A materials transfer agreement was signed between the National Reference Laboratory (NRL) in Kigali, and the Department of Medical Microbiology at Makerere University College of Health Sciences, Uganda.

Study setting

Rwanda has a population of about 320 persons per square Kilometer (2005 National Housing Census). Samples were obtained from sputum smear positive TB suspects presenting to several health units in Rwanda, between March and September 2010. These samples were brought to NRL in Kigali. According to the National TB algorithm, the NRL receives samples from all health centres in the country, mainly: new cases with contact of known MDR patients; cases that had been on treatment for three months and remained sputum smear positive; and retreatment cases. At the Hospitals and Health Centres where sampling was done, suspects provided a spot sputum sample on the first day, and were given another container to collect an early morning sample, and finally another spot sample was requested when the patient returned with the early morning sample. The sample with the highest ZN score was shipped to the National Reference Laboratory in Kigali using cetylpyridinium chloride-sodium chloride (CPC-NaCl) transport medium for on ward processing and culture. Suspects were also requested to provide 3mls of blood for HIV testing after pre-test counselling as per routine national policy for HIV testing in all TB patients in the country. Rapid screening for HIV was performed at the Hospitals and Health Centres that received the patients. All the HIV positive patients received post-test counselling and were referred to national HIV treatment centres for professional health care. Demographic data for each patient sample, consisting of age, sex, and TB treatment history were also obtained.

Sample processing

At the NRL, about 5mls of specimen were homogenized by digestion for 1 minute at room temperature with 1 ml of N-acetyl L-cysteine (NALC, 25mg/ml) in phosphate buffer (pH 6.8) and vortexed with several 4 mm glass beads for 30 seconds. A 5 ml aliquot was decontaminated using 1% NaOH [19] and concentrated at 4000g for 15 minutes. The sediment was then reconstituted to 2.5 mls, using phosphate buffer pH 6.8, to make the inoculum for smears and cultures. Colonies were harvested in 400μl of sterile Tris-EDTA (TE) buffer, heat inactivated at 80°C for two hours and then shipped to the Department of Medical Microbiology at the College of Health Sciences, Makerere University, for identification and typing.

Culture and drug susceptibility testing

Sediments were cultured on Lowenstein-Jensen medium (L-J), incubated at 37°C and read weekly for growth for a maximal duration of 10 weeks. Positive cultures were subjected to Ziehl-Neelsen (ZN) staining for confirmation of mycobacterial growth, and isolates were later confirmed as MTC at the molecular level by a previously described PCR typing panel [4]. Drug Susceptibility Testing (DST) was performed by the indirect proportion method on L-J media at the following drug concentrations: rifampicin, 40μg/ml and isoniazid, 0.2μg/ml as recommended elsewhere [20]. For all test panels, drug susceptible strain (H37Rv) and specific drug resistant strains (TMC 303 for isoniazid and TMC 331 for rifampicin) internal controls were included.

DNA extraction

Cultures with ample growth were harvested, isolates heat killed for 2 hours and DNA extracted by the phenol-

chloroform method using standard protocols [21]. For cultures that did not have ample harvests, heat killed isolates were used directly for PCR in subsequent analyses.

RD analyses and spoligotyping

All the target genomic loci were previously well characterized [22,23]. Strains were analyzed for presence of the MTC specific 16S rRNA gene, and then RD9 (deleted in *M. africanum* but present in *M. tuberculosis*), as well as TbD1 (a *M. tuberculosis* specific deletion that is intact in *M. africanum*) using previously described PCR methods which detail primer sequences and amplification conditions [4,24]. Standard spoligotyping [25] was performed using a commercially available kit (Isogen Bioscience BV, Maarssen, The Netherlands) following manufacturer's instructions.

Data analysis

Spoligotypes were analyzed by the BioNumerics software, version 5.0 (Applied Maths, Kortrijk, Belgium) as character types. Binary outcomes were fed into the international spoligotyping database of the Pasteur Institute of Guadeloupe [17], which provides information on the spoligotype international type (SIT) distributions of *M. tuberculosis* spoligotypes worldwide. Statistical associations between strain types, drug susceptibility and HIV sero-status were generated by Stata 10 using the Pearson's chi-square test, and a P value of <0.05 was considered evidence of a significant difference.

Results

Study population

Samples from 153 patients were brought to the NRL between March and September 2009 for culture, with 39 of the patients providing more than one sample for internal control, but these duplicate samples were not considered in the final statistical analysis. Furthermore, two isolates did not amplify for the 16srRNA locus even on repeat analysis and were thus considered atypical mycobacteria and excluded from further analysis. Therefore, only isolates from 151 patients were assayed in this study. Ninety of the 151 (59.6%) of the isolates were from male patients. The sample median age was 36 (Interquartile range [IQR] 28, 48). Stratification according to age showed that 70 (49.6%) of the patients were between 18 and 35 years old (youths) while 71 (50.4%) were over 35 years of age.

Species identification

From the resulting PCR patterns for the three targeted RD loci, all the 151 isolates were identified as *M. tuberculosis* (all deleted at the TbD1 locus), with consistent amplification for RD9, a region that is invariably deleted from all *M. africanum* → *M. bovis* lineage strains as previously shown elsewhere [22].

Spoligotypes

To determine the strain lineages present in the sample, the 151 isolates were spoligotyped and binary outcomes

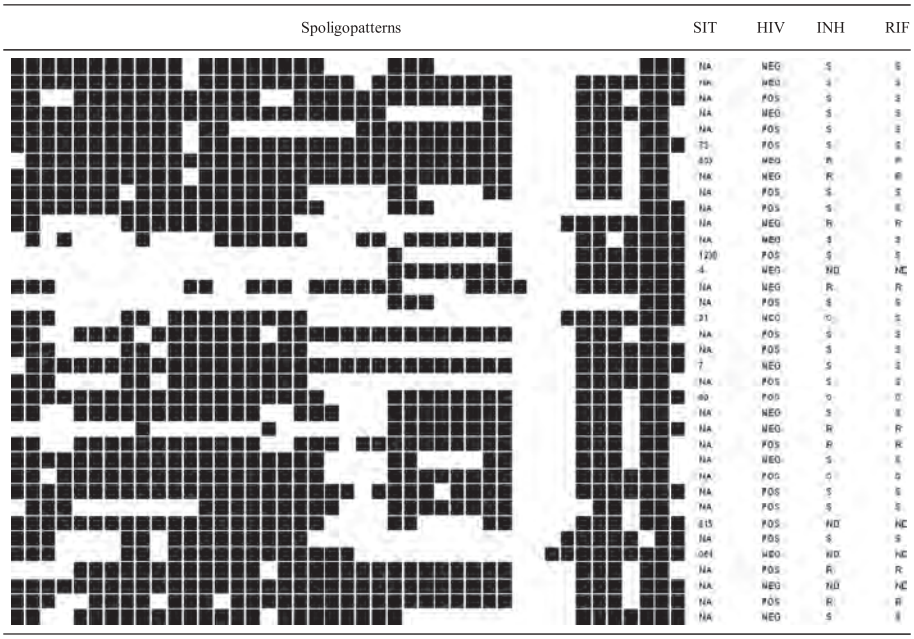

Figure 1 Spoligotype patterns of non-clustered *M. tuberculosis* strains in the study (N=36). SIT, spoligotype international type; filled boxes represent positive hybridization while empty boxes represent absence of spacers; label defines the lineage/sub lineage; NA, not available in SpolDB4.0; HIV, sero-status of the patients; INH, resistance to isonaizid; RIF, resistance to rifampicin; S, sensitive; R, resistant; ND, not determined.

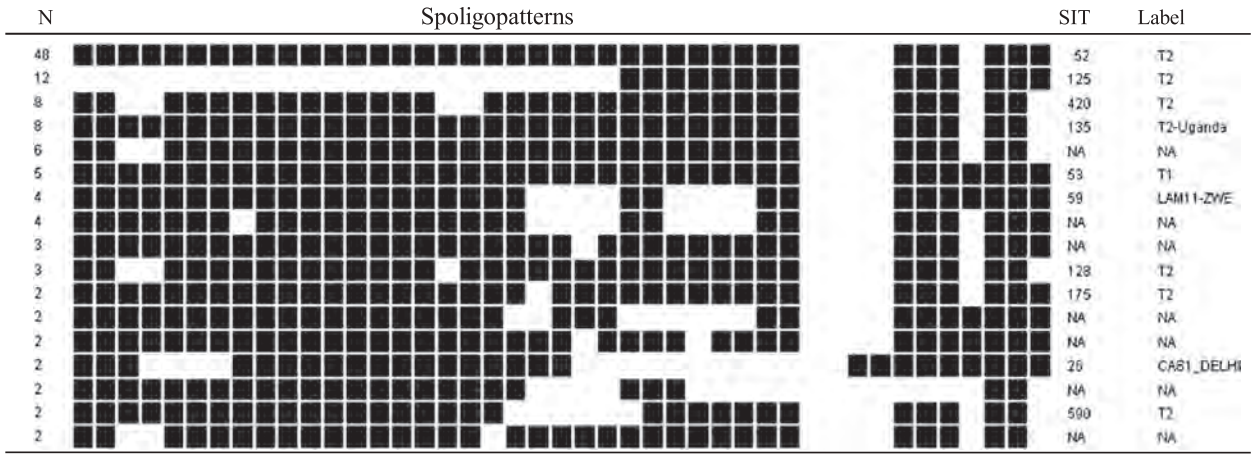

Figure 2 Spoligotype patterns of 115 clustered *M. tuberculosis* strains in the study. N, number of isolates per cluster; SIT, spoligotype international type; filled boxes represent positive hybridization while empty boxes represent absence of spacers; label defines the lineage/sub lineage; NA, not available in SpolDB4.0.

compared with those existing in SpolDB4 so as to assign spoligotype international type (SIT) designations. A total of 115 isolates (76.2% of the sample) were grouped into 17 clusters (2 to 48 isolates per cluster), while the remaining 36 (23.8%) of the strains did not cluster. Of these 36 strains that did not cluster, 27 did not exist in the SpolDB4.0 data base, hence represented the true orphans in the study sample. The remaining nine of the un clustered isolates were all present in SpolDB4 with labels SIT 73 (T2-T3), SIT 853 (T2), SIT 1208 (H1), SIT 4 (LAM 3/S Convergent), SIT 21 (CAS_KILI), SIT 7 (T1), SIT 60 (LAM 4), SIT 815 (LAM11_ZWE) and SIT 954 (CAS_DELHI). The associated drug susceptibility patterns for the un clustered isolates as well as HIV sero-status of the corresponding patients for each isolate are indicated in Figure 1.

Among the 17 clusters, only two included more than ten isolates each and were defined as major spoligotypes, while minor spoligotypes, in this study, were defined as SITs that contained two to eight isolates per cluster. The two major shared spoligotypes in our sample were SIT 52 (T2) with 48/151 (31.8%) and SIT 125 (T2) with 12/151 (7.9%) of the isolates. Other significant clustered spoligotypes in the sample were SIT 420 (T2) and SIT 135 (T2-Uganda) with eight strains each (Figure 2). Furthermore seven clusters, ranging from two to six strains per cluster, formed a total of 20 strains and were not yet defined in SpolDB4.0. Among all the clustered strains, 83 of 115 (72%) were identified in SpolDB4 as T2, while a further 15 strains that were not identified in SpolDB4 also lacked hybridization to either spacer 40 or both 40 and 43, characteristic of the T2 Euro-American lineage of strains previously erroneously identified in Uganda as *M. africanum* genotypes Uganda II and I respectively [26] but later termed *M. tuberculosis* Uganda genotype strains [4].

Drug susceptibility patterns

Susceptibility testing results for the two key anti-tuberculosis drugs (isoniazid and rifampicin) showed that 67 isolates were susceptible to both drugs, three isolates were monoresistant (two to rifampicin and one to isonaizid), resistance to isoniazid was 65/151 (43%), and that to rifampicin was 66/151 (43.7%), while 17 cases did not have interpretable susceptibility results. Sixty four of the 65 isonaizid resistant strains were also rifampicin resistant hence MDR. Of the 151 patients in the study, 94 were retreatment cases, of the 46 new patients, 3 new cases were MDR know contact patients whereas 43 new patients were on treatment for three months and remained microscope smear positive, while treatment history for 11 patients could not be established. Among the retreatment cases, 48/94 (51.1%) were MDR, while 13/46 (28.3%) of the new cases were MDR ($p = 0.01$). A summary of patient demographic characteristics and associated drug susceptibility pattern is shown in Table 1.

Analysis of drug resistance in the major clusters revealed that SIT 52 (T2) with 48 strains had 34/65 (52.3%) of the total isoniazid resistant strains in the sample. Furthermore, this strain type had 35/66 (53%) of the rifampicin resistant strains and 34/64 (51.3%) of the MDR isolates. SIT 125 (T2), on the other hand, had eight of its12 strains resistant to both rifampicin and isoniazid, hence MDR. Categorization of the patients into retreatment and new cases within the two major

Table 1 Patient demographic characteristics and associated drug susceptibility pattern

Demographic characteristics		Total	Sensitive[a]	Resistant		
				INH[b]	RIF[c]	MDR[d]
Number of strains		151	67 (44.4%)	1 (0.7%)	2 (1.3%)	64 (42.4%)
Sex	Male	95	47 (49.5%)	1 (1.1%)	1 (1.1%)	34 (35.8%)
	Female	56	20 (35.7%)	0	1 (1.8%)	30 (53.6%)
Treatmenthistory	New cases	46	28 (60.9%)	0	0	12 (26.1%)
	Retreatment	94	39 (41.5%)	1 (1.1%)	2 (2.2%)	48 (51.1%)
	Unknown	11	2 (18.2%)	0	0	0
HIV status	Positive	69	34 (49.3%)	0	2 (2.9%)	30 (43.5%)
	Negative	76	35 (46.1%)	1 (1.3%)	0	32 (42.1%)
	unknown	6	0	0	0	0

[a]Sensitive indicates isolates susceptible to both isoniazid and rifampicin; [b]Resistance to isonaizid only, [c]resistance to rifampicin only, [d]resistance to both isonaizid and rifampicin. Seventeen isolates did not have complete susceptibility testing results and were excluded from the table.

spoligotypes revealed that 35/48 strains in SIT 52 were retreatment cases while 11 of the 12 cases in SIT 125 were retreatment. There were no significant statistical associations between genotypes and drug resistance. The relationship between the different spoligotypes in the non clustered strains and resistance to rifampicin and isoniazid is summarized in Figure 1.

HIV sero-status and associated spoligotypes

In the sample analyzed, 69 patients (45.7%) were HIV sero-positive, 76 (50.3%) sero-negative, while 6 (4%) did not have test results hence their status unknown. Of the 69 sero-positive cases, 42 (60.9%) were TB retreatment cases while 52/76 (26.3%) of the sero-negative cases were retreatment. An analysis of the drug susceptibility pattern of isolates from the 69 HIV sero-positive individuals showed that 31 had strains resistant to isoniazid, 32 to rifampicin while 30 (43.5%) were MDR isolates. Analysis of the two major spoligotypes above (SIT 52 and SIT 152) vs. HIV sero-status of patients showed that 19 of the 48 SIT 52 strains (39.6%) were from HIV positive patients while 26/48 (54.2%) strains were from HIV negative patients (p =0.15). Likewise 7 of the 12 SIT 152 strains (58.3%) were isolated from HIV positive patients while 5/12 (41.7%) were from HIV negative patients (p = 0.41). There was no statistical relationship between HIV sero-status of the patients and any particular spoligotypes pattern. The sero-status of the patients carrying un clustered strains in the study is shown in Figure 1.

Discussion

This, to the best of our knowledge, is the first report describing the species and strain diversity of *M. tuberculosis* complex isolates from TB patients in Rwanda. Characterization of prevailing *M. tuberculosis* strains focusing on different geographical levels is important for locating the origin, evolution and spread dynamics of particular *M. tuberculosis* clones, which is often difficult to be identified by traditional epidemiological investigations. In low-resource, high-disease burden settings, it is critical to identify circulating strains in order to understand the dynamics of spread of the causative agent. In Rwanda, there is no data about the species and strains of *M. tuberculosis* circulating in the country. This report, therefore, will provide baseline data for future country-wide molecular epidemiological studies to understand transmission dynamics of TB.

Regions of Difference (RD) analysis using 16S-rRNA, RD9 and TbD1 loci showed that all the strains investigated were characterized by presence of both 16S-rRNA and RD9 loci, and deletion in the TbD1 regions, a pattern confirming that they all were *M. tuberculosis* strict sense. Most studies in the East African region have reported predominance of *M. tuberculosis* [4,26,27], while most *M. africanum* strains isolated to date are from West Africa [2,7,28,29].

A majority (68.2%) of the spoligotypes obtained in this study belong to previously identified shared spoligotype international types (SITs). A significant proportion of the total isolates (48/151, 31.8%) belonged to SIT 52, while only 8/151 (5.3%) were SIT 135, a strain type commonly seen in Uganda. SIT 52 was found to be 7.6% (26/344) of isolates in a study in Central Uganda [18] and 4.8% (6/125) of isolates from South Western Uganda [30], while not a single strain of this type was seen in a collection of 130 isolates from Northern Tanzania [31]. Generally, this genotype together with the related SIT 135 and SIT 128 are known to be the commonest strain types causing TB in Central African human host populations [4].

The 151 isolates in the study show 53 different spoligopatterns, displaying a wide diversity of the spoligotypes in this collection. It is known that the structure of the TB populations is determined by geography, demography, and human migration. The large diversity of

strains observed in this study may be attributed to increased transborder human movement in this region due to a large influx of former refugees from different neighboring countries in the last 15 years. Additionally, true orphan spoligotypes accounted for only 17% of all the spoligotypes in this study, this low percentage further supporting the hypothesis of increased recent human traffic in this setting, since countries with a history of isolation have been shown to have a large number of new spoligotypes, which is not the case in this scenario [32].

Spoligotyping identified T2 to be the most predominant family of strains in Rwanda, accounting for up to 55.0% (83/151) of the total sample (Figures 1 and 2). Results from a previous molecular study of recurrent TB in Rwanda by spoligotyping and mycobacterial interspersed repetitive unit variable number of tandem repeat (MIRU-VNTR) typing did not show species and strain types in the collection [16] hence we cannot compare the two studies. Findings from the current study, however, are in agreement with the previous data from Uganda, in which two studies showed predominance of T2 family, the first having been conducted at the National referral hospital, Kampala, in which 67% of the isolates were T2 [33] and the second a systematic community based study in Rubaga, one of the divisions of Kampala, which reported 70% isolates being of the T2 family [18]. This result is in further agreement with those elsewhere reporting predominance of single genotypes in the respective populations across Africa [2,6,7,28,34]. Collectively, these results depict a tendency for local genotypes that are well established to form a larger proportion of circulating strains compared to others as previously postulated [3,35]. Since our sample collection may not reflect a national picture, a future national survey could genotype all isolates so as to give a clear situation of strain types as well as transmission pattern in this locale.

In Rwanda, the most recent national anti-tuberculosis drug resistance survey (2002–2005) on 616 new cases [14] showed that 6.2% of the isolates were resistant to isoniazid, 3.9% to rifampicin and 3.9% were multi-drug resistant. In neighboring Uganda, a much earlier national survey (1996–1997) showed that of 586 patients, resistance to isoniazid was 6.7 %, that to rifampicin was 0.8% while MDR was 0.5% [36]. The current study tested 46 new TB case, 94 retreatment cases and 11 cases with no known history. Overall MDR was 42.4%, a very high increase, most likely attributed to the high proportion of retreatment cases (94/115) in our study population as opposed to new TB cases in the previous studies.

Conclusion

Mycobacterium tuberculosis is the most prevalent species of *Mycobacterium tuberculosis* complex in Rwanda, and SIT 52 (T2) the predominant strain. There is significantly more MDR in retreatment cases but no significant difference was observed by HIV status in relation to any spoligotypes.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JG participated in the planning of the study, acquisition of samples, culture and isolation of mycobacteria and molecular analysis of isolates; BBA participated in planning of the study, training JG, supervision of the molecular assays, data analysis and drafting of the manuscript. ANU participated in data collection, seeking ethical clearance and material transfer agreement, supervision of the work, and drafting of the manuscript. All authors read and approved the final manuscript.

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Southern Med Review

The burden of adverse events during treatment of drug-resistant tuberculosis in Namibia

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Abstract

Objective: Namibia faces a dual burden of HIV/AIDS and tuberculosis (TB). In 2010, HIV prevalence was 18.8%, the TB case notification rate was 634 cases per 100,000 population and the TB/HIV co-infection rate was 58%. There were 372 cases of drug-resistant TB (DR-TB) in 2009. The objective of this study was to assess the prevalence, profile and outcome of adverse events (AEs) associated with treatment of DR-TB and to explore possible influences of HIV disease on the occurrence of adverse events.

Methods: This was a cross-sectional descriptive study. After ethical approval, data were collected from treatment records of all patients treated for DR-TB at the study facility between January 2008 and February 2010 using a structured data collection form.

Results: A total of 141 adverse events of varying severity were experienced in 90% (53/59) of patients.The TB/HIV co-infection rate was 53% (n=31). The prevalence of gastrointestinal tract adverse events (abdominal pains, constipation, diarrhea, nausea and vomiting) was 64%, tinnitus 45%, joint pain 28%and decreased hearing 25%. Abdominal pains, rash, nausea, decreased hearing and joint pain were more common in HIV infected than in HIV uninfected patients.

Conclusions: Adverse events of varying severity are common during treatment of DR-TB, particularly in the intensive phase of therapy. Some adverse events were more prevalent in DR-TB patients co-infected with HIV. The study concludes that the characteristics and risk factors of serious adverse events should be further examined.

Keywords: tuberculosis, drug resistance, second-line drugs, adverse events, Namibia

Introduction

Tuberculosis (TB) exerts a huge burden of disease in Namibia, with a case notification rate (CNR) of 634 cases per 100,000 population in 2009 [1]. This is one of the highest tuberculosis CNRs in Africa. The TB/HIV co-infection rate was 58% in 2009 [1, 2]. Resistance to first-line regimens is a growing issue and could be due to various factors, including sub-optimal patient adherence to treatment schedules and defaulting in treatment [3]. Namibia reported 372 cases of drug resistant TB (DR-TB) in 2009, of which 74% of cases were`multi-drug resistant TB (MDR-TB), 22% poly-drug resistant TB and 5% were extensively drug resistant TB (XDR-TB) [1].

Although a number of studies [4-15] have examined the occurrence and characteristics of adverse events among patients

on second-line anti-TB medicines, very few have specifically examined occurrence of adverse events in sub-Saharan Africa [16], especially in the context of high HIV prevalence and high TB/HIV co-infection rates. Most reviewed studies have mainly focused on adverse events of either one or two anti-TB medicines, but not on the entire treatment regimen [4-16].

This study describes the epidemiology of adverse events associated with treatment of DR-TB in a sub-Saharan country with a dual burden of TB and HIV. It further explores possible influences of HIV disease and antiretroviral treatment on the occurrence of adverse events.

The study thereby contributes to the existing body of epidemiologic and public health knowledge about treatment of DR-TB, focusing on a sub-Saharan country. This will assist managers of tuberculosis control programs, clinicians, and patients in similar socio-economic and epidemiologic settings in making evidence-based decisions for optimizing treatment outcomes for DR-TB patients, particularly in HIV co-infected patients. In this context, we aimed at assessing the profile, frequency and outcomes of adverse events associated with the use of second-line anti-TB medicines. The specific objectives of the study were:

1) To determine the types and frequency of adverse events associated with the use of second-line anti-TB medicines in a selected DR-TB treatment facility in Namibia.

2) To describe the characteristics, duration and outcomes of the adverse events, focusing on differences in adverse event occurrence between HIV infected and HIV uninfected persons.

Methods

Settings

The study was conducted in a 25-bed district hospital DR-TB ward with the second largest number of patients on DR-TB treatment in Namibia. Patients diagnosed with DR-TB are hospitalized in this TB ward, which is physically isolated from the rest of the wards in the hospital. This isolation is part of the infection control measures put in place at the facility to minimize nosocomial transmission of *Mycobacteria tuberculosis*. The patients with DR-TB infection are initiated on second-line treatment for about six months of intensive chemotherapy that includes injectable agents (amikacin, kanamycin or capreomycin). Until 2008, amikacin was the preferred aminoglycoside but this was later changed to kanamycin from 2009 onwards. The daily patient doses for each medicine used in the regimen were calculated and individualized according to the recommended World Health Organisation (WHO) body weight-based dosing scheme for anti-TB drugs (Table 3). Continuation therapy using oral anti-TB agents that includes a fluoroquinolone is maintained through an outpatient directly observed treatment short-course (DOTS)-plus programme. This DOTS-plus treatment is implemented through the health center closest to the patient. Patients on continuation therapy visit the health facility every day (Monday - Friday) for daily doses of second-line anti-tuberculosis medicines. Doctors and nurses elicit information on adverse events from patients and record them on a structured, pre-printed DR-TB treatment side effects monitoring form.

Study participants and data collection

For this cross-sectional descriptive study, the study population included all patients treated with second-line anti-TB medicines at the DR-TB treatment facility from 01 January 2008 to 24 February 2010. Treatment records were reviewed for all the patients treated for DR-TB during this period. Further, data on patient demographics, *Mycobacterium tuberculosis* drug resistance, medications and other clinical variables, including occurrence of adverse events and the characteristics of the adverse events, were collected from patient records using a structured data collection form. Since the present study did not involve direct contact with patients, informed patient consent was not required. Ethical approval of the study protocol was obtained from the research unit of the Ministry of Health and Social Services of Namibia (MoHSS) and the Higher Degrees Committee of the University of the Western Cape, South Africa.

Occurrence of adverse events and the analysis of data

The main outcome variable was the occurrence of adverse events. Further, a detailed characterization of the adverse events was conducted, which included: the adverse event description, time to onset of the adverse event, grading of severity of the adverse event, duration of the adverse event, actions taken to clinically manage the adverse event, and the outcome of the adverse event. Data were single-entered into Epi Info version 3.5.3 and the accuracy of entry verified against the original paper forms. The data were further checked for any errors and then analyzed using descriptive statistics. Absolute and relative frequency counts and measures of central tendency (mean, median and mode) were calculated. Measures of dispersion including range, interquartile range and standard deviation were also calculated.Student's T-tests were used to assess differences in age and weight between the genders. A P-value of less than 0.05 was considered to be statistically significant. All statistical analyses were performed using Epi Info version 3.5.3.,while Microsoft Excel® (2010) was used to draw charts.

Results

Fifty-nine (59) patients were treated for DR-TB during the study period. There were more male patients than females (66% vs. 34%). The mean patient age was 34.7 ± 9.4 (SD) years (Table 1). Males were slightly older than females (36.9 versus 31 years;P=0.02). The mean baseline weight was 52.5 ± 11.3 (SD) kilograms (kg), with no statistically significant gender difference (53.6 ± 7.8 kg males, versus 49.8 ± 16.4 kg females; P=0.23). About one-third of patients were unemployed.

Table 1: Demographic and clinical characteristics of the 59 patients treated with DR-TB therapy

Characteristic	n (%)
Gender	
Male	38 (64%)
Female	20 (34%)
Missing	1 (2%)
Age (years), SD	**34.7 ± 9.4**
Male	36.9 ± 8.4
Female	31.0 ± 10.2
Weight (kg), SD	**52.5 ± 11.3**
Male	53.6 ± 7.8
Female	49.8 ± 16.4
Occupation	
Unemployed	18 (31%)
Employed	20 (34%)
Student	1 (2%)
Missing	20 (34%)
Type of TB	
PTB smear +	55 (93%)
PTB smear -	3 (5%)
EPTB	1 (2%)
Diagnostic category of DR-TB	
Previously treated with 1st line medicines	46 (78%)
Previously treated with 2nd line medicines	8 (14%)
New patient, never treated for TB	5 (8%)
TB drug resistance pattern	
MDR	36 (61%)
Poly resistant	18 (28%)
XDR	1 (2%)
Missing	4 (6%)
Number of medicines in anti-TB regimen; median (range)	
Intensive phase regimens	5 (4-7)
Continuation phase regimens	3 (3-5)
Days on intensive phase treatment; Median (IQR) n=53	
Male	182 (154-186)
Female	184 (165-211)
Days on continuation phase treatment; Median (IQR) n=49	
Male	389 (185-503)
Female	522 (451-584)
HIV co-infection	
Male	19 (32%)
Female	12 (20%)
Unknown	3 (5%)
Proportion of HIV positive persons on HAART*	**13 (42%)**
D4T/3TC/EFV	5 (16%)
AZT/3TC/EFV	3 (10%)
AZT/3TC/NVP	2 (6%)
TDF/3TC/EFV	2 (6%)
D4T/3TC/NVP	1 (3%)

* As percentage of number of patients with HIV co-infection

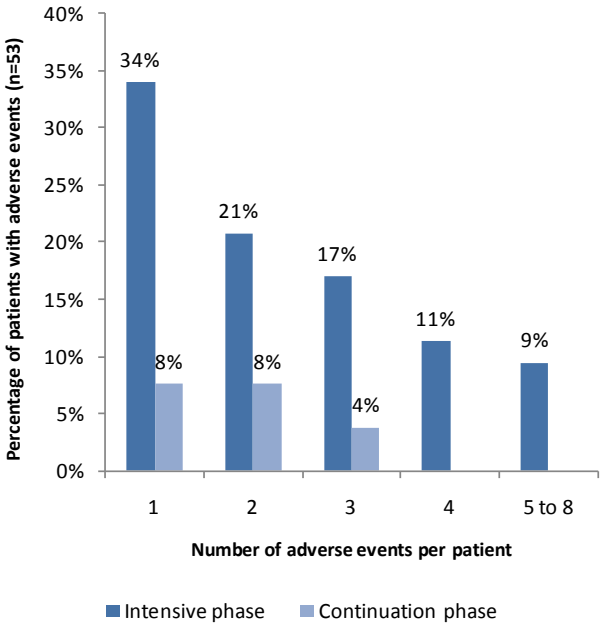
SD=standard deviation; kg=kilogrammes; TB=tuberculosis; PTB=pulmonary tuberculosis; + = positive; - = negative; EPTB=extra pulmonary tuberculosis; MDR=multidrug-resistant; XDR=extensively drug-resistant; IQR=interquartile range; HIV=human immunodeficiency virus; HAART= highly active antiretroviral therapy; d4T=stavudine; AZT=zidovudine; 3TC=lamivudine; EFV=efavirenz; TDF=tenofovir disoproxil fumarate; NVP=nevirapine

Almost all (92%) of the 59 patients had a prior history of treatment with either first-line or second-line anti-tuberculosis medicines. Approximately half of the patients (31/ 59 or 53%) were co-infected with the human immuno deficiency virus (HIV). Of the 31 HIV co-infected TB patients,13 (42%) were on highly active antiretroviral treatment (HAART).

In total, there were fifteen different anti-tuberculosis medicines that were used by the patients included in this study (Table 3). Most of the patients were treated with DR-TB regimens containing pyrazinamide (93%) and ethionamide (92%). All patients were treated with an injectable anti-tuberculous agent (amikacin, kanamycin or capreomycin) during the intensive phase of treatment,with kanamycin being the most frequently used aminoglycoside in 54% of the patients. Fluoroquinolones (ciprofloxacin and levofloxacin) were used in almost all of the patients (98%), of which levofloxacin was used twice as much as ciprofloxacin (66% versus 32%). There were 30 individualized regimens that were used in the intensive phase of treatment and 18 in the continuation phase of treatment. These individualized regimens were determined according to the drug sensitivity patterns of the infecting *Mycobacterium tuberculosis* strain.

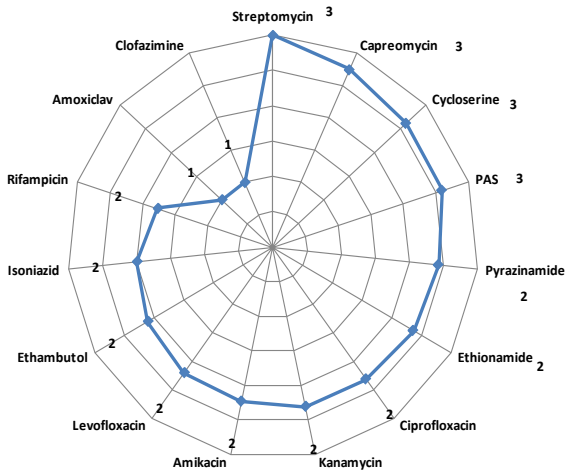
Fifty-three of the 59 patients experienced at least one adverse event of varying severity grading (90% prevalence). A total of 141 adverse events were reported by these patients. The number of adverse events experienced by an individual patient ranged from one to eight. The proportion of patients experiencing a given number of adverse events dramatically reduced from the intensive to the continuation phase of treatment (Figure 1).

Figure 1: Distribution of percentage of patients by number of adverse events experienced per patient in the intensive and continuation phases of treatment



The average number of adverse events experienced by patients treated using specific anti-tuberculosis medicines ranged from one to three (Figure 2). Patients using regimens that contained streptomycin, capreomycin, cycloserine, and para-amino salicylic acid (PAS) experienced the highest average number (3) of adverse events, while patients using amoxycillin/ clavulanic acid and clofazimine experienced the fewest, with an average of one adverse event per drug. The rest of the medicines were associated with a similar average number of two adverse events per patient (Figure 2).

Figure 2: Average number of adverse events experienced per patient exposed to specific anti-tuberculosis drug.



Hearing loss (decreased hearing), tinnitus, gastrointestinal tract (GIT)-related events (nausea, abdominal pains, vomiting, diarrhea and constipation) and joint pain were the predominant adverse events (Table 2). Five adverse events were more prevalent in HIV infected patients than in HIV uninfected patients (the figures in brackets show the excess frequency of occurrence in HIV infected patients as compared to HIV negative patients). These adverse events were: abdominal pains (22%); rash (16%); nausea (10%); decreased hearing (7%) and joint pain (6%). Contrarily, fever and fatigue are examples of adverse events that were reported less frequently by these patients (Figure 3).

Fourteen (93%) of the 15 reported cases of joint pain were observed in patients treated with pyrazinamide-containing regimens.

Seventy three percent of the moderate-to-severe adverse events lasted for more than three (3) months, while 60% of the mild adverse events resolved within 3 months of onset. Overall, in 53% of patients, the adverse events resolved within 3 months of onset, while 47% of patients experienced adverse events that persisted beyond 3 months. Adverse events were severe and warranted discontinuation of the suspected offending medicine in four (4) out of 26 (15%) patients. Four (4) out of the 42 (9%) patients for whom data was available recovered from their adverse reactions with sequelae.

Table 2: Frequency of adverse events in both treatment phases; intensive and continuation phases respectively

Grouped adverse events	Specific adverse events	Both phases (N=53)*	%	Intensive phase (N=53)	%	Continuation phase (N=49)†	%
Hearing loss & Tinnitus	Tinnitus	24	45%	21	40%	3	6%
	Decreased hearing	13	25%	12	23%	1	2%
	Hearing loss & Tinnitus Total	**37**	**70%**	**33**	**62%**	**4**	**8%**
GIT-related	Nausea	12	23%	8	15%	4	8%
	Abdominal pain	9	17%	8	15%	1	2%
	Vomiting	6	11%	6	11%	0	0%
	Diarrhea	5	9%	5	9%	0	0%
	Constipation	2	4%	2	4%	0	0%
	GIT Total	**34**	**64%**	**29**	**55%**	**5**	**10%**
Others	Joint pain	15	28%	13	25%	2	4%
	Headache	11	21%	10	19%	1	2%
	Fatigue	10	19%	8	15%	2	4%
	Dizziness	8	15%	7	13%	1	2%
	Rash	7	13%	7	13%	0	0%
	Neuropathy	4	8%	2	4%	2	4%
	Fever	3	6%	3	6%	0	0%
	Vision changes	3	6%	2	4%	1	2%
	Depression	2	4%	2	4%	0	0%
	Psychosis	2	4%	2	4%	0	0%
	Severe hepatitis	1	2%	1	2%	0	0%
	Decreased urine	1	2%	1	2%	0	0%
	Anemia	2	4%	2	4%	0	0%
	Loss of libido, delayed ejaculation	1	2%	0	0%	1	2%
Total of all adverse events		**141**		**122**		**19**	
Percent of all adverse events		**100%**		**87%**		**13%**	

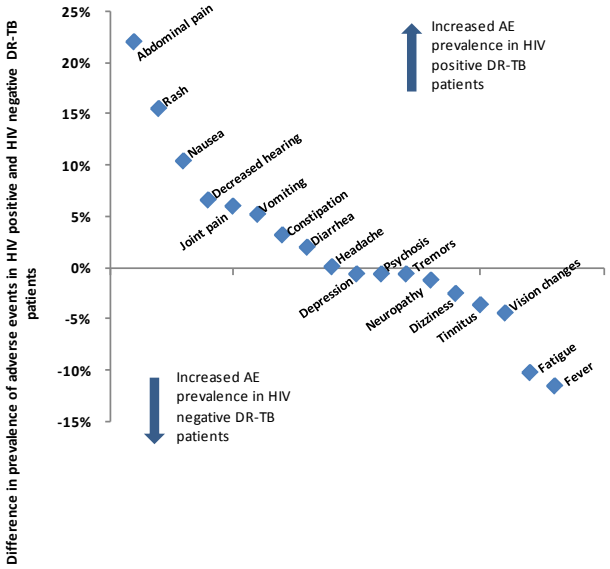
*53 of the 59 patients reported to have experienced at least one DR-TB treatment-related adverse event. All the 53 patients had either completed or were still in the intensive phase of treatment at the time of data collection. †49 of the patients had progressed into the continuation phase of treatment and were either still on continuation phase treatment or had completed treatment at the time of data collection. %= percent. Sum of column percentages may exceed 100% because a patient may experience more than one adverse event. GIT =gastrointestinal tract

Table 3: Prevalence of use and the weight-based dosing of specific anti-tuberculosis drugs in the treatment of drug-resistant tuberculosis in Namibia

Drug name	DRUG EXPOSURE		DOSING BY WEIGHT CLASS			
	Number of patients	Percent (n=59)	<33 KG	33–50 KG	51–70 KG	>70 KG (Maximum dose)
Pyrazinamide	55	93%	30–40 mg/ kg , daily	1000–1750 mg, daily	1750–2000 mg , daily	2000–2500 mg ,daily
Ethionamide	54	92%	15–20 mg/ kg daily	500 mg	750 mg	750–1000 mg
Levofloxacin	39	66%	Usual adult dose is 750 mg	750 mg	750 mg	750–1000 mg
Ethambutol	36	61%	25 mg/ kg , daily	800–1200 mg, daily	1200–1600 mg , daily	1600–2000 mg daily
Kanamycin	32	54%	15–20 mg/ kg daily	500–750 mg	1000 mg	1000 mg
Cycloserine	29	49%	15–20 mg/ kg daily	500 mg	750 mg	750–1000 mg
Amikacin	21	36%	15–20 mg/ kg daily	500–750 mg	1000 mg	1000 mg
Ciprofloxacin	19	32%	20–30 mg/ kg daily	1500 mg 1500 mg	1500 mg	
Rifampicin	13	22%	10–20 mg/ kg, daily	450–600 mg, daily	600 mg, daily	600 mg, daily
Para-aminosalicylic acid	5	8%	150 mg/ kg daily			
Capreomycin	4	7%	15–20 mg/kg	500–750 mg	1000 mg	1000 mg
Isoniazid	4	7%	4–mg/ kg daily	200–300 mg daily	300 mg daily	300 mg daily
			or 8–12 mg, 3 x wk	or 450–600 mg, 3 x wk	or 600 mg , 3 x wk	or 600 mg, 3 x wk
Streptomycin	3	5%	15–20 mg/ kg daily	500–750 mg	1000 mg	1000 mg
Clofazimine	1	2%	Efficacy and dosing in the treatment of drug-resistant TB not fully determined			
Amoxicillin/ Clavulanate	1	2%	Efficacy and dosing in the treatment of drug-resistant TB not fully determined			

Source: WHO, (2006). Guidelines for the programmatic management of drug-resistant tuberculosis: 147-8. mg=milligrammes; Kg=kilogrammes; wk = week

Figure 3: Comparison of difference in prevalence of adverse events in HIV positive and HIV negative DR-TB patients.



Discussion

Adverse events of varying severity, particularly tinnitus, hearing loss, GIT-related adverse events and joint pains were experienced by most (90%) of the patients included in this study. Most of the adverse events were reportedly experienced in the intensive phase of DR-TB treatment. Some differences in the occurrence of adverse events were observed between patients who were HIV infected and those who were HIV uninfected. Abdominal pains, rash, nausea, decreased hearing and joint pain were among the adverse events more frequently reported by HIV infected patients, whereas fever and fatigue were reported relatively less frequently, when compared with HIV uninfected patients.

The 90% prevalence of adverse events observed in the current study is higher than that reported in other studies, where it ranged from 69%-86% [4-14, 16]. It was slightly lower than the 96% reported by Tupasi and colleagues in their study of 117 patients in the Philippines [15]. The reasons for the heterogeneity in the prevalence of adverse events across the various studies is unclear, but might be related to several possible factors such as: differences in definitions of adverse events terminologies across settings, whether the adverse event was symptomatic and patient-reported (subjective) or clinician-validated (objective), whether all or only the severe and serious adverse events were studied, variations in the use of specific anti-TB agents, and/or the differences in co-morbidities and other covariates between study settings. Our study's cohort is similar to other cohorts in terms of demographics and number of anti-TB medicines used and treatment duration. In addition, treatment was according to existing guidelines [3, 17]. However, the HIV co-infection rate and the specific anti-TB agents used may differ between settings and this should be borne in mind when interpreting and comparing results of adverse events reported from different countries. Although the present study found the TB/HIV

co-infection rate to be higher than that reported in Europe and South East Asia (where HIV prevalence rates are low) [6,13,18], it is lower than that observed for Lesotho, a country in Southern Africa, which has a high prevalence of HIV infection [16].

The frequency of tinnitus (45%) in the present study was higher than the 5.1% - 24% range reported in the literature [4, 14, 15], while that of hearing loss (25%) was within the range of 6.7% - 33% reported in the literature [5, 11, 14, 15]. From the review of the literature, the reported rates of ototoxicity (tinnitus and hearing loss) ranged from 12% to 42% [6, 7, 16]. Our study found an almost double rate of ototoxicity, when compared to the 36% reported by Seung et al. [16], whose study population and HIV prevalence rates are similar to our population. It is unclear why this is so, but one possible reason could be that the majority of patients in the Seung study were still in the early stages of treatment, hence not all potential adverse events may have occurred by the time of completion of their study. The high degree of heterogeneity of ototoxicity observed in the literature could have been brought about by differences in the use of specific ototoxic anti-TB agents, as well as by the differences in the profiles of co-morbidities in the different patient population groups of the various studies.

Ototoxicity (tinnitus and decreased hearing) is predominantly associated with the use of parenteral anti-tuberculous agents (aminoglycosides and aminopeptides) [19-24]. The drug-specific rate of patient-reported tinnitus in the current study ranged from 33%- 50%, while hearing loss was 13% - 67%. These findings are above the range of 15.4% - 33% reported in studies conducted elsewhere [5, 19, 20]. The high prevalence of tinnitus and hearing loss found in our study is probably because they were symptomatic or patient-reported (subjective) and may not have been clinically validated by audiometric tests. In addition, there could have been additive effects of interaction with other concomitant and potentially ototoxic anti-TB drugs that were used in the anti-TB regimens, such as fluoroquinolones and cycloserine. Additionally, there are possibilities of interactive effects from HIV disease and the concomitant use of antiretroviral medicines, which may have contributed to this high rate of ototoxicity. This needs further investigation to uncover the possibility of these interactive effects.

The gastrointestinal tract (GIT)-related adverse events were the second most observed group of adverse events, reported by 64% of the patients. The specific GIT-related adverse events were: nausea (23%), abdominal pain (17%), vomiting (11%), diarrhea (9%), and constipation (4%). The frequency of occurrence of these specific GIT-related adverse events fall within the wide range (10.8% - 100%) which has been reported in the literature [4, 6, 7, 11, 14, 15, 16]. Since some studies have reported higher rates of specific GIT-related adverse events, it is possible that patients in our study may have selectively under-reported these adverse events during the course of their treatment.

The possibility of drug-drug interactions [10], drug-disease and disease-disease interactions should be reflected on in the present study, particularly considering that an average of five different anti-TB agents were used by each patient in the study and that over 50% of the patients had HIV co-infection, 42% of whom were on concomitant antiretroviral medication.

In our study, adverse events were severe and warranted discontinuation of the suspected offending medicine in 15% of patients. This prevalence of treatment discontinuation is lower than that reported in the literature [4, 5, 12, 14]. Generally, our findings are similar to the findings of Furin et al. (2001) that adverse events of the anti-TB medicines were bearable and did not cause discontinuation of the treatment apart from the occasional suspension of an offending agent in 11.7% of the patients [11].

Strength of the study

The data used in this study reflect real-life DR-TB treatment practices and patient experiences. The cross-sectional descriptive design enabled us to examine and describe the prevalence and profile of adverse events in the patient sample. We were able to generate a tentative hypothesis that some adverse events occur more in DR-TB patients co-infected with HIV, which is clinically important when treating this sub-group of patients.

Limitation of the study

By using retrospective data, we encountered instances of missing patient treatment records and missing data on specific variables. Furthermore, it was not possible to perform qualitative causality assessment of the adverse events using the available data, especially given the paucity of laboratory data. The adverse events recorded on the patients' side-effects monitoring form were based on patient-reported symptoms. Hence, there was a possibility of subjectivity and of selective under-reporting of adverse events by patients or the selective recording of adverse events by clinicians, which may have biased the results away from the true prevalence. Some symptoms of reported adverse events may have overlapped with symptoms of HIV/ AIDS. The small sample size and the use of data from one facility may not allow for generalization of findings beyond the studied sample.

Conclusion

This study found that adverse events, of varying severity, most commonly occur in the intensive phase of DR-TB treatment. While most patients tolerated the second-line anti-TB medicines used in Namibia's DR-TB treatment program, about 10% of patients experienced serious adverse events, with a possibility of suffering permanent disability. Some adverse events were more prevalent in DR-TB patients co-infected with HIV. The characteristics, magnitude of risk and risk factors of these serious and potentially permanent adverse events should be thoroughly examined and elucidated in subsequent prospective active surveillance pharmacovigilance or cohort studies. Therefore, clinicians, including pharmacists, should closely monitor and aggressively manage adverse events during the intensive phase of DR-TB treatment and should always consider the possibility of increased occurrence of adverse events in patients co-infected with HIV.

Authors' contributions

Evans Sagwa conceived and designed the study; collected, analyzed the data, drafted and finalized the manuscript. Brian van Wyk, Panganai Dhliwayo, Nunurai Ruswa, and Jean Paul Musasa reviewed the study protocol and manuscript. Aukje Kaija Mantel-Teeuwisse and Shanthi Pal critically reviewed the manuscript.

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Conflict of interest

None

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TB Diagnostic Capacity in Sub-Saharan African HIV Care Settings

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Abstract

As HIV care services continue to scale-up in sub-Saharan Africa, adequate tuberculosis diagnostic capacity is vital to reduce mortality among HIV-infected persons. A structured survey was administered at 663 health facilities providing HIV care to 908,043 patients in across 9 sub-Saharan African countries to estimate the proportion of facilities and HIV patients at these facilities with access TB-related diagnostic tests. Sputum smear microscopy was available at 87% of facilities (representing 97% of patients), chest x-ray at 26% of facilities (representing 56% of patients), tuberculin skin tests were available at 12% of facilities (representing 33% of patients). Acid-fast bacillus culture was available on-/off-site at 53% of facilities (representing 77% of patients). Primary health facilities had lower availability of tuberculosis diagnostic tests compared with secondary and tertiary health facilities. As HIV care continues to decentralize to primary health facilities, a corresponding expansion of diagnostic capacity to lower levels of the health system will be essential.

Keywords

tuberculosis diagnostics; laboratory capacity; TB/HIV integration; HIV care; implementation science; resource-limited settings

INTRODUCTION

Fueled by the HIV epidemic, tuberculosis (TB) remains a global public health challenge. In 2010, there were 8.8 million incident cases of TB worldwide and 1.45 million deaths.[1] An estimated 1.1 million incident cases were HIV-coinfected; 82% of these were in sub-Saharan Africa (SSA), where drug-resistant TB is also an emerging threat.[1]

Intensified TB case finding and prompt initiation of TB treatment are important strategies to improve patient outcomes and curb transmission, particularly among HIV-infected patients,

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who often present with atypical disease. However, lack of adequate diagnostic capabilities in resource-limited settings where HIV-infected persons receive care often delays diagnosis. In turn, initiation of treatment for active TB and isoniazid preventive therapy (IPT) for those in whom active TB was excluded is often delayed.[1] According to the most recent WHO estimates, in SSA, smear microscopy coverage is at 1.4 laboratories per 100,000 population, acid-fast bacilli (AFB) culture coverage at 0.7 laboratories per 5 million population, and drug susceptibility testing (DST) coverage at 0.4 laboratories per 10 million population. By contrast, in resource-rich countries such as Germany, coverage of AFB culture and DST is at 12 laboratories per 5 million population and 4.4 laboratories per 10 million population, respectively.[1] Improving the coverage and capacity of laboratories with adequate TB diagnostic services is a global health priority, especially in SSA where HIV prevalence is high and the incidence of multidrug and extensively drug-resistant TB (MDR/XDR-TB) is increasing.[2] We describe the availability of TB diagnostic services at 663 diverse health facilities across 9 SSA countries.

METHODS

In September 2010, a structured survey was administered to staff in 663 health facilities supported by ICAP-Columbia University providing HIV care and treatment across 9 SSA countries funded by the President's Emergency Plan for AIDS Relief (Cote d'Ivoire, Ethiopia, Kenya, Mozambique, Nigeria, Rwanda, South Africa, Swaziland, and Tanzania). These facilities represented 97% of all HIV care and treatment facilities that received support from ICAP at the time. The survey consisted of 101 questions about the HIV program and facility characteristics, of which 23 questions were TB-related. The survey was administered by ICAP field staff to the director of the health facility, HIV clinic, or another staff member most familiar with the day-to-day operations of the facility. The protocol was reviewed by Columbia University Institutional Review Board and received nonhuman subject research determination, as the subjects of data collection were facilities and not individuals.

Outcome variables for the present analysis included availability of sputum smear microscopy, chest x-ray (CXR), and tuberculin skin test (TST) on-site and availability of AFB culture and DST on-site or through referral to another facility (data cannot be disaggregated). Covariates in the present analysis were facility characteristics, including location (urban and rural), facility type (public primary, public secondary, public tertiary, and private/other), and time since first quarter of reporting as a proxy for years providing comprehensive HIV care. In addition, patient load at the HIV clinic was derived from cumulative enrollment data reported during the July–September 2010. We examined the frequencies of available TB diagnostic tests stratified by facility characteristics. Furthermore, we estimated the proportion of HIV-infected patients enrolled in care at facilities that might have access to these tests, disregarding operational barriers, such as provider knowledge, fees for tests, and equipment malfunction, by dividing the number of patients enrolled in facilities reporting availability of various TB diagnostic tests by the total number of patients enrolled. Statistical significance was assessed with χ^2 tests, with $P < 0.05$ as threshold for significance. Statistical analyses were performed using SAS software version 9.2 (SAS, Cary, NC).

RESULTS

As of September 2010, 908,043 HIV-infected patients were cumulatively enrolled in HIV care at the 663 facilities included in this analysis (Table 1). The majority (59%) of facilities surveyed was public sector primary care facilities and was evenly distributed between urban and rural areas. However, in terms of number of patients, most patients were enrolled at

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public sector secondary and tertiary facilities (63%) and in urban facilities (78%). The median cumulative number of patients ever enrolled across the surveyed facilities was 365 (IQR: 96–1419), with children aged 0–14 comprising 9.3% of the patients. The median time since a facility began providing comprehensive HIV care was 2.0 years (IQR: 0.75–3.5). Most facilities reported offering TB treatment within the facility (80%).

Sputum smear microscopy, CXR, and TST were reported available on-site at 87% [range across country programs (RAC): 28%–100%], 26% (RAC: 8%–79%), and 12% (RAC: 0%–60%) of facilities, respectively. Fifty-three percent (RAC: 2%–94%) of facilities had AFB culture availability either on-site or through another facility, and of these facilities, 35% (RAC: 0%–75%) had availability of DST on-site or through another facility.

Table 2 compares on-site availability of each diagnostic test by facility characteristics. While sputum smear microscopy was widely available across urban and rural areas at all types of facilities (public primary, public secondary, public tertiary, and private/other), CXR availability varied substantially from 0% to 94%, and TST availability was low across facilities (Table 2). Availability of CXR was high in urban secondary and tertiary facilities (74% and 94%, respectively) and lower in urban private and rural secondary facilities (55% and 48%, respectively). CXR was rarely available in urban and rural primary facilities (both at 3%). TST availability was highest at urban tertiary facilities (44%), while all other facilities reported very low availability.

Availability of AFB culture on-site or through referral to another facility was also variable and was highest at urban tertiary (81%) and rural secondary (77%) facilities. Among 352 facilities with AFB culture availability, DST was most available in urban tertiary facilities (69%), followed by private (56%) and public primary facilities (41%). Facilities providing HIV care for ≥5 years or having ≥352 cumulative patients in HIV care were more likely to have all specified types of diagnostic tests available (with the exception of DST), as compared with facilities that more recently initiated HIV care programs and/or had fewer patients enrolled in care. Facilities providing HIV care for ≥5 years were less likely to have availability of DST compared with facilities providing HIV care for <1 year (26% vs 50%).

When examining the proportion of HIV-infected patients at facilities that reported having availability of TB diagnostic tests, disregarding operational barriers, a higher proportion of patients as compared with facilities had availability of diagnostic tests. This is mainly because, as stated above, most HIV-infected patients accessing care in surveyed facilities do so at secondary and tertiary facilities where there is relatively high availability of TB diagnostics tests. Of all HIV-infected patients receiving care at surveyed facilities, 97%, 56%, and 33% of patients attended facilities that had on-site sputum smear microscopy, CXR, and TST, respectively. Seventy-seven percent and 35% of patients attended facilities that had AFB culture availability and DST either on-site or through another facility, respectively.

DISCUSSION

In this survey of the availability of TB diagnostic tests at 663 HIV care and treatment facilities from 9 SSA countries, we found that sputum smear microscopy was widely available across the spectrum of healthcare facilities, irrespective of location and type of facility. However, availability of CXR, TST, and AFB culture were generally limited to secondary and tertiary facilities. Surprisingly, DST was more commonly available at primary as opposed to secondary facilities, and at those providing HIV care for <1 as opposed to ≥5 years, findings partly driven by the large number of primary and less mature facilities included in the survey from Kenya and South Africa, respectively, where DST was

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reportedly available at all health facility levels. Still, with exception of South Africa, none of the countries included in the analysis have achieved the Global Plan to Stop TB goal for countries with high prevalence of HIV (and consequently smear-negative TB) of at least one laboratory with AFB culture and DST capability per 5 million population.[4] TST was only available at a small number of facilities. The lack of CXR and TST availability demonstrates the difficulty in operationalizing TB diagnostic algorithms developed in many countries for HIV-infected patients that include CXR, and in the case of children TST,[5] given the high prevalence of paucibacillary disease[6] and the challenges inherent to diagnosing TB in such patients.[7] The lack of availability of TST capacity also demonstrates the difficulty in attempting to identify HIV-infected patients most likely to benefit from IPT, that is, those with positive TST.[8]

In our analysis, only 53% of facilities reported on-site or off-site availability of AFB culture, most likely because in many resource-limited settings, particularly with high TB incidence, AFB culture is not included in national diagnostic algorithms for patients without a history of TB because of its cost and a turnaround time that can span 6–8 weeks.[9] Nevertheless, because most patients were enrolled in secondary and tertiary facilities, culture availability in terms of the number of HIV-infected patients was relatively high, at 77%. Similarly, only 12% and 26% of facilities reported having on-site availability of TST and CXR, respectively. However 33% and 56% of HIV-infected patients attended facilities that reported having these diagnostic tests. These proportions may decrease in the near future, as HIV care becomes further decentralized and increasing numbers of patients receive HIV care in primary care settings where availability of such tests is more limited. As HIV care expands to primary health facilities across SSA, it is anticipated that TB incidence will decline because of increased ART coverage.[2] Nonetheless, continued scale-up of laboratory and CXR service availability to lower levels of the health care system is critical to prevent delays in TB diagnosis and treatment, particularly in the context of the rapid increase in incidence of MDR/XDR-TB noted in recent years.[3]

The study had some limitations worth noting. The data were based on responses of health facility staff and were not always independently verified by survey staff. As such, we cannot rule out the possibility of facility staff over- or underreporting availability of diagnostic tests. In addition, the facility survey only determined the availability of diagnostic tests and did not assess patient access and routine use of these tests, which may have been limited by factors such as provider awareness, equipment malfunction, and direct and indirect costs to patients. For example, the finding that AFB culture is available at 53% of clinics may not always reflect routine use of this test for TB diagnostic purposes and should be interpreted with caution. In many cases, clinics must transport specimens to central laboratories in the capital cities for AFB culture testing. Routine utilization of the test and access to test results in a timely fashion are likely present at less than 53% of facilities (and subsequently less than 77% of HIV patients).

Strengths of this study include the breadth of the HIV care facilities surveyed, which included predominantly public facilities at all levels of the health care system in both urban and rural areas in 9 SSA countries with high TB case rates.[1] Furthermore, the survey was found to have good test–retest reliability; a data quality assurance exercise performed in 2010 that recollected data on a sample of questions (including 3 TB screening and diagnostic test questions) from the 2009 facility survey found 81% (IQR: 74%–85%) agreement.[10]

In conclusion, as HIV care expands to primary health facilities across SSA, a corresponding expansion of TB-related laboratory and radiology services to lower levels of the health care system is essential to meet the expected increase in demand for such services. Without it,

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availability of timely TB diagnosis and treatment for HIV-infected individuals may decrease in the coming years. These efforts should include increasing availability of CXR and TST to implement comprehensive TB diagnostic algorithms and ensure timely initiation of treatment for active TB and uptake of IPT for latent TB infection. Given the increasing threat of MDR/XDR-TB in the region,[3] increasing availability of AFB culture and DST through strengthened linkages between lower and higher level facilities is critical, including improvements in specimen transportation systems. Given the various performance and implementation issues with existing tests, especially in settings with high TB/HIV coinfection,[6] expanding coverage of rapid molecular tests, such as Xpert MTB-RIF (Xpert; Cepheid, Inc, Sunnyvale, CA), is also a potentially important strategy.[11–13] However, scale-up of molecular tests will face challenges similar to those of AFB culture because of their relatively high cost and prerequisite environmental conditions, such stable electrical supply and adequate room temperature, which are difficult to achieve in primary health care facilities in resource-limited settings.[13,14] Existing diagnostic tests can improve timely diagnosis and treatment of TB among HIV-infected patients. Resources are needed to expand the coverage of these tests to lower level health facilities where a substantial number of patients are expected to receive HIV care and treatment in the near future.

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TABLE 1

Clinic Characteristics at 663 HIV Care and Treatment Programs in 9 SSA Countries, September 2010

	Total Facilities, n (%)	Total Patients, n (%)
HIV Care and Treatment Clinics	663	908,043
Country		
Cote d'Ivoire	60 (9)	9868 (1)
Ethiopia	62 (9)	96,762 (11)
Kenya	157 (24)	137,002 (15)
Mozambique	60 (9)	278,083 (31)
Nigeria	33 (5)	83,382 (9)
Rwanda	46 (7)	46,139 (5)
South Africa	69 (10)	121,835 (13)
Swaziland	49 (7)	67,697 (7)
Tanzania	127 (19)	67,275 (7)
Location and clinic type		
Urban		
Public primary*	157 (24)	184,119 (20)
Public secondary†	129 (19)	400,792 (44)
Public tertiary‡	16 (2)	101,012 (11)
Private/other§	32 (5)	31,571 (3)
Rural		
Public primary	229 (35)	100,708 (11)
Public secondary	53 (8)	75,308 (8)
Private/other	47 (7)	14,533 (2)
Cumulative in number of patients in HIV care (proxy for program size)‖		
<365	328 (50)	41,288 (5)
≥365	328 (50)	866,755 (95)
Missing	7	
Years providing comprehensive HIV care (proxy for program maturity)		
≥5 yrs	51 (8)	251,906 (28)
ge;3 and <5 yrs	160 (24)	375,389 (41)
≥1 and <3 yrs	362 (55)	260,000 (29)
<1 yr	90 (14)	20,748 (2)
Provide treatment of active TB within the facility		
Total	530 (80)	793,700 (87)

*Health centers and clinics.

†District/provincial hospitals.

‡Teaching/national referral hospitals.

§Private: any facility run by private, nongovernmental, or faith-based organization; Other: mixed private–public clinics, workplace clinics, VIP clinic, and other clinic types.

[||]Cumulative through September 30, 2010. The categories were created using the median.

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TABLE 2

Bivariate Analysis of Factors Associated With Availability of Sputum Smear, Sputum Culture, DST, CXR, and TST Diagnostic Services at HIV Care and Treatment Programs in 9 SSA Countries, September 2010 (N = 663)*

	Sputum Smear Microscopy (n = 660)		AFB (n = 663)		DST (n = 352)†		CXR (n = 653)		TST (n = 663)	
	n (%)	*P*	n (%)	*P*	n (%)	*P*	n (%)	*P*	n (%)	*P*
Overall (% facilities)	574 (87)		352 (53)		123 (35)		170 (26)		81 (12)	
Overall (% patients)	881,972 (97)		699,968 (77)		242,640 (35)		508,757 (56)		301,117 (33)	
Location and clinic type										
Urban										
Public primary	**118 (76)**	**0.0039**	**71 (45)**	**0.0106**	27 (38)	0.7075	4 (3)	0.7813	**41 (26)**	**<0.0001**
Public secondary	**127 (99)**	**<0.0001**	72 (56)	0.568	**17 (24)**	**0.0208**	**93 (74)**	**<0.0001**	**17 (13)**	**0.0003**
Public tertiary	15 (94)	0.3768	**13 (81)**	**0.0152**	**9 (69)**	**0.0124**	**15 (94)**	**<0.0001**	**7 (44)**	**<0.0001**
Private/other	27 (84)	0.5776	**9 (28)**	**0.0102**	5 (56)	0.3259	**17 (55)**	**<0.0001**	**3 (9)**	**0.0389**
Rural										
Public primary	202 (88)	Ref	135 (59)	Ref	55 (41)	Ref	7 (3)	Ref	5 (2)	Ref
Public secondary	**52 (98)**	**0.0005**	**41 (77)**	**0.0033**	**7 (17)**	**0.0156**	**25 (48)**	**<0.0001**	**8 (15)**	**0.0004**
Private/other	**33 (70)**	**0.0199**	**11 (23)**	**0.0006**	3 (27)	0.4251	**9 (19)**	**0.0001**	0 (0)	—
Cumulative number of patients in HIV care										
<365	250 (77)	Ref	124 (38)	Ref	45 (36)	Ref	30 (9)	Ref	14 (4)	Ref
≥365	**319 (98)**	**<0.0001**	**227 (69)**	**<0.0001**	78 (34)	0.716	**139 (43)**	**<0.0001**	**67 (20)**	**<0.0001**
Years providing comprehensive HIV care										
≥5 years	**50 (98)**	**0.000**	**39 (76)**	**<0.0001**	**10 (26)**	**0.037**	**43 (84)**	**<0.0001**	**15 (29)**	**0.005**
≥3 and <5 years	159 (100)	—	**110 (69)**	**0.000**	44 (40)	0.273	**74 (48)**	**<0.0001**	28 (18)	0.120
≥1 and <3 years	**302 (84)**	**0.046**	167 (46)	0.312	**51 (31)**	**0.015**	42 (12)	0.870	29 (8)	0.541
<1 year	63 (71)	Ref	36 (40)	Ref	18 (50)	Ref	11 (12)	Ref	9 (10)	Ref
Country										
Cote d'Ivoire	17 (28)	—	**1 (2)**	**0.000**	0 (0)	—	5 (8)	**0.014**	1 (2)	0.082
Ethiopia	62 (100)	1.000	37 (60)	0.406	1 (3)	0.152	49 (79)	**<0.001**	1 (2)	0.077
Kenya	147 (94)	0.639	**135 (86)**	**0.023**	41 (30)	0.077	21 (13)	**0.021**	0 (0)	0.999
Mozambique	57 (95)	0.714	**52 (87)**	**0.028**	**19 (37)**	**0.038**	17 (28)	0.962	**36 (60)**	**<0.001**
Nigeria	32 (100)	1.000	**10 (30)**	**0.005**	2 (20)	0.577	14 (48)	0.079	6 (18)	0.079

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	Sputum Smear Microscopy (n = 660)		AFB (n = 663)		DST (n = 352)†		CXR (n = 653)		TST (n = 663)	
	n (%)	*P*	n (%)	*P*	n (%)	*P*	n (%)	*P*	n (%)	*P*
Rwanda	45 (100)	Ref	31 (67)	Ref	4 (13)	Ref	12 (28)	Ref	5 (11)	Ref
South Africa	67 (99)	0.889	**65 (94)**	**0.002**	**49 (75)**	**0.000**	15 (22)	0.510	**28 (41)**	**0.003**
Swaziland	37 (76)	0.118	**10 (20)**	<**0.0001**	1 (10)	0.810	9 (18)	0.281	0 (0)	—
Tanzania	110 (87)	0.350	**11 (9)**	<**0.0001**	**6 (55)**	**0.008**	28 (22)	0.442	4 (3)	0.056

*The table excludes missing values.

†Only answered by facilities with sputum culture diagnostic services.

Bold values indicate significance at $P < 0.05$.

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DEBATE Open Access

Can Brazil play a more important role in global tuberculosis drug production? An assessment of current capacity and challenges

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Abstract

Background: Despite the existence of effective treatment, tuberculosis is still a global public health issue. The World Health Organization recommends a six-month four-drug regimen in fixed-dose combination formulation to treat drug sensitive tuberculosis, and long course regimens with several second-line drugs to treat multi-drug resistant tuberculosis. To achieve the projected tuberculosis elimination goal by 2050, it will be essential to ensure a non-interrupted supply of quality-assured tuberculosis drugs. However, quality and affordable tuberculosis drug supply is still a significant challenge for National Tuberculosis Programs.

Discussion: Quality drug production requires a combination of complex steps. The first challenge is to guarantee the quality of tuberculosis active pharmaceutical ingredients, then ensure an adequate manufacturing process, according to international standards, to guarantee final product´s safety, efficacy and quality. Good practices for storage, transport, distribution and quality control procedures must follow. In contrast to other high-burden countries, Brazil produces tuberculosis drugs through a strong network of public sector drug manufacturers regulated by a World Health Organization-certified national sanitary authority. The installed capacity for production surpasses the 71,000 needed treatments in the country. However, in order to be prepared to act as a global supplier, important bottlenecks are to be overcome. This article presents an in-depth analysis of the current status of production of tuberculosis drugs in Brazil and the bottlenecks and opportunities for the country to sustain national demand and play a role as a potential global supplier. Raw material and drug production, quality control, international certification and pre-qualification, political commitment and regulatory aspects are discussed, as well recommendations for tackling these bottlenecks. This discussion becomes more important as new drugs and regimens to treat tuberculosis are expected in a close future.

Summary: International manufacturers of raw material for tuberculosis treatment should undergo certification and pre-qualify their active pharmaceutical ingredients as a first step to ensure quality of tuberculosis drugs. At the country level, Brazilian public manufacturers should apply for international certification and tuberculosis drugs should be pre-qualified by international organisms. Finally, only with political commitment and large-scale production will Brazilian public sector manufacturers be able to partially supply the global market.

Keywords: Antitubercular agents, Certification, Fixed dose combination, Pharmaceuticals, Quality control, Tuberculosis

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Background

The World Health Organization (WHO) estimates that one third of the world population is infected by *M. tuberculosis*. WHO also estimates that in 2010, 8.7 million (range 8.3-9.0 million) people developed tuberculosis (TB) and 0.99 million (range 0.84-1.1 million) died from TB, with 0.43 million (range 0.40-0.46 million) additional deaths from HIV-associated TB. [1] Worldwide, TB is the second leading cause of death from infectious diseases [1] and the first among people living with HIV/Aids. [2] To combat TB worldwide, the United Nations [3] and WHO [4] propose that by 2050, TB global incidence rate should decrease to less than 1/1,000,000 inhabitants per year. By 2015, global targets aim to reduce global TB prevalence and death rates by 50% compared to 1990 [3].

Among other challenges, the rapid spread of drug resistant TB in Africa, Eastern Europe and Asia [5,6] jeopardizes the achievement of these goals [1]. Drug resistant strains emerged mainly from the inadequate use of TB drugs, or use of low quality drugs, poor TB program performance and lack of regulation [7]. The incorporation at country level of promising advances on new drug, vaccine and diagnostic technologies will still take time before they can effectively contribute to global TB control [8,9]. In the meantime, it is important to guarantee an uninterrupted supply of quality-assured drugs at the country level.

This article will introduce key issues on the Brazilian model for TB control and focus on the production of quality TB drugs in Brazil, highlighting current strengths and obstacles of the Brazilian Public Pharmaceutical Manufacturing Laboratories (PPML) [10] as potential suppliers for the global market.

Discussion

Specificities of Brazilian Context for TB Control

Brazil is one of the 22 countries that account for 80% of the global burden of TB [1]. In 2010, the country reported 71,337 new TB cases [1]. In Brazil, TB treatment is offered exclusively in the public sector, according to current rules and treatment protocols recommended by the Ministry of Health (MoH) [11]. Public manufacturers provide TB drugs, including fixed-dose combination (FDC) of rifampicin and isoniazid since the 1970s, [9] which are distributed free of charge across the country [12]. The drugs are purchased centrally by the MoH and distributed to the municipalities [13]. Except for quinolones and aminoglycosides, TB drugs are not available in private pharmacies; they are exclusively distributed in the public health system. Treatment of TB is based on national recommendations and guidelines edited jointly by the MoH and professional associations [11,14]. There is no private market for TB drugs or TB treatment. As a consequence, the rate of multidrug-resistant TB in the country has remained low (1.4%, personal communication by Brazilian National TB Control Program (NTP), based on national survey conducted in 2008–2009).

Opportunities for TB drug manufacturing in Brazil

Drug production is regulated by Brazil's National Regulation Authority (ANVISA) [15]. ANVISA was established in 1999 to regulate health products and services in Brazil, following the model of international regulation authorities, [15] and is WHO pre-qualified for regulation of vaccine production [15]. The PPML produce 11 billion pharmaceutical units per year to meet the needs of government-run public health programs [10,16]. This manufacturing network has improved technologically and gained recognition through its broadly acknowledged capacity for antiretroviral production [13,17]. First-line TB drugs, including fixed dose combination formulations, and some second-line TB drugs are currently manufactured by these PPML. [17] Farmanguinhos, one of the most innovative manufacturers of this network, developed the Rifampicin/Isoniazid (RH) 2:1 FDC tablet (currently undergoing registration process) and is working on the pharmacotechnical development of the Rifampicin/Isoniazid/Pyrazinamide/Ethambutol (RHZE) 4:1 FDC, through a public-private partnership (PPP) agreement with a WHO-pre-qualified Indian manufacturer [18].

Under this new context, PPML produce TB drugs with formulations and dosages/strengths aligned with WHO recommendations, opening new opportunities to supply the international market [17]. Entering the global supply chain would likely contribute to leverage production scale, and maintenance of quality standards without significant extra costs. However, in order to reach international certification requirements, like compliance to WHO's pre-qualification program, [19] and attain financial sustainability, a few bottlenecks should be overcome.

Bottlenecks for TB drug manufacturing in Brazil

Economic incentives for production

The costs of drugs and the impact of imported supplies on the national trade balance are important issues for the sustainability of any public health system, often influencing priorities for investment. However, the majority of TB drugs are available at low cost in national and international markets [10,20] and therefore have limited budgetary impact for the Brazilian National Health System (*Sistema Único de Saúde* - SUS) [21]. Thus, most TB drugs have low commercial interest for manufacturers, [10,20] including PPML. More expensive second-line drugs, such as capreomycin, cycloserin/terezidon, 4-aminosalicylic acid (PAS) or ultimate generation quinolones, at least while they are not part of first-line regimen, are also not considered a priority for local production, because of Brazil's low drug resistance rates and limited demand.

[1,5] Instead, industrial interests are focused on the most innovative technological approaches to maximize return on investments. The same logic applies to the public sector based industry, which frequently chooses to produce, promote and fund innovation focusing on high-cost drugs that can boost revenues for the PPML, and reduce costs for the health system [10,22]. TB drugs do not represent such an incentive [21,23].

Nevertheless, TB is a national and global priority [10]. It is critical to engage diverse stakeholders, including regulatory agencies, media, civil society and political organizations to support domestic production of TB drugs in Brazil. Even if not profitable, domestic production would benefit job creation, technological development and supply security, and above all, meet an important public health need.

Active pharmaceutical ingredients (API)

Manufacturing of most molecules employed in TB treatment does not impose significant technological challenges [24]. In addition to international API manufacturers directly linked to large pharmaceutical companies, countless independent medium-sized companies manufacture API. However, challenges remain, including an economic disincentive (due to low cost and low demand) and gaps in the parameters and mechanisms to guarantee API quality standards [25]. Limited official control from national and international regulatory agencies also leads to highly variable quality of API [1,19,23]. This severely impacts the quality of final products and production consistency.

In order to guarantee drug quality, physicochemical and microbiological characteristics of API must be standardized and kept constant, [24] through an expanded certification process. Certification should be based on specific description of quality parameters for API, and pre-qualification of raw materials is an essential step for the manufacturing of quality drugs [25,26]. Private industries ensure compliance and consistency by establishing supplier-manufacturer agreements. However, Brazilian PPML must follow public sector procurement rules, [27] and government regulations prohibit procurement notices conditioned to specific technical requirements. This has occasionally made it difficult for PPML to purchase critical pharmaceutical ingredients in accordance with characteristics approved by the health regulatory agencies, or to establish a consistent relationship with a selected supplier. These legal procurement aspects, as they apply to API, may hamper the uniformity of nationally manufactured drugs.

The manufacturing process

Drug quality control, whether carried out by the private industry or by the national regulatory inspection framework, involves a set of legal, technical and administrative requirements [24,28]. In Brazil, quality control is insured by the Brazilian Sanitary Surveillance System, headed by the Brazilian National Institute of Metrology [29] and ANVISA [15]. One potential limiting factor of this highly regulated sector is the availability of reference materials for bioavailability and bioequivalence studies in the national market [30]. In addition, standardized proficiency testing programs must be carried out on a regular basis. Although the government implemented a dedicated quality control program for TB drugs in 2005, [31] and reference substances were prioritized for local development by the Brazilian Pharmacopeia, [30] strong political will and support are necessary to ensure the continuation of such a program. Additionally, it is critical to ensure effective mechanisms for drug certification [25].

Internal technological development

Over the last few decades, Brazil has increased its investment in scientific and technological innovation. Numerous examples can be found in other fields of knowledge, such as the country's expanded participation in the petroleum/biodiesel and agricultural global markets [32]. This investment has also led to growth in scientific publications around health, including scholarships and research grants for TB projects [33].

In the past decade, Brazil identified the pharmaceutical sector as a priority for industrial policy [34]. PPPs supporting technology transfers from international companies to domestic public sector manufacturers are a core strategy of that policy. The consolidated experience of the numerous PPPs coupled with national investment in development of new technologies by Brazilian investigators represent an important push for pharmaceutical innovation in the country.

Despite these recent efforts, significant investment is still needed. In the 1990s, rapid changes in importation policies led to a lack of prioritization of industrial drug manufacturing capacity, which had been strengthened under previous national development cycles [34]. This created a gap in pharmaceutical research and development capabilities that is still felt today. Going forward, progress will require strong science and technology policies that encourage later-stage pharmaceutical-technical development and industrial-scale drug manufacturing.

Recommendations for addressing the identified bottlenecks

Economic incentives for production

The SUS strategic product policy could incorporate some of the innovative thinking developed through national and international initiatives such as the Drugs for Neglected Disease Initiative program [35]. To incentivize drug development, this program successfully balanced economic interests and public health needs, including

market/supply forecasts, safety and quality-related issues regarding these drugs.

Brazil has been playing an important role in South-South cooperation on health and other development sectors [36]. This has enhanced the country's political credibility worldwide, and could facilitate access to global markets for domestically-produced TB drugs. Since national demand for TB drugs is relatively limited in scale, participating in international markets through global initiatives would help justify required investments, benefiting manufacturing capacity overall. Additionally, product development efforts focusing on needed innovations for TB control, such as paediatric, geriatric as well as parenteral formulations, may further expand the potential international market for PPML.

Finally, if PPML are fully compliant with international requirements for drug quality, innovative models guaranteeing advanced purchase commitments from international mechanisms would facilitate Brazil engagement for investing in TB drug production.

API

The legal requirements regarding the bidding process for API in Brazil need to be revisited to address the PPML specificities and to incorporate a new legal paradigm to increase efficiency for public sector companies. This will require strong political advocacy and commitment, along with improved harmonization across government agencies to further define and adapt legal mechanisms and administrative processes to leverage suitable levels of efficiency in API purchasing. In addition, it will be necessary to define requirements for API certification by national or international organizations. TB API suppliers could be encouraged to register their quality, safety and efficiency standards with national regulatory authorities. Issues to be considered as part of the registration process should include detailed information on the different synthetic routes, specific and significant toxicological impurities, polymorphism among other physicochemical characteristics, which would allow for comparison between API from diverse manufacturers.

This process would allow Brazil and other manufacturing countries to share key updated information on API suppliers. Above all, this approach would enable the Brazilian MoH to monitor API market dynamics so that in critical situations, such as when there are limited manufacturers or competition for specific API, risks of shortages would be minimized and overall API quality standards improved. If WHO and other international organizations standardize and expand their pre-qualification mechanisms, Brazil – and other interested countries - should take part in the process.

If coordinated with WHO and other international organizations, this registration process would likely increase API supplier interest in applying for health registration.

The manufacturing process

The Brazilian government should encourage PPML to apply for the WHO pre-qualification program [26] and initiate first and second-line drug regulatory registration procedures in other countries. This could be leveraged through a more unified global strategy approach. In partnership with key international stakeholders and donors, the Brazilian government could develop a priority agenda for global and regional production of TB drugs. In a short time span, Brazil could play an important role in supplying TB drugs to the international market, particularly given the organizational strengths of SUS [13] and the fact that standards for good manufacturing practices (GMP) certification are aligned with the international ones. Farmanguinhos, one of the main PPML, is already GMP certified for some of its products. So is the Navy Forces Laboratory (*laboratório da Marinha*), a fluoroquinolone producer. This needs to be expanded, monitored and encouraged so that it becomes a model for drug development programs at other PPML.

Internal technological development

If Brazil wishes to play a significant role as a global TB drug producer, it is essential to continue with the PPP approach for technology transfer and take additional measures to foster domestic investment on pharmaceutical research and innovation.

Incentivizing more interaction between public sector research institutes and pharmaceutical manufacturers through the Brazilian TB Research Network [37] may be an adequate approach to establish innovative partnerships. Moreover, lessons learned during the implementation of a quality-control program for TB drugs in Brazil indicated that there is strong interest in more interactions between the manufacturing sector and the national regulation authority. A closer collaboration between manufacturers and ANVISA would help address, as early as possible, manufacturing challenges that may impact quality of final products. If implemented, these measures may provide the basis for later stage development processes, in case new molecules currently under development are launched as new drugs [38] and attract the attention of the manufacturing sector.

Summary

Considering the technical capacity, regulation framework and industrial network established by PPML, Brazil has a strong potential for supplying TB drugs to the international market in the near future. However, several issues and bottlenecks still need to be addressed. At the global level, an important step is to ensure the availability of quality API. Brazilian manufacturers should be allowed to purchase of API exclusively from pre-qualified manufacturers, which will require new mechanisms for API certification and procurement by the Brazilian agencies and

public administration. Furthermore, the Brazilian public laboratory network needs to seek broader recognition by pursuing certification through international quality mechanisms like the WHO pre-qualification program. TB drug production for international markets could also be included in Brazil's South-South cooperation agenda. In addition to benefiting global access, these efforts would provide synergistic effects to consolidate capacity for regular quality-assured TB drug production for Brazil's own domestic demand.

Abbreviations

4:1: Drug containing four active ingredients (RHZE) in one unit, the tablet; ANVISA: National Health Surveillance Agency; API: Active Pharmaceuticals Ingredients; FDC: Fixed-dose combination; PPML: Public Pharmaceutical Manufacturing Laboratories; MoH: Ministry of Health; NTP: National Tuberculosis Control Program; PPP: Public-Private Partnership; RH: Rifampicin/Isoniazid; RHZE: Rifampicin/Isoniazid/Pyrazinamide/Ethambutol; SUS: Brazilian Unified National Health System; TB: Tuberculosis; WHO: World Health Organization.

Competing interests

The authors declare no competing interests. The sponsors (Fundação Ataulpho de Paiva, through a grant by Bill and Melinda Gates Foundation) are not responsible for any statements in this manuscript.

Authors' contributions

AG interviewed MoH partners, public laboratory leaders, international and non-governmental organizations. All authors discussed the contents of interviews and the recommendations included in the manuscript. AT and AM edited the manuscript. All authors approved the final version of the present manuscript.

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Determinants of multidrug-resistant tuberculosis in patients who underwent first-line treatment in Addis Ababa: a case control study

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Abstract

Background: Worldwide, there were 650,000 multidrug-resistant tuberculosis (MDR-TB) cases in 2010, and in 2008 the World Health Organization estimated that 150,000 deaths occurred annually due to MDR-TB. Ethiopia is 15th among the 27 MDR-TB high-burden countries. This study identifies factors associated with the occurrence of MDR-TB in patients who underwent first-line TB treatment in Addis Ababa City.

Methods: A case control study was conducted at St. Peter Hospital and five health centers in Addis Ababa from 1 November 2011 to February 30, 2012. Cases were MDR-TB patients who were confirmed with culture and drug-susceptibility testing and were in treatment at St. Peter Hospital during the study period. Controls were patients who were on first-line anti-TB treatment and were registered as cured or having completed treatment in the period 9 April 2009– 28 February 2010, in five health centers of Addis Ababa City. Accordingly, 134 cases and an equal number of controls were included in this study. A structured interview questionnaire was used to assess factors that could potentially be associated with the occurrence of MDR-TB.

Results: Factors that were significantly associated with MDR-TB: drug side effects during first-line treatment (adjusted odds ratio (AOR): 4.5, 95% CI; 1.9 - 10.5); treatment not directly observed by a health worker (AOR = 11.7, 95% CI; 4–34.3); interruption of treatment of at least a day (AOR = 13.1, 95% CI 3.0-56.6); duration of treatment between 2 and 7 months (AOR = 14.8, 95% CI 2.3-96.4); and retreatment with the Category II regimen (P = 0.000). In the current study, HIV infection was not significantly associated with the occurrence of MDR-TB.

Conclusions: Patients who were not in strict DOTS programs and did not adhere to first-line TB treatment and patients who experienced side effects during first-line treatment and Category II retreatment were at significantly increased risk of developing MDR-TB. The DOTS program should, therefore, be strengthened to increase patient adherence. Drug-susceptibility testing is also highly recommended for all Category I treatment regimen failures before those patients begin the Category II regimen.

Keywords: TB, MDR-TB, TB treatment, TB treatment regimens, Adherence to TB treatment, TB treatment failure, DOTS

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Background

Multidrug-resistant tuberculosis (MDR-TB) is a type of TB that is resistant to at least the first line anti-TB drugs, Rifampacin and Isoniazid. MDR-TB occurs either when a person is infected with a resistant strain or when improper treatment leads to drug selection of the resistant strain [1]. When an individual who has no history of first-line TB treatment develops MDR-TB, it is termed primary. When insufficient treatment leads to selection of spontaneously resistant strains (i.e., drug resistance is acquired), the disease is termed secondary MDR-TB [2].

Worldwide, there were 650,000 MDR-TB cases in 2010, and in 2008 World Health Organization (WHO) estimated that there were 150,000 deaths annually due to MDR-TB [3]. Overall, the 27 high MDR-TB burden countries accounted for 85% of all MDR-TB cases. China, and India, was the top two countries accounting 50% MDR-TB cases [3]. A 2010 WHO report showed that the number of MDR-TB cases is rising in Africa [1]. Ethiopia is 15th among the 27 MDR-TB high-burden countries, with an estimated 5,200 cases occurring each year [4].

The occurrence of MDR- TB is mainly attributable to human error, although genetic factors are also believed to contribute to a certain extent [5]. The principal patient-related factor that predicts the occurrence of MDR-TB is non-adherence to treatment [6]. The first-line anti-TB drugs used in Ethiopia in 2009/2010 were rifampicin (R), ethambutol (E), isoniazid (H), and pyrazinamide (Z) [7]. The category II treatment regimen (S (ERHZ) for two months, ERHZ for one month and E (RH) for five months three times a week), which adds streptomycin to the category I regimen (ERHZ for two months and RH for four months) has been blamed for increasing the risk of developing MDR-TB [8], despite the fact that patients have already been exposed to most of the drugs.

The emergence of MDR-TB is a threat for the populations of resource-limited countries. In Ethiopia, the low socioeconomic status of the people, high prevalence of infectious diseases and limited access to well-equipped health care facilities worsens the effect of MDR-TB. Furthermore, poor treatment outcomes, longer treatment time (about two years), higher treatment costs, and many more complications make MDR-TB a more complex disease than TB [1,9]. In 2010, less than 5% of new and previously treated TB patients were tested for MDR-TB because of limited availability of the test in most developing countries [10]. For example in Ethiopia, in 2010 the ratio of laboratories capable of performing mycobacterial culture was 0.1 per 5 million populations [10]. Similarly, the ratio of laboratories capable of running line probe assays (LPA) for rapid detection of MDR-TB was 0.1 per 5 million populations [10]. At the time of this study in Ethiopia, the LPA, or culture using Lőwenstein-Jensen media (LJ), and drug-susceptibility testing (DST) were provided only at the Ethiopian Health Nutrition and Research Institute (EHNRI) in Addis Ababa.

MDR-TB occurs mostly in relation to improper treatment of drug-susceptible TB. In countries like Ethiopia MDR-TB is becoming a challenge because of poor adherence to treatment and an increase in the use of illegal and unapproved treatment regimens for MDR-TB [9]. To make things worse, in these TB and MDR-TB high-burden countries patients stay in their communities for longer periods without being diagnosed or getting proper treatment. Even after diagnosis, because there are few diagnostic and treatment facilities and a lack of trained health professionals and drugs, patients do not start treatment immediately. This delay potentially allows easy spread of the disease to a large number of individuals within a short time. The aim of this study is to asses factors that determine the occurrence MDR-TB among patients who had taken first line anti-TB treatment in Addis Ababa City.

Methods

Study area and study design

This health institution–based case control study was conducted between 1 November 2011 and 28 February 2012 in Addis Ababa, the capital city of Ethiopia. The estimated population size of Addis Ababa is 2.74 million and the male population constitutes 48% [11]. Administratively, the city is divided into 10 sub-cities and further classified into 99 *kebeles* (lowest government administrative unit). The health institutions in the city includes 47 hospitals, 204 private higher clinics, 226 private mid-level clinics (known as medium clinics), 143 private lower clinics, and 37 government health centers [Addis Ababa Health Bureau report].

Study setting

Cases were selected from St. Peter Hospital, one of the two MDR-TB patient treatment centers in Addis Ababa, and controls were selected from Addis Ketema Health Center in Addis Ketema sub-city; Woreda 9 Health Centers in Kolfe Keranyo sub-city; Lideta Health Center in Lideta sub-city; Kasanches Health Center in Kirkos sub-city; and Woreda 19 and Nifas Silk Lafto health centers in Nifas Silk Lafto sub-city.

Eligibility of study participants

MDR-TB patients diagnosed by LPA, or culture using LJ, and DST at the EHNRI and who were being treated at St. Peter Hospital during the study period were considered as cases. In Ethiopia a patient is a suspect for MDR-TB if he/she is a symptomatic close contact of a

confirmed MDR-TB patient; a symptomatic individual from a known high-risk group such as health workers; a case of treatment failure; a new TB patient who remains smear positive after 2 months of treatment (for new cases) and after 3 months of retreatment with first-line treatment or retreatment (e.g., return after default, relapse) [12]. The controls were patients who had completed first-line anti-TB treatment and were declared cured or treatment completed using the WHO criteria and adopted by FMOH of treatment outcomes [13] between 9 April 2009 and 28 February 2010. Additionally, the controls were those with no clinical symptoms of TB based on the WHO criteria.

Recruitment of study participants

During the study period there were 147 eligible confirmed MDR-TB cases at St. Peter Hospital, 134 of who consented to participate in the study. These patients were residents of Addis Ababa who had a history of taking their first course of first-line TB treatment and were on MDR-TB treatment during the period of data collection. Prior to identification of the controls, five health facilities were identified based on the number of MDR-TB cases that they referred to St. Peter Hospital. The same number of controls was selected from each of these five health facilities. The sampling frame comprised all patients who had completed first-line anti-TB treatment and were registered as cured or treatment completed. Following this, the required sample size of the control group was selected using systematic random sampling. When a selected patient declined to participate in the study, the next person in the register was taken.

The contact information of controls and cases was obtained from the health center's TB clinic patient registration book. The selected individuals were contacted by telephone and given information about the study. Individuals who were willing to participate and gave verbal consent were scheduled for an interview at the health facility.

Data collection

A structured questionnaire was used to collect information from study participants. Secondary data were collected from TB and MDR-TB registers. Patient charts and the data collection format were used to determine and record their initial TB episode. The FMOH screening tool was used to identify controls free of suspected TB at the time of the study [7]. Day-long training was provided to the nurses and health officers involved in the data collection process. The main variables included in study instrument were sex, age, socioeconomic status, ethnicity, HIV status, adherence or non-adherence to the first course of anti-TB treatment, number of previous anti-TB treatments, treatment with the Category II regimen, ever- interruption in taking medicine for a day, and occurrence of drug side effects during the first course of TB treatment.

Data management and analysis

Data were entered using Epidata version 3.1 and exported to STATA version 11 for analysis. Data completeness and consistency were checked by running frequencies of each variable. Bivariate analyses were carried out for categorical variables, and odds ratios were used to quantify the strength of association between potential risk factors and MDR-TB. Multiple logistic regressions were used to control the confounding effect of different variables while assessing the effect of each variable on the likelihood of MDR-TB occurrence. A p-value of 0.05 was used as the cut-off point for statistical significance. Variables having a p-value of at most 0.05 in bivariate analysis were included in the multivariate logistic regression model. In multivariate logistic regression, the adjusted effects of three variables (the number of pulmonary TB episodes, ever-interruption in anti-TB treatment for at least a day in the first course, and duration of the first course of TB treatment) were estimated without concurrently adjusting for each other to avoid multicollinearity.

Ethical considerations

Ethical clearance was obtained from the institutional review board of the Aklilu Lemma Institute of Pathobiology at Addis Ababa University and St. Peter Hospital. Written permission to conduct the study was also obtained from the managers of each health facility. A statement about the purpose of the study was read to each study participant, and those who gave verbal consent to participate in the study were interviewed. Study participants were interviewed privately, and their names were not written on the questionnaire to ensure confidentiality.

Results

Sociodemographic characteristics of study participants

A total of 134 cases and an equal number of controls were included in the study. A total of 81 (60.5%) of the MDR-TB cases were males, but females represented the majority in the control group (70 females, or 52.5%). Single or divorced individuals accounted for the majority 101 (75.3%) of the MDR-TB cases but only about half (69, or 51.5%) in the control group (Table 1). The mean age was 25.1 (SD = 10.94) years for MDR-TB cases and 30.72 (SD = 11.4) years for controls.

TB-related conditions

Table 2 summarizes TB-related conditions in the cases and controls. Of the 134 MDR-TB cases, 96 (71.6%) had had two or more episodes of TB treatment before they

Table 1 Sociodemographic characteristics of MDR-TB cases and their controls in Addis Ababa, 2011

Characteristics (variables)	Cases (n = 134)		Controls (n = 134)	
	Number	Percentage	Number	Percentage
Sex				
Male	81	60.5	64	47.5
Female	53	39.5	70	52.5
Age at the time of first anti-TB treatment (years)				
5–25	85	63.4	47	35.1
26–45	40	29.9	70	52.2
46–72	9	6.7	17	12.7
Marital status				
Single	85	63.4	60	44.8
Married	32	23.8	56	41.8
Divorced	16	11.9	9	6.7
Widow/widower	1	0.75	9	6.7
Educational status				
Up to fourth grade	15	11.2	25	18.6
Completed 5th –8th grade	16	11.9	20	15
Completed 8th –10th grade	27	20.1	25	18.6
Above 10th grade	76	56.7	64	47.8
Occupation				
No work	31	23.1	31	23.1
Student	36	26.9	9	6.7
Daily laborer	2	1.5	13	9.7
Government worker	24	17.9	24	17.9
Private worker	31	23.1	42	31.3
Businessman	10	7.5	15	11.2
Number of rooms in residence				
1	61	45.5	37	27.6
2–3	57	42.5	63	47
4–5	11	8.2	34	25.4
6–9	5	3.7	0	0
Family size				
1–3	57	42.5	49	36.6
4–6	57	42.5	70	52.2
7–11	20	15	15	11.2

Table 2 Tuberculosis disease-related conditions in each category (case/control) in Addis Ababa, 2011

Characteristics	Cases (n = 134)		Controls (n = 134)	
	Number	Percentage	Number	Percentage
No. of pulmonary TB episodes				
One	29	21.6	119	88.8
Two	66	49.3	14	10.5
Three	30	22.4	0	0
Four or more	9	6.7	1	0.75
HIV status				
Negative	116	86.6	94	70.2
Positive	18	13.4	40	29.9
Ever lived with MDR-TB patient				
No	122	91.0	134	100
Yes	12	9.0	0	0
Site of TB infection during first episode				
Pulmonary	130	97	90	67.2
Extrapulmonary	4	3.0	44	32.8
Smear-positive during first anti-TB treatment				
No	11	8.2	82	61.2
Yes	123	91.8	52	38.8
Ever counseled by health worker				
No	44	32.8	1	0.75
Yes	90	67.2	133	99.25
Presence of other disease				
No	111	82.8	115	85.5
Yes	23	17.2	19	14.2
Ever smoked cigarettes				
No	125	93.3	115	85.8
Yes	9	6.7	19	14.2
Perception about the care provided				
Very good	5	3.7	87	64.9
Good	13	9.7	36	26.9
Satisfactory	77	55.5	8	6.0
Poor	39	29.1	3	2.2
Weight measured by health worker before starting treatment				
No	3	2.2	0	0
Yes	120	89.6	134	100
Doesn't remember	11	8.2	0	0

were diagnosed as MDR-TB, and 9 (6.7%) of the cases had had four or more episodes of TB. In the control group, only 14 (10.4%) had undergone two rounds of TB treatment, and one case had suffered four or more episodes of TB. HIV positivity was significantly lower in the MDR-TB cases than in the control group (13.4% versus 29.9%; p-value <0.001). The quality of care provided by health care providers was perceived as poor by 39 (29.1%) of MDR-TB cases and by 3 (2.2%) of the controls.

Treatment-related conditions

Conditions related to anti-TB treatment are summarized in Table 3. During first-line anti-TB treatment, drug side

Table 3 First-line tuberculosis treatment-related conditions in MDR-TB cases and their controls in Addis Ababa, 2011

Characteristics	Cases		Controls	
	(n = 134)		(n = 134)	
	Number	Percentage	Number	Percentage
Encountered drug side effect				
No	67	50.0	109	81.3
Yes	67	50.0	25	18.7
Suffered the most common drug side effect (vomiting)				
No	85	63.4	124	92.5
Yes	49	36.6	10	7.5
Duration of first-time TB treatment				
2–4 months	3	2.2%	1	0.75%
5–7 months	22	16.4%	2	1.5%
8 months	103	76.9%	128	95.5
9–13 months	6	4.5%	3	2.2%
Directly observed by health worker while taking anti-TB				
No	65	48.5	7	5.2
Yes	69	51.5	127	94.8
If yes, how many months				
1–2 weeks	11	15.95	0	0
One month	32	46.4	1	0.8
Two months	26	37.7	126	99.2
Reason for interruption for at least a day				
Side effects	34	36.6	3	30.0
Forgot to take it	23	24.7	7	70.0
Symptoms were gone and felt good	29	31.2	0	0
Shortage of drug	7	7.5	0	0
Ever interrupted anti-TB for at least a day				
No	41	30.6	124	92.5
Yes	93	69.4	10	7.5
Took the medication at a regular time				
No	81	60.5	25	18.7
Yes	53	39.5	109	81.3
Outcome of first anti-TB treatment				
Treatment success	64	47.7	132	98.5
Defaulted	16	11.9	2	1.5
Treatment failure	54	40.3	0	0
Drug regimen (category) for the second time				
Category II	101	94.4	3	23.1
Category I	6	5.6	10	76.9

effects were encountered in 60 (50%) of the MDR-TB cases and 25 (18.7%) of the controls. Among the current MDR-TB patients, their first-line anti-TB treatment was directly observed by health workers in only 69 cases (51.5%), while 127 (94.8%) of the controls were treated in accordance with the strict DOTS guidelines of the country. First-line anti-TB treatment was interrupted for at least a day in 93 (69.4%) of the MDR-TB cases, and in only 10 (7.5%) of the controls. Out of the 16 MDR-TB patients who were poor adherers of treatment in category I treatment 10(62.5%) were male. Reasons for interruption among MDR-TB cases were drug side effects in 34 cases (36.6%), followed by improved/disappeared symptoms and the perception that TB was cured 29 cases (31.2%), and forgetfulness about taking the medicine 23 cases (24.7%). Duration of first-line anti-TB treatment was exactly 8 months in 103 (76.9%) of the MDR-TB cases and 128 (95.5%) of the controls. Among the MDR-TB cases, the outcomes of the first course of anti-TB treatment was reported as treatment success in 64 cases (47.7%), defaulter in 16 cases (11.9%), and treatment failure in 54 cases (40.3%). In the controls, 132 (98.5%) were declared treatment successes. Of the MDR-TB cases, 107 (79.9%), and 13 (9.7%) of the controls, were treated at least twice with first-line anti-TB treatment. Of the 107 current MDR-TB cases, 101 (94.4%) were also treated with the Category II regimen, while only 3 (23.1%) of the 13 controls were treated with the Category II regimen.

Results from logistic regression analysis

After adjusting for possible confounding factors (Table 4), the study found that MDR-TB development is significantly associated with two or more episodes of TB illness (AOR = 31.8; 95% CI; 8.7–115.5), interruption of first-line anti-TB treatment for at least a day (AOR = 13.1; 95% CI; 3.0–56.6), education above 10th grade (AOR = 3.7; 95% CI; 1.1–12.1), and male sex (AOR = 2.7; 95% CI; 1.1–6.5).

The number of rooms in the patient's household also showed a significant association with MDR-TB (AOR = 10.1; 95% CI; 2.0–49.4). Pulmonary TB (AOR = 10.9; 95% CI; 2.8–41.9), drug side effects during first-line treatment (AOR = 4.5; 95% CI; 1.9–10.5), lack of direct observation by health workers (AOR = 11.7; 95% CI; 4.0–34.3), and less than 7 months of first-line anti-TB treatment (AOR = 14.8 95% CI; 2.3–96.4) were also significantly associated with MDR-TB development. Fischer's exact test showed that being treated with the Category II regimen was associated with MDR-TB development (P = 0.000).

HIV status, history of smoking, experience of drug shortages, and family size were not significantly associated with MDR-TB development.

Discussion

A case control study with equal number of cases and controls was conducted by recruiting a total of 268 study participants to determine factors associated with developing

Table 4 Determinants of multidrug-resistant tuberculosis from logistic regression model

Characteristics	Case Number	Control Number	Crude OR (95% CI)	Adjusted OR (95% CI)
Individually adjusted for the remaining variables				
Number of pulmonary TB episodes				
One	29	119	1	1
Two or more	105	15	28.7 (14.6-56.5)	31.8 (8.7-115.5)
Ever interrupted anti-TB for at least a day				
No	41	124	1	1
Yes	93	10	28.1 (13.4-58.1)	13.1 (3.0-56.6)
Duration of first course of TB treatment (months)				
2–7	25	3	10.0 (2.9-34.1)	14.8 (2.3-96.4)
≥8	109	131	1	1
Adjusted for all variables				
Age when taking first-line anti-TB for the first time (years)				
46–72	9	17	1	1
26–45	40	70	1.1 (0.4-2.6)	1.4 (0.3-5.8)
5–25	85	47	3.4 (1.4-8.3)	4.6 (1.1-20.5)
Marital status				
Single	85	60	2.5 (1.4-4.3)	1.2 (0.5-3.3)
Married	32	56	1	1
Divorced/ separated	17	1	1.7 (0.75-3.7)	3.1 (0.7-13.2)
Educational status				
Up to fourth grade	15	24	1	1
Completed 5th–8th grade	16	20	1.3 (0.5-3.2)	1.2 (0.3-5.1)
Completed 8th–10th grade	27	25	1.7 (0.7- 4.0)	1.4 (0.4-5.1)
Above 10th grade	76	64	1.9 (0.9-3.9)	3.7 (1.1-12.1)
Sex				
Female	53	70	1	1
Male	81	64	1.7 (1.0-2.7)	2.7 (1.1-6.5)
Number of rooms in residence				
4–9	16	34	1	1
2–3	57	63	1.9 (1.0-3.9)	3.3 (1.0-10.9)
1	61	37	3.5 (1.7-7.2)	10.1 (2.0-49.4)
Number of rooms in residence				
4–9	16	34	1	1
2–3	57	63	1.9 (1.0-3.9)	3.3 (1.0-10.9)
1	61	37	3.5 (1.7-7.2)	10.1 (2.0-49.4)
Family size				
1–3	57	49	1	1
4–6	57	70	0.7 (0.4-1.2)	1.6 (0.5-5.0)
7–11	20	15	1.2 (0.5-2.5)	2.9 (0.7-13.0)
HIV status				
Negative	116	94	2.7 (1.5-5.1)	2.8 (0.9-8.5)
Positive	18	40	1	1
Site of TB infection during first episode				
Extrapulmonary	4	44	1	1
Pulmonary	130	90	15.9 (5.5-45.8)	10.9 (2.8-41.9)
Encountered drug side effect				
No	67	109	1	1
Yes	67	25	4.4 (2.5-7.6)	4.5 (1.9-10.5)
Encountered shortage of drug				
No	106	124	1	1
Yes	28	10	3.3 (1.5-7.1)	2.7 (0.8-9.5)
Directly observed by health worker while taking anti-TB				
Yes	69	127	1	1
No	65	7	17.1 (7.4-39.3)	11.7 (4.0-34.3)
Took the medication at a regular time				
No	69	127	1	1
Yes	65	7	17.1 (7.4-39.3)	11.7 (4.0-34.3)
Ever smoked cigarettes				
No	125	115	1	1
Yes	9	19	0.4 (0.19-1.0)	0.4 (0.1-1.8)

MDR-TB after taking first line anti-TB treatment. Factors which were associated with MDR-TB: the first site of TB infection being pulmonary, encountering drug side effects during the first course of treatment, having more than one TB episode, undergoing the Category II regimen, and taking anti-TB treatment for less than 7 months.

The study also found that being male was a risk factor for MDR-TB development. A study in Nigeria showed that being male was a risk factor for defaulting from anti-TB medication [14]. Similarly, this study showed that among MDR-TB cases who were defaulters in their first-line TB treatment, 62.5% were males. The association between being male and having MDR-TB could be due to the fact that males have a higher tendency not to adhere to anti-TB treatment than females, thus increasing their risk of developing MDR-TB. Another study showed that individuals who do not take anti-TB medication regularly have increased risk for MDR-TB [15]. Our study also showed that individuals who did not take first-line anti-TB drugs regularly had increased risk for development of MDR-TB.

Evidence from a previous study has shown that poor treatment adherence was a risk factor for MDR-TB [8]. The current study also showed that individuals who took first-line anti-TB treatment for duration of 2 to 7 months

had increased risk of developing MDR-TB. In Ethiopia, the previous guideline for first-line anti-TB treatment was 8 months' duration, but the standard has been changed to 6 months. TB therapy requires more than 90% adherence to facilitate cure [16], and 2 to 7 months (25%–87.5% of the prescribed duration) is less than the required duration to result in cure.

Additionally, individuals who were not under strict DOTS per national guidelines during their first anti-TB treatment had an 11.7 times increased risk for MDR-TB. An analysis that used empirical data to determine the impact of the expansion of the DOTS strategy on TB case finding and treatment success found that countries with full DOTS coverage had at least an 18% increase in the treatment success rate [17]. An individual who is supervised by a health worker is more likely to take the appropriate dose of medicine and less likely to miss a treatment. Furthermore, individuals who come for DOTS have frequent contact with health workers and thus have increased opportunities to get advice and counseling, which might help them to adhere to medication protocol.

As expected, individuals who encountered drug side effects during the first course of TB treatment had a 4.5 times increased risk of developing MDR-TB. Studies done in three districts of Arsi Zone, Ethiopia, found that anti-TB drug side effects were significantly associated with a high rate of defaulting [18]. When patients develop side effects, they tend to stop treatment, which favors the development of MDR-TB. If the DOTS strategy of the nation were followed in all cases, there would be a chance to counsel patients and even treat adverse drug reactions before treatment interruption. In our study, the first-line anti-TB treatment of 48.5% of the MDR-TB cases was not directly observed. A systematic review of 29 published reports on risk factors associated with MDR-TB in Europe revealed that previous treatment was the strongest determinant of MDR-TB and that the pooled risk of MDR-TB was 10.23 times higher in previously treated than in never-treated cases [19]. A study in Uganda also showed that multiple TB episodes and treatment failure were significantly associated with MDR-TB [20]. Similarly, in Ethiopia, according to a nationwide anti-TB drug resistance survey conducted in 2005, 1.6% of newly diagnosed TB cases were infected with MDR-TB, while 11.8% of the MDR-TB cases were previously treated TB cases [10].

One can see how MDR-TB is prevalent in individuals who have a history of treatment compared to new patients. Similarly, the current study showed that having more than one TB episode also increased risk for MDR-TB. This may be related to the previous treatment outcome, default, treatment failure, or relapse, or the patient may have had MDR-TB initially.

Having pulmonary TB during first anti-TB treatment was associated with increased risk for MDR-TB. This may also be associated with the fact that smear-positive pulmonary TB individuals have a high bacterial load and may not respond to the treatment within a short period of time, as do those with a low bacterial load [21]. For this reason, smear-positive pulmonary TB patients might be more prone to develop MDR-TB. The other explanation might be associated with diagnostic difficulties. In case of extra pulmonary MDR- TB the bacterial load is lower and difficult for definite diagnosis comparing to pulmonary MDR-TB. Limited capacity of the existing laboratory facilities especially for the diagnosis of extra pulmonary MDR-TB might explain the association of being Pulmonary TB and having MDR-TB.

This study showed that individuals who were treated by the Category II regimen had increased risk for MDR-TB. More than one explanation may be given for the association of Category II treatment and MDR-TB. These individuals might have had a previous TB treatment history and registered for the treatment as treatment failures, defaulters, or relapse cases, or they might have already had MDR-TB at the initiation of the Category II regimen. Another explanation is that adding one drug in the failing regimen could change susceptible strains and lead to multidrug resistance. "Michael Iseman, the US-based MDR-TB specialist, had 10 commandments for the physicians not to change fully drug susceptible organisms to MDR-TB; the first one was never to add a single drug to a failing regimen and the other nine were to repeat the first commandment to make sure it was well understood" [8]. WHO recommends that DST should be done for all previously treated patients before they are treated with the Category II drug regimen, and in conditions where DST is not available, the Category II regimen can be used for relapse, default, and treatment failure for low- or medium-MDR-TB-burden countries [9]. A cross-sectional study in South Africa showed that retreatment patients had increased risk for any drug resistance and MDR-TB [22]. Having a DST before embarking on the Category II regimen is very important. In Ethiopia, because of low laboratory capacity, performing DST for all previously treated patients is difficult even though the country is one of the high-MDR-TB- burden countries. An individual's treatment may fail because they have already had MDR-TB or because drug resistance was caused by the retreatment regimen [23]. This is because the patient has already taken all the drugs in the Category II regimen in the previous treatment, except streptomycin, which is the oldest drug.

In the current study, HIV status had no significant association with MDR-TB. A study in Thailand showed also that HIV status was not significantly associated with MDR-TB [23]. In France, being HIV positive was

associated with primary MDR-TB but it was not associated with secondary MDR-TB [24]. A cross-sectional study in South Africa showed that in retreated patients, HIV had no significant association with MDR-TB [25]. The study participants in the current study were patients who had a history of first-line anti-TB treatment. It is possible that the result could have been different if all study participants were primary MDR-TB cases rather than MDR-TB cases who had a history of previous treatment. A study in Ukraine showed that HIV-positive individuals had a 50% higher risk of developing MDR-TB at their first TB infection [26]. This is because being HIV positive is one risk factor for drug-susceptible TB, which is related to immune system suppression. Being HIV positive might carry the same risk of infection with MDR-TB but may not contribute to the change of a drug-susceptible strain of TB to MDR-TB.

The strengths of the current study are that study participants in the control group finished first-line anti-TB treatment two years before the study period, which reduced the chance of relapse. They were selected from the five health facilities in Addis Ababa that reported the most MDR-TB cases to St. Peter Hospital, so that cases and controls would have a better likelihood of coming from similar backgrounds and be most likely to receive the same service. Regarding the case group, all cases that fulfilled the eligibility criteria that were available during the study period and willing to respond were included in the study. This was helpful to decrease sampling error.

The current study is not without limitations, however. Recall bias could be considered one potential challenge, since some of the information was based on the recall of the study participants. Furthermore, it was not clear whether all cases had MDR-TB before or after undergoing first-line TB treatment, since DST was not done before they took first-line TB treatment or Category II regimens.

Conclusions

Non-adherence to the first line anti-TB treatment was significantly associated with MDR-TB. Taking medication without interruption, taking medication regularly, and having supervision (DOTS) had a protective effect against MDR-TB. Having more than one pulmonary TB episode had a significant association with MDR-TB. Individuals who were treated with the Category II regimen were also found to have an increased risk for MDR-TB. HIV status was not significantly associated with MDR-TB among individuals who had been previously treated with first-line anti-TB drugs. Hence, strengthening DOTS programs to enhance patient adherence to anti-TB treatment and giving special attention to individuals at high risk for MDR-TB and prioritizing them for DST are recommended.

Abbreviations

AFB: Acid fast bacilli; AOR: Adjusted odds ratio; CI: Confidence interval; DOTS: Directly observed treatment short course; DST: Drug sensitivity test; EHNRI: Ethiopia health nutrition and research institute; FMOH: Federal Ministry of Health; HBC: High burden country; HIV: Human immune deficiency virus; IRB: Institutional Ethical Review Board; MDR-TB: Multi drug resistant tuberculosis; OR: Odds ratio; PI: Principal investigator; TB: Tuberculosis; WHO: World Health Organization; XDR-TB: Extensive drug resistant tuberculosis.

Competing interests

All authors declare that they have no competing interests.

Authors' contributions

SH conceived the idea of the study, prepared the study proposal, collected data in the field, performed the data analysis, and drafted the manuscript. GA and GM assisted with the preparation of the proposal and the interpretation of data, participated in data analysis, and critically reviewed the manuscript. BG participated in the proposal preparation, interpretation of data, and critical review of the manuscript. AM participated in the interpretation of data and critically reviewed the manuscript. MM and PS critically reviewed the proposal and the manuscript. All authors read and approved the final manuscript. All authors participated in critical appraisal and revision of the manuscript.

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Determinant Factors Associated with Occurrence of Tuberculosis among Adult People Living with HIV after Antiretroviral Treatment Initiation in Addis Ababa, Ethiopia: A Case Control Study

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Abstract

Introduction: Tuberculosis (TB) is a leading morbidity and mortality, and the first presenting sign in majority of people living with Human Immune deficiency Virus (PLWH). Determinants of active TB among HIV patients on anti retroviral treatment (ART) are not well described in resource limited settings. The aim of this study was to assess determinant factors for the occurrence of TB among people living with HIV after ART initiation in public hospitals and health centers in Addis Ababa, Ethiopia.

Methods and Findings: A case control study was conducted from December 2011 to February 2012 in 2 public hospitals and 13 health centers in Addis Ababa. The study population consisted of 204 cases and 409 controls. Cases were adult people living with HIV who developed TB after ART initiation and controls were adult people living with HIV who did not develop TB after ART initiation. An interviewer administered structured questionnaire was used to collect information. - After adjustment for potential confounders, presence of isoniazid prophylaxis (adjusted odd ratio [AOR] 0.35, 95% confidence interval [CI] 0.125, 0.69) and cotrimoxazole prophylaxis (AOR = 0.19; 95% CI: 0.06, 0.62) had protective benefit against risk of TB. In contrary, bedridden (AOR = 9.36; 95% CI: 3.39, 25.85), having World Health Organization (WHO) clinical stage III/IV (AOR = 3.40; 95% CI: 1.69, 6.87) and hemoglobin level $<$10 mg/dl (AOR = 7.43; 95% CI; 3.04, 18.31) at enrollment to ART care were predictors for increased risk of tuberculosis in PLWH after ART initiation.

Conclusion: Increasing coverage of isoniazid preventive therapy and cotrimoxazole preventive therapy reduced risk of TB among HIV patients who started treatment. All PLWH should be screened for TB, but for patients who have advanced disease condition (WHO clinical stage III/IV, being bedridden and having hemoglobin level $<$10 mg/dl) intensified screening is highly recommended during treatment follow up.

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Introduction

In high HIV prevalence population, tuberculosis (TB) is a leading cause of morbidity and mortality, and the first presenting sign in the majority of acquired immune deficiency syndrome (AIDS) patients [1,2]. It is also the most common presenting illness among people living with HIV, including those who are taking antiretroviral treatment (ART) [3–5]. Despite major reductions with ART, however, risk of TB remains high in Africa [6].

According to the 2012 World Health Organization (WHO) global TB control report, Ethiopia ranks 8th among the 22 high-burden countries in the world and the prevalence rate of TB including HIV positive TB (HIV+TB) is 237 per 1000,000 population with incidence rate of 258/100000 in 2011. There were 8% of HIV+TB patients in the country. The incidence rate of HIV+TB patients is 45/100000 [7] and number of TB case is more likely to increase in the country as HIV/AIDS epidemic expands [8].

The life time risk of developing active TB in HIV-negative individuals is approximately 10%, but the annual risk among HIV-infected patients is ~10%, while the lifetime risk approaches 50% among them [9]. It is estimated that about one-third of people with HIV are also infected with TB [1]. Even though ART is known to decrease incidence of TB, still studies have reported TB incidence from HIV patients on ART [10–15].

In developing countries incidence of TB occurrence has been associated with factors like socio-economic [16–21], lifestyle/habits [17,21,22], clinical [16,23–27], laboratory [10,16,19,28,29] and other co-morbidities, example, diabetes [30]. Many patients either have a history of TB when they start ART, or they develop

TB while receiving ART in the developing world [6]. It has not been well delineated what factors influence the development of TB in patients on ART [23]. In sub-Saharan Africa including Ethiopia, the incidence of tuberculosis in adults receiving highly active antiretroviral therapy (HAART) is higher than in HIV-negative adults [3]. Studies on risk factors of TB were done in the general population but determinants of active TB among HIV patients are not well described in resource limited settings. There are no enough studies in Ethiopia on factors associated with development of TB among HIV infected patients who started ART. This study assessed the determinant factors for the occurrence of TB in people living with HIV (PLWHIV) who were already enrolled on ART in public hospitals and health centers, Addis Ababa.

Methods

From December 2011 to February 2012 this case control study was conducted in two hospitals and thirteen health centers in Addis Ababa, the capital city of Ethiopia and seat of African Union & Economic Commission for Africa.

Cases were defined as adult people living with HIV who developed TB after ART initiation and on anti TB treatment in the last 6 months before data collection and controls were adults living with HIV who did not develop TB after ART initiation. Diagnosis of TB in HIV-positive patients was made based on the national TB guideline [31].

Smear positive pulmonary tuberculosis (PTB+) diagnosed if one sputum smear examination positive for Acid Fast Bacilli (AFB) by direct microscopy, **and** laboratory confirmation of HIV infection. And **smear negative pulmonary tuberculosis (PTB−)** diagnosed if at least two sputum specimens negative for AFB and radio graphical abnormalities were consistent with active tuberculosis and laboratory confirmation of HIV infection and decision by a clinician to treat with a full course of anti tuberculosis chemotherapy. **Extra-pulmonary tuberculosis** diagnosed if one specimen from an extra-pulmonary site culture-positive for *mycobacterium tuberculosis* or smear-positive for AFB **or** histological or strong clinical evidence consistent with active extra-pulmonary tuberculosis **and** laboratory confirmation of HIV infection **or** strong clinical evidence of HIV infection **and** decision by a clinician to treat with a full course of anti tuberculosis chemotherapy

People living with HIV who were ≥18 years of age and started ART treatment and have follow up at the study sites were included in this study. People lining with HIV who presented with TB before commencing ART, taking TB therapy at the time of HAART initiation, not on ART or discontinued, and severely ill were excluded.

Sample size determination

The sample size was calculated using Epi Info version 3.5.1 software (Center for Disease Control and Prevention, Atlanta, 2004) using the following parameters: proportion of CD4<50 cells/μl of 31.8% among the controls and 43.9% among cases [32], 5% significance level, power of 80%, a case to control ratio of 1:2 and by using the two proportion formula. The calculated sample size was 186 for cases and 372 for controls, adding 10% for none response, the resulting minimum sample size was 613 (204 cases and 409 controls). Sample size was calculated for exposure status in different variables of the most significant predictors of TB. First the sample size was calculated for exposure status in different variables; body mass index (BMI<18 kg/m^2), CD4<50 cell/μl, and low Hgb level. We took the largest sample among these most significant predictors of TB in most literatures that is CD4 cell count less than 50 cell/μl as exposure variable.

Sampling Technique/Procedure

First, the governmental hospitals and health centers were assessed whether they have adequate cases or not. Two hospitals and thirteen health centers were found to be eligible and included in the study purposely to get adequate number of cases. Identification of cases and controls was done by the principal investigator through the help of the ART and TB registries. All TB–HIV patients on ART who were on anti TB treatment (cases) and fulfilled inclusion criteria were included in the study for their relative small number. Since controls were adequate enough to be sampled, they were selected by simple random sampling method. For those controls that fulfill inclusion criteria, unique identification numbers were given in increasing order by using the registries. Then simple random sampling technique was employed to select samples from each facility. Controls were allocated and selected from each facility based on the number of cases available in each facility with the control to case ratio of 2:1. I.e. for each case two controls.

Data Collection and analysis

The data were collected by trained nurses using structured questionnaire, which was translated into Amharic from English, back translated and pre-tested for consistency. The data were collected from two sources: the primary data collected by face to face interview of patients to asses: Socio demographical variables, (age, sex, religion, ethnicity, marital status, employment and educational status), use of substances such as smoking, alcohol and Chat/Khat, medical history like presence of asthma and history of diabetes mellitus, contact history with a TB patient in the family, living conditions (e.g. persons per household (crowding), availability of separate kitchen in the house hold, having latrine in the compound). And to supplement clinical and laboratory information at the ART initiation variables like (CD4 cell count (cells/μL), hemoglobin level mg/dl, WHO clinical stage, functional status, opportunistic infection, chemoprophylaxis) extracted from ART card and log books.

Data were entered and cleaned using Epi-info version 3.5.1 and exported to SPSS software version 16 for analysis. Frequencies and proportions were used to describe the study population in relation to relevant variables. Bivariate analysis was performed to examine the effect of each variable of interest on the risk of TB. Crude odds ratios (COR) and their 95% confidence intervals (CIs) were estimated using binary logistic regression, with TB as an outcome. To identify confounding factors and to measure the independent effects of each exposure variable on occurrence of tuberculosis, a multivariate logistic regression model was used with the variables having a p-value <0.05 in the bivariate analysis. To decide whether the model adequately describes the data, we used the Hosmer-Lemeshow test which indicates a poor fit if the significance value (p) is less than 0.05 and good fit greater than 0.05. Here, in this study the model adequately fits the data since p-value is 0.78.

Ethical issues

Ethical clearance was obtained from the Institutional Review Board (IRB) of the Addis Ababa University, College of Health science, School of Public Health and from Addis Ababa City Health Bureau Ethics Review committee. Since there were illiterate study participants, the data collectors inform each respondent and confirmed the willingness of the participants by signing on the informed consent sheet. So that consent was

obtained from each study participants and confidentiality assured for all the information provided. Moreover, personal identifiers were not included on questionnaire.

Results

Socio-demographic, clinical and immunological characteristics of study participants

Of 613 participants selected, 593 study subjects responded (196 (33%) cases and 397(67%) controls) with over all response rates of 96.7% (96.1% for cases and 97.1% for controls).

The mean and inter quartile range (IQR) for the age of cases were 36.7 and 29–42.75 years, respectively. The corresponding values for controls were 35.7 and 30–40 years. More proportions of case and control patients were in the age group of 30–39; 37.2% and 45.6% respectively. High proportions of women were repoted in both groups; 56.6% (111) in cases and 69.3% (275) in controls respectively. More than three fourth of the patients have completed primary school and above; 83.2% in cases and 80.9% in controls. The majority of subjects; 60.2% in cases and 59.9% in controls were single and widowed/divorced.

Majority of cases; 78.4% (152) were in WHO clinical stage III or IV. In contrary, 55.5% (213) control groups were in WHO clinical stage I or II. During ART initiation 85% of cases and 64.9% of controls did not use INH preventive therapy. Of the total 183 patients in cases; three fourth, 73.2% of patients had CD4+ cell count less than 200 cells/μl. But half, 53.6% of patients in controls had CD4+ cell count less than 200 cells/μl. Among cases; 39% of them had Hgb level less than 10 mg/dl. In contrary, 7.2% of controls had Hgb level less than 10 mg/dl (**Table 1**).

Clinical presentation of Tuberculosis in HIV positive persons after ART initiation

Half, 50.5% (99) of the TB patients presented with smear negative pulmonary TB followed by extra pulmonary TB, 31.1% (61) and 18.4% (36) patients had smear positive pulmonary TB.

Bivariate analysis of factors associated with TB

The bivariate analysis showed that higher proportion of male patients (COR = 1.73; 95% CI: 1.23, 2.46) develop TB compared to female patients. The divorced/widowed (COR = 0.560; 95% CI: 0.36, 0.87) patients were less likely to develop TB compared with unmarried (single) individuals. But educational status and occupation were not associated with occurrence of Tuberculosis (**Table 2**).

The cases are more likely to be smoker (COR = 3.34; 95% CI: 2.087, 5.35), alcohol drinker (COR = 2.39; 95% CI: 1.63, 3.52) as well as chat chewer (COR = 2.31; 95% CI: 1.57, 3.40). But Tuberculosis is not associated with diabetes (COR = 1.893; 95% CI: 0.54, 6.62) and history of asthma (COR = 1.3030; 95% CI: 0.59, 2.87). Patients who lived in other place for at least 6 months were about 1.7 times more likely to develop TB after ART initiation (p = 0.017). In addition, controls were more likely to have separate kitchen (p = 0.032) and latrine (p = 0.02). Using gas/kerosene as a source of energy in house hold associated with increased risk of TB (COR = 2.5; 95% CI: 1.74, 3.61). Those who lived in households having a size of 6–10 members were more likely to develop TB compared with the number of persons in the household between 1 and 5 (COR = 1.914; 95% CI: 1.23, 2.99). Similarly, the number of adults in the household between 6 and 10 were 1.89 times more likely to develop TB than adults in the household between 1 and 5 ($P = 0.043$). But, previous family history of TB, history of imprisoned, living in his/her own or family's house and house floor made of cement or mud did not show significant difference between cases and controls (**Table 3**).

Other important predictors for the TB occurrence were base line clinical variables. TB patients are more likely to have baseline WHO clinical stage III or IV (COR = 4.51; 95% CI: 3.032, 6.70). Those study subjects with INH prophylaxis (COR = 0.32; 95% CI: 0.21, 0.52) and cotrimoxazole prophylaxis (COR = 0.27; 95% CI: 0.14, 0.53) were less likely to develop TB. Individuals with hemoglobin level <10 mg/dl were more likely to have TB than individuals with hemoglobin level ≥ 12.5 mg/dl (COR = 10.5; 95% CI: 6.26, 17.68). Patients who were bedridden (COR = 8.87; 95% CI: 4.91, 16.05) and ambulatory (COR = 17.7; 95% CI: 9.98, 31.39) by their functional status were at increased risk of developing TB compared to working status. Similarly, patients whose CD4 cell count ≤ 50 cell/μL were more likely to develop TB compared to patients who had ≥ 350 cell/μL cd4 cell count (COR = 5.47; 95% CI: 2.56, 11.97) (**Table 4**).

Multivariate analysis: Factors independently associated with active TB

To identify independent predictors of developing tuberculosis, a multivariate logistic regression model was fitted with the variables having a p-value <0.05 in the bivariate analysis. So, some variables remained independent predictors for the occurrence of TB after controlling for the other factors. From these factors, being widowed or divorced were at lower risk of TB compared to single individuals (AOR = 0.36; 95% CI: 0.16, 0.82). Patients who had separate kitchen were less likely to have TB (AOR = 0.5; 95% CI: 0.26, 0.96; $P<0.038$). Presence of INH prophylaxis (AOR = 0.35; 95% CI: 0.125, 0.69; P = 0.005) and cotrimoxazole prophylaxis (AOR = 0.19; 95% CI: 0.06, 0.62) had an independent protective benefit against tuberculosis. Study subjects who were bedridden (AOR = 9.36; 95% CI: 3.39, 25.85) and ambulatory (AOR = 19.4; 95% CI: 7.44, 50.78) by their functional status were more likely to develop TB compared to working status. Study subjects with baseline WHO clinical stage III or IV had higher risk of developing TB (AOR = 3.4; 95% CI: 1.69, 6.87). As well individuals with hemoglobin level <10 mg/dl are more likely to develop TB than individuals with hemoglobin level ≥ 12.5 mg/dl (AOR = 7.43; 95% CI: 3.04, 18.31). Having opportunistic infection at ART initiation (AOR = 5.22; 95% CI: 2.67, 10.27), the ART regimen initiated at base line and using gas (kerosene) as energy source in the house hold (AOR = 2.67; 95% CI: 1.36, 5.2) were independently associated with increased risk of TB occurrence. But occupational status, smoking, alcohol intake, family history of TB, sex, lived other place, number of people living in the house hold and CD4 cell count lost their statistical significance in the multivariate analysis (**Table 5**).

Discussion

This case-control study has identified several determinant factors for the occurrence of TB among HIV infected people enrolled on ART in Addis Ababa. Housing condition, living standard and isoniazid preventive therapy were risk factors for TB in this setting. Patients who have advanced condition (WHO clinical stage III or IV disease, being bedridden and having hemoglobin level less than 10 mg/dl) were also associated with development of new TB infection.

In this study, among determinant factors, marital status was significantly associated with TB. Divorced or widowed Patients were less likely to develop TB compared to unmarried (single), which is consistent with other reports in West Africa and Ethiopia [17,33]. It might be explained by unmarried (single) persons are

Table 1. Socio-demographic, clinical and immunological characteristics of study participants in Addis Ababa, 2012.

Variables		Cases n(%)	Controls n(%)	Total n (%)
Sex	Male	85(43.4)	122(30.7)	207(34.9)
	Female	111(56.6)	275(69.3)	386(65.1)
Age	≥40	70(35.)	120(30.2)	149(25.1)
	30–39	73(37.2)	181(45.6)	254(42.8)
	18–29	53(27)	96(24.2)	190(32.0)
Education	No education	33 (16.8)	76 (19.1)	109 (18.4)
	Primary	85 (43.4)	159 (40.1)	244 (41.1)
	Secondary	61 (31.1)	122 (30.7)	183 (30.9)
	Tertiary	17 (8.7)	40 (10.1)	57(9.6)
Marital status	Married	78(39.8)	159(40.1)	237(40.0)
	Divorced/Widowed	55(28.1)	145(36.5)	200(33.7)
	Single	63(32.1)	93(23.4)	156(26.3)
WHO Clinical Stage	Stage III or IV	152(78.4)	171(44.5)	323(55.88)
	Stage I or II	42(21.6)	213(55.5)	255(44.12)
INH prophylaxis	Yes	27(15.0)	137(35.1)	164(28.8)
	No	153 (85.0)	253 (64.9)	406 (71.2)
CTX prophylaxis	Yes	164 (87.2)	380 (96.2)	544 (93.8)
	No	24(12.8)	15(3.8)	36(6.2)
Hgb level (mg/dl)	<10	73(39.0)	28(7.2)	101(17.6)
	10–12.49	54(28.9)	118(30.4)	172 (29.9)
	> = 12.5	60(32.1)	242(62.4)	302(52.5)
CD4 cell count (cell/μL)	≤50	26(13.9)	22(5.6)	48(8.3)
	51–200	112(59.9)	187(47.7)	299(51.6)
	201–349	33(17.6)	109(27.8)	142(24.5)
	≥350	16(8.6)	74(18.9)	90(15.5)

WHO = World Health Organization, INH = Isoniazid, CTX = Cotrimoxazole, Hgb = Hemoglobin.
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Table 2. Socio-demographic determinant factors for occurrence of TB among people living with HIV after ART initiation: comparison of TB cases and controls by bivariate analysis in Binary logistic regression, Addis Ababa, 2012.

Variables		Cases n(%)	Controls n(%)	COR	95% CI	p-value
Sex	Male	85(43.4)	122(30.7)	1.73	1.21, 2.46	0.003*
	Female	111(56.6)	275(69.3)	1		
Age	≥40	70(35.)	120(30.2)	1.057	0.68, 1.65	0.81
	30–39	73(37.2)	181(45.6)	0.731	0.47, 1.13	0.15
	18–29	53(27)	96(24.2)	1		
Education	No education	33 (16.8)	76 (19.1)	1.02	0.508,2.06	0.952
	Primary	85 (43.4)	159 (40.1)	1.26	0.673,2.35	0.472
	Secondary	61 (31.1)	122 (30.7)	1.18	0.617,2.24	0.622
	Tertiary	17 (8.7)	40 (10.1)	1		
Marital status	Married	78(39.8)	159(40.1)	0.72	0.48–1.10	0.131
	Divorced/Widowed	55(28.1)	145(36.5)	0.56	0.36, 0.87	0.011*
	Single	63(32.1)	93(23.4)	1		
Occupation	Employed	57(29.1)	125(31.5)	0.892	0.61,1.30	0.55
	Unemployed	139(70.9)	272 (68.5)	1		

*__Significant at α = 0.05__.
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Table 3. Host and environmental determinant factors for occurrence of TB among HIV patients after ART initiation, Addis Ababa, 2012.

Variables		Cases n(%)	Controls n(%)	COR	95% CI	p-value
Chat chewing	Yes	70 (35.7)	77 (19.4)	2.31	1.57, 3.40	<0.0001*
	No	126 (64.3)	320 (80.6)	1		
Smoking	Yes	49(25.0)	36(9.1)	3.34	2.087,5.35	<0.0001*
	No	147 (75.0)	361(90.9)	1		
Alcohol drinking	Yes	71 (36.2)	76 (19.1)	2.39	1.63, 3.52	<0.0001*
	No	125 (63.8)	321 (80.9)	1		
TB history	Yes	63 (32.1)	108 (27.2)	1.08	0.74,1.59	0.68
	No	120 (61.2)	223(56.2)	1		
Asthma	Yes	11(5.6)	16(4.0)	1.303	0.59, 2.87	0.511
	No	181(92.3)	343(86.4)	1		
Diabetes mellitus	Yes	5 (2.6)	5(1.3)	1.893	0.54, 6.62	0.318
	No	187(95.4)	354(89.2)	1		
Family Hx of TB	Yes	33(16.8)	75(18.9)	0.847	0.54, 1.33	0.471
	No	159(81.1)	306(77.1)	1		
Imprisoned	Yes	15(7.7)	39(9.8)	0.761	0.41, 1.42	0.389
	No	181(92.3)	358 (90.2)	1		
Have kitchen	Yes	109(55.6)	257(64.7)	0.682	0.481,0.97	0.032*
	No	87(44.4%)	140(35.3)	1		
Owen house	Yes	52 (26.5)	137 (34.5)	0.685	0.47,1.00	0.05*
	No	144(73.5)	260(65.5)	1		
Latrine	Yes	160(81.6)	352(88.7)	0.568	0.35, 0.94	0.02*
	No	36 (18.4)	45 (11.3)	1		
kerosene as source of energy in HH	Yes	139(70.9)	196(49.4)	2.501	1.74, 3.61	<0.0001*
	No	57(29.1)	201(50.6)	1		
Number of people living in HH	>10	3(1.5)	8(2.0)	0.85	0.22, 3.24	0.81
	6–10	44(22.4)	52(13.1)	1.914	1.23, 2.99	0.004*
	1–5	149(76.0)	337(84.9)	1		
Numbers of room	1–2	153(78.5)	299(75.3)	1.194	0.79, 1.80	0.397
	> = 3	42(21.5)	98(24.7)	1		

***significant at $\alpha = 0.05$.**
Hx = history.
HH = Houshold.
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younger than married persons and have a different lifestyle, especially males, who often migrate to towns in search of a job where they live alone or with friends.

Similarly, low level of education was not associated with TB. But it is not consistent with the study from south west Ethiopia [16]. This could be due to the high prevalence of literates in our study population as it was from the capital of the country.

Smoking was identified as risk factor for the development of TB in clinic-based case-control study in West Africa [17]. But, in a case control study in Gambia, smoking was not associated with active TB [18]. Similarly, in this study smoking was not associated with TB occurrence in multivariate analysis. This could be due to the low prevalence of smoking in our study population. There could also be a social desirability bias whereby smokers denied their smoking status.

In a case control study from West Africa, history of asthma became protective against TB [17]. But, in this study history of asthma was not associated with TB. This is consistent with the case control study in Gambia [18].

Studies demonstrated that contact with TB patients in the family associated with increased occurrence of TB [16–18]. But in this study family history of TB showed some degree of association with TB in bivariate analysis, but it did not have an independent effect on the occurrence TB in multivariate analysis when adjusted for other variables. This could be due to that the influence of TB history in the family as a risk factor for TB would differs by setting and background of HIV burden.

Other independent predictors of tuberculosis were WHO stage III or IV; patients with WHO stage III or IV have higher risk of developing TB than those with WHO stage I or II. It is consistent with other studies done in South Africa and South West Ethiopia [16,23]. This suggests that who had WHO stage III or IV might be immune-compromised and predisposed to TB.

TB patients were 8.87 times more likely to be bedridden at the initiation of ART than working patients. This is consistent with the retrospective cohort study in Ethiopia [33]. High degree of suspicion while administering ART towards patients with this condition should be instituted.

Table 4. Clinical and immunological factors for occurrence of TB among HIV patients after ART initiation: bivariate analysis in Binary logistic regression, Addis Ababa, 2012.

Variables		Cases n(%)	Controls n(%)	COR	95% CI	p-value
WHO clinical stage	Stage III orIV	152(78.4)	171(44.5)	4.51	3.032, 6.70	<0.0001*
	Stage I or II	42(21.6)	213(55.5)	1		
INH prophylaxis	Yes	27(15.0)	137(35.1)	0.33	0.21, 0.52	<0.0001*
	No	153 (85.0)	253 (64.9)	1		
CTX prophylaxis	Yes	164 (87.2)	380 (96.2)	0.27	0.14, 0.53	<0.0001*
	No	24(12.8)	15(3.8)	1		
Functional status	Bed ridden	39(20.9)	20(5.1)	8.87	4.91, 16.05	<0.0001*
	Ambulatory	70(37.4)	18(4.6)	17.7	9.98, 31.39	<0.0001*
	Working	78(41.7)	355(90.3)	1		
Opportunistic infection	Yes	110(59.8)	91(23.6)	4.80	3.29, 7.00	<0.0001*
	No	74(40.2)	294(76.4)	1		
ART Regimen	1b	45 (23.0)	35 (8.8)	3.75	1.96, 7.16	<0.0001*
	1c	33(16.8)	115(29.0)	0.84	0.45, 1.54	0.566
	1d	38(19.4)	49(12.3)	2.26	1.197, 4.26	0.012*
	1e	52(26.5)	109(27.5)	1.39	0.78, 2.48	0.246
	1f	5(2.6)	22(5.5)	0.66	0.23, 1.95	0.454
	1a	23 (11.7)	67 (16.9)	1		
Hgb level (mg/dl)	<10	73(39.0)	28(7.2)	10.5	6.26, 17.68	<0.0001*
	10–12.49	54(28.9)	118(30.4)	1.85	1.20, 2.83	<0.0001
	> = 12.5	60(32.1)	242(62.4)	1		
CD4 count (cell/μL)	≤50	26(13.9)	22(5.6)	5.47	2.56, 11.97	<0.0001*
	51–200	112(59.9)	187(47.7)	2.77	1.54, 4.99	0.001*
	201–349	33(17.6)	109(27.8)	1.400	0.72, 2.73	0.322
	≥350	16(8.6)	74(18.9)	1		

***significant at α = 0.05**.

WHO = World Health Organization, INH = Isoniazid, CTX = Cotrimoxazole, ART = Antiretroviral Therapy, Hgb = Hemoglobin, 1a = Stavudine, lamivudine, neverapine→d4t-3TC-NVP, 1b = Stavudine, lamivudine, efavirenz→d4t-3TC-EFV, 1c = Zidovudine, lamivudine, neverapine→AZT-3TC-NVP,1d = Zidovudine, lamivudine, efavirenz→AZT-3TC-EFV, 1e = TDF, lamivudine, efavirenz→TDF-3TC-EFV, 1f = TDF, lamivudine, neverapine→TDF-3TC-NVP.

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Besides, availability of separate kitchen in the household associated with decreased risk of TB development which is consistent with a study from south west Ethiopia [16]. It might be explained by increased indoor air pollution if there is no separate cooking kitchen in the house. Likewise using gas (kerosene) as energy source in the household associated with TB as it was commonly used cooking fuels in urban areas.

Studies have shown that risk of TB was associated with the number of people living together in the household (over Crowding) [18,19,21]. But, this study did not find the association between TB and number of people in the household. This might be related to high proportions of unmarried persons in the study population resulted in low number of family size in the house hold. The other reason may be due to TB development is a reactivation of an infection acquired years ago due to HIV infection, with no relation to current living and crowding conditions.

In addition, patients having a hemoglobin level of ≤10 mg/dl have 2.4 times higher risk of developing TB than those patients having hemoglobin level ≥12.5 mg/dl, similar to other study findings in south west Ethiopia [16]. This shows that patients having higher hemoglobin level were less likely to develop TB than those with low hemoglobin level. TB and hemoglobin level might be indirectly associated with advanced stage of HIV disease. When HIV positive patients have chronic disease and high viral load, it resulted in immune-suppression and suppression of red blood production in bone marrow. This is also consistent with the previous findings that predict the occurrence of TB which implied that advance disease condition in HIV patients may predict occurrence of Tuberculosis after ART initiation.

Different studies have shown that isoniazed (INH) preventive therapy reduces the risk of TB infection in people living with HIV [24–27]. Similarly, in this study, patients who were on INH preventive therapy were at the lower risk of developing TB. The initiation of cotrimoxazole preventive therapy has also been independent predictor. TB/HIV collaborative actions should give priority high level of coverage to the implementation of these interventions as they have proven effectiveness in improving patients' conditions.

A Study from West Africa showed that ownership of the house by the TB patient's family associated with lower risk for TB [17]. But, this study didn't show statistical difference between those who had house and those who hadn't. This inconsistency might be due to source population difference, as the source population of this study was from the capital of the country.

This study has the following limitations: Case control study design could not set up temporal relationships and can only show associations; it could not proof causations. Recall bias might have also affected the accuracy of information related to substance use

Table 5. Factors independently associated with active tuberculosis among HIV infected patients after ART initiation, Addis Ababa, 2012.

Variables		COR(95% CI)	p-value	AOR(95% CI)	p-value
Kerosene as source of energy in HH	Yes	2.5(1.7, 3.6)	<0.0001	2.67 (1.36, 5.2)	0.004
	No	1		1	
Separate kitchen	Yes	0.68(0.48,0.9)	0.032	0.50 (0.26,0.96)	0.038
	No	1		1	
WHO clinical stage	Stage IIIorIV	4.508 (3.03,6.7)	<0.0001	3.40 (1.69, 6.87)	0.001
	Stage IorII	1		1	
INH preventive therapy	Yes	0.33(0.21,0.20)	<0.0001	0.35 (0.125,0.69)	0.005
	No	1		1	
CTX preventive therapy	Yes	0.27(0.14,0.53)	<0.0001	0.19 (0.06, 0.62)	0.006
	No	1		1	
Functional status	Bed ridden	8.88(4.91,16.05)	<0.0001	9.36(3.39, 25.85)	<0.0001
	Ambulatory	17.8 (10,31.4)	<0.0001	19.44(7.44,50.78)	<0.0001
	Working	1		1	
Opportunistic infection	Yes	4.80(3.29, 7.0)	<0.0001	5.22 (2.67, 10.27)	<0.0001
	No	1		1	
Hgb level	<10	10.52(6.26,17.7)	<0.0001	7.43(3.04, 18.31)	<0.0001
	10–12.49	1.85 (1.2, 2.83)	<0.0001	1.34 (0.65, 2.77)	0.430
	≥12.5	1		1	
Marital status	Married	0.72 (0.48,1.1)	0.131	0.99 (0.48, 2.00)	0.985
	Divorced/widowed	0.56(0.36,0.87)	0.011	0.36 (0.16, 0.82)	0.015
	Single	1		1	

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such as cigarette smoking and alcohol consumption. Lastly, challenges to diagnosis of tuberculosis in HIV patients might result in low sensitivity and specificity of available diagnostic approaches.

Conclusion

Having poor clinical and biochemical status were found to be predicators of occurrence of Tuberculosis. All people living with HIV/AIDS should be screened for TB. But, in the presence of the risk factors mentioned in this paper, intensified screening is highly recommended during follow up of treatment. In addition, increasing coverage of INH and cotrimoxazole preventive therapy is necessary to reduce the overall risk of TB among HIV patients who started ART. Household condition related to kerosene use in household was also associated with outcome of interest.

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Author Contributions

Conceived and designed the experiments: KTK AWY BGB MMA. Performed the experiments: KTK AWY BGB MMA. Analyzed the data: KTK AWY BGB MMA. Contributed reagents/materials/analysis tools: KTK AWY BGB MMA. Wrote the paper: KTK AWY BGB MMA.

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Free tuberculosis diagnosis and treatment are not enough: patient cost evidence from three continents

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SUMMARY

SETTING: The National Tuberculosis Programs of Ghana, Viet Nam and the Dominican Republic.

OBJECTIVE: To assess the direct and indirect costs of tuberculosis (TB) diagnosis and treatment for patients and households.

DESIGN: Each country translated and adapted a structured questionnaire, the Tool to Estimate Patients' Costs. A random sample of new adult patients treated for at least 1 month was interviewed in all three countries.

RESULTS: Across the countries, 27–70% of patients stopped working and experienced reduced income, 5–37% sold property and 17–47% borrowed money due to TB. Hospitalisation costs (US$42–118) and additional food items formed the largest part of direct costs during treatment. Average total patient costs (US$538–1268) were equivalent to approximately 1 year of individual income.

CONCLUSION: We observed similar patterns and challenges of TB-related costs for patients across the three countries. We advocate for global, united action for TB patients to be included under social protection schemes and for national TB programmes to improve equitable access to care.

KEY WORDS: tuberculosis; Dominican Republic; Ghana; Viet Nam

THE CONNECTION between tuberculosis (TB) and poverty is well established.[1] TB patients face a number of barriers in seeking diagnosis and treatment, including financial costs related to charges for health services, transportation, accommodation, nutrition, and lost income, productivity and time.[1–3] These barriers cause delays in seeking health care, resulting in more advanced disease and continued transmission of TB.[4] Direct out-of-pocket costs for public or private services and indirect opportunity costs can trigger a spiral into deeper poverty for TB patients and their families.[5] A number of studies have been published on patient costs in developing countries;[6–17] however, comparisons of study results are difficult due to the different tools employed. To date, comparative studies on patient costs have mainly been conducted in Western countries.[18,19] Our aim was therefore to assess whether similar patterns in cost burden can be found in different settings using the same cost-assessment tool and closely involving the national TB programmes (NTPs).

The main objective of the present study was therefore to evaluate the direct and indirect costs of TB patients on three continents before/during diagnosis and during treatment using the Tool to Estimate Patients' Costs,[20] which has been described elsewhere in detail.[21] We also aimed to identify relevant interventions to reduce patient costs in each country. This article describes the key results of the implementation of the tool in Ghana, Viet Nam and the Dominican Republic, and the resulting recommendations and interventions.

STUDY POPULATION AND METHODS

Setting

All three countries studied follow the World Health Organization (WHO) recommended DOTS strategy

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for TB control. While basic TB diagnostics (sputum smear microscopy) and treatment (first-line TB drugs) are provided free of charge, X-rays and hospitalisation are charged in all countries. With an estimated population of 24 million in 2010, Ghana notified 14 607 TB patients in 2010 and treated 87% of patients notified in 2009 successfully.[22] The Dominican Republic had an estimated population of 10 million in 2010, with 3964 TB patients notified in 2010; 85% of patients notified in 2009 were successfully treated.[22] Compared to the other countries, Viet Nam had the largest population, with 88 million (2010), and the largest number of TB patients (n = 94 867). Viet Nam treated 92% of its TB patients notified in 2009 successfully.[22] Ghana is the poorest country among the three (Human Development Report Index Rank 135), followed by Viet Nam (rank 128) and the Dominican Republic (rank 98).[23]

Methods

Each country adapted and translated the generic questionnaire,[21] based on local circumstances (NTP, economy, culture, language, social values and norms). In Ghana, the questionnaire was translated into English, Twi, Ga, Kassim, Nankam and Frafra. Interviews took place in two purposively selected regions: Eastern, a wealthier region, and Upper Eastern, a more deprived region. Urban and rural areas were included. Of 242 patients registered at all 25 public health facilities in both regions, 159 were interviewed either at the health facility or at home. Due to inclusion of retreatment patients in the interviews and their exclusion from the analysis, complete information was available for 135 patients.

In Viet Nam, the questionnaire was translated into Vietnamese. Three provinces were purposively selected: Hanoi, Quangnam and Binh Duong. In each province, two districts were randomly selected, one urban and one rural. Interviews were conducted at six public sector sites. Of 300 randomly selected patients recorded at selected facilities, all 300 were interviewed. As retreatment patients were included in the interviews but excluded from the analysis, information is available for 258 patients. Due to the sensitive nature of questions on costs and payments, as well as some challenges faced in interviewer training, not all questions were answered by all patients, resulting in fewer total records for some sections.

In the Dominican Republic, the questionnaire was translated into Spanish. Interviews took place at 32 randomly selected facilities in three purposively selected provincial health directorates, Santiago, La Vega and San Cristobal, and three health area directorates, Areas IV, V and VIII. These included urban and rural areas and public and private sector institutions. A total of 150 new patients who visited the selected facilities on the days of the survey were interviewed.

All countries back-translated the questionnaire to ensure accuracy of translation, pre-tested the questionnaire with adjustments made as needed, and received approval from the appropriate ethical review committees. All participants in the studies provided informed consent (written consent in Ghana and the Dominican Republic and oral consent in Viet Nam). All interviews took place with patients on treatment for at least 1 month. Table 1 provides an overview of the methodologies employed in each country. All three countries followed the tool guidelines for calculating costs;[21] indirect costs were calculated as income lost due to TB. For income lost prior to treatment, time off work was multiplied by the reported individual income prior to the onset of TB. For income lost during treatment, time off work was multiplied by the reported individual income since the onset of TB.

RESULTS

The results for all countries are summarised and compared in Tables 2–5. Factors related to local circumstances and health systems differed, such as patient education levels (Table 2), type of facility visited to seek care (Table 3), magnitude of specific costs incurred (Table 4), place of treatment provision, and health insurance coverage (Table 5). The average time to collect drugs, including travel and waiting time, was similar across countries, at about 1 h 20 min (Table 5).

Table 1 Overview of study methodology

	Ghana	Viet Nam	Dominican Republic
Sample population	135	258	150*
Age, years	⩾15	>15	18–65
Type of TB patients	New out-patients	New out-patients	New out-patients*
Treatment regimen	All: 2(RHZE)/4(RH)	2S(RHZ)/6(EH) (n = 245) 2(RHZE)/6(EH) (n = 13)	New (n = 150): 2(RHZE)/4$(RH)_3$†
Robustness of income data	Assessed	Not assessed	Not assessed

*The team in the Dominican Republic also interviewed retreatment out-patients and MDR-TB patients; however, in this article we present data on new patients only. Results of retreatment and MDR-TB patients have been submitted for publication.
†Three times weekly.
TB = tuberculosis; R = rifampicin; H = isoniazid; Z = pyrazinamide; E = ethambutol; S = streptomycin; MDR = multidrug-resistant TB.

Table 2 Characteristics of study population

	Ghana %	Viet Nam %	Dominican Republic %
Type of TB			
Smear-positive	65	58	69
Smear-negative	26	23	11
EPTB	9	19	20
Place of treatment			
Hospital	72	5	56
Primary care unit (health centre)	21	—	43
Community	6	95	1
Private facility (public-private-mix)	1	—	—
Sex			
Male	61	72	55
Female	39	28	45
Age, years			
15–24	10	9	20
25–44	38	36	54
⩾45	47	54	26
Unknown	5	1	—
Education			
Illiterate	38	3	5
Primary school	19	21	80
Secondary school	40	36	1
High school	—	29	—
College/university	30	10	14
Unknown	—	1	—
HIV status			
HIV-positive	22	4	11
HIV-negative	67	57	66
Not known	11	39	23

TB = tuberculosis; EPTB = extra-pulmonary TB; HIV = human immunodeficiency virus.

Factors related to the impact of TB on the welfare of individuals and their households are similar across the three countries. A substantial percentage of TB patients had to stop working due to TB (70% in Ghana, 27% in Viet Nam, 60% in the Dominican Republic) and therefore experienced reduced income (Table 5). In all countries (Table 5), nearly a third of all patients were hospitalised at some stage for TB, incurring enormous (mean) costs (Table 4), equivalent to 67% of monthly individual income in Ghana, 149% in Viet Nam and 34% in the Dominican Republic.* Furthermore, many interviewed patients sold property (37% in Ghana, 5% in Viet Nam, 19% in the Dominican Republic) or borrowed money (47% in Ghana, 17% in Viet Nam, 45% in the Dominican Republic), affecting future welfare and socio-economic status.

The main direct cost items before and during TB diagnosis in all three countries were drugs and tests that were not directly related to TB diagnosis and treatment (Table 4). Hospitalisation costs and additional food items form the largest part of direct costs during treatment.

*Applicable to individuals with a monthly income of >US$166 before onset of disease, see also Table 5.

Table 3 Health care seeking behaviour

	Ghana %	Viet Nam %	Dominican Republic %
Type of facility visited			
Regional hospital	—	35	21
District hospital	43	11	23
Private clinic	1	17	23
Primary care unit	28	12	23
Pharmacy	—	1	1
Others	28*	24	9
Symptoms and delay†			
Cough	88	73	83
Fever/chest pain/cold	53	54	82
Weight loss	51	45	78
Haemoptysis	14	13	23
Night sweats	51	9	46
Mean delay, weeks	7	NA	6

*Mission hospital.
†In presenting to a facility with TB diagnostic services.
NA = not available.

Health care seeking behaviour

In all three countries, more than 40% of patients visited hospitals during care seeking, and a considerable number in Viet Nam and Ghana visited private clinics (Table 3). In Viet Nam and the Dominican Republic, those patients who visited non-public facilities were asked for their reasons for doing so. In Viet Nam, 21% cited distance as the main reason and 29% mentioned waiting times; 46% reported other reasons such as habit or convenience. In the Dominican Republic, 27% cited mistrust of public services as the main reason, while 23% mentioned obtaining private health insurance; 16% mentioned distance as the main reason. Men prolonged health care seeking for the same symptoms by on average one more week than women. In Ghana and the Dominican Republic, the mean patient delay from experiencing symptoms to seeking care at a facility offering TB services was quite similar (7 and 6 weeks, respectively). In Viet Nam, data on this are not available, as the question was not well understood by the interviewers, and non-response was very high.

Comorbidities

In the Dominican Republic, 26% of TB patients had chronic comorbidities other than human immunodeficiency virus (HIV) infection such as diabetes, high blood pressure and arthritis. In Viet Nam, 40 TB patients (15.5%) were also treated for other diseases, of whom 4% were HIV-positive. Patients treated for other diseases in addition to TB incurred a mean additional cost of US$37. In the Dominican Republic, 30% of HIV-positive TB patients were on antiretroviral therapy. HIV-positive TB patients in the Dominican Republic had more direct (+US$2) and indirect (+US$600) costs than HIV-negative patients due to more health facility visits. However, HIV-negative patients had higher costs due to hospitalisation

Table 4 Summary of direct and indirect patient costs, US$*

	Ghana			Viet Nam†			Dominican Republic		
	Mean	Median [IQR]	*n* (%)‡	Mean	Median [IQR]	*n* (%)‡	Mean	Median [IQR]	*n* (%)‡
Subtotal direct pre-/diagnosis costs	31	14 [4–39]	135 (100)	92	8 [10–87]	193 (75)	38	8 [2–19]	149 (99)
Administrative charges	3	0 [0–4]	135 (100)	8	2 [1.8–5.0]	40 (16)	14	0 [0–0.8]	148 (99)
Non-TB tests	1	0 [0–0]	135 (100)	47	9 [4.1–47.1]	67 (26)	6	0 [0–0.4]	127 (85)
X-rays	3	0 [0–3]	135 (100)	11	3 [1.8–5.9]	108 (42)	17	0 [0–5.5]	125 (84)
Non-TB drugs	12	4 [0–14]	135 (100)	26	12 [5.9–26.5]	51 (20)	2	0 [0–4.2]	117 (78)
Transport	4	1 [0–4]	135 (100)	6	2 [1.2–3.5]	130 (50)	2	0.8 [0.6–2.8]	133 (89)
Food	6	1 [0–4]	135 (100)	27	3 [1.2–29.4]	38 (15)	2	0.6 [0–1.4]	114 (77)
Accommodation	2	0 [0–0]	135 (100)	32	29 [8.8–58.8]	3 (1)	0	0 [0–0]	21 (14)
Subtotal direct treatment costs	114	18 [5–52]	135 (100)	73	22 [10–64]	245 (95)	110	12 [5–27]	140 (93)
Hospitalisation	42	16 [0.1–46]	135 (100)	118	44 [28–61]	58 (22)	94	0 [0–1.7]	49 (33)
Food	17	11 [3.3–21.3]	135 (100)	22	12 [8.8–17.6]	218 (84)	21	8 [0–41.6]	25 (57)
Total costs for:									
DOT visits	27	0 [0–25]	135 (100)	18	8 [4–12]	68 (26)	5	4 [2.2–6.7]	130 (87)
Follow-up test visits	1	0 [0–0]	130 (96)	5	3 [2–6]	90 (35)	18	8 [1.2–18.4]	7 (5)
Drug collection visits	27	2 [0–9.4]	135 (100)	1	0.6 [0.6–1.2]	118 (46)	5	4 [2.2–6.9]	128 (85)
Sum of subtotals direct costs	145	32		165	30		148	20	
Subtotal indirect pre-diagnosis costs	381	170 [43–340]	135 (100)	830	721 [478–1029]	51 (20)	1051	666 [275–1186]	112 (75)
Inability to work	381	170 [43–340]	135 (100)	830	721 [478–1029]	51 (20)	1051	666 [275–1186]	112 (75)
Subtotal indirect treatment	12	0 [0]	135 (100)	26	7 [3–12]	165 (64)	69	56 [20–79]	137 (91)
Hospitalisation	8	0 [0–4.4]	135 (100)	92	43 [15–123]	35 (14)	57	48 [21.2–78.2]	118 (79)
Drug collection visits	1	0 [0–0.4]	135 (100)	1	0.4 [0.2–0.8]	141 (55)	2	2 [1–4.6]	125 (84)
DOT visits	3	0 [0–2.9]	135 (100)	3	3 [2–5]	165 (64)	6	3 [1.1–9.0]	117 (78)
Follow-up test visits	0	0	130 (96)	5	2 [1–5]	82 (32)	2	2 [1–4.6]	126 (85)
Sum of subtotals indirect costs	393	170		856	728		1120	722	
Total patient costs (direct + indirect totals)	538	202		1021	758		1268	742	

*Subtotal mean and median numbers were calculated using totals of subcosts from each individual answer; subtotals may therefore differ from the sum of the mean and median individual cost items.
†Some patients only provided (sub)total direct costs without specifying individual cost items.
‡Percentage of interviewed patients who answered this question (response rate).
IQR = interquartile range; TB = tuberculosis; DOT = directly observed treatment.

Table 5 Financial impact of TB on patients

	Ghana %	Viet Nam %	Dominican Republic %
Patients who stopped working due to TB	70	27	60
Patients who stopped working for more than 6 months	51	26	48
Patients hospitalised for TB	33	23	33
Time spent per drug collection visit	1 h 22 min	1 h 13 min	1 h 20 min
Coping costs			
Patients who sold property	37	5	19
Land	2	21	8
Livestock	44	57	3
Other	54	22	89
Patients who took out loans	47	17	45
At interest >10%	8	7	37
Without interest	84	84	8
Monthly individual income, US$			
Before onset of TB	62	79	0 (for 1%)*
After onset of TB	10	59	0 (for 54%)†
% income change due to TB	84	25	100 (for 54%)
Expenditures on health care as % of monthly household income	108	12	360‡
Patients with health insurance	67	48	32
Patients who received reimbursements	4	26	3

*Data available only in ranges: US$0 = 1% of interviewed patients; <US$42 = 8% of interviewed patients; US$42–83 = 14% of interviewed patients; US$83–166 = 27% of interviewed patients; >US$166 = 50% of interviewed patients.
†Data available only in ranges: US$0 = 54% of interviewed patients; <US$42 = 2%; US$42–83 = 6%; US$83–166 = 16%; >US$166 = 26% of interviewed patients.
‡Applies only to the lowest income group (data available only in ranges for income groups, see *).
TB = tuberculosis.

(US$127 vs. US$51). Costs during diagnosis and treatment in Ghana were lower for HIV-positive TB patients than for HIV-negative patients (US$393 vs. US$793).

Impact of TB

In the Dominican Republic, the proportion of patients with zero income increased from 1% to 54% due to TB (Table 5). The lowest income group, with <US$42 per month, spent 360% of its monthly household income on health care. In Ghana, the individual mean monthly income dropped by 79% due to TB. The change was particularly acute for women, whose mean monthly individual income changed from US$57 to US$3 (men US$67 to US$16). Here, TB patients spent 108% of monthly household income on health care. In Viet Nam, household expenditures on food and health care increased by almost 50% due to TB. Expenditures on health care amounted to 12% of monthly household income due to TB. TB patients in Ghana and the Dominican Republic face catastrophic health expenditures, defined by the WHO[24] as ⩾40% of non-subsistence household income. Moreover, the percentage of interviewed TB patients with incomes below the poverty line of US$1 per day increased in all three countries due to TB (Figure).

In all countries, costs were incurred for a treatment supporter or family member (guardian). These were as follows: Ghana, median US$26 direct and US$0 indirect costs; in Viet Nam, median US$85 direct and US$0 indirect costs; and in the Dominican Republic median US$51 direct and US$66 indirect costs.

DISCUSSION

The mean total direct costs as a percentage of total patient costs were higher in Ghana (27%) than in Viet Nam (16%) and the Dominican Republic (12%) due to higher costs for health facility visits for DOTS and drug collection. The increase in patients with incomes <US$1 per day due to TB was high in the Dominican Republic, while it was comparatively low in Viet Nam. The latter confirms the findings of van Doorslaer and O'Donnell that Viet Nam relied heavily on out-of-pocket payments but were 'more successful in limiting their impoverishing effect'.[25] Total patient costs (including direct and indirect costs) in all countries were equivalent to approximately 1 year of individual income (Table 5). The differences in guardian costs across countries are probably related to the fact that health care facilities in Ghana are further from patients' homes, resulting in higher transport costs and more investment of time.

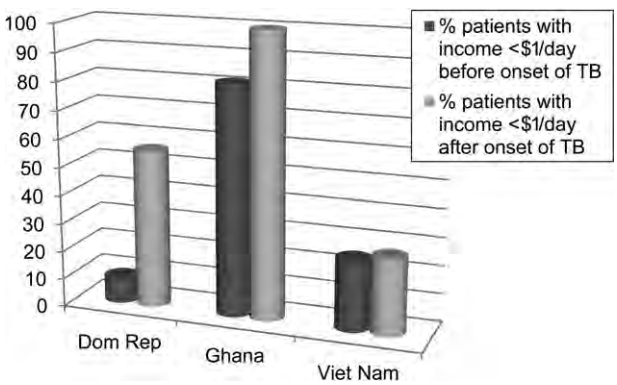

Figure Patients below US$1/day poverty line before and after onset of TB. TB = tuberculosis.

Recommendations based on the studies in all three countries were similar: bringing services closer to patients, reducing expenditures on transport and invested time, increasing efforts to find cases early to reduce indirect costs related to inability to work, informing health care workers and the public about TB diagnosis and treatment to reduce costs unrelated to TB, and including TB-related out-patient costs in social protection schemes.

Following the presentation of the results, each country took action to improve identified bottlenecks. In Ghana, the NTP presented the study findings to the Ministry of Health (MoH). As a result, policy makers agreed to include TB care interventions as part of its pro-poor strategies in the delivery of health care. The Nutrition Department of the MoH has since developed nutrition guidelines to address the specific needs of TB patients. Second, the evidence generated from the study findings was key in informing and developing the successful Global Fund Round 10 TB proposal. Given the identified high burden for female TB patients in Ghana, the NTP is currently focused on addressing gender-sensitive challenges of poor TB patients. Third, the parliamentary sub-committee on health has considerably advanced insurance coverage for all TB patients for health-related costs other than (free) anti-tuberculosis treatment. Lastly, study findings were presented at Union conferences in Lille, France, and Abuja, Nigeria.

As a result of the study, the NTP in Viet Nam is working toward increased involvement of the private sector in public-private-mix projects focusing on reducing travel, accommodation and hospitalisation costs for TB patients and guardians. Second, the study contributed to the decision to switch from the 8-month to the 6-month anti-tuberculosis treatment regimen, which will help reduce the treatment time and travel costs for follow-up tests. Third, the NTP is working on the expansion of its NTP network to provide TB services at provincial general hospitals, all major public non-MoH hospitals and private hospitals. Fourth, the NTP has started planning for a way to provide social and economic support to TB patients in each district. Finally, the NTP has been mobilising support for TB patients by organisations such as farmers and womens' unions.

In the Dominican Republic, the MoH evaluated the study findings in depth and explored the possibilities for implementing the recommendations. In 2011, the MoH moved forward with increased efforts to allocate public funds for food supplements for TB patients and for the inclusion of in- and out-patient TB services in the national health insurance schemes.

In summary, using the tool[21] provided results pointing towards similar patterns and challenges across the three countries. These triggered similar conclusions and recommendations. TB patients worldwide are in danger of spiralling into deeper poverty. As this effect is not limited to individual NTPs, it requires global action. Together with other research evidence,[9–14,26] our results strongly suggest that it is time for global institutions to improve social protection for TB patients. In the meantime, NTPs need to minimise costs for patients by providing services that are completely free, decentralising care with appropriate supervision and quality assurance, and improving access to care.

Limitations

All study teams reported difficulties with recall bias and conveying cost and payment concepts to patients. In Viet Nam, several patients could only provide (sub-)total direct costs, without specifying individual cost items (Table 4). Although absolute costs in US$ are difficult to compare, the relative burden and impact of TB on the welfare of the individual and the household can nevertheless be demonstrated. The costs incurred by TB patients as described here do not directly account for costs of comorbidities, although these additional costs are reflected in the indirect costs and coping strategies. Free TB care is only partly helpful if patients incur additional substantial costs due to comorbidities. We did not investigate whether the financial burden affected treatment completion. We do not intend to compare results closely across these countries, which have very different cultural settings, values, norms, health systems and purchasing power parities; however, the results still indicate that TB patients on different continents face similar catastrophic events unmediated by existing health systems and social protection schemes.

CONCLUSIONS

These results from the Dominican Republic, Ghana and Viet Nam show that patients face very high direct and indirect costs before and during TB diagnosis and treatment, which often translate into catastrophic financial events and increased poverty. It is time for the international community to come together and address the need for greater social protection of TB patients.

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RÉSUMÉ

CONTEXTE : Programmes Nationaux de Tuberculose (PNT) au Ghana, au Viet Nam et en République Dominicaine.

OBJECTIF : Evaluer les coûts directs et indirects du diagnostic et du traitement de la tuberculose (TB) encourus par les patients et les ménages.

SCHÉMA : Un questionnaire structuré, le Tool to Estimate Patient's Costs, a été traduit et adapté dans chaque pays. On a interviewé dans les trois pays un échantillon aléatoire de nouveaux patients adultes sous traitement depuis au moins un mois.

RÉSULTATS : Dans les divers pays, 27–70% des patients ont arrêté le travail et ont subi des réductions de revenus, 5–37% ont dû vendre leurs biens et 17–47% ont dû emprunter de l'argent à cause de la TB. Les coûts d'hospitalisation (US$42–118) et les compléments alimentaires constituent la plus grande partie des coûts directs au cours du traitement. Les coûts moyens totaux par patient (US$538–1.268) représentent approximativement le revenu individuel d'une année.

CONCLUSION : Dans les trois pays, nous avons observé des types et défis similaires en ce qui concerne les coûts-patient liés à la TB. Nous plaidons en faveur de l'introduction dans les schémas de protection sociale d'une action mondiale et unifiée en faveur des patients TB ainsi qu'en faveur de l'amélioration d'un accès équitable aux soins à charge des PNT.

RESUMEN

MARCO DE REFERENCIA: El Programa Nacional contra la Tuberculosis (PNT) de Ghana, Viet Nam y la República Dominicana.

OBJETIVO: Evaluar los costos directos e indirectos del diagnóstico y el tratamiento de la tuberculosis (TB) para los pacientes y los hogares.

MÉTODO: En cada país se tradujo y se adaptó la herramienta de cálculo de los costos para los pacientes, que consiste en un cuestionario estructurado. Se escogió de manera aleatoria una muestra de pacientes nuevos que habían recibido como mínimo 1 mes de tratamiento en los tres países.

RESULTADOS: En todos los países, de 27% a 70% de los pacientes interrumpieron su trabajo y sufrieron una disminución de los ingresos, de 5% a 37% vendieron propiedades y de 17% a 47% prestaron dinero por causa de la TB. La mayor parte de los costos directos correspondieron a los costos de hospitalización (entre US$42 y US$118) y los complementos de alimentación durante el tratamiento. En promedio, los costos de la enfermedad para el paciente (entre US$538 y US$1268) fueron equivalentes a los ingresos individuales de 1 año.

CONCLUSIÓN: Se observó que las características de los costos relacionados con la TB y las dificultades que estos generan en los pacientes son análogas en los tres países estudiados. Se recomienda promover una acción mundial y unificada en favor de estos pacientes, en el marco de los programas de protección social y de los PNT, con el fin de optimizar el acceso equitativo a la atención de salud.

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EDITORIAL

Planning for the invisible: projecting resources needed to identify and treat all patients with MDR-TB

THE REPORT by Royce et al. in this issue of the *Journal* estimates the burden of multidrug-resistant tuberculosis (MDR-TB) among notified new cases of TB in countries with high MDR-TB caseloads.[1] Previously, the MDR-TB burden among new TB cases was estimated by multiplying the MDR fraction (derived from population representative resistance surveys) by the estimated total incidence of new TB cases (i.e., including both cases who are and those who are not notified).[2] Royce et al. produce estimates of MDR-TB among TB cases who could have been detected under existing program conditions if drug susceptibility testing (DST) had been available for all notified new cases. They sharpen the focus on expected numbers of cases of MDR-TB among TB patients who present to notifying facilities. In addition to revealing the important role of transmission of MDR-TB in these high-burden settings, their paper highlights the urgent need to improve access to DST and effective treatment for MDR-TB among notified cases.

What is not reflected in these estimates is the substantial number of patients whose TB—and MDR-TB—goes undetected, for whom diagnostics and drugs are not purchased, budgeted, manufactured, or even projected. Although the number of invisible patients is uncertain, recent estimates are that up to a third of global TB cases are not notified[3] and therefore would lack access to appropriate diagnosis and care, even if universal DST for notified cases were implemented. These invisible patients will continue to transmit TB (and MDR-TB) to their families and communities until their disease resolves spontaneously or they die.

As the authors note, improved surveillance systems—in which the number of notified cases approximates the true number of incident cases—would permit the true burden of cases requiring second-line treatment to be known. This longer-term solution requires investment in public health infrastructure so that all TB cases can access the health system and all diagnostic centers have adequate capacity to diagnose and notify TB. The World Health Organization, and several of the authors cited in the article by Royce et al.,[1] are among those actively working to improve TB surveillance within countries.[4]

In parallel, solutions are urgently needed to bring appropriate care to the full half million—visible and invisible—patients newly suffering from MDR-TB each year. Unprecedented opportunities exist to improve the diagnosis and treatment of MDR-TB, with new interest in enhanced TB screening,[5] innovative efforts to diagnose TB cases that might previously have gone undiagnosed,[6,7] new technologies that allow for rapid detection of drug resistance in the periphery,[8] and promising new drugs on the horizon.[9] Use of the new technologies can also provide important updates to estimates of drug resistance prevalence. Twenty-one of the 29 country estimates used in the paper by Royce et al. rely on survey data from 2007 or earlier. In a number of these settings, planned or ongoing implementation of drug resistance surveillance systems—with rapid diagnostics—provides an opportunity to update these dynamic figures and inform planning for global drug supply and financial needs. We believe that projections of the resources required to confront this problem should be based on the best estimates of true numbers of patients suffering from MDR-TB, and not only those who are currently notified and visible to TB programs. Failure to secure resources that permit access to diagnosis and effective MDR-TB treatment for all patients, even if invisible, will result in continued transmission and needless deaths.

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BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Predictors of mortality among TB-HIV Co-infected patients being treated for tuberculosis in Northwest Ethiopia: a retrospective cohort study

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Abstract

Background: Tuberculosis (TB) is the leading cause of mortality in high HIV-prevalence populations. HIV is driving the TB epidemic in many countries, especially those in sub-Saharan Africa. The aim of this study was to assess predictors of mortality among TB-HIV co-infected patients being treated for TB in Northwest Ethiopia.

Methods: An institution-based retrospective cohort study was conducted between April, 2009 and January, 2012. Based on TB, antiretroviral therapy (ART), and pre-ART registration records, TB-HIV co-infected patients were categorized into "On ART" and "Non-ART" cohorts. A Chi-square test and a *T*-test were used to compare categorical and continuous variables between the two groups, respectively. A Kaplan-Meier test was used to estimate the probability of death after TB diagnosis. A log-rank test was used to compare overall mortality between the two groups. A Cox proportional hazard model was used to determine factors associated with death after TB diagnosis.

Results: A total of 422 TB-HIV co-infected patients (i.e., 272 On ART and 150 Non-ART patients) were included for a median of 197 days. The inter-quartile range (IQR) for On ART patients was 140 to 221 days and the IQR for Non-ART patients was 65.5 to 209.5 days. In the Non-ART cohort, more TB-HIV co-infected patients died during TB treatment: 44 (29.3%) Non-ART patients died, as compared to 49 (18%) On ART patients died. Independent predictors of mortality during TB treatment included: receiving ART (Adjusted Hazard Ratio (AHR) =0.35 [0.19-0.64]); not having initiated cotrimoxazole prophylactic therapy (CPT) (AHR = 3.03 [1.58-5.79]); being ambulatory (AHR = 2.10 [1.22-3.62]); CD4 counts category being 0-75cells/micro liter, 75-150 cells/micro liter, or 150-250 cells/micro liter (AHR = 4.83 [1.98-11.77], 3.57 [1.48-8.61], and 3.07 [1.33-7.07], respectively); and treatment in a hospital (AHR = 2.64 [1.51-4.62]).

Conclusions: Despite the availability of free ART from health institutions in Northwest Ethiopia, mortality was high among TB-HIV co-infected patients, and strongly associated with the absence of ART during TB treatment. In addition cotrimoxazol prophylactic therapy remained important factor in reduction of mortality during TB treatment. The study also noted importance of early ART even at higher CD4 counts.

Keywords: Predictors, Mortality, TB-HIV, Co-infection

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Background

The human immunodeficiency virus (HIV) pandemic presents a massive challenge to the control of tuberculosis (TB) at all levels. The synergy between TB and HIV is strong; in high HIV prevalence population, TB is a leading cause of morbidity and mortality, and HIV is driving the TB epidemic in many countries, especially those in sub-Saharan Africa [1]. TB is often the first clinical indication that a person has an underlying HIV infection and, as a result, TB services can be a critical entry point for HIV prevention, care, and treatment [2].

The syndemic interaction between HIV and TB epidemics has had deadly consequences around the world, and disproportionately affects people in Africa [3].

In patients with advanced acquired immune deficiency syndrome (AIDS) and active TB, highly active antiretroviral therapy (HAART) may be administered concurrently with the TB treatment to prevent opportunistic infections which may superimpose and accelerate HIV disease progression [4]. The World Health Organization (WHO) currently recommends that ART should be initiated for all TB-HIV co-infected patients irrespective of their CD4 counts [5].

Despite international recommendations and the proven benefit of ART, physicians remain reluctant to prescribe ART to HIV-infected TB patients, due to concerns about overlapping toxicity, drug-drug interactions, pill burden, and immune reconstitution inflammatory syndrome (IRIS) [6].

Understanding the predictors of mortality for TB-HIV co-infected patients in the local context is critical for Ethiopia to improve TB-HIV co-infected patients' co-management. To date, there is inadequate data on predictors of mortality among TB-HIV co-infected patients in Ethiopia. To address this, the USAID-funded Help Ethiopia Address Low TB (HEAL TB) project conducted a retrospective study in Northwest Ethiopia to determine predictors of mortality among TB-HIV co-infected patients. The study also aimed to compare the survival rate between TB-HIV co-infected patients who received ART and did not receive ART. It is anticipated that findings from this study will contribute to the body of knowledge that informs TB-HIV program planers, decision makers, and project implementers by providing predictors of mortality among TB-HIV co-infected patients during TB treatment in Ethiopia.

Methods

Setting

We conducted a retrospective cohort study in governmental health institutions in Bahir Dar, Northwest Ethiopia, from August, 2011 to January, 2012. Bahir Dar is located in Northwest Ethiopia, 565 kilometers from Addis Ababa. In these health institutions, patients diagnosed as having HIV in any of HIV counseling and testing protocols (i.e., Voluntary counseling and testing, Provider initiated HIV counseling and testing units) are registered in Pre-ART and ART log books according to the status of disease progression. Patients are also referred to ART clinics for pre-ART and ART follow up from private health facilities within Bahir Dar and health facilities outside of Bahir Dar. Felege Hiwot Referral Hospital and Bahir Dar Health Center have provided pre-ART and ART services since 2005 and other health centers in the town began providing these services in 2009. Felege Hiwot Referral Hospital's 2011 annual report showed that the facility had detected 1,600 TB cases, enrolled 13,590 people living with HIV/AIDS (PLWHA) in ART clinic, and started 9,222 PLWHA on ART. As of 2011 annual report, there were 5,547 PLWHA taking ART at Felege Hiwot Referral Hospital. According to 2011/12 report of Bahir Dar Health Center, a total of 4, 420 PLWHA ever enrolled of which 1, 133 were currently on ART. In the same year the health center reported 135 TB patients. The 2011/12 report of Abay Health Center showed 756 PLWHA enrolled of which 326 were currently on ART. The health center also reported 162 TB patients. Han Health Center reported 1, 726 PLWHA were ever enrolled (407 currently on ART) and 112 TB patients were registered in the year 2011/12.

Participants

All TB-HIV co-infected patients who started ART before initiating TB treatment, and those who started ART while being treated for TB, were included in the "On ART" cohort. Patients who did not receive ART until completion of TB treatment were included in the "Non-ART" cohort. For both cohorts, inclusion criteria included TB-HIV co-infected patients, aged 15 years or older, who were diagnosed with TB at any time during pre-ART and or ART follow-up since April 2009, and who completed TB treatment before January 2012. Patients who had been diagnosed for both TB and HIV during their initial visit to the health facility were also included for the study.

Enrollment procedures for study subjects

Bahir Dar town was chosen purposely to get adequate number of sample with proper and complete patient record profile. In the town there are seven governmental health institutions, of which three were newly opened during data collection period. Therefore we included four health institutions (Felege Hiwot Refferal Hospital, Bahir Dar Health Center, Han Health Center and Abay Health Center) for the study which delivers TB service, Pre-ART and ART service for TB/HIV co-infected patients. During April 2009 – September 2011, 849 TB-HIV co-infected patients were registered in four

health institutions. A total of 422 TB-HIV co-infected patients (272 'On ART' and 150 'Non-ART' cohorts) were included for the study [Figure 1].

Data collection

Nurses who work in TB and ART clinics were selected to collect data from August, 2011 to January, 2012. Data was collected retrospectively by reviewing the files of TB-HIV co-infected patients in Bahir Dar. All profiles of TB-HIV co-infected patients between April 2009 and January 2012 were considered for data collection. Pre-ART registers, lab requests, follow-up forms, anti-TB record forms, ART intake forms, and patient cards were reviewed. The patients' date of death was extracted from TB registration log books. Data quality was assured by using a pre-tested data collection tool and trained data collectors. Two public health professionals (Master of public health) had provided continuous supervision and monitoring. Supervisors, data clerks and investigators had checked completeness and consistency of data before and after data entry.

Measurement of variables

Death from any cause during TB treatment was listed as "on-treatment TB death," according to the WHO's TB treatment outcomes definitions [7]. If the date of ART was more than one week before TB treatment initiation, that person was classified as "on ART prior to TB treatment". Patients who initiated ART at any time before TB treatment was completed were classified as "having received ART during TB treatment".

Patients were diagnosed with smear positive pulmonary tuberculosis (PTB+), if one of the sputum examinations was positive for acid fast bacilli (AFB). Patients were diagnosed with extra pulmonary tuberculosis (EPTB) if physicians suspected or observed that the TB infection had spread outside of the respiratory organs [5].

Functional status is measured at base line, and a person is categorized into working "able to perform usual work in or out of the house"; Ambulatory "able to perform activities of daily living" and Bedridden "not able to perform activities of daily living".

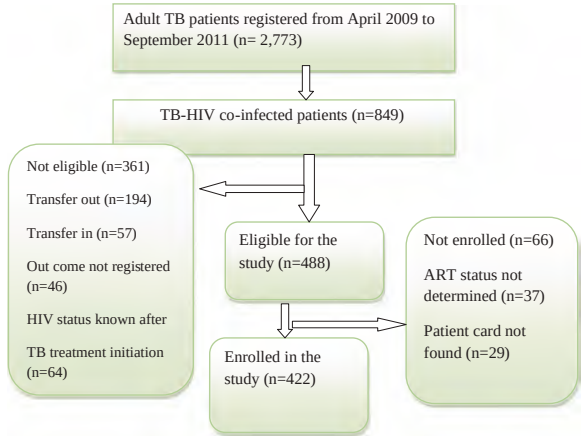

Figure 1 Enrollment of TB-HIV co-infected patients in the study, 2012.

Statistical analysis

Data was entered to EpiData 3.1[a] for Windows. Statistical package for social science (SPSS) version 16.0 for Windows and Stata version 11.0 were used for analysis. Data was cleaned and edited by simple frequencies and cross tabulation before analysis. The response variable was survival time, defined as "time in days transpired from the date of initial TB treatment to death" or, in the case of individuals who did not die (censored), "the time in days transpired to complete TB treatment".

Mean (with standard deviation), median (with inter quartile range [IQR]), and frequencies (as percentages) were used to describe patients' characteristics in each cohort. A Chi-square test and a *T*-test were used to compare categorical and continuous variables between the two cohorts, respectively. The Kaplan-Meier test was used to estimate the probability of death and the median time to death after TB diagnosis. The log-rank test was used to compare time to death between the two groups. The Cox proportional hazard model was used to determine predictors of death after TB diagnosis. All statistically significant ($p < 0.05$) factors in the bivariate analysis were included in the final model. The crude and adjusted hazard ratio (HR) and its 95% confidence interval (CI) were estimated.

Ethical issues

Ethical clearance for this study was obtained from the Review Ethics Committee of the School of Public Health at Addis Ababa University. To preserve patient confidentiality, nurses working in the ART clinics extracted the data from patients' medical records. Moreover, no personal identifiers were used on the data collection form.

Results

A total of 422 TB-HIV co-infected patients (272 On ART patients and 150 Non-ART patients) were included for the study and followed for a median of 197 days with an IQR of 140 to 221 days among On ART patients and 191 days among Non-ART patients with an IQR of 65.5 to 209.5 days.

Baseline socio-demographic characteristics of the study subjects

In this study, the two cohorts were not statistically different in any of the identified socio-demographic attributes.

The median age of study subjects in both cohorts was 30 years with an IQR of 27 to 37.5 years in the On ART cohort and 25 to 38 years in the Non-ART cohort. There were more female than male subjects in both cohorts, with 141 (53.4%) women in the On ART cohort and 83 (56.5%) women in the Non-ART cohort. More than one third of patients in both cohorts had completed secondary school with 93 (34.8%) in the On ART cohort and 50 (35.7%) in the Non-ART cohort (see Table 1).

Clinical characteristics of the study subjects

The clinical condition of study subjects within the two cohorts was not statistically different among any of the identified variables, except for history of prophylactic medication. In the On ART cohort, a higher proportion (51.6%) of patients had used prophylactic medication, as compared to patients in the Non-ART cohort (27.1%), (X^2 = 21.721; df (1); p = 0.000). Among all study subjects, more than one third had had at least one past opportunistic infection. In the On ART cohort, 58 (22.4%) study subjects had a history of past TB treatment, as compared to just 31 (21.7%) in the Non-ART cohorts. Data showed that the On ART and Non-ART cohorts had statistically different median CD4 counts (T = 10.305; p = 0.000): the On ART cohort had a much lower CD4 count with, a median of 114 cells/micro liter (μl) and an IQR of 58 to 185 cells/μl, as compared to the Non-ART cohort, which had a median of 291 cells/μl and an IQR of 183.5 to 448 cells/μl (see Table 2).

There was a statistically significant difference in the type of TB diagnosis between the cohorts. In the On ART group, 107 (39.3%) study subjects had smear negative PTB, whereas only 36 (24.0%) had smear negative PTB in the Non-ART group (X^2 =10.434; df = 2; p = 0.005). A higher proportion (93.3%) of study subjects in the On ART cohort had received CPT, as compared to those in the Non-ART cohort (77%) (see Table 2).

Comparison of mortality between the on ART and Non-ART cohorts

The 422 study subjects contributed a cumulative total of 2,274.4 person month observations (PMO) to this study; the On ART cohort contributed 1,545.03 PMO and the Non-ART cohort contributed 729.37 PMO. In the Non-ART cohort, 44 (29.3%) of TB-HIV co-infected patients died during TB treatment, which represented a higher percentage than the 49 patients (18%) who died in the On ART cohort. The incidence rate of mortality in the Non-ART cohort was 6.03 per 100 person months observations (PMO), (95% CI: 4.5, 8.1) and the mortality incidence in the

Table 1 Baseline socio-demographic characteristics of TB-HIV co- infected patients in Bahir Dar town, 2012

Base line variable	On ART (n = 272)	Non-ART (n = 150)	*X*2 Value (df)	P-Value
Residency (n = 407)				
Urban	235 (90.7%)	129 (87.2%)	1.271	0.260
Rural	24 (9.3%)	19 (12.8%)	(1)	
Age (n = 408)				
Mean ± SD	32.58 ± 9.123	31.98 ± 9.837	0.753♦	0.452
Median (IQR)	30 yrs (27-37.5)	30 yrs (25-38)		
Sex (n = 411)				
Male	123 (46.6%)	64 (43.5%)	0.355	0.551
Female	141 (53.4%)	83 (56.5%)	(1)	
Religion (n = 411)				
Orthodox	226 (85.3%)	117 (80.2%)	5.962	0.183
Muslim	26 (9.8%)	18 (12.3%)	(2)	
Others	13 (4.9%)	11 (7.5%)		
Marital status (n = 415)				
Single	76 (28.1%)	55 (37.9%)	7.901	0.131
Married	108 (40.0%)	57 (39.3%)	(3)	
Divorced	52 (19.2%)	24 (16.6%)		
Widowed	34 (12.6%)	9 (6.2%)		
Educational status (n = 407)				
Not educated	77 (28.8%)	40 (28.6%)	0.765	0.858
Primary	61 (22.8%)	35 (25.0%)	(3)	
Secondary	93 (34.8%)	50 (35.7%)		
Tertiary	36 (13.5%)	15 (10.7%)		

♦ = *T*-test Statistic for independent sample test used.

Table 2 Baseline clinical characteristics of TB-HIV co- infected patients in Bahir Dar town, 2012

Base line variable	On ART (n = 272)	Non-ART (n = 150)	X^2 Value (df)	P- Value
Past OIs (n = 366)				
Yes	105 (43.6%)	55 (44.0%)	0.006	0.937
No	136 (56.4%)	70 (56.0%)	(1)	
Past TB Treatment (n = 402)				
Yes	58 (22.4%)	31 (21.7%)	0.027	0.869
No	201 (77.6%)	112 (78.3%)	(1)	
Functional status (n = 397)				
Working	159 (60.9%)	80 (58.8%)	1.363	0.506
Ambulatory	72 (27.6%)	44 (32.4%)	(2)	
Bedridden	30 (11.5%)	12 (8.8%)		
CD4 count (n = 408)				
Mean ± SD	132.9 ± 94.42	312.78 ± 192.8	10.30♦	0.000*
Median (IQR)	114 (58-185)	291 (183.5-448)		
Hgb level (mmHg)(n = 357)				
Mean ± SD	11.36 ± 2.3	11.46 ± 1.83	0.063♦	0.95
Median (IQR)	11.3 (10.0-13.0)	12.0 (10.12-13.0)		
TB diagnosis				
Smear Positive PTB	53 (19.5%)	40 (26.7%)	10.434	0.005*
Smear Negative PTB	107 (39.3%)	36 (24.0%)	(2)	
Extra PTB	112 (41.2%)	74 (49.3%)		
CPT (n = 397)				
Prescribed	239 (93.0%)	109 (77.9%)	19.19	0.000*
Not Prescribed	18 (7.0%)	31 (22.1%)	(1)	
Outcome of TB Treatment (n = 417)				
Cure	37 (13.7%)	16 (11.0%)	8.039	0.045*
Treatment completed	167 (61.6%)	77 (52.7%)	(3)	
Defaulter	18 (6.6%)	9 (6.2%)		
Death	49 (18.1%)	44 (30.1%)		

* Significant at α = 0.05, ♦ = *T*-test Statistic for independent sample test used.

On-ART cohort was 3.2 per 100 PMO (95% CI: 2.40, 4.20). The overall incidence rate of mortality during TB treatment was 4.09 per 100 PMO (95% CI: 3.34, 5.01). Results from the On ART cohort showed that incidence of mortality in the first month of TB treatment was 5.4 per 100 PMO and, in the second month of TB treatment, was 4.8 per 100 PMO. The corresponding values in Non-ART cohort was 16.9 per 100 PMO and 5.9 per 100 PMO in the first and second months of TB treatment, respectively. The median time to death was 59 days in the On ART cohort and 29.5 days in the Non-ART cohort. The overall probability of survival in the On ART cohort was significantly greater than in the Non-ART cohort (log rank statistic = 8.93, df = 1, P = 0.003); (see Figure 2).

Predictors of mortality in TB-HIV Co-infected patients during TB treatment

The bivariate analysis showed that the risk of death decreased by 46% (HR = 0.54, 95% CI: 0.36-0.82) in the On-ART cohort. Compared to smear negative PTB patients, smear positive PTB patients had a 2.02 (95% CI: 1.07-3.83) times higher risk of death and EPTB patients had a 2.77 (95% CI: 1.61-4.75) times higher risk of death. In addition, patients who did not start CPT had a 3.15 times higher risk of mortality (95% CI: 1.95-5.11). Compared to the reference group, TB patients 45 years old or more (HR = 2.58, 95% CI: 1.34-4.92), patients with ambulatory and bedridden functional status (HR = 2.76, 95% CI: 1.71-4.47 and HR = 3.88, 95% CI: 2.15-7.02 respectively), and patients with CD4 count less than 75 cells/μl (HR = 2.08, 95% CI: 1.17- 3.70) had an increased risk of mortality during TB treatment. In the study, completing primary school -reduced risk of death by 55% (HR = 0.45, 95% CI: 0.22-0.90), compared to not educated TB-HIV co-infected patients (see Table 3).

ART status, CPT status, CD4 count, functional status, type of TB diagnosis, and type of health institution were independent predictors of mortality after controlling for

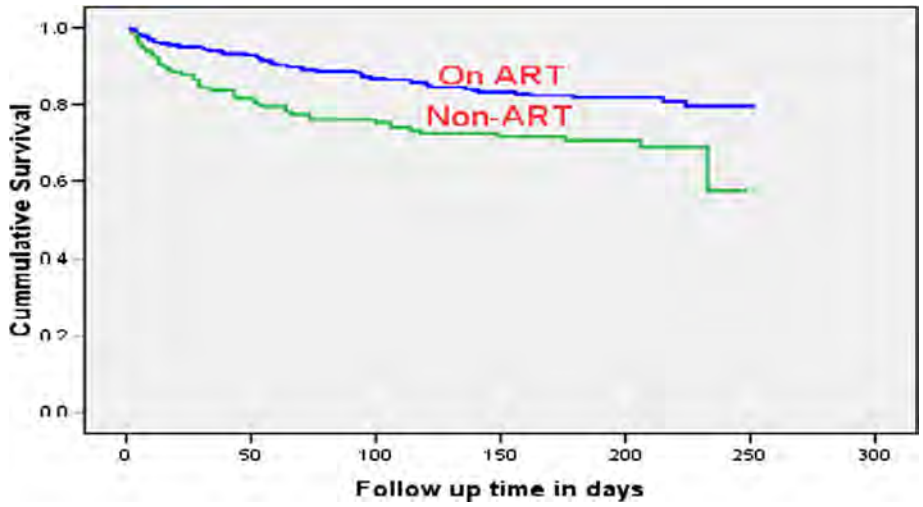

Figure 2 Kaplan-Meier estimate of survival among TB-HIV co-infected patients in Bahir Dar town, 2012.

the other factors. From these factors, receiving ART during TB treatment had decreased risk of mortality by 65% (AHR = 0.35, 95% CI: 0.19-0.64). In addition, CPT remained an important factor in reduction of mortality during TB treatment, in which patients without CPT were at a 3.03 times higher risk of mortality (95% CI: 1.58, 5.79). In this study CD4 count categories 0-75 cells/μl, 75-150 cells/μl, and 150-250 cells/μl; EPTB type; being ambulatory; and treatment in a hospital were independent predictors of increased risk of mortality during TB treatment (see Table 4).

Discussion

This study revealed the overwhelming problem of the high mortality of TB-HIV co-infected patients during TB treatment. More than 1 in 5 TB-HIV co-infected individuals died during TB treatment. Results from this study demonstrated that ART remained independently protective against mortality during TB treatment. In addition not having initiated cotrimoxazole prophylactic therapy; being ambulatory; CD4 count and treatment in a hospital were independent predictors of mortality during TB treatment.

In our study, the median CD4 count in the Non-ART cohort was twice as high as the median CD4 count in the On ART cohort. Non-ART cohorts may have been diagnosed as having HIV and TB, before their clinical and immunological conditions deteriorate. The median CD4 count among participants in this study was much higher than the median CD4 count among participants in other studies [8-15]. The difference may be due to the fact that researchers in our study took CD4 counts while the study subjects were being treated for TB or one month before they began TB treatment and, in most cases, these study subjects had started ART before TB diagnosis, which may have improved their immunological status. In addition, the results showed that 86.3% of study subjects had a CD4 count below 350 cells/μl. This is similar with a study conducted in Zimbabwe where 84.6% of study participants had a CD4 count below 350 cells/μl [16]. This showed that most study subjects were in progressive immunodeficiency condition.

There was no statistical difference in type of TB diagnosis between the two cohorts; 55.9% of study subjects were diagnosed with PTB and 44.1% were diagnosed with EPTB. This is in line with other studies [11,13,17] but the proportion of EPTB in this study is high compared to two studies conducted in India (22.9% and 31%) and one study conducted done in Thailand, which reported that 31% of study subjects had EPTB [10,12,18]. The variation could be a result of stage of HIV disease, difference in TB diagnosis or epidemiology of TB in different countries.

We found that mortality rate was high (22%) among TB-HIV co-infected patients during TB treatment. In line with this, previous studies have reported high mortality rates ranging from 8.5% to 30% among TB-HIV co-infected patients prior to successful completion of TB treatment [4,8-10,12,13,15,17-19]. In our study, death occurred in 49 of 272 patients (18%) exposed to ART during TB treatment, compared with 44 of 150 patients (29.3%) never exposed to ART. This finding is similar to a study conducted in India, where death occurred in 11.3% of patients exposed to ART during TB treatment and 24.6% of TB patients never exposed to ART [10]. However, results from a study conducted in Thailand showed 46% proportion of death among TB-HIV co-infected patients who did not start ART [13]. Another study in Thailand reported that 5 of 71 patients (7%) who received ART died, compared with 94 of 219 patients (43%) who did not receive ART (RR 0.2; 95%

Table 3 Predictors of mortality among TB-HIV co-infected patients in Bahir Dar town, 2012

Variable	Number at risk	Number of death	Incidence of mortality per 100 person month observation (95% CI)	Crude hazard ratio (95% CI)
ART				
Started	272	49	3.17 (2.39, 4.19)	**0.54 (0.36, 0.82)***
Not started	150	44	6.03 (4.49, 8.11)	1
CPT prophylaxis				
Prescribed	348	60	3.59 (2.66, 4.87)	1
Not prescribed	49	23	10.18 (6.77, 15.32)	**3.15 (1.95, 5.11)***
Type of TB				
Smear negative PTB	143	17	2.02 (1.26, 3.25)	1
Smear positive PTB	93	21	4.31 (2.81, 6.61)	**2.02 (1.07, 3.83)***
Extra PTB	186	55	5.81 (4.46, 7.57)	**2.77 (1.61, 4.78)***
Past OIs				
No	206	50	4.62 (3.50, 6.09)	1
Yes	160	31	3.53 (2.48, 5.02)	0.77 (0.49, 1.20)
Past TB treatment				
No	313	66	3.95 (3.10, 5.03)	1
Yes	89	18	3.58 (2.25, 5.68)	0.91 (0.54, 1.54)
Functional status				
Working	239	31	2.21 (1.55, 3.14)	1
Ambulatory	116	36	6.39 (4.61, 8.87)	**2.77 (1.71, 4.47)***
Bedridden	42	17	7.31 (3.81, 14.05)	**3.88 (2.15, 7.02)***
CD4 count				
< 75	107	33	6.22 (4.42, 8.75)	**2.08 (1.17, 3.30)***
75-150	91	21	4.44 (2.90, 6.81)	1.50 (0.80, 2.82)
150-250	95	19	3.57 (2.28, 5.59)	1.24 (0.65, 2.37)
> = 250	115	18	2.89 (1.82, 4.59)	1
Health institution				
Health center	226	34	2.67 (1.91, 3.72)	1
Hospital	196	59	5.89(4.57, 7.61)	**2.18 (1.43, 3.33)***
Age(n = 408)				
15-24	100	18	3.30 (2.08, 5.24)	1
25-34	193	40	3.79 (2.78, 5.17)	1.15 (0.66, 2.01)
35-44	69	16	4.40 (2.70, 7.18)	1.30 (0.66, 2.55)
> = 45	46	19	8.97 (5.72, 14.06)	**2.58 (1.34, 4.92)***
Sex				
Male	187	45	4.53 (3.36, 6.07)	1
Female	224	45	3.69 (2.75, 4.94)	0.82 (0.54, 1.24)
Educational status				
Not educated	117	26	4.47 (3.05, 6.57)	1
Primary	96	11	1.93 (1.07, 3.49)	**0.45 (0.22, 0.90)***
Secondary	143	37	4.82 (3.49, 6.66)	1.10 (0.66, 1.81)
Tertiary	51	13	4.48 (2.60, 7.72)	1.05 (0.54, 2.05)

*Significant at $\alpha = 0.05$.

CI: 0.1–0.4) [18]. In Malawi, a total of 132 of 660 patients (20%) died during an eight-month course of anti-TBs treatment, which is consistent with our finding of 22% [20].

In this study, we have documented that the risk of mortality was high among subjects in the first month of TB treatment. This may be due to delayed presentation

Table 4 Multivariate predictors of mortality among TB-HIV co-infected patients in Bahir Dar town, 2012

Variable	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
ART		
Started	0.54 (0.36, 0.82)	**0.35 (0.19, 0.64)***
Not started	1	1
CPT prophylaxis		
Prescribed	1	1
Not prescribed	3.15 (1.95, 5.11)	**3.03 (1.58, 5.79)***
Type of TB		
Smear negative PTB	1	1
Smear positive PTB	2.02 (1.07, 3.83)	2.11 (0.95, 4.65)
Extra PTB	2.77 (1.61, 4.78)	**2.39 (1.23, 4.66)***
CD4 count		
< 75	2.08 (1.17, 3.30)	**4.83 (1.98, 11.78)***
75-150	1.50 (0.80, 2.82)	**3.57 (1.48, 8.61)***
150-250	1.24 (0.65, 2.37)	**3.07 (1.33, 7.07)***
> = 250	1	1
Functional status		
Working	1	1
Ambulatory	2.77 (1.71, 4.47)	**2.10 (1.22, 3.62)***
Bedridden	3.88 (2.15, 7.02)	2.11 (0.98, 4.53)
Health Institution		
Health center	1	1
Hospital	2.18 (1.43, 3.33)	**2.64 (1.51, 4.62)***
Age(n = 408)		
15-24	1	1
25-34	1.15 (0.66, 2.01)	1.17 (0.60, 2.29)
35-44	1.30 (0.66, 2.55)	0.98 (0.43, 2.23)
> = 45	2.58 (1.34, 4.92)	2.20 (0.97, 4.59)
Educational status		
Not educated	1	1
Primary	0.45 (0.22, 0.90)	0.49 (0.22, 1.12)
Secondary	1.10 (0.66, 1.81)	0.88 (0.49, 1.58)
Tertiary	1.05 (0.54, 2.05)	0.65 (0.29, 1.47)

*Significant at α = 0.05. ART status, health institution type, age, educational status, functional status, CD4 count, type of TB diagnosis, and CPT initiation were included in the model.

of patients and, thus, advanced TB and HIV/AIDS, late diagnosis of TB within health institutions, and the presence of life-threatening HIV related complications. These results are similar to results from a study conducted in Thailand which showed the first month of TB treatment is the time of the maximum number of deaths [21]. Another study conducted in sub-Saharan Africa concluded that ART should be started soon after TB diagnosis because the majority of deaths among TB-HIV patients in this study occurred during the patients' first two months of TB treatment [22].

In our retrospective, institution-based study, we found that TB-HIV co-infected patients who took ART during TB treatment had a lower risk of death. This is consistent with studies from several other settings [8-11,13,15,17-19,23,24] that demonstrate the positive impact of ART on the survival outcomes among TB-HIV co-infected patients, including successful immune restoration and reductions in morbidity and mortality.

In addition to ART, we found other immunological factors associated with mortality. For example, mortality rates increased in TB-HIV co-infected patients with

lower CD4 counts. This finding is consistent with a study in Zimbabwe, which showed that HIV-TB co-inflected patients with a CD4 count of <50 cells/micro litter had a 13 percent increased risk of death compared to patients with CD4 count greater or equal to 200 cells/micro litter [16]. Oppositely, a study conducted in southern India showed that a CD4 count below 200/mm3 was not associated with a higher rate of mortality [17]. The difference between our results and these others may be that we categorized CD4 counts into smaller intervals, which better enabled us to see the effect of CD4 counts on mortality.

The risk of death during TB treatment was higher in patients treated at a hospital compared to those treated at a health center. The reason could be that those who are taking care in hospitals might have advanced disease conditions. As a result, the severely ill hospitalized patients appeared to have a greater incidence of mortality, as compared to the less ill health center patients.

In this study TB-HIV co-infected patients with extra PTB were at increased risk of mortality during TB treatment compared to smear negative PTB patients. In other studies PTB is associated with high risk of mortality [10]. The possible reason may be HIV infected patients with extra PTB were highly immune-compromised.

In our study not initiating CPT was associated with high risk of mortality. In line with this, studies from South India and Sub-Saharan Africa showed that not taking CPT was significantly associated with mortality [17,22]. In our study, however, patients who died shortly after being diagnosed with TB and HIV may not have had the chance to initiate CPT. This may have led us to overestimate the benefit of CPT.

Our study was subject to several important limitations. All TB-HIV co-infected patients who started ART before initiating TB treatment, and those who started ART while being treated for TB, were included in the same group which may introduce bias. Information about other biomedical predictors for death that may have confounded this study, such as drug resistance, severity of immune suppression, or co-morbidities, adherence of medication were not available. We were also unable to collect adequate information about specific types of EPTB and patients' recent CD4 counts. Since most deaths in Ethiopia occur at home [25], it was difficult to trace all deaths. Exclusion of patients who transferred out of care may have also slightly confounded our results.

Conclusions

A significant difference was observed in the mortality rate during TB treatment between the On ART and Non-ART cohorts. Despite the fact that ART is available in most governmental health institutions throughout Ethiopia, death was strongly associated with the absence of ART during TB treatment. Risk of death was 65% lower in TB-HIV co-infected patients treated with ART, as compared to those not treated with ART. In addition cotrimoxazol prophylactic therapy remained important factor in reduction of mortality during TB treatment. The study also noted importance of early ART even at higher CD4 counts. To alleviate this, expanding ART use among TB-HIV co-infected patients is critical to improving the survival of these patients. Health institutions in Ethiopia should begin treating all TB-HIV co-infected patients with ART, irrespective of CD4count levels, as per the WHO recommendation.

Endnotes

[a] EpiData Association, Odense, Denmark.

Abbreviations

AFB: Acid fast bacilli; AHR: Adjusted hazard ratio; AIDS: Acquired immune deficiency syndrome; ALT: Alanine transaminase; AST: Aspartate aminotransferase; ART: Antiretroviral therapy; CD4: Cluster of differentiation 4; CI: Confidence interval; CPT: Cotrimoxazole prophylactic therapy; Df: Degree of freedom; EPTB: Extra pulmonary tuberculosis; HAART: Highly active antiretroviral therapy; HEAL TB: Help Ethiopia Address Low Tuberculosis (project); HIV: Human immunodeficiency virus; HR: Hazard ratio; IQR: Inter-quartile range; IRIS: Immune reconstitution inflammatory syndrome; MSH: Management Sciences for Health; OR: Odds ratio; PLWHA: People living with HIV and AIDS; PMO: Person months observed; PTB: Pulmonary tuberculosis; PTB+: Smear-positive pulmonary tuberculosis; RR: Relative risk; TB: Tuberculosis; USAID: United States Agency for International Development; WHO: World Health Organization; μl: Micro liter.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

BS designed the study, performed statistical analysis, and drafted the manuscript. ND participated in the study design and analysis. BG participated in the study design, analysis, and helped to draft the manuscript. MM and PS participated in the study design and helped to draft the manuscript. All of these authors provided critical comments for revision and approved the final version of the manuscript.

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The tuberculosis profile of the Philippines, 2003–2011: advancing DOTS and beyond

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The Philippines is one of the highest tuberculosis (TB) burden countries in the world with nationwide coverage of directly observed treatment, short-course (DOTS) achieved in 2003. This study reports on the National TB Control Programme (NTP) surveillance data for the period 2003 to 2011. During this period, the number of TB symptomatics examined increased by 82% with 94% completing the required three diagnostic sputum microscopy examinations. Of the 1 379 390 cases diagnosed and given TB treatment, 98.9% were pulmonary TB cases. Of these, 54.9% were new smear-positive cases, 39.3% new smear-negative cases and 4.7% were cases previously treated. From 2008 to 2011, 50 030 TB cases were reported by non-NTP providers. Annual treatment success rates were over 85% with an average of 90%; the annual cure rates had an eight-year average of 82.1%. These surveillance data represent NTP priorities – the large proportion of smear-positive cases reflected the country's priority to treat highly infectious cases to cut the chain of transmission. The performance trend suggests that the Philippines is likely to achieve Millennium Development Goals and Stop TB targets before 2015.

The Philippines is an archipelago of more than 7107 islands with an area of 300 000 km^2 in south-eastern Asia. The country is divided into 17 administrative regions with 81 provinces, 136 cities including 16 highly urbanized centres, 1495 municipalities and 42 008 barangays.[1] The population of the Philippines was 92.3 million in 2010 with 33.4% aged between zero and 14 years, 62.3% in the working age group of 15–64 years, and 4.3% being 65 years and older.[2] Poverty incidence in the population was 26.5% in 2009.[3]

Tuberculosis (TB) is the sixth leading cause of morbidity and mortality in the Philippines; the country is ninth out of the 22 highest TB-burden countries in the world and has one of the highest burdens of multidrug-resistant TB. Directly observed treatment, short-course (DOTS)[4] strategy for TB control commenced in 1997 and nationwide coverage was achieved in 2003.[5] The prevalence of TB in 2007 was 2.0 per 1000 for smear-positive TB and 4.7 per 1000 for culture-positive TB. Compared with 1997, there was a 28% and 38% decline in prevalence for smear-positive and culture-positive TB, respectively.[6]

The National TB Control Programme (NTP) is managed by a central team at the National Center for Disease Prevention and Control of the Department of Health.[4] This team develops policies and plans and provides technical guidance to regional and provincial/city-level NTP management teams, overseeing the implementation of the programme at the municipal and *barangay* levels based on NTP policies and standards.

Under NTP, TB control services are provided mainly through public primary health care facilities (also called DOTS facilities) operated by local government units in a devolved set-up. There are additional DOTS facilities within the NTP's network of service providers that either refer diagnosed TB patients for treatment or directly provide TB treatment services using DOTS strategy. These include private outpatient clinics; public and private primary, secondary and tertiary care hospitals; workplaces; clinics under faith-based organizations and community-based nongovernmental organizations (NGOs); and public institutions such as military facilities, jails and prisons. The NTP has also established public–public and public–private partnerships for TB control consisting of public non-NTP providers such as public hospitals, public medical colleges, prisons/detention centres and military facilities; private DOT providers include private physicians, private hospitals, private clinics, private workplaces and NGOs. Nationwide expansion of TB testing in children has been part of NTP

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since 2004,[7] while the programmatic management of drug-resistant TB was mainstreamed into NTP starting in 2008.[8]

The NTP surveillance system is based on the standardized recording and reporting system used in all DOTS facilities under the NTP network of providers. Reports from rural health units, health centres and other DOTS providers include data for laboratory, case finding and case holding activities. These are reported quarterly and annually to the provincial or city health offices on paper-based, standardized forms. The provincial or city health offices then consolidate these paper-based reports and convert them into an electronic format (in tabular form using Microsoft Excel or Word). These are then forwarded to the respective regional health offices for consolidation and further analysis. The regional electronic-based reports are then forwarded to the central NTP team at the Department of Health.

Modernization of the TB registry was initiated in 2005 with the launching of the electronic TB registry in two regions (National Capital Region and CHD III Central Luzon). However, the initiative was discontinued in 2010 and was replaced by the Integrated TB Information System in 2011. This system is being implemented in phases and is currently used in selected facilities in four of the country's 17 regions including South Luzon, National Capital Region, Central Luzon and Western Visayas.

The objective of this report is to provide a national summary of TB cases reported to the NTP surveillance system from 2003 to 2011.

METHODOLOGY

Data submitted to the central NTP team for the nine-year period 2003 to 2011 were consolidated and summarized. Descriptive statistics were used to analyse the data. Treatment outcome data are for 2003 to 2010 only; 2011 data are not yet complete and not included in the report.

As case finding and treatment outcome data for drug-resistant TB are not fully integrated into the system, they are not included in this report. Data for pulmonary TB (PTB) cases previously treated were disaggregated by case classification starting only in 2008 and are only reported for 2008 to 2011.

RESULTS

TB cases

From 2003 to 2011, a total of 4 638 939 TB symptomatics were examined with sputum smear microscopy (**Figure 1**). On average, 94% of TB symptomatics completed the required three diagnostic sputum microscopy examinations each year. Compared to 2003, the number of TB symptomatics examined increased by 82% in 2011.

From these, a total of 1 379 390 cases of TB all forms were diagnosed and given TB treatment from 2003 to 2011. PTB comprised 98.9% of all TB cases notified; extra-pulmonary TB (EPTB) made up the remaining 1.1%. The nine-year average proportions of PTB cases are disaggregated as follows: new smear-positive, 54.9%; new smear-negative, 39.3%; and cases previously treated, 4.7% (**Figure 2**). Compared to 2003, the number of new smear-positive PTB cases increased by 34% in 2011; new smear-negative PTB cases increased by 70%.

Non-NTP providers

From 2008 to 2011, a total of 50 030 TB cases were reported by non-NTP providers – 7.4% of total cases reported to NTP in this time (**Table 1**). Most of these were from the private sector (38 565, 77.1%); 11 465 were from public partners (22.9% from 2010 to 2011 only).

New smear-positive PTB cases

The case notification rate (CNR) for new smear-positive PTB cases increased from 2003 to 2011 (**Figure 3**). The lowest CNR was in 2003 (86 per 100 000) and the highest was in 2006 (100 per 100 000). During the nine-year period, 63% of new smear-positive cases were aged 25 to 54 years, with 20% in the 25–34 years age group, 22% in the 35–44 years age group and 21% in the 45–54 years age group (**Figure 4**). The average male-to-female ratio for the period was 2.3.

Cases previously treated

The number of PTB cases previously treated increased from 2008 to 2011 (**Table 2**). On average, relatively large proportions of PTB cases previously treated were

Figure 1. **Number of TB symptomatics examined and proportion that had three diagnostic sputum microscopy examinations by year, the Philippines, 2003 to 2011**

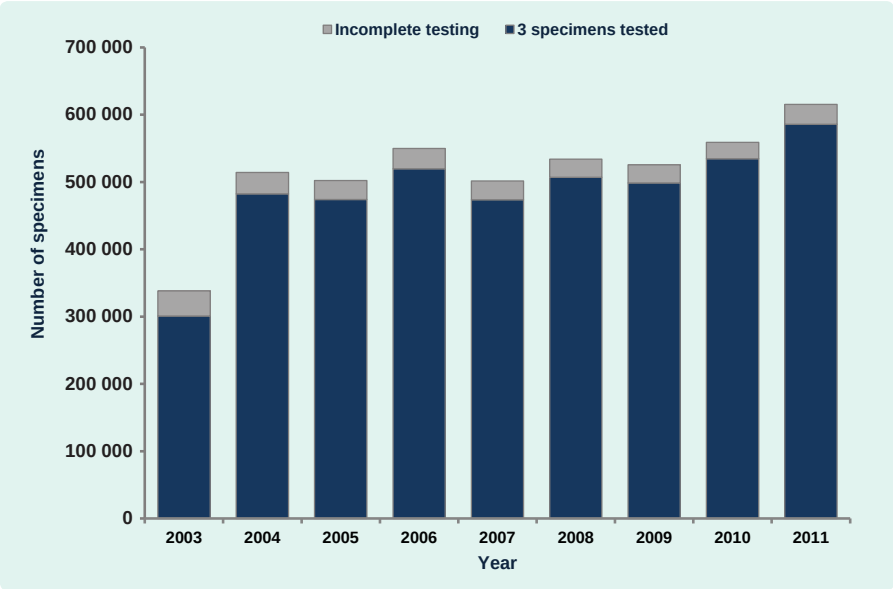
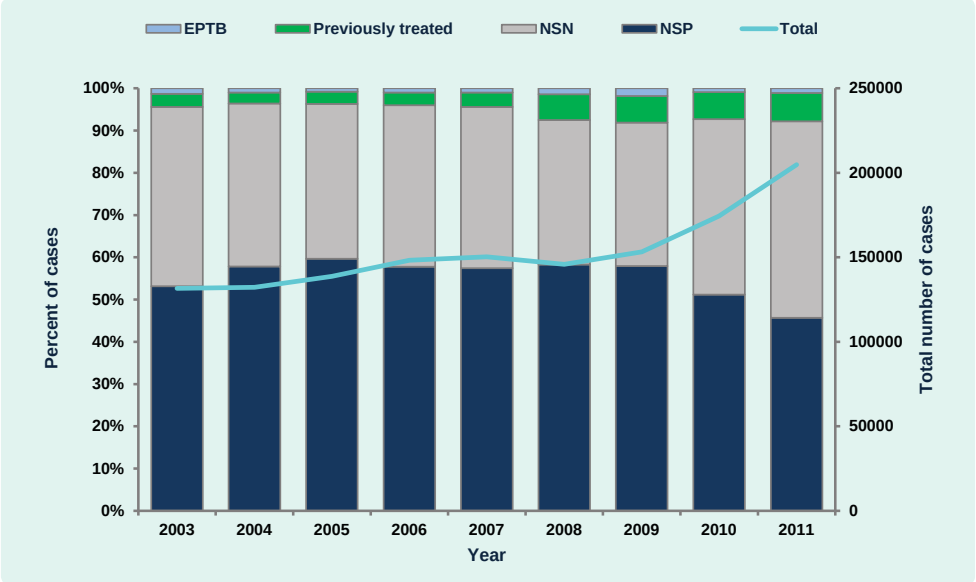


Figure 2. **Total number of TB cases and the proportion by case classification, the Philippines, 2003 to 2011**



EPTB – extrapulmonary TB; NSN – new smear-negative TB; NSP – new smear-positive TB

from relapses (27%) or other smear-negative cases (50%).

Treatment outcomes

Treatment outcomes for successive yearly cohorts of new smear-positive cases from 2003 to 2010 showed treatment success rates of over 85% with an average of 90% (**Table 3**). The average annual cure rate for eight years was 82.1%. The eight-year annual average for the other treatment outcomes were: treatment completed at 7.9%, death at 2.3%, treatment failure at 1%, defaulted from treatment at 4.4%, and transferred out at 2.4%.

DISCUSSION

Changes observed in the TB surveillance data in the Philippines from 2003 to 2011 reflected NTP priorities. The increase in the number of reported TB cases can be attributed to various NTP initiatives to improve access

Figure 3. **Case notification rate of new smear-positive cases by year, the Philippines, 2003 to 2011**

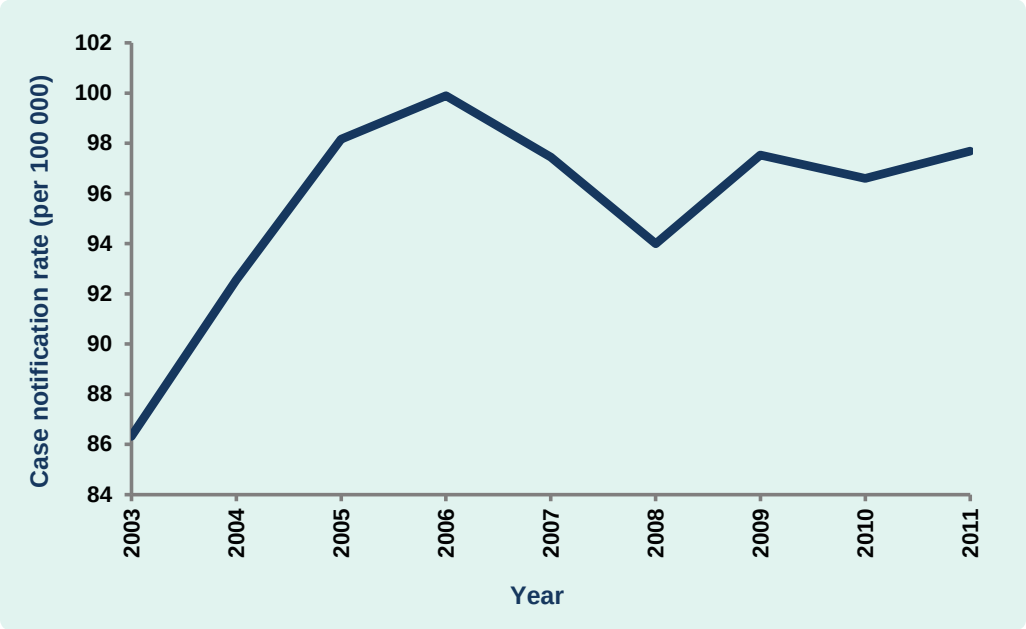


Figure 4. **Proportion of all new smear-positive cases by age group, the Philippines, 2003 to 2011**

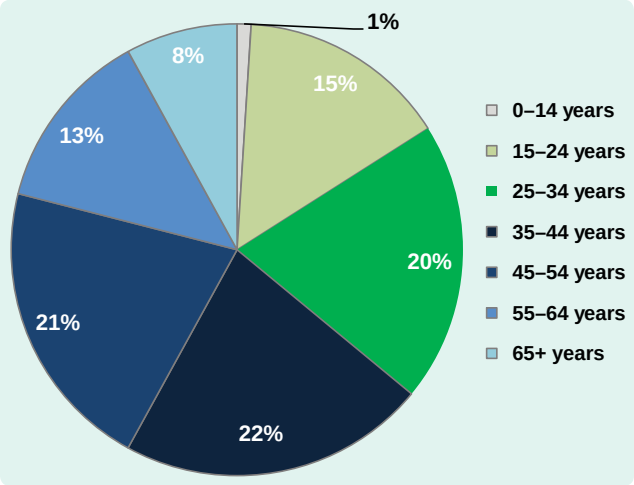


Table 1. **Number of TB cases reported by non-NTP public and private health providers, the Philippines, 2008 to 2011**

Year	Private providers	Non-NTP public providers	Total
2008	6 914	–	6 914
2009	4 866	–	4 866
2010	12 081	2 138	14 219
2011	14 704	9 327	24 031
Total	**38 565**	**11 465**	**50 030**

NTP – National TB Control Programme

to diagnostic and treatment services especially for the vulnerable sectors. Examples of these initiatives include the expansion of laboratory services and establishing partnerships with public and private health providers. The number of cases contributed by the non-NTP public and private partners also increased from 2008 to 2011; in 2011, these partnerships contributed 11.7% of the total number of cases notified.

More than half the cases per year were new smear-positive cases (apart from 2011 at 46%). This reflects NTP's high priority for the detection and treatment of highly infectious TB cases to cut the chain of transmission. The increase in the number of new smear-negative cases in 2010 and 2011 reflects a change in programme priorities to detect all forms of TB following the new WHO recommendations issued at that time.[9] It also explains the decrease in the proportion of new smear-positive cases in 2011. The increasing trend in the number of cases previously treated from 2008 may be due to the heightened efforts to detect drug-resistant TB cases among these cases. Also in 2008 the management of drug-resistant TB cases was mainstreamed into NTP.

The global target for treatment success rate is 85%,[10] this has been exceeded in the Philippines with an

Table 2. **Number and proportion of pulmonary tuberculosis cases previously treated by case classification and year, the Philippines, 2008 to 2011**

Year	Relapses		Returns after default		Treatment failure		Other (smear-positive)		Other (smear-negative)		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
2008	2 577	29	720	8	522	6	864	10	4 183	47	8 866	100
2009	2 973	31	804	8	585	6	947	10	4 266	45	9 575	100
2010	3 075	28	914	8	566	5	1 135	10	5 451	49	11 141	100
2011	3 217	23	900	7	466	3	1 205	9	7 957	58	13 745	100
Total	**11 842**	**27**	**3338**	**8**	**2139**	**5**	**4 151**	**10**	**21 857**	**50**	**43 327**	**100**

Table 3. **Proportion of new smear-positive cases by treatment outcome and year, the Philippines, 2003 to 2010**

Year	Treatment outcome indicators (%)						
	Cure	Treatment completed	Success	Death	Failure	Defaulted	Transferred out
2003	80.5	7.9	88.4	3.0	1.0	5.0	3.0
2004	81.0	7.8	88.8	2.4	1.0	5.0	2.6
2005	82.4	7.4	89.8	2.5	1.0	4.3	2.4
2006	82.2	8.2	90.4	2.4	1.0	3.9	2.4
2007	79.9	9.6	89.5	2.0	1.1	4.4	2.5
2008	82.0	8.4	90.4	2.0	1.1	4.4	2.5
2009	84.1	6.9	91.0	2.0	1.0	4.0	2.0
2010	84.8	6.7	91.5	2.1	0.9	3.8	2.0
Average	**82.1**	**7.9**	**90.0**	**2.3**	**1.0**	**4.4**	**2.4**

eight-year average of 90%. However, the country's target of 85% for annual cure rates[11] was met only in 2010. The low cure rates in previous years were mainly due to the high number of patients who completed treatment without laboratory confirmation of cure (i.e. treatment completed). The average rate of cases defaulting from treatment for the eight-year study period was 4.4%, contributing to the low cure rate and therefore treatment success rates. Moreover, these defaulters may become the future drug-resistant cases.

The death rate of notified TB cases, while low, still contributed to the overall unfavourable treatment outcome as did those cases that transferred out as their outcome is unknown. However, the sustained high treatment success rate reflects ongoing efforts to improve case holding through various NTP strategies such as the administration of DOT in workplaces, homes and other acceptable venues in the community other than the health facility using community volunteers as treatment partners.

In this study, EPTB comprised only 1% of cases, compared to the 15% to 20% reported from other countries.[12,13] The low case detection for EPTB in the Philippines may be due to the limited capability of primary care facilities to diagnose these cases or because EPTB cases are diagnosed in hospitals that are not part of NTP. Only 7% of public and 4% of private hospitals report to NTP. However, the higher number of EPTB cases reported from 2008 onwards may reflect the inclusion of more private and non-NTP public providers to NTP. This limitation to the surveillance system is being addressed by increasing the number of NTP-engaged hospitals and improving capacities to confirm EPTB diagnosis.

The proportion of children aged zero to 14 years notified to NTP was 1% for the whole study period,

and although there was an increase over this time, its proportion relative to other TB cases did not exceed 2% from 2003 to 2011. It has been estimated that the 0–14 age group should comprise around 15% of cases in low-income countries,[14] suggesting that cases in children are either not being diagnosed or if being diagnosed they are not being reported to NTP.

There are some limitations in using NTP surveillance system data to report on TB in the Philippines. Cases diagnosed and treated in health facilities outside the NTP network of providers, including private clinics and hospitals, are not included, therefore the surveillance system is underreporting the total number cases of TB in the Philippines. The submission of case reports are still paper-based, particularly at the peripheral level, which contributes to delays and errors in reporting. Not all regional health units have the capacity to consolidate their data in an electronic format because of gaps in infrastructure and equipment.

CONCLUSION

The Philippines has achieved improvements in case detection and exceeded the target for treatment success despite numerous challenges, particularly in making services accessible in difficult geographic and socioeconomic settings. The country aims to further improve access to diagnostic and treatment services, especially for highly vulnerable groups, while sustaining high cure and treatment success rates particularly among smear-positive PTB cases. Efforts will be directed at improving diagnostic capabilities in DOTS facilities and hospitals, addressing barriers to follow-up examinations for patients under treatment as well as the factors that promote treatment default and improving the referral system to reduce transfer-outs. Factors that contribute to TB mortality such as diagnostic and treatment delay and co-morbidities need to be addressed as well. Finally, the TB information system will be strengthened to improve its usefulness for surveillance, planning and decision-making. With the current trend of NTP performance, it is predicted that the country will achieve Millennium Development Goals and Stop TB partnership targets before 2015.[10]

Conflicts of interest

None declared.

Funding

None.

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Drug resistance of *Mycobacterium tuberculosis* in Malawi: a cross-sectional survey

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Objective To document the prevalence of multidrug resistance among people newly diagnosed with – and those retreated for – tuberculosis in Malawi.

Methods We conducted a nationally representative survey of people with sputum-smear-positive tuberculosis between 2010 and 2011. For all consenting participants, we collected demographic and clinical data, two sputum samples and tested for human immunodeficiency virus (HIV).The samples underwent resistance testing at the Central Reference Laboratory in Lilongwe, Malawi. All *Mycobacterium tuberculosis* isolates found to be multidrug-resistant were retested for resistance to first-line drugs – and tested for resistance to second-line drugs – at a Supranational Tuberculosis Reference Laboratory in South Africa.

Findings Overall, *M. tuberculosis* was isolated from 1777 (83.8%) of the 2120 smear-positive tuberculosis patients. Multidrug resistance was identified in five (0.4%) of 1196 isolates from new cases and 28 (4.8%) of 581 isolates from people undergoing retreatment. Of the 31 isolates from retreatment cases who had previously failed treatment, nine (29.0%) showed multidrug resistance. Although resistance to second-line drugs was found, no cases of extensive drug-resistant tuberculosis were detected. HIV testing of people from whom *M. tuberculosis* isolates were obtained showed that 577 (48.2%) of people newly diagnosed and 386 (66.4%) of people undergoing retreatment were positive.

Conclusion The prevalence of multidrug resistance among people with smear-positive tuberculosis was low for sub-Saharan Africa – probably reflecting the strength of Malawi's tuberculosis control programme. The relatively high prevalence of such resistance observed among those with previous treatment failure may highlight a need for a change in the national policy for retreating this subgroup of people with tuberculosis.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

Although the World Health Organization (WHO) has monitored the emergence of drug resistance of *Mycobacterium tuberculosis* since 1994,[1] there have been few national surveys of such resistance in sub-Saharan Africa.[2]

In 2012, it was estimated that about 1.9% of people newly diagnosed and 9.4% of those undergoing retreatment in Africa had multidrug-resistant (MDR) tuberculosis.[3] The prevalence of MDR tuberculosis in Africa varies between countries[4] and might be generally increasing.[3,5]

Over several years, attempts have been made – at the Central Reference Laboratory in Lilongwe – to isolate *M. tuberculosis* from all smear-positive patients undergoing retreatment in Malawi to investigate drug susceptibility. In 2008, about 8% of people investigated in this manner were found to have MDR tuberculosis (James Mpunga, Malawi National Tuberculosis Control Programme, personal communication, 2008) – although most of the samples came from urban centres and the laboratory's attempts to isolate *M. tuberculosisM. tuberculosis* often failed.[6] The only published data on MDR tuberculosis in Malawi indicated that just 0.5% of people newly diagnosed with tuberculosis and 0.9% of people being retreated in Karonga district had MDR tuberculosis in 1996–1998.[7]

In 2007, the nationally recommended treatment regimen for people newly diagnosed with tuberculosis in Malawi changed. The initial supervised treatment remained the same – i.e. daily isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months – but the unsupervised continuation phase changed from 6 months of isoniazid and ethambutol to 4 months of isoniazid and rifampicin.[8,9] There are four problems since this change that need monitoring. The first is that poor adherence during this currently-recommended continuation phase could lead to the emergence of MDR tuberculosis. Another problem is that nothing is known about the resistance of Malawian isolates of *M. tuberculosis* to the second-line drugs that began to be used routinely in Malawi in 2007. A third problem is the high prevalence of human immunodeficiency virus (HIV) infection among people with tuberculosis.[10] In 2010, 63% of Malawian tuberculosis patients tested for HIV were found positive.[4] Finally, the national prevalence of drug-resistant tuberculosis may be affected by migration of people from neighbouring countries, where such outbreaks have occurred.[11] Given these issues, we conducted a national survey of resistance to anti-tuberculosis drugs in Malawi.

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Methods

Study setting and design

We engaged all of Malawi's 48 tuberculosis registration centres to conduct a prospective, cross-sectional survey. The centres were grouped into three zones – northern, central and southern – for phased sample collection.

Data collection and management

Health workers in each registration centre formed a recruitment team and attended a three-day training course about the survey protocol. They subsequently collected data on each consenting smear-positive tuberculosis patient, including the patient's age, sex, level of education, occupation, marital status and HIV status – if known – and details of any previous tuberculosis treatment. After each patient was asked if they had received tuberculosis treatment, the patient's medical records at the health facility of recruitment were checked for evidence of such treatment.

Following national policy in Malawi,[8] each participant in the survey was offered HIV testing and counselling. At the time of the survey, two rapid blood tests – Uni-Gold Recombigen HIV-1/2 (Trinity Biotech, Bray, Ireland) and Determine HIV-1/2 (Alere, Waltham, United States of America) were used in the registration centres. Any samples giving inconclusive results were sent to the Central Reference Laboratory for retesting.

Data were collected on piloted forms and double-entered into an Epi Info (Centers for Disease Control and Prevention, Atlanta, United States of America) spreadsheet.

Participants and case definitions

Using the definitions recommended by WHO,[12] new cases were defined as people who had never been treated for tuberculosis – or had previously received anti-tuberculosis medications for less than one month – and retreatment cases were defined as those who had previously received tuberculosis treatment for at least one month. Retreatment cases were grouped according to the outcome of previous treatment: cured, completed, defaulted or failed. A patient was defined as cured when the person was smear-negative at, or one month before, treatment completion and on at least one previous occasion. A completed treatment was defined as a patient who completed treatment but without smear microscopy proof of cure. Persons who had treatment interruption for two consecutive months or more were grouped as defaulted. Those who remained smear-positive when tested five or six months after initiation of their previous treatment were defined as treatment failures.

For our survey, sputum samples were collected from each newly-diagnosed person with sputum-smear-positive tuberculosis seen at a registration centre in the northern, central and southern zones in May–July 2010, August–October 2010 and November 2010–January 2011, respectively. Sputum samples were also collected from each person with smear-positive tuberculosis undergoing retreatment at any registration centre between February 2010 and March 2011.

Drug resistance definition

Isolates of *M. tuberculosis* were defined as MDR if they were at least resistant to isoniazid and rifampicin, and extremely drug resistant (XDR) if they were also resistant to an injectable drug and a quinolone of the second-line medications.

Sample size projections

Assuming that 1.8% and 20% of the people newly diagnosed would have MDR tuberculosis and be lost to follow-up, respectively, we estimated that we needed to enrol 1260 new cases to estimate the prevalence of MDR tuberculosis among such cases with a precision of ± 1%. Similarly, assuming that 5.0% and 20% of our retreatment sample would have MDR tuberculosis and be lost to follow-up, respectively, we estimated that we would have to enrol 770 people undergoing retreatment to estimate the prevalence of MDR tuberculosis with a precision of ± 2.0%.

Laboratory procedures

Prior to enrolment, each participant had been found positive for tuberculosis by the microscopic examination of three smears of sputum.[12,13] Each month, a random selection of sputum smears from the registration centres – five from each health centre and 25 from each district hospital – was re-examined by a visiting laboratory supervisor. Concordance between the registration centres' results and the supervisor's remained above 96% during our survey.

For our survey, two additional sputum samples were collected – under supervision and approximately one hour apart – from each enrolled patient and stored at 2–8 °C in the registration centre. Efforts were made to ensure that these samples were collected before anti-tuberculosis treatment was commenced. The samples were transported to the Central Reference Laboratory, in cooler boxes, by bus or in a district health vehicle or study team vehicle.

Once a sample had reached the laboratory, it was decontaminated and further homogenized.[14] Part of the pellet produced by centrifuging the sample was smeared, stained with auramine phenol stain and then checked for acid-fast bacilli. Another part was inoculated into two tubes of Lowenstein–Jensen medium – one containing glycerol and the other containing sodium pyruvate – which were examined for growth weekly for up to 8 weeks. Each contaminated culture was discarded and replaced with a new culture that was set up using another part of the relevant pellet – which had been kept in a refrigerator. The Capilia tuberculosis test[15] was used to identify isolates belonging to the *M. tuberculosis* complex. Indirect susceptibility testing to isoniazid, rifampicin, ethambutol and streptomycin was performed, on one isolate per participant, using the proportion method on Lowenstein–Jenson medium.[16]

All isolates defined as MDR tuberculosis were sent to the South African Medical Research Council's Supranational Reference Laboratory in Pretoria. There, they were retested for their susceptibility to first-line drugs – using a line probe assay and automated liquid culture[17,18] – and tested for their susceptibility to the second-line drugs amikacin, kanamycin, capreomycin, ofloxacin and ethionamide – using automated liquid culture.

Statistical analysis

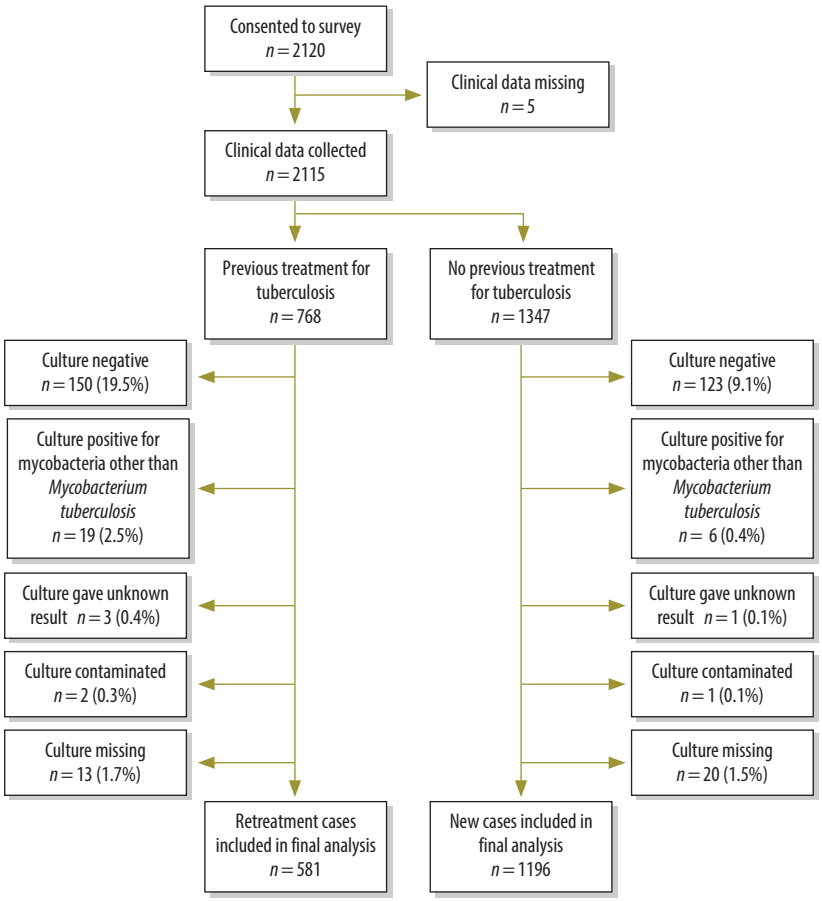
For our final analysis, we excluded those cases from which *M. tuberculosis* was not isolated in culture. Categorical and

non-parametric continuous variables were compared using χ^2 and Wilcoxon rank-sum tests, respectively. Data on new tuberculosis cases were analysed independently from retreatment cases. Associations between MDR tuberculosis and patient age, sex, HIV status, year of previous tuberculosis treatment and outcome of previous tuberculosis treatment were compared using Poisson logistic regression analysis. Unadjusted and adjusted incidence rate ratios (IRRs) were calculated in univariate and multivariate analyses, respectively. Stata 10.0 (StataCorp. LP, College Station, United States of America) was used for the statistical analysis.

Ethical considerations

Ethical approval was granted by the Malawi National Health Sciences Research Committee in April 2009. This study commenced in 2009, before requirements for review of all WHO-supported research by the WHO research ethics review committee were fully implemented. Written informed consent was obtained from adult participants and the caregivers of child participants. As recommended by the relevant national guidelines,[8] all cases of MDR tuberculosis were given six months of capreomycin, levofloxacin, ethionamide, cycloserine and pyrazinamide followed by 18 months of levofloxacin, ethionamide and cycloserine.

Fig. 1. **Flowchart to determine multidrug resistance in people diagnosed with tuberculosis in Malawi, 2010–2011**



Results

During the study period, 2120 smear-positive individuals consented to participate. Five were excluded as their baseline data were missing, another 1347 were classified as newly diagnosed with tuberculosis and the remaining 768 were classified as retreatment cases (Fig. 1). *M. tuberculosis* was isolated from 1196 (88.8%) of the new cases. There was no difference in the distribution of age, sex, region or HIV status between these and new cases from which *M. tuberculosis* was not isolated. *M. tuberculosis* was isolated from 581 (75.7%) of people undergoing retreatment. Those in whom *M. tuberculosis* was not isolated were older than the other retreatment cases, with mean ages of 40.7 and 36.4 years, respectively.

Compared with the new cases, people undergoing retreatment were more frequently found to be culture-negative or to be culture-positive for mycobacteria other than *M. tuberculosis*.

Of 86 treatment failures, 31 samples were culture-positive for *M. tuberculosis*, six were culture-positive for other mycobacteria and 49 were culture-negative.

The median transit time of all samples, from collection to arrival at the Central Reference Laboratory was 4 days (interquartile range, IQR: 2–7 days). Transit time had no apparent effect on the probability that a sample would be found culture-positive for *M. tuberculosis* ($P = 0.71$).

Culture-positive tuberculosis

Culture-positive individuals in both new and retreatment groups were similar in terms of their sociodemographic characteristics (Table 1).

Overall, 66.4% (386) of the retreatment cases and 48.2% (577) of the new cases were known or found to be infected with HIV, demonstrating a significantly higher HIV prevalence among people retreated ($P < 0.01$). The retreatment cases reported that they had received tuberculosis treatment between 1978 and 2010 with a median of 2.4 years (IQR: 1.1–5.9 years) before their enrolment. Just 31 (5.3%) of the culture-positive retreatment cases had failed their previous treatment (Table 1).

Among the 1196 *M. tuberculosis* isolates from new cases, ethambutol, isoniazid, rifampicin and streptomycin resistance was present in 0.5%, 3.2%, 0.8% and 4.2%, respectively (Table 2). The corresponding values for the 581 isolates from the retreatment cases were all higher (Table 2).

Five (0.4%) of the 1196 new cases had MDR tuberculosis (Table 2 and Fig. 2). Other types of resistance (mono-resistance or any combination of drug resistance excluding MDR tuberculosis) were identified in 75 (6.3%) of the new cases but the remaining 1116 (93.3%) *M. tuberculosis* isolates from new cases were found to be sensitive to all four first-line drugs.

Table 1. **Characteristics of people newly-diagnosed with, and retreated for, tuberculosis, Malawi, 2010–2011**

Characteristic	New cases ($n = 1196$)		Retreatment cases ($n = 581$)	
	No.	% (95% CI)	No.	% (95% CI)
Mean age (years)	1196	35.6 (34.8–36.4)	581	36.4 (35.5–37.4)
Sex (% male)	1196	53.7 (50.8–56.5)	581	60.6 (56.6–64.6)
Marital status (%)				
Married	750	63.2 (60.5–66.0)	346	60.3 (56.3–64.3)
Single	232	19.6 (17.3–21.8)	106	18.5 (15.3–21.7)
Divorced	103	8.7 (7.1–10.3)	70	12.2 (9.5–14.9)
Widowed	101	8.5 (6.9–10.1)	52	9.1 (6.7–11.4)
Occupation (%)				
Business	226	19.5 (17.2–21.8)	120	21.1 (17.8–24.5)
Formal employment	195	16.8 (14.7–19.0)	126	22.2 (18.8–25.6)
Subsistence farmer	330	28.4 (25.8–31.0)	148	26.1 (22.4–29.7)
Unemployed	409	35.3 (32.5–38.0)	174	30.6 (26.8–34.4)
Educational level achieved (%)				
Tertiary	23	2.0 (1.2–2.8)	13	2.3 (1.0–3.5)
Secondary	262	22.5 (20.1–24.9)	171	29.9 (26.1–33.7)
Primary	729	62.6 (59.8–65.4)	319	55.8 (51.7–59.9)
None	151	13.0 (11.0–14.9)	69	12.1 (9.4–14.7)
HIV status (%)				
Positive	577	48.2 (45.4–51.1)	386	66.4 (62.6–70.3)
Negative	474	39.6 (36.9–42.4)	165	28.4 (24.7–32.1)
Unknown	145	12.1 (9.4–14.8)	30	5.2 (2.6–7.7)
Region of residence (%)				
Northern	115	9.6 (7.9–11.3)	85	14.6 (11.8–17.5)
Central west	283	23.7 (21.3–26.1)	108	18.6 (15.4–21.8)
Central east	135	11.3 (9.5–13.1)	46	7.9 (5.7–10.1)
South-west	359	30.0 (27.4–32.6)	207	35.6 (31.7–39.5)
South-east	304	25.4 (22.9–27.9)	135	23.2 (19.8–26.7)
Outcome of previous treatment (%)				
Cured[a]	NA	NA	389	67.0 (63.1–70.8)
Completed[b]	NA	NA	104	17.9 (14.8–21.0)
Defaulted[c]	NA	NA	49	8.4 (6.2–10.7)
Failed[d]	NA	NA	31	5.3 (3.5–7.2)
Unknown	NA	NA	8	1.4 (0.4–2.3)
Smear score (%)[e]				
Scanty	101	8.6 (7.0–10.2)	66	11.6 (8.9–14.2)
1+	135	11.5 (9.6–13.3)	66	11.6 (8.9–14.2)
2+	295	25.0 (22.6–27.5)	115	20.1 (16.8–23.4)
3+	647	54.9 (52.1–57.8)	324	56.7 (52.7–60.8)

CI: confidence interval; HIV: human immunodeficiency virus; NA: not applicable.

[a] Cured defined as a smear-positive patient who was smear-negative at, or one month before, treatment completion and on at least one previous occasion.[12]

[b] Treatment completed defined as a patient who completed treatment but without smear microscopy proof of cure.[12]

[c] Defaulted defined as treatment interruption for two consecutive months or more.[12]

[d] Failed defined as remaining smear-positive when tested five or six months after initiation of previous treatment.[12]

[e] Smear scores indicate the density of acid-fast bacilli seen on a sputum smear.[13]

Note: Data are missing for some characteristics. The sum of the percentages for some characteristics may not equal 100 due to rounding.

Twenty-eight (4.8%) of the 581 *M. tuberculosis* isolates from retreatment cases showed multidrug resistance (Table 2). Other types of resistance were identified in 83 (14.3%) of the retreatment cases but the remaining 470 (80.9%) *M. tuberculosis* isolates from retreatment cases were found to be sensitive to all four first-line drugs (Table 2 and Fig. 2).

In the multivariate analysis, sex, age and HIV status were not found to be significantly associated with MDR tuberculosis among new or retreatment cases. There was also no evidence of a significant association between region of residence and MDR tuberculosis. All of the 28 retreatment cases with MDR tuberculosis had received treatment in the previous five years – 23 (82%) within the previous two years. MDR tuberculosis in people undergoing retreatment was found to be significantly and inversely associated with time since previous treatment (adjusted IRR: 0.7, 95% confidence interval, CI: 0.5–0.9). Previous treatment failure – but no other previous treatment outcome – was strongly associated with MDR tuberculosis (adjusted IRR: 3.7, 95% CI: 1.6–8.4). Of the 31 treatment failures, nine (29.0%) cultured multi-drug resistant *M. tuberculosis*.

Of the 33 isolates of *M. tuberculosis* found to be multidrug-resistant in Malawi, 30 successfully underwent retesting in South Africa, and 11 of these were sensitive to either isoniazid or rifampicin or both of these drugs. If the results from South Africa are used as the gold standard, this indicates a 36.7% false-positive rate (11/30 in Table 3). When a random sample of 106 isolates of *M. tuberculosis* found not to be multidrug-resistant in Malawi were retested in South Africa, one was identified as MDR tuberculosis – giving a 0.9% false-negative rate (1/106 in Table 3).

The 20 isolates found to show multidrug resistance in South Africa were re-cultured in South Africa and tested for resistance to several second-line drugs. Although 18 of these isolates were successfully re-cultured and tested, none showed extensive drug resistance (Table 4).

Discussion

This is the first national survey of anti-tuberculosis drug resistance done in Malawi. We found the prevalence of MDR tuberculosis among people

Table 2. **Resistance to first-line anti-tuberculosis drugs among *Mycobacterium tuberculosis* isolates, Malawi, 2010–2011**

Resistance	Isolates from new cases ($n = 1196$)		Isolates from retreatment cases ($n = 581$)	
	No.	% (95% CI)	No.	% (95% CI)
Fully sensitive	1116	93.3 (91.7–94.7)	470	80.9 (77.5–84.0)
Any resistance[a]				
R	9	0.8 (0.4–1.4)	38	6.5 (4.7–8.9)
H	38	3.2 (2.3–4.3)	66	11.4 (8.9–14.2)
E	6	0.5 (0.2–1.1)	18	3.1 (1.9–4.9)
S	50	4.2 (3.1–5.5)	49	8.4 (6.3–11.0)
Multidrug resistance	5	0.4 (0.1–1.0)	28	4.8 (3.2–6.9)
RH	2	0.2 (0.0–0.6)	13	2.2 (1.2–3.8)
RHE	0	0.0 (0.0–0.3)	1	0.2 (0.0–1.0)
RHS	1	0.1 (0.0–0.5)	6	1.0 (0.4–2.2)
RHES	2	0.2 (0.0–0.6)	8	1.4 (0.6–2.7)
Other forms of resistance	75	6.3 (5.0–7.8)	83	14.3 (11.5–17.4)
R only	3	0.3 (0.1–0.7)	9	1.5 (0.7–2.9)
H only	22	1.8 (1.2–2.8)	32	5.5 (3.8–7.7)
E only	2	0.2 (0.0–0.6)	4	0.7 (0.2–1.8)
S only	35	2.9 (2.1–4.1)	30	5.2 (3.5–7.3)
RS	1	0.1 (0.0–0.5)	0	0.0 (0.0–0.6)
RE	0	0.0 (0.0–0.3)	1	0.2 (0.0–1.0)
HE	1	0.1 (0.0–0.5)	2	0.3 (0.0–1.2)
HS	10	0.8 (0.4–1.5)	3	0.5 (0.1–1.5)
ES	1	0.1 (0.0–0.5)	1	0.2 (0.0–1.0)
HES	0	0.0 (0.0–0.3)	1	0.2 (0.0–1.0)

CI: confidence interval; E: ethambutol; H: isoniazid; R: rifampicin; S: streptomycin.
[a] Any resistance indicates resistance to the anti-tuberculosis medication tested, independent of resistance results to the other medications.

newly diagnosed to be low, at 0.4%. As about 7200 new cases of smear-positive tuberculosis have occurred annually in Malawi over recent years,[4] we can expect there to be 29 cases of primary MDR tuberculosis in Malawi annually. Although we found the prevalence of MDR tuberculosis among retreatment cases to be significantly higher, as generally observed,[19] this could be expected to produce only 27 secondary cases of MDR tuberculosis annually.

The rates described here represent the lowest values reported in sub-Saharan Africa up to 2011.[3] Neighbouring Mozambique identified multidrug resistance in 3.5% of new tuberculosis cases and 11.2% of retreatment cases in 2007. In 2009, Swaziland reported corresponding values of 7.7% and 33.9%, respectively.[5] During our survey, the Central Reference Laboratory successfully isolated *M. tuberculosis* from the sputum samples from 88.8% of new cases and 75.7% of retreatment cases. Although the sample transit times recorded during our survey were disappointing, long transit times were not associated with isolation failures. Mycobacteria could not be grown from 49 of 86 samples from treatment failures, probably because the bacilli in the 49 samples were dead. Mycobacteria other than *M. tuberculosis* were cultured from six treatment failures. The proportion of sputum samples from retreatment cases that were found culture-positive for *M. tuberculosis* was significantly lower than the corresponding value for the new cases. This difference is partly explained by (i) the low isolation rate from treatment failures; (ii) the fact that samples from retreatment cases were relatively more likely to grow mycobacteria other than *M. tuberculosis*; and (iii) the fact that sputum samples from retreatment cases are relatively more likely to be collected from patients who have already begun treatment for their current episode of tuberculosis.

Since the results recorded by Malawi's Central Reference Laboratory were associated with a 36.7% false-positivity rate and a 0.9% false-negativity rate, the prevalences of MDR tuberculosis that we recorded in Malawi – although low – could overestimate the true values. Given the laboratory's limited capacity and the observation that resistance patterns probably do not vary between smear-positive and smear-negative cases of tuberculosis,[20] we did not investigate the drug resistance of any *M. tuberculosis* isolates from smear-negative tuberculosis patients.

We found HIV prevalence among new smear-positive cases of pulmonary tuberculosis to be 48.2%. The HIV prevalences reported among all tuberculosis cases by Malawi's National Tuberculosis Programme in 2010 and 2011 were higher, at 63% and 60%, respectively.[21] The programme's observations indicate that HIV prevalence among smear-negative cases of pulmonary tuberculosis exceeded 65% in 2010–2011. By focusing on smear-positive cases, we probably limited the extent to which we could explore associations between HIV and MDR tuberculosis. Although we found no association between HIV and MDR tuberculosis, it is possible that such an association exists in the overall population of people with tuberculosis. The existence of such a link remains a matter of controversy[3,5,22,23] but concomitant HIV infection certainly poses some unique challenges in the management of tuberculosis.[10]

Although we collected samples from different areas of Malawi at different times of the year, a retrospective analysis of new tuberculosis case notifications between 1999 and 2007 suggested that there was little variation in the number of new cases occurring in each quarter of the year (James Mpunga, Malawi National Tuberculosis Control Programme, personal communication, 2010).

The low prevalence of MDR tuberculosis that we recorded may be attributable to the success of Malawi's tuberculosis control programme. The frequencies of success in the treatment of tuberculosis in Malawi – 88% for new cases and 85% for retreatment cases – are among the highest recorded in sub-Saharan Africa.[4] We recorded higher prevalences of streptomycin resistance than of rifampicin or isoniazid resistance, perhaps because streptomycin was included in the recommended first-line treatment for tuberculosis in Malawi until 1992.

Fig. 2. **Resistance patterns of *Mycobacterium tuberculosis* to anti-tuberculosis drugs, Malawi, 2010–2011**

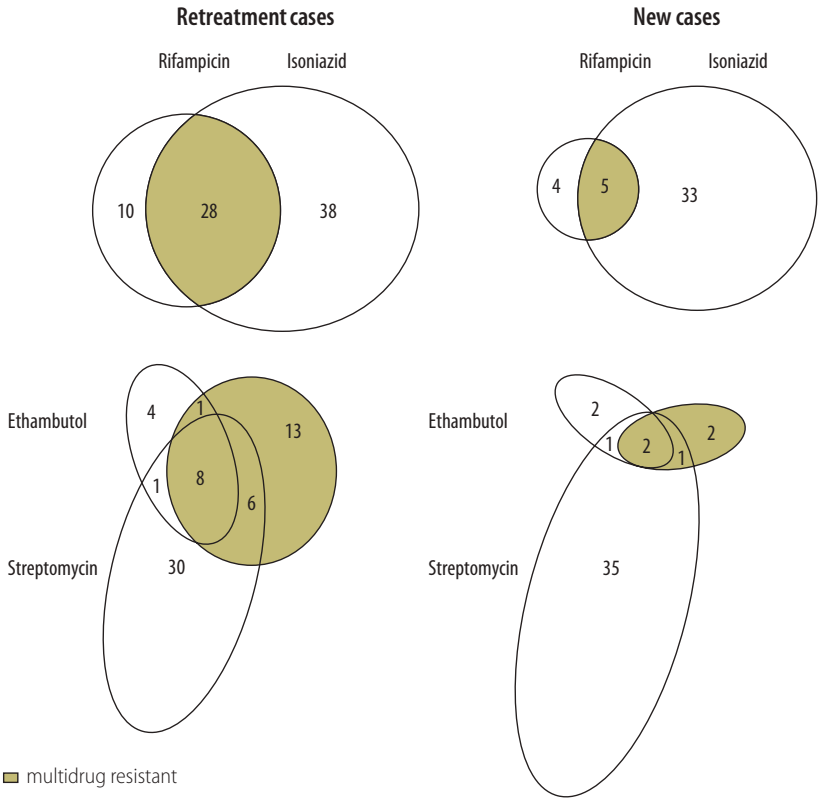


Table 3. **Comparison of anti-tuberculosis drug susceptibility testing of Malawian *Mycobacterium tuberculosis* isolates, 2010–2011**

Malawian result	South African result[a]			
	Sensitive to all drugs	Resistant to rifampicin only	Resistant to isoniazid only	MDR
Sensitive to all drugs	87	1	2	0
Resistant to rifampicin only	2	0	0	0
Resistant to isoniazid only	6	0	7	1
MDR	4	2	5	19

MDR: multidrug-resistant.

[a] The table shows the numbers of *M. tuberculosis* isolates, from Malawian cases of smear-positive pulmonary tuberculosis, that were tested for resistance to isoniazid, rifampicin, ethambutol and streptomycin in both the Central Reference Laboratory (Lilongwe, Malawi) and the South African Medical Research Council's Supranational Reference Laboratory (Pretoria, South Africa).

Table 4. **Resistance to second-line anti-tuberculosis drugs among 18 multidrug-resistant *Mycobacterium tuberculosis* isolates, Malawi, 2010–2011**

Isolate	Resistance[a]				
	Amikacin	Kanamycin	Capreomycin	Ofloxacin	Ethionamide
1–14	susceptible	susceptible	susceptible	susceptible	resistant
15	susceptible	resistant	susceptible	susceptible	resistant
16	susceptible	susceptible	resistant	susceptible	resistant
17	resistant	resistant	resistant	susceptible	resistant
18	resistant	susceptible	resistant	susceptible	resistant

[a] Amikacin, kanamycin, capreomycin, ofloxacin and ethionamide were tested at concentrations up to 1.0, 5.0, 2.5, 2.0 and 5.0 µg/mL, respectively.

We detected no XDR tuberculosis but did observe some resistance to second-line drugs. Since all of our isolates tested for resistance to ethionamide were found positive, the currently recommended 24-month regimen for the treatment of MDR tuberculosis in Malawi needs to be revised. Resistance to the second-line injectables was detected but not resistance to ofloxacin. At the time of the survey, Malawi's Central Reference Laboratory relied entirely upon the South African Supranational Reference Laboratory for the identification of Malawian cases of XDR tuberculosis.[8]

Treatment failure – frequently a forewarning for the development of drug-resistant tuberculosis[24] – was associated with a 29.0% risk of MDR tuberculosis in our survey. The initiation of a standard retreatment regimen while awaiting the results of drug susceptibility testing may amplify resistance in cases with pre-existing MDR tuberculosis.[25,26] Although use of an empirical MDR treatment regimen has been suggested as a replacement for the standard retreatment regimen for all treatment failures,[24,27,28] such a change in Malawi would expose most treatment failures – i.e. those who do not have MDR tuberculosis – to a more toxic and less effective therapy. During our survey, all patients with MDR tuberculosis who were diagnosed by phenotypic testing at the Central Reference Laboratory – including the 11 cases classified as drug sensitive when their sputum samples were investigated in South Africa – were managed with the nationally recommended second-line regimen. This was because (i) the phenotypic results were seen as more predictive of clinical response; (ii) the South African results became available several months after the patients had started second-line therapy; and (iii) it was felt that any changes to treatment made after the South African results became available would be confusing to patients.

Conclusion

The prevalence of MDR tuberculosis is currently low in Malawi – probably as the result of a strong tuberculosis control programme – whereas HIV-coinfection, which has been associated with high mortality in the presence of drug-resistant tuberculosis, is common. Almost a third of the treatment

failures we investigated had MDR tuberculosis. Given the discovery of ethionamide resistance in all 18 of the MDR tuberculosis isolates investigated for such resistance, ethionamide should be replaced with an alternative drug in Malawi's current MDR tuberculosis treatment regimen. Given an increasing prevalence of drug resistance in some neighbouring countries and the recent introduction of unsupervised rifampicin into tuberculosis treatment regimens in Malawi, we recommend repeating this survey within three years. ■

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Competing interests: None declared.

ملخص

مقاومة الأدوية للبكتريا المتفطرة السليّة في ملاوي: دراسة استقصائية متعددة القطاعات

الغرض توثيق انتشار مقاومة الأدوية المتعددة بين الأشخاص الذين جرى تشخيص إصابتهم حديثاً بالسل – والذين تكرر علاجهم من السل – في ملاوي.

الطريقة أجرينا دراسة استقصائية تمثيلية على الصعيد الوطني للأشخاص المصابين بالسل وسجلوا نتائج إيجابية لاختبار لطاخة البلغم بين 2010 و2011. وقمنا بجمع البيانات الديمغرافية والسريرية وعينتين من البلغم واختبارهما لتحديد الإصابة بفيروس العوز المناعي البشري من جميع المشاركين الذين أبدوا موافقتهم. وتم إجراء اختبار المقاومة للعينات في المختبر المرجعي المركزي في ليلونغوي، بملاوي. وتم تكرار اختبار جميع مستفردات البكتريا المتفطرة السليّة التي تبين مقاومتها للأدوية المتعددة من أجل تحديد مقاومتها لأدوية الخط الأول – واختبارها من أجل تحديد مقاومتها لأدوية الخط الثاني – في مختبر مرجعي للسل على الصعيد فوق الوطني في جنوب أفريقيا.

النتائج بشكل عام، تم استفراد البكتريا المتفطرة السليّة من 1777 (83.8 ٪) مريضاً من أصل 2120 مريضاً بالسل سجلوا نتائج إيجابية لاختبار اللطاخة. وتم تحديد مقاومة الأدوية المتعددة في خمس (0.4 ٪) من أصل 1196 مستفردة من حالات جديدة و28 (4.8 ٪) من أصل 581 مستفردة من الأشخاص الذين تكرر علاجهم. وأظهرت تسع (29.0 ٪) من أصل 31 مستفردة من الحالات التي تكرر علاجها بعد فشل علاجها في السابق مقاومة للأدوية المتعددة. وعلى الرغم مما تبين من مقاومة لأدوية الخط الثاني، لم يتم اكتشاف حالات للسل الشديد المقاوم للأدوية. وتبين من اختبار فيروس العوز المناعي البشري للأشخاص الذين تم الحصول على مستفردات البكتريا المتفطرة السليّة منهم أن 577 (48.2 ٪) من الأشخاص الذين جرى تشخيصهم حديثاً و386 (66.4 ٪) من الأشخاص الذين تكرر علاجهم سجلوا نتائج إيجابية.

الاستنتاج كان انتشار مقاومة الأدوية المتعددة بين الأشخاص المصابين بالسل الذين سجلوا نتائج إيجابية لاختبار اللطاخة منخفضاً في أفريقيا جنوب الصحراء الكبرى – بما يوضح على نحو محتمل قوة برنامج مكافحة السل في ملاوي. من المحتمل أن يؤكد الارتفاع النسبي لانتشار هذه المقاومة التي لوحظت بين الأشخاص الذين فشل علاجهم في السابق على الحاجة للتغيير في السياسة الوطنية من أجل تكرار علاج هذه الفئة الفرعية من الأشخاص المصابين بالسل.

摘要

马拉维分枝杆菌肺结核耐药性：横断面调查

目的 记录马拉维肺结核新诊以及复治人群多耐药性流行率。

方法 我们针对 2010 年和 2011 年之间痰涂片阳性肺结核患者进行了具有全国代表性的调查。对于所有的参与者，我们都收集了人口和临床数据、两份唾液样本并进行艾滋病毒（HIV）检测。这些样本在马拉维隆圭中央参考实验室接受耐药性检测。在南非超国家结核病参考实验室对发现具有多耐药性的所有分枝杆菌肺结核分离菌再次进行一线药物的耐药性检测，然后进行二线药物耐药性检测。

结果 总的来说，在 2120 名痰涂片阳性肺结核患者中，从 1777 名（83.8%）患者中分离出肺结核分枝杆菌。从新患者的 1196 个分离菌中确定了 5 个（0.4%）有多耐药性，从复治患者的 581 个分离菌中确定了 28 个（4.8%）有多耐药性。在曾经治疗失败的复治病例中获得的 31 个分离菌中，9 个（29.0%）显示出多耐药性。尽管发现二线药物耐药性，但未发现广泛耐药性的肺结核病例。对获得肺结核分枝杆菌分离菌人群的艾滋病毒检测显示，新患者中有 577 例（48.2%）为阳性，复治患者中有 386 例（66.4%）为阳性。

结论 撒哈拉以南非洲痰涂片阳性肺结核患者多耐药性的流行率较低——可能反映了马拉维的肺结核病控制规划的效力。在先前治疗失败的人群中观察这种耐药性的流行率相对较高，这可能凸显了对这个肺结核患者子群的全国性复治政策作出改变的需求。

Résumé

Pharmacorésistance du *Mycobacterium tuberculosis* au Malawi: une enquête transversale

Objectif Documenter la prévalence de la résistance polymédicamenteuse de la tuberculose parmi les personnes nouvellement diagnostiquées et les personnes traitées à nouveau au Malawi.

Méthodes Nous avons mené une enquête nationale représentative des personnes atteintes de tuberculose à frottis d'expectoration positif entre 2010 et 2011. Pour tous les participants consentants, nous avons recueilli les données démographiques et cliniques, deux échantillons d'expectoration et effectué le dépistage du virus de l'immunodéficience humaine (VIH). Les échantillons ont subi des tests de résistance au Laboratoire central de référence de Lilongwe, au Malawi. Tous les isolats de *Mycobacterium tuberculosis* qui ont présenté une résistance polymédicamenteuse ont été retestés pour la résistance aux médicaments de première intention - et testés pour la résistance aux médicaments de deuxième intention – dans un laboratoire de référence supranational pour la tuberculose en Afrique du Sud.

Résultats Dans l'ensemble, *M. tuberculosisM. tuberculosis* a été isolé chez 1777 (83,8%) des 2120 patients atteints de tuberculose à frottis positif. La résistance polymédicamenteuse a été identifiée dans 5 (0,4%) des 1196 isolats obtenus à partir des nouveaux cas et dans 28 (4,8%) des 581 isolats obtenus à partir des personnes qui recevaient à nouveau un traitement. Parmi les 31 isolats issus des cas retraités qui ont connu un échec de traitement, 9 (29%) isolats ont présenté une résistance polymédicamenteuse . Bien que la résistance aux médicaments donnés en deuxième intention ait été identifiée, aucun cas de tuberculose ultrarésistante aux médicaments n'a été détecté. Les dépistages du VIH des personnes à partir desquelles les isolats de *M. tuberculosisM. tuberculosis* ont été obtenus ont montré que 577 (48,2%) des personnes nouvellement diagnostiquées et 386 (66,4%) des personnes recevant à nouveau le traitement étaient séropositives.

Conclusion La prévalence de la résistance polymédicamenteuse chez les personnes atteintes de tuberculose à frottis positif était faible en Afrique subsaharienne – reflétant probablement la force du programme de contrôle de la tuberculose du Malawi. La prévalence relativement élevée de cette résistance observée chez les personnes pour lesquelles le traitement précédent a échoué peut mettre en évidence un besoin de changement dans la politique nationale en matière de retraitement de ce sous-groupe de personnes atteintes de tuberculose.

Резюме

Лекарственная устойчивость *микобактерий туберкулеза* в Малави: перекрестное исследование

Цель Задокументировать распространенность множественной лекарственной устойчивости при первичном и повторном лечении больных туберкулезом в Малави.

Методы В 2010-2011 гг. было проведено национальное репрезентативное исследование больных туберкулезом легких с бактериовыделением. У всех согласившихся принять участие в исследовании были собраны демографические и клинические данные и взяты два образца мокроты; кроме того, они прошли тестирование на вирус иммунодефицита человека (ВИЧ). Лекарственная устойчивость полученных образцов была проверена в Центральной референс-лаборатории г. Лилонгве, Малави. Все изоляты микобактерий туберкулеза с выявленной множественной лекарственной устойчивостью были подвергнуты дополнительному тестированию на устойчивость к лекарственным препаратам первой и второй линии в наднациональной туберкулезной референс-лаборатории в Южной Африке.

Результаты В итоге, наличие *микобактерий туберкулеза* было выявлено у 1777 (83,8%) из 2120 больных туберкулезом легких с бактериовыделением. Множественная лекарственная устойчивость была обнаружена у пяти (0,4%) из 1196 изолятов, взятых у лиц, получавших первичное лечение туберкулеза, и у 28 (4,8%) из 581 изолятов, взятых у лиц, получавших повторное лечение. Из изолятов, взятых у лиц, получавших повторное лечение после неудачного первичного, множественная лекарственная устойчивость была выявлена в девяти (29%) случаях из 31. Притом, что устойчивость к лекарствам второй линии была обнаружена, случаев туберкулеза с широкой лекарственной устойчивостью выявлено не было. Тестирование на ВИЧ лиц, у которых были выделены изоляты микобактерий туберкулеза, показало наличие вируса у 577 (48,2%) больных, у которых туберкулез был выявлен впервые, и у 386 (66,4%) больных, получавших повторное лечение.

Вывод Распространенность лекарственной устойчивости среди больных туберкулезом легких с бактериовыделением в странах Африки южнее Сахары невелика, что, по-видимому, свидетельствует об эффективности противотуберкулезной программы Малави. В то же время, довольно высокая распространенность таких случаев среди лиц, лечение которых в прошлом не принесло результата, может указывать на необходимость изменения национального подхода к повторному лечению этой подкатегории больных туберкулезом.

Resumen

Resistencia medicamentosa a la *Mycobacterium tuberculosis* en Malawi: una encuesta transversal

Objetivo Documentar la prevalencia de la resistencia a medicamentos múltiples entre pacientes a quienes se ha diagnosticado recientemente o han vuelto a recibir tratamiento para la tuberculosis en Malawi.

Métodos Llevamos a cabo una encuesta representativa a nivel nacional de pacientes con tuberculosis que dieron positivo en el análisis de esputo entre 2010 y 2011. Para todos los participantes adultos, se recogieron datos demográficos y clínicos, dos muestras de esputo y realizamos pruebas del virus de inmunodeficiencia humana (VIH). Las muestras se sometieron a pruebas de resistencia en el Laboratorio Central de Referencia en Lilongwe (Malawi). Se volvieron a examinar todas las cepas de *Mycobacterium tuberculosis* multirresistentes para probar la resistencia a los medicamentos de primera línea y se probó su resistencia a los medicamentos de segunda línea en un laboratorio de referencia supranacional para la tuberculosis en Sudáfrica.

Resultados En general, la *M. tuberculosisM. tuberculosis* se aisló en 1777 (83,8%) de los 2120 pacientes de tuberculosis con baciloscopia positiva. Se detectó multirresistencia a medicamentos en cinco (0,4%) de las 1196 cepas de casos nuevos y en 28 (4,8%) de las 581 cepas de pacientes que se volvieron a someter al tratamiento. De las 31 cepas de casos de repetición del tratamiento que no habían respondido

previamente al tratamiento, nueve (29,0%) mostraron multirresistencia a medicamentos. Pese a que se halló resistencia a los medicamentos de segunda línea, no se detectaron casos de tuberculosis con resistencia extendida a medicamentos. Las pruebas del VIH de quienes se obtuvieron cepas de *M. tuberculosisM. tuberculosis* mostraron que 577 (48,2%) de los pacientes con diagnóstico reciente y 386 (66,4%) de los pacientes que se volvieron a someter al tratamiento dieron positivo.
Conclusión La prevalencia de la multirresistencia a medicamentos entre los pacientes con tuberculosis que dieron positivo en la baciloscopia positiva fue baja en el África subsahariana, lo cual probablemente refleja la eficacia del programa de control de la tuberculosis de Malawi. La prevalencia relativamente alta de dicha resistencia observada entre los pacientes que no respondieron al tratamiento anterior puede poner de manifiesto la necesidad de un cambio en la política nacional para volver a tratar a este subgrupo de pacientes con tuberculosis.

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SUPPLEMENT: THE ETHIOPIAN OR INITIATIVE

Poor symptomatic tuberculosis screening practices in a quarter of health centres in Amhara Region, Ethiopia

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Setting: In 2011, Ethiopia introduced a strategy of symptomatic tuberculosis (TB) screening for patients attending out-patient services to increase identification of presumptive TB.

Objective: To assess implementation and factors affecting symptomatic TB screening at out-patient departments in health centres in the Amhara Region, Ethiopia.

Design: Using a cross-sectional study design, 86 randomly selected public health centres providing DOTS were included in the study. Data were captured by reviewing TB registers and interviewing key informants at out-patient services.

Results: Of 86 health centres, 24 (28%) had poor symptomatic TB screening practices, defined as screening <80% of attending out-patients. Having an actively functioning multidisciplinary health centre team to assess TB services (aOR 2.29, 95%CI 2.23–30.80) and partner support for TB activities (aOR 4.84, 95%CI 1.05–22.40) were associated with higher TB screening rates, whereas availability of antiretroviral therapy was negatively associated. In all health centres combined, 1.6% of out-patient department attendees were identified as having presumptive TB.

Conclusion: A quarter of health centres had poor symptomatic TB screening practices in the out-patient services in this study. Strengthening multidisciplinary teams and expanding partner support are recommended to improve TB screening practices at out-patient services in Ethiopia.

In 2012, Ethiopia ranked eighth among the world's 22 high TB burden countries.[1] The Ethiopian TB case finding strategy for TB control consists of the detection of TB among all persons presenting to health services with symptoms indicative of TB.[2] By implementing the DOTS strategy, the country achieved a case detection rate of 64%.[1] The Amhara Region reports a case detection rate of 56%,[3] which is below both the international target of 70% and the national average.

In 2011, Ethiopia introduced a strategy to implement symptomatic TB screening for all persons attending out-patient services. This coincided with the introduction of the reformed Health Management Information System out-patient department (OPD) register to capture data on the screening and identification of patients with presumed TB. This strategy was supplemented by the updated national comprehensive training manual for clinical and programmatic management of TB, leprosy and TB-HIV (human immunodeficiency virus), which also highlights the need to screen every person visiting a health facility for TB.[4] There is no published information on the implementation of the strategy in the region or the country at large.

The objective of the present study was to assess the level of implementation and factors affecting symptomatic TB screening among out-patients attending public health centres in the Amhara Region.

STUDY POPULATION, DESIGN AND METHODS

An institution-based cross-sectional study was conducted from 30 September to 18 October 2013 in selected health centres in the Amhara Region, which has an estimated population of 18.9 million, of whom 87% live in rural areas.[3] There are 801 health centres in the region; each health centre provides services for on average 25 000 people within a 10 km radius. TB diagnostic and treatment services are provided free of charge at all government facilities. Public health centres providing DOTS services in OPDs were included.

A sample size of 86 health centres was obtained using the single-population proportion formula for finite populations in Open-Epi software (Emory University, Atlanta, GA, USA). We assumed 50% of the health centres to have good TB screening practices on review, with a 10% margin of error and 95% confidence levels.

Of the 10 administrative zones (defined as a group of adjacent districts) in Amhara, five (North Gondar, South Wollo, West Gojam, Awi and Oromia) were purposively selected based on their geographical distribution in the region, population size and accessibility. The 86 health centres were allocated to the selected zones proportionate to the number of health centres. The number of health centres in each zone was then selected using simple random sampling.

Data were collected using interviews with OPD case managers, record reviews (OPD and laboratory registration books) and observation (availability of TB screening job aids). A pre-tested structured questionnaire was used to assess the profile of the health centres, health professionals and TB screening-related variables for the period from 1 April to 30 June 2013. Data collectors were experienced health professionals trained and supervised by the study team during data collection.

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TABLE 1 Operational definitions

The following definitions were used:

- Functioning multidisciplinary team: clinic team composed of ART pharmacist, ART officer, ART nurse, TB focal person, laboratory personnel, OPD case team leader, counsellors, prevention of mother-to-child HIV transmission focal person, infection prevention officer, ART adherence case manager and head of health centre who meet every 2 weeks to discuss TB and HIV issues; minutes of meetings are kept
- Infection prevention committee: team consisting of representatives from each service delivery unit that meets every 2 weeks to discuss overall infection prevention and control, including TB infection control, and keeps minutes of meetings
- Patient overload: average number of patients per OPD room exceeds 24/day
- Presumptive TB case: any person who presents with symptoms and/or signs suggestive of TB, in particular, cough of ⩾2 weeks and/or constitutional symptoms (loss of appetite, weight loss, fever, night sweats and fatigue)
- Regular supervision by *woreda* health office: at least monthly supervision visits to health centres by *woreda* health officers
- Review meeting: a quarterly meeting conducted to evaluate performance against quarterly plan and recommendations made by health centres, *woreda* health office, the zonal health department and the regional health bureau, partners and other stakeholders
- Symptomatic TB screening practice: considered good if a health centre screened ⩾80% of all OPD attendants for TB during the study period
- TB training: training of OPD staff in the previous year on TB, TB-HIV, TB/leprosy or infection prevention
- *Woreda* officers: health professionals assigned at *woreda* (district) level and responsible for planning, supervising and evaluating health centres in their territory
- Written feedback from supervisors: reports outlining strengths and weaknesses of OPD services observed during supervision visits

ART = antiretroviral therapy; TB = tuberculosis; OPD = out-patient department; HIV = human immunodeficiency virus.

Each questionnaire was reviewed and checked for accuracy and completeness by the study team. Epi-Info™ version 3.5.1 (Centers for Disease Control and Prevention, Atlanta, GA, USA) was used for double data entry. STATA version 11.0 (Stata Corp, College Station, TX, USA) and SPSS version 16 (Statistical Package for the Social Sciences, Chicago, IL, USA) statistical packages were used for data analysis. The health centre was used as the unit of analysis, and descriptive statistics were used to determine the proportion of health centres with good screening practice (Table 1) and the yield of the screening. The mean was calculated for normally distributed data, while for skewed data the median was calculated. The association between response and explanatory variables was measured using odds ratios (OR) with 95% confidence intervals (CI) obtained from multivariate logistic regression analysis.

Ethics clearance was obtained from the Regional Ethical Review Committee of the Amhara Regional Health Bureau (Bahir Dar, Ethiopia). A letter of permission was obtained from each Zonal Health Department and the heads of health centres. Verbal consent was provided by study participants.

RESULTS

Characteristics of health centres

All 86 selected health centres were included in the study. The median number of out-patients seen per day and room was 15.8 (interquartile range 8.2). The median number of OPD rooms per health centre was 2.0, ranging from 1 (33.7% of the health centres) to 5 (2.3% of the health centres). Of the 83 health centres with sputum microscopy services, 13 (15.7%) experienced service interruptions of an average duration of 20 days during the study period.

Fifty-two (60.5%) health centres had an actively functioning multidisciplinary team (MDT) or infection prevention (IP) team, with existing documentation of meetings held. The mean number of meetings in a quarter was 2.7 (standard deviation ± 1.3). *Woreda* officers carried out supervisory visits to 79 (91.9%) of the health centres, and the number of visits ranged from 1 to 8 (median = 1). Supervision was monthly for a quarter of the health centres, while two thirds were irregularly supervised and nearly 10% were not supervised at all in 2012–2013 (Table 2). Seventy-four (86%) health centres had a partner organisation supporting TB activities in terms of supervision (94.6%), training (83.8%), provision of microscope (83.4%) and job aids (33.8%), furniture (28.4%) and other items, such as computers (14.9%). In the study facilities, 24.2% (89/368) of the health professionals had received training in TB or TB-HIV on at least one occasion during the previous year.

Proportion of health centres implementing symptomatic TB screening

Of the 86 health centres, three (3.5%) did not screen OPD patients for TB at all and two (2.3%) documented only bacteriologically confirmed TB patients and not presumptive TB cases; 24 (28%) screened <80% of OPD patients. The overall yield of the symptomatic TB screening was 1.6%, i.e., 16 presumptive TB patients/1000 screened OPD patients. The yield differed in centres with good (⩾80% screened) and poor (<80% screened) screening rates (1.8% and 0.8%, respectively). This difference was significant ($P = 0.002$). Variations in screening practice across the zones were observed. All health centres in the North Gondar Zone screened at least 80% of OPD patients, while health centres in the Awi and West Gojjam Zones screened only about one third of patients (Figure).

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Conflicts of interest: none declared.

TABLE 2 Frequency distribution of health centre characteristics, Amhara Region, Ethiopia, 2013

Variable	*n* (%)
Availability of job aids for symptomatic TB screening	
Yes	81 (94.2)
No	5 (5.8)
Sputum microscopy available	
Yes	83 (96.5)
No	3 (3.5)
Availability of ART service	
Yes	52 (60.5)
No	34 (39.5)
Functional MDT/IP team	
Yes	52 (60.5)
No	34 (39.5)
Supervision by *woreda* health officers	
Yes	79 (91.9)
No	7 (8.1)
Provision of supervision feedback	
Yes	69 (80.2)
No	17 (19.8)
Partner support for TB activities	
Yes	74 (86.0)
No	12 (14.0)
Conduct review meeting	
Yes	74 (86.0)
No	12 (14.0)

TB = tuberculosis; ART = antiretroviral therapy; MDT = multidisciplinary team; IP = infection prevention; *woreda* = district.

Factors associated with the implementation of symptomatic TB screening

TB training, availability of antiretroviral therapy (ART), partner support for TB activities, feedback from supervision, supervision, MDT/IP meetings, patient overload and conducting review meetings were investigated for association with good screening practice. In the bivariate logistic regression analysis, screening practice was only significantly associated with MDT/IP meetings. In multivariate logistic analysis, three independent variables (MDT/IP, $P = 0.002$; ART service, $P = 0.028$; and availability of partners, $P = 0.044$) were significantly associated with screening practice.

Health centres with an actively functioning MDT/IP team were 8.3 times more likely to screen ⩾80% of OPD patients than health centres without a team (Table 3). Health centres with partner support for TB activities were 4.8 times more likely to screen ⩾80% of OPD patients than health centres without partner support. Screening practice was significantly lower among health centres with ART services: centres without ART service were five times more likely to screen OPD patients for TB.

DISCUSSION

This study showed that 72.1% of the health centres screened ⩾80% of OPD patients for TB. This supports the finding of a study from Ghana that concluded that systematic active screening of OPD attendees is feasible under programme conditions.[5] One of the factors significantly associated with good screening practice was holding regular MDT/IP meetings to monitor TB activities. In addition, availability of partners to support TB activities and not having an ART service were also significantly associated with good screening practice at the OPD.

Twenty-four (27.9%) of the health centres had unsatisfactory symptomatic TB screening of OPD patients. This is higher than the proportion (10.9%) reported earlier by Heal TB among the Management Sciences for Health supported health centres in four zones.[6] This difference could be attributed to the continuous clinical mentorship, regular programme monitoring and other capacity building activities provided by the partner. In our study, in addition to Heal TB, other partners, such as the International Training and Education Centre for Health (I-TECH) and the Ethiopia Network for HIV/AIDS Treatment, Care & Support (ENHAT-CS), were active in the study zones. Although partner support differs in scope and content, all were providing support for TB activities. Health centres supported by partners focusing on TB were 4.8 times more likely to have good screening practice.

Having a functioning MDT/IP team was significantly associated with good TB screening practice, as health centres with teams were eight times more likely to screen ⩾80% of OPD patients. In these TB programme-specific facility level meetings, health professionals discuss case-finding efforts, such as symptomatic TB screening, community suspect referrals, contact screening, intensified case finding activities and the quality of DOTS provided. Health care workers (HCWs) working at different

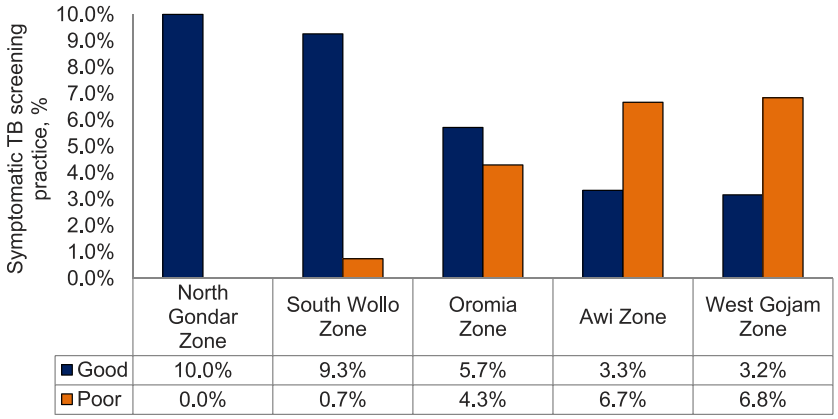

FIGURE Symptomatic TB screening practice at health centre out-patient departments by zone in the Amhara Region, Ethiopia, 2013. TB = tuberculosis.

TABLE 3 Bivariate and multivariate analysis of factors affecting screening practice, Amhara Region, Ethiopia, 2013

Variables	Screening practice		OR (95%CI)	aOR (95%CI)
	Good (⩾80%)	Poor (<80%)		
TB training				
Yes	36	15	0.83 (0.32–2.19)	0.49 (0.14–1.69)
No	26	9	1	1
Availability of ART service				
Yes	35	17	0.53 (0.19–1.47)	0.22 (0.06–0.85)*
No	27	7	1	1
Partner support for TB activities				
Yes	56	18	3.11 (0.89–10.86)	4.84 (1.05–22.4)*
No	6	6	1	1
Supervision by *woreda* health officers				
Yes	58	21	2.07 (0.43–10.04)	4.08 (0.69–24.12)
No	4	3	1	1
Functional MDT/IP team				
Yes	43	9	3.77 (1.41–10.12)*	8.29 (2.23–30.80)*
No	19	15	1	1
Patient overload				
Yes	10	3	0.74 (0.19–2.97)	0.53 (0.10–2.78)
No	52	21	1	1
Conduct review meeting				
Yes	52	22	0.47 (0.10–2.34)	0.18 (0.02–1.56)
No	10	2	1	1

*Statistically significant.
OR = odds ratio; CI = confidence interval; aOR = adjusted OR; TB = tuberculosis; ART = antiretroviral therapy; MDT = multidisciplinary team; IP = infection prevention; *woreda* = district.

entry points participate in these meetings.[7] MDT/IP team meetings help HCWs to evaluate their performance every 2 weeks and identify local solutions to strengthen services.

In this study, screening practices were significantly poorer among health centres with ART services. This could be a result of a shift in focus among health care providers to screen patients for TB in the HIV clinic rather than in the OPD. As ART clinics were not included in this study, this assumption needs further investigation. However, if confirmed this would be disturbing, as screening would then only focus on people living with HIV (PLHIV) and not all health centre attendees. Although PLHIV are at higher risk of TB, only 40% of TB cases in the region were co-infected with HIV.[3]

Reported OPD patient load was not associated with screening practice in the current study. However, a study in South Africa showed that clinics with a high patient load were less likely to screen than clinics with fewer attendees.[8] A study in Pakistan reported that both excessive workload and extremely low workload were associated with poor performance.[9] In our study, recent TB training of HCWs was not associated with TB screening practice. The study from South Africa indicated that follow-up training of HCWs increased the effectiveness of integrated TB-HIV screening.[8] This could be due to fact that some HCWs who attended training in our setting may not have been working in OPDs due to work rotation. HCWs with TB training should be assigned to TB clinics to strengthen anti-tuberculosis treatment.

The observed yield of presumptive TB at OPDs was 1.6%. This is lower than the World Health Organization estimate (5–10%) and reports from South India that 6.7% of out-patients in health centres were symptomatic for TB.[10,11] The possible reasons for the lower yield include lower magnitude of TB symptoms, poor screening quality and poor documentation. This should be investigated further.

Our study was limited by the small sample size, leading to wide CIs. Data were collected from existing records that may have been inaccurate. We were unable to link the health centre's OPD activity with TB-related laboratory activities, as both have different log books.

In conclusion, although the TB screening policy has been implemented widely in the Amhara Region, a quarter of the health centres still had poor symptomatic TB screening practices in the OPD services. To enhance TB detection, strengthening health centre TB meetings and expanding partner support for TB control are proposed. The negative association between the presence of ART services and OPD performance in TB screening needs to be further investigated.

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Contexte : En 2011, l'Ethiopie a introduit une stratégie de dépistage de la tuberculose (TB) basé sur les symptômes parmi les patients venant en consultation externe afin d'augmenter l'identification de patients suspects de TB.
Objectif : Evaluer la mise en œuvre et les facteurs affectant le dépistage symptomatique de la TB en consultation externe dans des centres de santé de la région d'Amhara, Ethiopie.
Schéma : Grâce à une étude transversale, 86 centres de santé publics, choisis au hasard et offrant des services DOTS, ont été inclus dans cette étude. Les données ont été recueillies grâce à une revue des registres et à des entretiens avec les personnes clé des services de consultations externes.
Résultats : Vingt-huit pour cent des centres de santé (24/86) avaient une pratique médiocre du dépistage symptomatique de la TB, définie comme un dépistage de <80% des consultants externes. Les facteurs associés à un dépistage plus exhaustif comprenaient le fait d'avoir un centre de santé actif et bien fonctionnel, une équipe multidisciplinaire discutant des services liés à la TB (aOR 2,29, IC95% 2,23–30,80) et un soutien d'un partenaire pour les activités liées à la TB (aOR 4,84, IC95% 1,05–22,40) ; par contre, la disponibilité du traitement antirétroviral y était négativement associée. Dans tous les centres de santé combinés, 1,6% des consultants externes ont été identifiés comme suspects de TB.
Conclusion : Dans cette étude, un quart des centres de santé avait une pratique de dépistage de la TB médiocre dans ses services de consultation. Il est recommandé de renforcer les équipes multidisciplinaires et d'étendre le soutien par un partenaire afin d'améliorer la pratique du dépistage de la TB dans les services de consultation externe en Ethiopie.

Marco de referencia: En el 2011 se introdujo en Etiopía una estrategia de detección sistemática de la tuberculosis (TB) sintomática en los pacientes que acuden a los servicios ambulatorios, con el objeto de mejorar el reconocimiento de los casos con presunción clínica de TB.
Objetivo: Evaluar la aplicación de la estrategia de detección sistemática y los factores que influyen sobre sus resultados en los servicios ambulatorios de los establecimientos de salud en la región de Amhara en Etiopía.
Método: En un examen transversal se seleccionaron de manera aleatoria, con el fin de participar en el estudio, 86 centros de atención sanitaria que prestan servicios de DOTS. Los datos se obtuvieron a partir del examen de los registros clínicos y mediante entrevistas a los informantes clave en los servicios ambulatorios.
Resultados: Se observó que en 28% (24 de 86) de los centros sanitarios las prácticas de detección sistemática de la TB sintomática eran deficientes, pues alcanzaban <80% de los pacientes ambulatorios. Los siguientes factores se asociaron con una tasa más alta de detección: un equipo multidisciplinario operativo que examine los servicios relacionados con la TB en el centro (ORa 2,29; IC95% 2,23–30,80) y el respaldo de los organismos asociados a las actividades relacionadas con la TB (ORa 4,84; IC95% 1,05–22,40); la oferta de tratamiento antirretrovírico ofreció una relación inversa con la detección de la TB. En general, se estableció el diagnostico presuntivo de TB en 1,6% de los pacientes ambulatorios que acudieron a todos los centros.
Conclusión: En un cuarto de los establecimientos sanitarios examinados en el presente estudio las prácticas de detección sistemática de la TB en los servicios ambulatorios eran deficientes. Se recomienda fortalecer los equipos multidisciplinarios y ampliar el respaldo de los asociados con el propósito de mejorar la detección de la TB en Etiopía.

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Research

Knowledge of tuberculosis management using directly observed treatment short course therapy among final year medical students in South Western Nigeria

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Key words: Tuberculosis, Directly observed treatment short course therapy (DOTS).

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Abstract

Introduction: Equipping medical graduates with the competence to manage tuberculosis is not just imperative but also urgent as the diseases have been consistently listed as one of the major causes of morbidity and mortality in Nigeria. However, there were no baseline studies done on knowledge of final year medical students on various aspects of TB diagnosis and management under directly observed treatment short course therapy (DOTS) which forms the basis of this study. **Methods:** A total of 241 final year medical students from three medical colleges in Nigeria were interviewed. The questions assessed their knowledge about various modes of transmission, symptoms and management of tuberculosis under DOTS. **Results:** More than half of the respondents (i.e. 69%) had poor knowledge on TB disease. Only 33.6% mentioned sputum smear as the best tool of diagnosing TB according to guideline. Poor knowledge was also exhibited when asked of various categories under DOTS treatment regimen, as 46.1% correctly mentioned cat 1 and 2. Minority 18.7% and 6.7% had complete knowledge of 6 months duration for new TB cases and 8 months for re-treatment cases respectively. Less than one tenth, i.e. 4.6% and 2.9% could correctly defined what is called a new TB case and re-treatment cases according to standard guideline. **Conclusion:** The study reveals gross inadequacies in TB knowledge and management practices among Nigerian final year medical students. There is urgent need for incorporation of National TB guideline into existing undergraduate medical education curriculum as well as students rotation through activities in DOTS clinic.

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Introduction

Tuberculosis (TB) has re-emerged as a major global public health concern since the mid-1980s. Globally, Tuberculosis accounted for 1.2 - 1.5 million deaths (including mortality due to Tuberculosis as well as TB and HIV co-infection), 85% of this occurring in developing countries and 26% in Africa [1]. Thus, TB ranks as the second highest cause of adult mortality after HIV in the world. It also tends to affect men more than women, mostly among the economically productive age group. [1] Factors contributing to the re-emergence include pervasive poverty and lack of good governance, the HIV/AIDS epidemic poor public health services, rapid population growth and rapid urbanization [2].

TB is a highly contagious and fatal disease of public health concern particularly in low income countries. [3] It remains a major cause of high morbidity and mortality in these countries despite considerable decline in prevalence in the developed world [4]. Unfortunately, it affects mainly the economically productive age group despite the availability of cure [5]. The disease spreads through air by droplet nuclei and the micro-organisms enter the body through lung inhalation. So, only people with pulmonary TB are infectious. This form of disease is the most frequent, [3] occurring in more than 80% of cases. The extra-pulmonary TB are almost never infectious, unless with concomitant pulmonary TB [3]. However, TB could actually affect any part of the body. Most infected people (80-90%) will never become ill with TB unless with seriously compromised immunity. Nevertheless, each active TB case will infect on average between 10 and 15 people every year [1,5].

In Nigeria, there were 33,000 deaths resulting from TB disease in year 2009. [1] Despite the availability of proven interventions such as the use of anti-TB drugs reported to produce a cure rate of up to 87%, there are differing trends in the incidence of re-treatment and new MDR cases. Likewise, there is a strong political commitment to combat TB and this has led to the establishment of National Tuberculosis and Leprosy Control Programme (NTBLCP), an arm of the Federal Ministry of health given the mandate to control TB and leprosy in Nigeria. The vision of the Programme is "Nigeria free of TB" while its goal is to reduce TB to a level at which it is no longer a public health problem. In line with this vision, the NTBLCP adopted the WHO recommended DOTS strategy in 1993 and the Stop TB strategy 2006 and has since then scaled-up implementation to all the 36states and FCT with significant improvement in DOTS expansion from 40% in 2006 to 63% in 2010 (1 DOTS centre/25,000 population) to achieve 70% case detection and 85% cure rate. [6] There has been a steady increase in total number of all forms of TB cases notified from 90,311 in 2008; 90,447 in 2010 to 93,050 in 2011 (the latter representing a CNR of 58/100,000 pop for all forms of TB) still below the 70% case detection target [7].

Medical schools are one of the important portals for management of patients with TB. DOTS centers have also been established in these colleges to increase access to TB treatment. Medical schools play an important role not only in the building of medical expertise but also in the socialization of future physicians. Societies expect these institutions to train students to competently and holistically handle common health problems. To widen access and improving quality of TB services as well as for giving hands on training to students, involvement of medical colleges is paramount. Knowledge of tuberculosis is assimilated in parts over all the years in the medical college. A TB clinic posting exposes the medical student to the practical aspects of Tuberculosis treatment, giving them an insight in to the day to day working of a DOTS clinic. Medical colleges play a central role in training and shaping the attitudes of the future generations of medical practitioners.

However, there is a dearth of data regarding the level of knowledge about TB and DOTS among medical students who are the budding doctors and can make an impact on TB control. Previous studies conducted in Nigeria and other countries worldwide focuses on the knowledge of TB and its management among practicing doctors, both in private or public sector showing considerable variation in prevention, evaluation and treatment strategies, indicates less than optimal performance and highlight the need for further education and training in issues relating to tuberculosis among physicians [8-12].

Physicians in the future need to be aware of the epidemiology, determinants, screening, and management of re-emerging infections such as tuberculosis. Increased exposure and education in both academic and clinical settings is crucial if medical students are to become competent in this arena. In view of the above background, this study was conducted with objective of assessing knowledge of the final year medical students in three medical colleges in Nigeria, about various aspects of diagnosis and management of TB under Directly observed treatment short course therapy (DOTS).

Methods

This study was carried out in Southwestern Nigeria. Government of Nigeria adopted the WHO recommended DOTS strategy as the national modality for the treatment of Tuberculosis, and the strategy had been effective in Nigeria like in many other parts of the world. However, most TB programmes are donor driven, though the federal Government through the NTBLCP coordinates TB response efforts in the country. There are 8 medical schools in the Southwestern region, 4 owned by Federal and 4 owned by states governments. Lectures on DOTs and rotation through PHCs and DOTs centers are usually incorporated into the medical school curriculum which final year medical students would have passed through before certified as a medical doctor

This is a descriptive cross sectional study among medical students in Southwestern Nigeria. All medical students in their final year constitute the target population. Eligible participants were registered final year MBBS students in selected medical schools. Sample size was estimated using the Leslie's Fischer's formular for single proportion using a prevalence of 16%. The minimum calculated sample size of 206 was increased to 242 to take care of non response.

Sampling was done in the multistage fashion. Three out of 8 medical schools in Southwestern Nigeria were selected using simple random sampling employing simple balloting. In stage 2 and for a medical school, 2 out of 4 groups of final year medical students on clinical rotation were also randomly selected using simple balloting. Questionnaires were equally allocated in each sampling stage. In stage three, a list of medical students per rotation group was made, and a systematic sampling method of 1 in 3 names on the list was made to reach the respondents for this study.

Research instruments were semi structured self administered pre tested questionnaires administered by trained lecturer assistant from each of the selected medical schools. Study variables include their knowledge, perception and practice of DOTs regimen including diagnosis and management and treatment of tuberculosis.. The

questionnaires had multiple choice questions, and also single or multiple responses of possible options that were correct. The subjects had a choice of not answering any question they did not know. Data were collected over a period of 3 months after making a total of 6 visits to the medical schools.

Ethical approval to conduct the study was obtained from LTH ethical review committee while a written consent was obtained from each respondent. A total of 241 finalists were interviewed. Data collected was analyzed using SPSS statistical package after data cleaning, and ensuring data validity through random checks and double entry of data. Frequency data were generated. Both bi and multivariate logistic regression were done in addition to Chi squared testing to demonstrate association between variables of interest. P value was set at less than or equal to 0.05 for all inferential statistics having to do with significance tests.

Results

All two hundred and forty one respondents returned useful and completely filled questionnaires. The respondent's age ranged between 20 - 49 years with a mean age 26 + 3 years and a modal age group 25 - 29 years. There were more males 147 (60.7%) than female 95 (39.3%). Majority of the respondents were Christians 189 (78.1%) while the remaining 52 (21.9%) were Moslems (**Table 1**).

Likewise in terms of TB diagnosis according to National guideline, 87 (33.6%), 85 (35.3%) and 73 (30.3%) mentioned sputum smear, chest x-ray and sputum culture respectively. In addition, only 29 (11.9%) was able to mention three methods used for diagnosis tuberculosis i.e. chest x-ray, sputum smear and sputum culture (**Table 2**).

The correct classification of patients into Cat 1 and Cat 11 was done by 111 (46.1%) of respondents while only 83 (34.5%), 16 (6.7%), 9 (3.7%) were able to identify correctly regimen duration for new tb, re-treatment and tb treatment among children. However, only 4 (1.7%), 7 (2.9%) were able to define correctly new tb and re-treatment tb cases (**Table 3**).

Discussion

The study revealed gross inadequacies in the knowledge of tuberculosis management according to DOTS regimen among final year medical students in South Western, Nigeria. Less than half of the respondents mentioned sputum smear, chest X-ray and sputum culture as means of diagnosing tb according to National guideline. A very similar finding was observed among medical interns in Turkey with 28.8% but higher findings recorded among interns in ido-ekiti, South Western Nigeria and Belgore where ZN staining for AFB was identified as the best diagnostic procedure/technique for PTB by 74 (62.7%) and 71.1% respectively [13-15].

Likewise, it is worrisome to know that only 34.5% and 6.7% were able to identify correctly regimen duration for new and re-treatment tuberculosis cases according to standard guidelines. This low level could be the result of deficiency in TB education in most Nigerian medical schools and affiliated teaching hospitals. This is made much worst by absence of effective DOTS centers in many tertiary centers including the teaching hospitals. However, since National Tuberculosis and Leprosy Control Program (NTBLCP) is already in place, though yet to achieve its global targets of 70% case detection despite adoption of DOTS strategy in the early 90s, there is need for additional support by effective and well trained medical practitioners towards achieving the target. The onus lies on the medical colleges and the curriculum to produce well trained and skilled medical practitioners. The knowledge level of graduating doctors and their attitudes may influence national TB control programs.

As far as the rank of Nigeria among the 22 high burden countries for TB, only 1.7% and 2.9% were able to define correctly new tb and re-treatment tb cases. Such low level was observed among final year medical students in tertiary level health facility in India where 16% 5th year medical students were able to classify patients according to drug regimen and category [16]. Knowledge about the terms as cured was also not satisfactory as only 1.7% correctly defined cure. Our result was lower when compared to a similar study among medical finalist in India where 30% of students mentioned correct definitions [16].

There is an urgent need for massive increase in awareness of DOTS among medical students. First, federal government must enforce the establishment of strict and dedicated DOTS clinic in all tertiary hospitals. Second, medical students must rotate through DOTS clinic and practically participate in all its activities, including performance of ZN staining for sputum smear microscopy. The revision of existing medical education curriculum in Nigeria should focus on incorporation of national TB guidelines into TB teachings in schools. The appropriate authority should ensure the circulation and availability of TB guidelines to every practicing medical doctor in the country. This will encourage medical practitioners to inculcate diagnostic and prescription practices that are in accordance with the national TB guidelines [17].

Conclusion

Tuberculosis being the major public health problem in Nigeria, needs a higher priority in the medical curriculum. The knowledge level of final year medical students in the present study was found to be poor for the various aspects of tuberculosis management under DOTS programme. This study highlights the inadequate and incomplete knowledge of medical undergraduates regarding TB treatment using DOTS, and emphasizes the need for more regular training sessions along with strict supervision of trainees. This study thus concludes that TB/DOTS clinic posting and training should be made mandatory for all the medical students to increase their knowledge and skills for effective management of patients with tuberculosis and thereby in the long run preventing the further rise of MDR and XDR TB cases. As long as TB continues to plague the country, empowering future physicians with competent knowledge of TB and DOTS remains a most viable solution. Based on the experience, we suggest the following: full integration of the TB control-DOTS curriculum across all levels and medical schools in Nigeria; faculty orientation and training on implementing the curriculum in their classes; access to instructional materials on TB control and DOTS; administrative support for the full implementation of the curriculum.

Competing interests

The authors declare no competing interests.

Authors' contributions

Olarewaju Sunday conceived the idea for the study, interviewed selected individuals and provide the result. He also performed the literature search and drafted introduction, results, discussion and conclusion of the study. Adebimpe Wasiu revised and edited the manuscript particularly the methodology aspect. Adenike Olugbenga-Bello and Olarewaju Oladimeji revised and edit the manuscript. All authors read and approved the final version of the manuscript.

Tables

Table 1: Socio-demographic status of respondents
Table 2: Knowledge on TB diagnosis and follow up by National Guideline
Table 3: Knowledge of respondents on TB classification and treatment by National Guideline

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Table 1: Socio-demographic status of respondents		
Variable (N=241)	**Frequency**	**Percentage**
Sex		
Male	147	60.7
Female	95	39.3
Marital status		
Single	204	84.0
Married	36	14.9
Separated	2	0.8
Religion		
Christian	189	78.1
Moslem	52	21.9
Ethnicity		
Yoruba	179	74.0
Hausa	10	4.0
Ibo	53	22.0
Age group		
20 -24	70	28.9
25- 29	150	62.0
30-34	18	7.0
35-39	3	1.2
40 -44	1	0.4

Table 2: Knowledge on TB diagnosis and follow up by National Guideline		
Variable (Multiple responses allowed)	**Frequency**	**Percentage**
Sputum smear	87	33.6
Chest x-ray	85	35.2
Sputum culture	73	30.3
Using three methods (Sputum smear, chest x-ray and sputum culture)	29	11.9
Using two methods (Sputum smear and chest x-ray)	29	11.9
Using one method (Sputum smear only)	88	36.4

Table 3: Knowledge of respondents on TB classification and treatment by National Guideline		
Variable	**Frequency**	**Percentage**
Cat 1 and Cat 11	111	46.1
6 months regimen for new cases	45	18.7
8 months regimen for new cases	38	15.8
8 months regimen for re-treatment cases	16	6.7
6 months regimen for children	9	3.7
Cured definition	4	1.7
New TB case definition	11	4.6
Re-treatment case definition	7	2.9

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Understanding private retail drug outlet dispenser knowledge and practices in tuberculosis care in Tanzania

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SUMMARY

SETTING: Private sector accredited drug dispensing outlets in Morogoro and pharmacies in Dar es Salaam, Tanzania.

OBJECTIVE: To assess 1) the level of knowledge about tuberculosis (TB) among dispensers in Tanzania's retail pharmaceutical sector; 2) practices related to identification of patients with suspected TB; 3) the availability of educational materials and training; and 4) the availability of first- and second-line anti-tuberculosis treatment in retail drug outlets.

DESIGN: A cross-sectional descriptive study involving the administration of a structured questionnaire among drug dispensers in 122 pharmacies and 173 accredited drug dispensing outlets.

RESULTS: Private retail drug outlets are convenient; most are open at least 12 h per day, 7 days/week. Although 95% of dispensers identified persistent cough as a symptom of TB, only 1% had received TB-related training in the previous 3 years; 8% of outlets stocked first-line anti-tuberculosis medicines, which are legally prohibited from being sold at retail outlets. The majority of respondents reported seeing clients with TB-like symptoms, and of these 95% reported frequently referring clients to nearby health facilities.

CONCLUSION: Private retail pharmaceutical outlets can potentially contribute to TB case detection and treatment; however, a coordinated effort is needed to train dispensers and implement appropriate referral procedures.

KEY WORDS: pharmacy; public-private partnerships; referral and consultation; drug seller

IN THE MID-1980s, Tanzania was the first African country to introduce DOTS, the World Health Organization's (WHO) internationally recommended strategy for tuberculosis (TB) control. By 2010, Tanzania had surpassed the global treatment success (88%) and case detection (77%) targets, and had halved the 1990 TB mortality rate.[1] However, in the same year Tanzania had approximately 60 000 new TB case notifications;[1] today, it remains one of the world's 22 high TB burden countries. Continued efforts are needed to reduce the number of new TB cases in Tanzania and take it off the list of high-burden countries.

An assessment of the private health sector in Tanzania revealed that it provides a substantial contribution to health care services in the country. While the use of private health services never exceeds 34% of all services provided, patients tend to be more likely to access the private sector for problems that can be treated with medical commodities, such as fever or cough.[2] Furthermore, while patients of all wealth quintiles utilise private facilities, those from the bottom three quintiles comprise nearly 50% of all people seeking treatment for fever and/or cough.[2] Low-income households are more susceptible to TB, and for many, private retail pharmaceutical outlets are their first point of contact with the health system. If properly engaged, private pharmaceutical outlets can be involved in many aspects of TB control, including case detection, providing treatment support and limited dispensing of anti-tuberculosis drugs to those with a prescription.[3]

The contribution of public-private mix (PPM) to TB control has been well documented in the literature. A study in India demonstrated that large-scale implementation of PPM for TB care and control was not only cost-effective, it also significantly reduced patient financial burden as a result of fewer

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patients seeking care outside of the scope of the national TB control program and therefore paying a higher price for anti-tuberculosis medicines.[4] Another study in Indonesia found that collaboration between the public and private sector increased TB case detection.[5] The value of PPM has also been recognized in international guidelines, with PPM comprising one of the core components of the global Stop TB Strategy,[6] and the WHO and the International Pharmaceutical Federation (FIP; The Hague, The Netherlands) issuing a joint statement encouraging the collaboration of national TB programs and national pharmacy associations to improve TB control.[7]

The Tanzanian Ministry of Health and Social Welfare, through the National Tuberculosis and Leprosy Programme (NTLP), has committed to engaging the private sector and expanding TB and TB-HIV (human immunodeficiency virus) services in private health facilities.[8] The present study was conducted to assess TB knowledge among dispensers in the retail pharmaceutical sector, to determine practices related to the identification and management of patients with suspected TB, to assess the availability of educational materials and training, and to determine the availability of first- and second-line anti-tuberculosis treatment. We defined private retail pharmaceutical outlets as pharmacies, predominantly in urban areas, and accredited drug dispensing outlets (ADDOs), predominantly in rural and peri-urban areas. The findings from this study will help enable the NTLP and partners to develop strategic interventions for engaging the retail pharmaceutical sector in Tanzania in TB diagnosis and care in line with the WHO/FIP 2011 recommendations.[9]

STUDY POPULATION AND METHODS

This was a cross-sectional descriptive study design involving the administration of a structured questionnaire to dispensers in retail drug outlets. The questionnaire assessed TB knowledge and pharmacy practices, and inquired as to whether anti-tuberculosis drugs were stocked at the outlet. All questionnaire items were structured to categorize responses. Before full deployment, the questionnaire was pre-tested and all questions were validated through field testing in outlets in Dar es Salaam, Tanzania. Outlets included registered private retail pharmacies authorized by the Tanzania Food and Drugs Authority (TFDA) to sell and dispense all prescription medicines, and ADDOs, described elsewhere,[10,11] which are legally authorized by the TFDA to sell and dispense a limited list of essential prescription medicines.

The study locations were Dar es Salaam City and the Morogoro region. Dar es Salaam has nearly 60% of all registered retail pharmacies in the country,[12] contributes 22% of all notified TB cases nationwide, and represents an urban population. The Morogoro region ranks seventh in national TB case notifications, has had ADDOs operating for several years, and represents peri-urban and rural populations. We estimated the sample size to include approximately 30% of all eligible registered pharmacies and ADDOs. We determined the sampling interval based on the total number of outlets in each region and randomly selected pharmacies and ADDOs by selecting the first on the list, then counting every second outlet from the list until the final sample included respondents from 122 private pharmacies and 173 ADDOs.

Interviews were conducted in person with dispensers, and the data were analyzed using SPSS statistical software version 16 (Statistical Product and Service Solutions, Chicago, IL, USA). Data collectors included representatives from the NTLP, Pharmacy Council and TFDA, along with community pharmacists, district pharmacists and district NTLP coordinators. To assure data quality, all data collectors were trained before being assigned to one of four teams, with each team led by a supervisor who ensured the completeness and accuracy of data during interviews. Two data entry clerks double-checked each entry to ensure accuracy.

Before data collection, approval was sought from the TFDA, the Pharmacy Council, and the NTLP. After being briefed on the purpose of the study, pharmacy and ADDO dispensers were asked to participate and were interviewed after providing informed consent. Data collectors verbally assured participants of the confidentiality of the information collected, their anonymity and the freedom to withdraw consent at any time during the process. Meetings were also held with district officials where the study was proposed before data collection.

RESULTS

Characteristics of the study population

The vast majority (83%) of dispensers interviewed in this study were female; 61% dispensers in pharmacies had secondary education compared to only 41% of those working in ADDOs, and 39% of all dispensers had primary education. Dispensers working in pharmacies had a statistically significantly higher level of education than those working in ADDOs ($P = 0.000$). Of those interviewed at pharmacies, 10% identified themselves as pharmacists; however, there were no pharmacists identified at the ADDOs. Of all dispensers in the pharmacies and ADDOs, 15% did not have any health training background.

Accessibility and referral linkages

Service accessibility was measured by the number of days and hours outlets were open for operation. Most ADDOs and pharmacies were open for at least 12 h

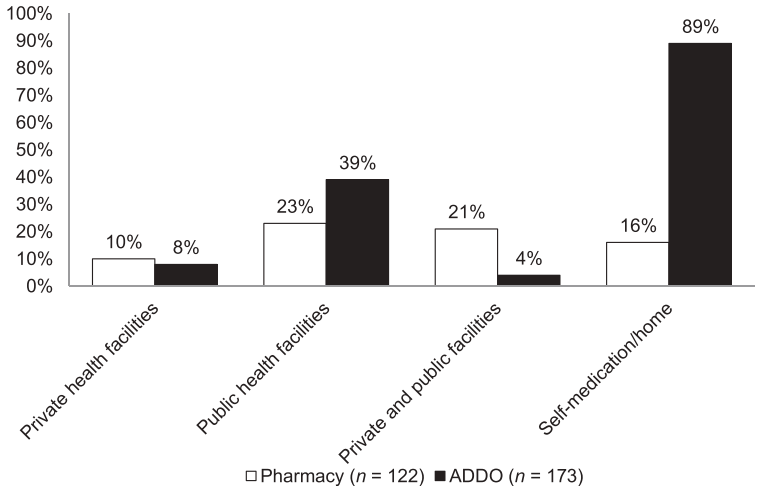

Figure Retail outlets' sources of clients (multiple responses allowed).

per day (85% and 67%, respectively), with approximately 70% of pharmacies and 60% of ADDOs operating 7 days per week. To assess referral linkages between ADDOs and pharmacies with other health services, we measured the walking time to the nearest public or private health facility and asked about the sources of clients at outlets. Approximately 88% of retail outlets were near a health facility, and dispensers reported that it took less than 30 min to walk to the closest facility. While most pharmacies reported that health facilities were their primary source of clients, the majority of ADDO clients came directly from home to seek care (Figure).

TB knowledge and practices among respondents

The vast majority of dispensers (91%) knew that TB is contracted by breathing air containing TB-causing micro-organisms. Many respondents, however, did not report knowing the factors that contribute to the spread of TB; 33% correctly identified poor ventilation in the house, approximately one half correctly noted overcrowding and one third correctly identified the presence of TB patients in the house or community. Dispensers working in retail pharmacies were significantly more likely to identify overcrowding ($P = 0.019$) or poverty ($P = 0.035$) as a factor contributing to TB transmission.

Patients with TB can present with a variety of symptoms, such as persistent cough lasting $\geqslant 2$ weeks, low grade fever, coughing blood and loss of weight. Among interviewed dispensers, 95% correctly identified persistent cough as a symptom, but the next most commonly recognized symptom—weight loss—was identified by only 49% of respondents (Table 1). ADDO dispensers were significantly more likely to name this symptom than those working in retail pharmacies (55% vs. 41%, respectively; $P = 0.018$).

While nearly all respondents recognized that there were negative consequences of not completing anti-tuberculosis treatment, including TB recurrence and death, only 30% were aware of the risk of developing drug-resistant TB (Table 1). ADDO dispensers were significantly more likely to recognize this risk, with 39% aware of resistance vs. 17% of pharmacy dispensers ($P = 0.000$). Two thirds of respondents had learned about TB symptoms during their formal education; the second most frequent source of knowledge cited was family members, relatives and friends. Other sources, such as community sensitization meetings, television, radio and billboards, contributed less than 5% each. Only 1% of respondents reported receiving any TB-related training in the previous 3 years.

Practice in TB case detection

Many respondents in both retail pharmacies and ADDOs (63% and 61%, respectively) reported seeing clients with TB-like symptoms in the 2 weeks before the interview. Of these, 95% reported referring the client to a nearby health facility, 8% dispensed broad-spectrum antibiotics and 14% dispensed cough syrup. Importantly, only 4% of both retail pharmacies and ADDOs referred patients with TB-like symptoms with a written note to a nearby health facility. Dispensers working in pharmacies were significantly more likely to report doing nothing when they saw clients come in with TB symptoms as compared to those working in ADDOs ($P = 0.025$).

Demand for and availability of anti-tuberculosis medicines

Despite the fact that first-line anti-tuberculosis medicines are prohibited from sale at retail outlets, 18% of surveyed pharmacies stocked at least one first-line anti-tuberculosis medicine, compared with 2% of ADDOs; however, none stocked fixed-dose combinations. For second-line anti-tuberculosis med-

Table 1 Knowledge about TB symptoms and the consequences of not completing anti-tuberculosis treatment among respondents

	Type of outlet		
	Pharmacy ($n = 122$) *n* (%)	ADDO ($n = 173$) *n* (%)	Total ($n = 295$) *n* (%)
TB symptoms*			
Persistent cough (⩾2 weeks)	115 (94)	166 (96)	281 (95)
Coughing blood	23 (19)	45 (26)	68 (23)
Fever for ⩾2 weeks	47 (39)	67 (39)	114 (39)
Loss of weight†	50 (41)	95 (55)	145 (49)
Excessive night sweats	47 (39)	48 (28)	95 (32)
Chest pains	25 (20)	30 (17)	55 (19)
Shortness of breath	12 (10)	18 (10)	30 (10)
Fatigue, malaise	32 (26)	48 (28)	80 (27)
Don't know	3 (2)	4 (2)	7 (2)
Consequences of not completing anti-tuberculosis treatment*			
Patient dies‡	63 (52)	118 (68)	181 (61)
Patient deteriorates	26 (21)	30 (17)	56 (19)
Recurrence of TB‡	67 (55)	120 (69)	187 (63)
Patient continues to infect others	15 (12)	27 (16)	42 (14)
Patient develops drug-resistant TB‡	21 (17)	67 (39)	88 (30)
Don't know	3 (2)	4 (2)	7 (2)

* Multiple responses allowed.
† ADDO dispensers were significantly more likely to name this symptom than those working in retail pharmacies (55% vs. 41%, respectively; $P = 0.018$).
‡ ADDO dispensers were significantly more likely to name patient death ($P = 0.009$), recurrence of TB ($P = 0.023$) and development of drug-resistant TB ($P = 0.000$) than pharmacy dispensers.
TB = tuberculosis; ADDO = accredited drug dispensing outlet.

icines, 68% of pharmacies and 50% of ADDOs stocked at least one second-line anti-tuberculosis medicine. In Tanzania, second-line regimens are authorized to be stocked at retail pharmacies because they are used for other diseases; however, ADDOs are not allowed to stock them (Table 2). A higher proportion of ADDO dispensers (43%) saw clients who specifically asked for anti-tuberculosis medicines as compared with pharmacy dispensers (35%).

Only half of the retail outlets (49%) surveyed reported keeping any kind of records for their clients, with ADDOs being significantly more likely to do so than pharmacies (39% and 10%, respectively, $P = 0.000$). Only 1% of all dispensers had any educational materials on TB available for their customers.

DISCUSSION

While similar studies have been conducted in Tanzania to assess knowledge and practices about malaria among drug sellers, and map care-seeking behavior for childhood illnesses and other health conditions,[13–15] this is the first study to assess TB awareness and practices among dispensers at Tanzania's private retail drug outlets. Our study found that many clients expect retail pharmaceutical outlets to supply and dispense anti-tuberculosis medicines, which is perhaps not surprising given that a previous study reported that 62% of retail pharmacy consultations were for cough.[16] While only 8% of dispensers in this study stocked first-line anti-tuberculosis medicines, approximately 4 in 10 saw clients who requested these medicines. Until the NTLP engages retail dispensers fully and ensures regulatory monitoring for anti-tuberculosis medicines, retail pharmaceutical outlets will continue to be under pressure to stock first-line medicines illegally and dispense them outside the DOTS strategy. These actions have the

Table 2 Availability of anti-tuberculosis medicines at retail outlets

	Type of outlet		
Anti-tuberculosis drugs stocked	Pharmacy ($n = 122$) *n* (%)	ADDO ($n = 173$) *n* (%)	Total ($n = 295$) *n* (%)
First-line drugs*	22 (18)	3 (2)	25 (8)
Second-line drugs†	83 (68)	86 (50)	169 (57)‡

* Sale prohibited by law at retail outlets.
† May be legally stocked in retail pharmacies because they are used to treat a variety of other conditions.
‡ Over 95% of pharmacies and ADDOs stocked fluoroquinolones (ciprofloxacin, levofloxacin and ofloxacin); the remaining pharmacies only stocked kanamycin and amikacin.
ADDO = accredited drug dispensing outlet.

potential to increase inappropriate use of anti-tuberculosis medicines and contribute to a rise in drug-resistant TB cases.

Studies carried out in other high TB burden countries have found similar misconceptions and knowledge gaps among retail pharmaceutical sellers regarding TB transmission, case detection and treatment; however, significantly higher rates of improper dispensing of TB medicines, mismanagement of TB cases, and development and spread of drug-resistant strains of TB were observed in countries that allow the sale of first-line anti-tuberculosis medicines in the private sector.[17–19] While Tanzania has largely managed to control the supply and sale of anti-tuberculosis medicines in its private retail pharmaceutical outlets (Sheikh K, Uplekar M. Regulating tuberculosis medicines: a policy analysis in six countries, unpublished), failure to involve the retail pharmaceutical sector in TB control efforts—including in the dispensing of anti-tuberculosis medicines—could lead to an increase in the unregulated distribution of these medicines as a result of client demand.

Although the dispensers' level of education was significantly lower in ADDO than pharmacies, their knowledge about TB was higher than in pharmacies. This is a result of years of investment to improve ADDO standards through training about all common illnesses including TB, regulatory monitoring, incentives and record keeping.[10,11,20] No similar efforts have been directed at retail pharmacies.

There are a variety of lessons to be learned from a similar effort to engage private pharmacists in Mumbai, India.[21] A total of 194 retail pharmacists were trained in case detection, a referral mechanism and DOTS protocols, and were provided with DOTS posters to display. In 2012, government TB clinic records showed a cumulative referral of 430 cases of persons suspected of having TB, of whom 17% had confirmed TB.[17] Training for pharmacists was scaled up and a significant number of pharmacists have since participated in the training and are administering DOTS. The system has proved beneficial for the pharmacists, who report that they enjoy offering a social service, as well as for the clients, who note that it is more convenient, more economical and less stigmatizing than receiving treatment at a TB clinic. A key component of the Indian effort to engage private pharmacists included listing those who completed the program in the DOTS directory of the local TB offices. The Indian Pharmaceutical Association then followed up with the pharmacists by telephone to inquire about their DOTS-related work.[21] This simple monitoring mechanism creates a sense of accountability and should be a part of any TB public-private intervention.

As retail pharmaceutical dispensers in this study rarely gave written referrals to health facilities for clients presenting with TB-like symptoms, any future dispenser training should include not only TB education, but also support for dispenser screening and referral. For example, a system could be established with a screening checklist for retail pharmacists and ADDO dispensers, standardized referral forms, a directory of facilities that provide NTLP TB diagnosis and treatment, and a register of pharmacy-referred TB patients. In addition, opportunities for health education could be enhanced by creating TB communication materials for pharmacies and ADDOs to display and distribute to clients.

CONCLUSION

The potential for retail pharmaceutical outlets to play a larger role in TB case detection is demonstrated by the fact that they are widely used, operate longer hours than health facilities, and most already see clients presenting with TB-like symptoms. However, the limited TB knowledge among staff, the lack of training and low rates of written referral indicate the need for a coordinated effort to engage this sector in TB case finding and to strengthen their linkage to TB diagnostic centers.

The NTLP, in collaboration with partners, used these study findings to develop an intervention to engage the retail pharmaceutical sector in TB control. The intervention includes a comprehensive training program covering proper identification and referral of TB patients, standard procedures for DOTS, and best practices for keeping client and drug registers. On completion of the training, private pharmacies and ADDOs will be certified by the NTLP to identify persons with TB symptoms and formally refer them to a nearby health facility (private or public) with diagnostic capacity. The outcomes of this intervention are currently being assessed and will be reported in a future publication.

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RESUME

CONTEXTE : Officines privées accréditées de délivrance de médicaments à Morogoro et pharmacies à Dar es Salaam, Tanzanie.

OBJECTIF : Evaluer 1) le niveau de connaissances en matière de tuberculose (TB) parmi les revendeurs dans le secteur de la pharmacie de détail en Tanzanie ; 2) les pratiques relatives à l'identification des patients suspects de TB ; 3) la disponibilité de matériel éducatif et de formation ; et 4) la disponibilité du traitement de première et de deuxième intention dans les officines de revente de médicaments.

SCHÉMA : Une étude descriptive transversale impliquant l'administration d'un questionnaire structuré à des vendeurs de médicaments dans 122 pharmacies et 173 officines de revente accréditées.

RÉSULTATS : Les officines privées de revente accréditées sont commodes car la majorité sont ouvertes au moins 12 h par jour, sept jours par semaine. Bien que 95% des revendeurs aient identifié une toux persistante comme un symptôme de TB, seulement 1% avaient bénéficié d'une formation relative à la TB pendant les 3 dernières années ; 8% des officines de revente disposaient d'un stock de médicaments anti-tuberculeux de première intention, dont la vente est interdite par la loi dans les officines. La majorité des répondants a affirmé avoir vu des clients présentant des symptômes évocateurs de TB et parmi eux, 95% ont déclaré référer fréquemment leurs clients à des centres de santé proches.

CONCLUSION : Les officines privées de revente pharmaceutiques peuvent contribuer à la détection des cas de TB et à leur traitement, cependant un effort coordonné est nécessaire pour former les revendeurs et mettre en place des procédures de référence appropriées.

RESUMEN

MARCO DE REFERENCIA: Los puntos autorizados de venta de medicamentos en el sector privado de Morogoro y las farmacias en Dar es Salaam, en Tanzania.

OBJETIVOS: Evaluar: 1) el grado de conocimientos sobre la tuberculosis (TB) de los proveedores del sistema de venta de medicamentos al público en Tanzania; 2) las prácticas en materia de detección de los pacientes con presunción de TB; 3) la existencia de materiales pedagógicos y de capacitación; y 4) la existencia de medicamentos antituberculosos de primera y segunda línea en los puntos de venta al público.

MÉTODO: Se llevó a cabo un estudio transversal descriptivo, mediante la administración de un cuestionario estructurado a los proveedores de medicamentos en 122 farmacias y 173 puntos autorizados de venta de medicamentos.

RESULTADOS: Los puntos de venta del sector privado son prácticos, pues en su mayoría atienden como mínimo 12 h al día y 7 días a la semana. Aunque el 95% de los proveedores reconoció la tos persistente como un síntoma indicativo de TB, solo 1% de ellos había recibido una capacitación en materia de TB en los últimos 3 años. El 8% de los puntos de distribución contaba con existencias de medicamentos antituberculosos de primera línea, cuyo comercio está prohibido en estos puntos de venta. La mayoría de los proveedores que respondieron al cuestionario manifestó haber atendido clientes con síntomas indicativos de TB y el 95% declaró que solía remitirlos a los establecimientos de salud cercanos.

CONCLUSIÓN: Los puntos de venta de medicamentos del sector privado podrían contribuir a la detección de casos de TB y a su tratamiento, siempre y cuando se emprenda un esfuerzo coordinado de capacitación de los proveedores y se pongan en práctica procedimientos de remisión apropiados.

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RESEARCH ARTICLE Open Access

Pre-ART retention in care and prevalence of tuberculosis among HIV-infected children at a district hospital in southern Ethiopia

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Abstract

Background: The Ethiopian epidemic is currently on the wane. However, the situation for infected children is in some ways lagging behind due to low treatment coverage and deficient prevention of mother-to-child transmission. Too few studies have examined HIV infected children presenting to care in low-income countries in general. Considering the presence of local variations in the nature of the epidemic a study in Ethiopia could be of special value for the continuing fight against HIV. The aim of this study is to describe the main characteristics of children with HIV presenting to care at a district hospital in a resource-limited area in southern Ethiopia. The aim was also to analyse factors affecting pre-ART loss to follow-up, time to ART-initiation and disease stage upon presentation.

Methods: This was a prospective cohort study. The data analysed were collected in 2009 for the period January 2003 through December 2008 at Arba Minch Hospital and additional data on the ART-need in the region were obtained from official reports.

Results: The pre-ART loss to follow-up rate was 29.7%. Older children (10–14 years) presented in a later stage of their disease than younger children (76.9% vs. 45.0% in 0–4 year olds, chi-square test, $\chi2 = 8.8$, $P = 0.01$). Older girls presented later than boys (100.0% vs. 57.1%, Fisher's exact test, $P = 0.02$). Children aged 0–4 years were more likely to be lost to follow-up (40.0 vs. 21.8%, chi-square test, $\chi2 = 5.4$, $P = 0.02$) and had a longer time to initiate ART (Cox regression analysis, HR: 0.50, 95% CI: 0.25-0.97, $P = 0.04$, controlling for sex, place of residence, enrolment phase and WHO clinical stage upon presentation). Neither sex was overrepresented in the sample. Tuberculosis prevalence upon presentation and previous history of tubercolosis were 14.5% and 8% respectively.

Conclusions: The loss to follow-up is alarmingly high and children present too late. Further research is needed to explore specific causes and possible solutions.

Keywords: HIV, TB, Ethiopia, Children, ART, Arba Minch, Resource-limited, WHO

Background

Recent global reports suggest considerably improved access to antiretroviral therapy (ART) in low and middle-income countries including in Sub-Saharan Africa. According to the 2013 global report, 9.7 million patients were receiving life-saving ART by the end of 2012 [1]. This is a remarkable acheivement as compared to a decade earlier when less than half a million patients were on ART in low and middle-income countries [2]. However, these gains in access are being challenged by emerging set of problems, one of which being retaining patients in care. A recent systematic review revealed problems with patient retention both before and after initiating ART [3]. This challenge and its associated factors are more clearly delineated in adult patient populations than in children.

During 2011, about 24 000 new infections were reported to have occurred and there were around 790 000 people infected with HIV living in Ethiopia, which is 1.5% of the entire population. The latter prevalence is projected to decline as well, along with mortality and incidence [4]. These encouraging results are believed to be the effect of concerted local and global actions including

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free delivery of HIV services at point of care, service decentralization, and task shifting [5,6]. The challenge of poor linkage to and retention in care has been well recognized in the Ethiopian HIV program. Published studies from Arba Minch and Gondar hospitals, for example, suggest high rates of pre-ART patient loss among adult patients living with HIV [6,7]. As elsewhere, there is limited information on the challenges of pre-ART patient retention among children living with HIV in Ethiopia [2].

Despite the success, many challenges still prevail [2,8]. There are problems with low condom use, violence against women and stigma leading to loss of job and income. One in five Ethiopians with HIV experience suicidal feelings. Another major problem is the low coverage of antiretroviral regimens to prevent mother-to-child transmission and rates of infant testing and prophylaxis remain very low [2,9].

Some of the most worrying statistics on HIV in Ethiopia concern the health of children. The deficient prevention of mother-to-child transmission in Ethiopia is central to the problem of HIV among children. Ethiopian studies have shown, similarly to findings from other low-income countries and international reports, that a majority of children with HIV in the country have acquired their infection vertically [9-11]. Apart from this, a big problem is the low ART coverage for children. Although the data are currently under review and may reveal an improvement, reports from 2010 announce that only 14–38% of the ART-need among children is met [9].

For those children who do present to care, further problems ensue. Timely initiation of treatment and retention in care are both crucial for patient outcome [12,13]. Late presentation to care among children have been identified as a problem in both high-income and low-income countries [11,14]. This implies that children in low-income countries are put in a particularly vulrerable situation as late presentation has been shown to be also a general problem in Sub-Saharan Africa [6,15]. A review from 2009 has found the reasons for this to be mainly population-based barriers to access such as lack of information, stigma and perceived high cost of treatment. However, the reviewer stresses that 'there is a paucity of studies on access barriers to ART for HIV-positive children' [16]. Furthermore, not all studies show that children present late. For instance, a study from India showed that children below 14 years of age actually were associated with a lower risk of late presentation [17]. This further underscores the importance of more local research. Extending the knowledge on HIV-infected children presenting to care in Ethiopia is critical for not letting children lag behind in the process to overcome the epidemic.

In this report, we present data from one of the longest-followed cohorts of paediatric HIV patients on TB prevalence and the magnitude and predictors of retention in care. The aim of this study was to describe the main characteristics and to analyze the predictors of pre-ART loss to follow up among children with HIV presenting to care at a district hospital in a resource-limited area in southern Ethiopia.

Methods

Participants

The data were collected at Arba Minch Hospital in southern Ethiopia. The hospital is a general public hospital located in the city of Arba Minch, in the Southern Nations, Nationalities, and People's Region (SNNPR), around 500 kilometres south of Addis Ababa, Ethiopia's capital. Arba Minch Hospital was the first hospital to introduce antiretroviral treatment in SNNPR in 2003—at a time when there were only few such centres in Ethiopia. The hospital serves a population of over 1.5 million in the Gamo Goffa zone of SNNPR. We established the HIV cohort database in 2003 and maintained it through this date. Since this is the longest-followed cohort in Ethiopia and resource constraint did not allow us to establish more of such centres, we opted to continue with analysis and learning from our existing cohort. This study did not entail any active data collection. We used de-identified data from the existing database and restricted our analysis to the paediatric age group as most of our earlier analyses did not involve this age group. All children with HIV presenting to care at Arba Minch Hospital from January 2003 through December 2008 were included in this study. The inclusion criteria were to be under 15 years old and to have an HIV infection. Children with a previous history of ART were excluded.

Procedure of therapy and data collection

The data for this study were collected along with data for adult patients at the same hospital. The findings on those data have been published elsewhere and the method described below is in part described in that study as well [6]. A trained health care worker did the initial evaluation and subsequent follow-up of the patients. During the initial years of the study this evaluation was made using only clinical and total lymphocyte count (TLC) criteria. From mid-2006 and onward CD4 testing was also available. The patients started ART according to the national guidelines issued by the Ethiopian Ministry of Health (MOH), which issued updated versions of the guidelines during the course of this study.

The first Ethiopian ART guidelines were published in 2003 and the paediatric treatment guidelines were included as a chapter in the adult guidelines. The first paediatric ART guidelines were published in 2008 and the recommendations did not change since then. Accordingly, treatment is recommended for all infants with confirmed HIV infection. Treatment is recommended for older children with stage III or IV diseases irrespectively of

CD4 count/percentage. For those with stage I or II disease a table is used as a guide outlining different CD4 count/percentage thresholds for different ages (12–35 months: < 750 cells/mm^3 or < 20%, 36–59 months: < 350 cells/mm^3 or < 20%, 5 years or older - same as adults: < 200 cells/mm^3 or < 15%). These thresholds did slightly change during the course of the study. In the 2003 guidelines the 15% threshold extended down to children of 18 months and the adult thresholds were applied to children 8 years or older. The guidelines also specify how to assess HIV infection and disease stage clinically if proper laboratory tests are unavailable [18-20].

Two data clerks recorded patient information both on paper and electronically. With a data abstraction form as a guide they recorded variables directly into an SPSS file. These variables include date of HIV-testing, date of pre-ART enrolment, WHO clinical stage, total lymphocyte count (TLC), CD4 count, haemoglobin level (HGB), history of TB (as reported by patient or caregiver), current TB (diagnosed within one month before or after presentation), sex, age, place of residence (rural or urban), pre-ART outcome and date of ART-initiation (if initiated).

During most of the time of the study, there was no strict guideline for pre-ART follow-up schedule neither for adults nor for children. Patients at the hospital were told to return after 3–6 months depending on their clinical condition. The 2008 paediatric guidelines formalised the schedule to recommend follow-up every 1–3 months depending on age and clinical condition (or more frequently than monthly if clinically indicated) [20]. However, there was no recording and reporting mechanism for the pre-ART visits and definitions for pre-ART outcomes such as loss to follow-up was not formalized. The Ethiopian Ministry of Health has recently finalized a nation-wide assessment of the status of pre-ART patient care. It is expected to lead to development of a comprehensive national framework for pre-ART care. In the mean time, we continued to use our own operational definition for pre-ART care. The pre-ART outcome was defined as: (a) 'still under pre-ART care' – if the patient was registered with the ART clinic of the hospital, had regular follow-up with the clinic and was not having follow up at another health facility; (b) 'lost to follow-up' – if patient did not have a follow-up visit at least 30 days after the last date of the most recent clinic appointment; (c) 'put on ART' – if patient was started on ART in the hospital clinic; (d) 'died before starting ART' – if patient was known to be dead as reported by treating clinicians or community health agents; and (e) 'transferred out' – if patient moved to another health facility with confirmed written documentation of transfer out.

For those patients that were put on ART, patients were defined as lost to follow-up if they had not attended the hospital within 30 days following the time for their clinical appointment. For patients lost to follow-up an extended follow-up was conducted in 2009 and involved a home visit or phone call using community health agents. Patient status after extended follow-up was defined as (a) 'died' – if a family member, neighbour or community leader reported death of the patient; (b) 'under follow up at another health facility' – if the patient was on treatment at any health facility in the region as reported by family, neighbours or community leaders; (c) 'stopped treatment but alive' – if the patient had not taken antiretroviral drugs (ARVs) for over a month and the patient was alive and did not get ART elsewhere; (d) 'on traditional treatment' – if the patient reported that he or she used traditional medicines or treatment instead of ART and (e) 'left the region' – if patient left the region as reported by family, neighbours or community leaders. If no information was available about the patient, this was defined as (f) 'unknown' ('true loss').

Patient data were updated at each visit. The database was updated on a quarterly basis 2003–2006 and yearly the last two years. In 2009, we undertook a more thorough cohort updating that involved home visits to determine the status of each patient declared to be lost as described above. The recorded data were updated, amended and cross-checked with paper records at the hospital in order to affirm their quality. In addition to the patient data, data on ART-need among girls and boys in SNNPR were obtained from an official report for statistical comparison with data on the participants of the study [4].

Ethics

The prospective cohort follow up system at Arba Minch hospital was established with the approaval of the the National Research Ethics Review Committee in Ethiopia. All patients were given standard care at the hospital, as prescribed in the national guidelines [18,19].

This particular analysis was done based on a separate protocol specifically designed to look into long-term treatment outcomes including pre-ART outcomes for which separate local approval was sought and granted. Since we used de-identified data for this analysis, obtaining patient consent was not feasible but permission was obtained from the hospital administration.

Statistical methods

SPSS was used for the analyses presented in this study. The data was entered into SPSS version 16 and later transferred to SPSS version 21. All data used for describing cohort profile and baseline characteristics were obtained from the SPSS file.

Data were grouped into three cohorts based on date of enrolment to pre-ART care and the chronology of Ethiopia's ART scale-up [5]. The three cohorts were decided to be (i) those enrolled January 2003-August 2006

(Early cohort), (ii) those enrolled September 2006-August 2007 (Rapid scale-up cohort) and (iii) those enrolled between September 2007-December 2008 (Recent cohort). For each cohort the proportion of patients presenting in the different WHO clinical stages of HIV/AIDS was compared. For the sake of clarity, a comparison was also made with the WHO clinical stage dichotomized into less advanced (stages I & II combined) and advanced (stages III and IV). In regard to the small sample size these distributions were only described for each cohort separately and no trend analyses were performed.

Logistic regression including the dichotomized WHO stage variable was used to identify potential risk factors for being in an advanced stage upon presentation. Because of the small sample size only four variables were screened: age, sex, place of residence and cohort. These variables were chosen on bases of biological and social plausibility and on the findings from the adult cohort [6]. A similar logistic regression was used to determine risk factors for being lost to pre-ART follow-up and the same variables were chosen for this analysis. Individual chi-square tests were performed to further analyse factors found to affect pre-ART loss and late presentation. For one analysis where the criteria for performing a chi-square test were not deemed to be met, Fischer's exact test was done instead.

Student's T test was used to determine whether the distribution between boys and girls presenting to care was significantly different from the distribution among HIV-infected children in general. Estimates for these numbers were obtained from official reports on the region, issued by the Ethiopian Ministry of Health [4].

Time to ART-initiation for different age groups was estimated using Cox regression, controlling for sex, place of residence, enrolment phase and WHO clinical stage upon presentation. Statistical significance was defined as $P < 0.05$.

The research adhered to strengthening the reporting of observational studies in epidemiology (STROBE) guidelines [21] (See Additional file 1 for more details).

Results

Cohort profile

Out of the 139 children who initiated pre-ART care from January 2003 through December 2008 all but one were enrolled in the study. The child who was not enrolled had a history of previous ART and thus failed to meet the inclusion criteria. Out of the 138 children included, 79 (57.2%) were put on ART, 15 (10.9%) were still under pre-ART care at the time of follow up, two (1.4%) had been transferred out of the hospital and one child (0.7%) had died. The remaining 41 children (29.7%) were lost to follow-up (Figure 1).

Of the 79 children who were put on ART, a majority was still enrolled in treatment at the time of follow-up, namely 65 children (82.3%). Five children (6.3%) had died, one (1.3%) had been transferred out and one had stopped treatment. The remaining 7 children (8.9%) were lost to follow-up. Three of these children were living in urban addresses and were traced for an extended follow-up. One had died and another was alive, receiving traditional treatment at 'holy water'. The outcome of the last child remains unknown.

The 138 patients enrolled in the study contributed 175.9 person years of observation (PYO). The median time to pre-ART outcome was 1.1 months (IQR: 0.2-6.1) and the median time from ART initiation to ART outcome (for the 79 patients put on ART) was 23.3 months (IQR: 5.1-30.1).

Characteristics of the children

The characteristics of the 138 children upon enrolment to pre-ART care are shown in Table 1. Their median age was 5 years (IQR: 3–8); 60 children (43.5%) were 0–4 years old, 52 children (37.7%) were 5–9 years old and 26 children (18.8%) were 10–14 years old. As for distribution between sexes, there were 79 boys (57.0%) in the entire sample. A vast majority of 121 children (87.7%) were urban residents and the remaining 17 (12.3%) had rural addresses. A previous history of TB was found for 11 children (8.0%) while 20 children (14.5%) had a TB infection upon presentation. CD4 count was recorded for 97 patients and the mean value was 529 cells/mm^3.

Differences between age groups

The distribution of presenting stage for different age groups is shown in Table 2. There were 26 children aged 10–14 years, 6 (23.1%) of these presented in a less advanced stage while the remaining 20 (76.9%) presented in an advanced stage. The higher proportion of children presenting late in the oldest age group was found to be statistically significant when compared to the reference group of 0–4 year olds (Chi-square test, $\chi^2 = 8.8$, $P = 0.01$). No significant difference was found between the middle and the youngest age group.

Pre-ART loss to follow-up proportion within different age groups is shown in Table 3. Among the 78 children who were 5 years or older, 17 (21.8%) were lost to follow-up. The number of children lost to follow-up among the 60 children aged 0–4 years was 24 (40.0%), a significantly higher proportion compared to the older children. (Chi-square test, $\chi^2 = 5.4$, $P = 0.02$).

Risk factors for longer time to ART initiation

The 138 patients enrolled in the study contributed 47.0 person years of observation (PYO) in pre-ART follow-up. The median time to ART initiation for all participants was 18 days (IQR 6–113). When controlling for sex, place of residence, enrolment phase and WHO clinical stage upon

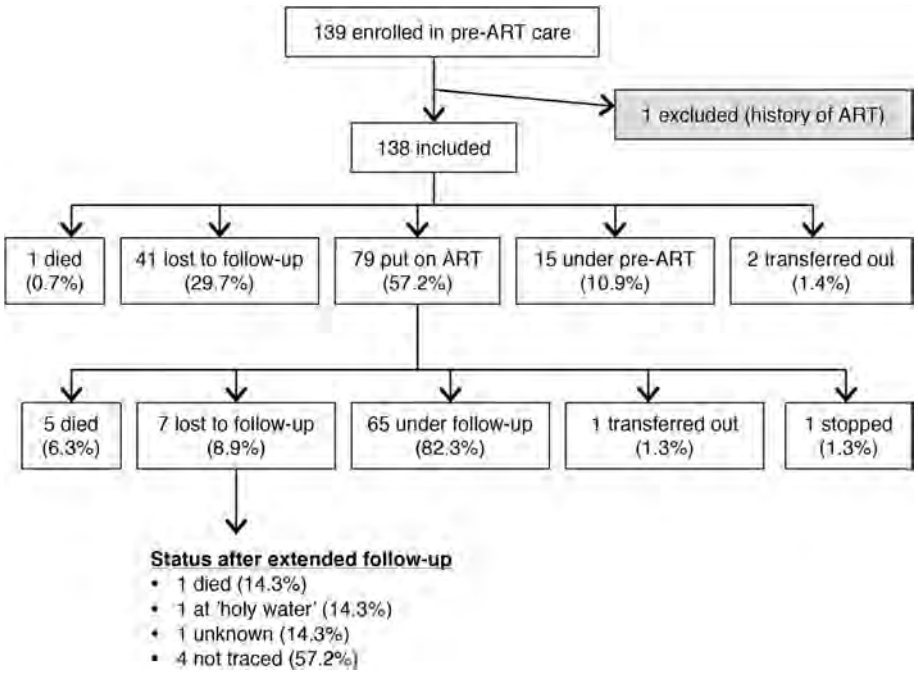

Figure 1 Cohort profile. Cohort profile of children treated at Arbaminch Hospital during the period 2003–2008, Arba Minch, Ethiopia.

Table 1 Presenting characteristics of children, Arba Minch Hospital, Ethiopia

Characteristic		Number (%)
Age	0-4 years	60 (43.4)
	5-9 years	52 (37.7)
	10-14 years	26 (18.8)
Sex	Female	59 (42.8)
	Male	79 (57.2)
Place of residence	Urban	121 (57.2)
	Rural	17 (12.3)
WHO clinical stage	Stage I	31 (22.5)
	Stage II	37 (26.8)
	Stage III	59 (42.8)
	Stage IV	11 (8.0)
Past history of TB	Yes	11 (8.0)
	No	127 (92.0)
TB upon presentation	Yes	20 (14.5)
	No	118 (85.5)
Characteristic		**Central tendency (variation)**
CD4 count*	Mean	529 cells/mm^3
Hgb**	Mean	10.7 g/dl
Time to ART***	Median (IQR)	18 days (6–113)

*97 cases analysed, 41 missing.
**101 cases analysed, 37 missing.
***For 79 patients put on ART.
Presenting characteristics for 138 children with HIV at Arba Minch Hospital, who initiated pre-ART care during the period 2003–2008.

presentation, it was found that children in the age group 0–4 years waited longer to initiate ART (HR: 0.50, 95% CI: 0.25-0.97, P = 0.04).

A longer time to ART initiation was also found for children presenting in stage I (HR: 0.27, 95% CI: 0.09-0.80, P = 0.02). Table 4 shows the adjusted hazard ratios for all variables mentioned above and Figure 2 shows the survival curves according to Cox regression with separate lines for different age groups.

Differences between sexes

The proportion of patients presenting in an advanced stage (in either stage III or stage IV) for boys and girls respectively is presented in Table 5. Out of the 59 girls in the sample, 35 (59.3%) presented in an advanced stage; for the boys the number was 35 (44.3%) out of 79. The table also shows sex difference in presenting stage stratified by different age groups. For ages 10–14, all 12 (100.0%) of the girls presented late, as compared to 8 (57.1%) out of the 14 boys and this distribution was determined to be statistically significant (Fisher's exact test, P = 0,02). However, the sample size was critically small for further statistical evaluation. The sex differences for the other two age groups were not statistically significant, neither was the difference between sexes for all age groups combined.

Neither boys nor girls were found to be overrepresented at the clinic. According to official reports, the proportion of girls in need of ART in SNNPR was 49.7% in 2011. It was not possible to obtain this proportion for the actual period studied (2003–2008) but the proportion was not

Table 2 Presenting stage of HIV/AIDS for different age groups

	Less advanced (%)	Advanced (%)	Total	χ^2 significance
0-4 years*	33 (55.0)	27 (45.0)	60	-
5-9 years	29 (55.8)	23 (44.2)	52	P > 0.05
10-14 years	6 (23.1)	20 (76.9)	26	P = 0.01

*reference category.
Less advanced = Stage I & II combined.
Advance = Stage III & IV combined.
Presenting stage of HIV/AIDS for different age groups in a cohort of 138 children who initiated pre-ART care during the period 2003–2008.

projected to change for the next five years despite an overall estimated decrease in total numbers [4]. On these grounds it was assumed that the proportion was similar during the period of the study. The proportion of girls in the sample was 43.0% – 6.7 percentage points lower than girls in need of ART in the region – but this difference was not found to be significant for P < 0.05 (two-tailed significance, P = 0.10).

Changes after the scale-up of ART

WHO clinical stage for children presenting to care at Arba Minch Hospital during the three phases of ART scale-up in Ethiopia is shown in Table 6. In the early phase, 17 (41.5%) out of 41 children presented in a less advanced stage, a proportion which in the recent phase rose to 35 (59.3%) out of 59 children. Due to the small size of the sample, an analysis to assess whether this trend was significant was not performed.

Discussion

This study shows that older children present later to care and that among the older children, girls present later than boys. Younger children face other problems, as they are shown to have a longer waiting time to initiate ART and to be more likely to discontinue their pre-ART program. The overall percentage of pre-ART loss to follow-up is alarmingly high and a notable TB prevalence (14,5%) is seen upon presentation. No sex difference was found in presentation to care among the children in need of ART in the region.

Another study was conducted on HIV-infected adults presenting to care at Arba Minch Hospital during the same period as the children participating in this study. In the adult cohort consisting of 2191 patients, 25% were lost to pre-ART follow-up [6]. As was discussed earlier, the ART coverage of children in Ethiopia is lower than that of adults [22]. This fact together with the loss to follow-up reported for adults at the same hospital suggest a worrying pattern where children not only have less access to care but also continue care to a lesser extent than adults. A likely explanation for this is the fact that the children presenting to care in this study were generally healthier (in a less advanced stage of HIV) than the adults but even so the issue ought not be disregarded. It is however worth noting that the new WHO guidance of starting ART for all children under 5 has been endorsed by the Ethiopian Ministry of Health but its cost and associated implications are being studied before its implementation. If implemented, this new guidance may alleviate some of the concerns noted in this study.

It may not be surprising that older children presented later. Studies from around world show that – although figures vary slightly in different settings – a majority of HIV infected children anywhere have acquired their infection vertically. If this is the case also for the area serviced by Arba Minch Hospital, it would mean the disease had had longer time to progress in the children aged 10–14 years. Yet, if perinatal transmission is indeed the dominating mode among these children, it is still troubling that so many cases go undiscovered so long – one in five being over 9 years old and the better part being 5 years or older. This is not unique for Ethiopia. Age distributions such as these have been reported elsewhere in low-income countries; a recent Ugandan study showed roughly similar proportions at two different district hospitals and children's ages were also high in a large Indian cohort [23,24]. The fact that older children present later could also be part of the explanation why younger children are lost to pre-ART follow-up more frequently, as being in a less advanced stage has been shown elsewhere to be a predictor for pre-ART loss to follow-up [6].

As for the older girls presenting later than the older boys, potential explanations are less obvious. Studies on adults have actually reported women in Sub-Saharan Africa to present earlier than men, but additional factors associated with early presentation are pregnancy and

Table 3 Pre-ART loss to follow-up for different age groups

	Not lost to follow-up (%)	Lost to follow-up (%)	Total	χ^2 significance
0-4 years	36 (60.0)	24 (40.0)	60	P = 0.02
5-14 years	61 (78.2)	17 (21.8)	78	

Loss to follow-up for different age groups in a cohort of 138 children who initiated pre-ART care during the period 2003–2008.

Table 4 Factors associated with longer waiting time to ART initiation, Arba Minch Hospital, Ethiopia

Variable		Adjusted HR (95% CI)	P-value
Sex	Male vs Female	0.90 (0.57-1.42)	>0.05
Address	Rural vs Urban	0.98 (0.46-2.05)	>0.05
Phase of enrolment	Early phase	1.36 (0.78-2.37)	>0.05
	Rapid scale-up	1.09 (0.59-2.00)	>0.05
	Recent phase*	1.00	
Age group	0-4 years	0.50 (0.25-0.97)	0.04
	5-9 years	0.40 (0.42-1.41)	>0.05
	10-14 years*	1.00	
WHO clinical stage	Stage I	0.27 (0.09-0.80)	0.02
	Stage II	0.69 (0.27-1.71)	>0.05
	Stage III	0.88 (0.38-2.04)	>0.05
	Stage IV*	1.00	

*reference category.
Hazard ratios for factors associated with having a longer time to ART initiation in a cohort of 138 children who initiated pre-ART care during the period 2003–2008.

having children less than 5 years [6,15]. These factors are naturally less occurrent among younger girls. Younger girls are also much less likely to be married, and being single is associated with presenting late not only in general but especially for women [15]. This kind of extrapolation however is somewhat speculative and probably does not tell the whole story.

On the other hand, previous research may provide a more straightforward explanation for the high loss to follow-up and longer waiting times among the youngest children. One reason that sufficient adherence can be hard to achieve for children is that they have to rely on their caregivers for it, caregivers who are often themselves in poor health due to HIV or difficult social circumstances [25]. The youngest children being most reliant on adults, this could explain their low retention. It could also explain the longer waiting time, since it is not recommended to initiate ART before it has been properly established that the patient is likely to adhere to the treatment [18,19].

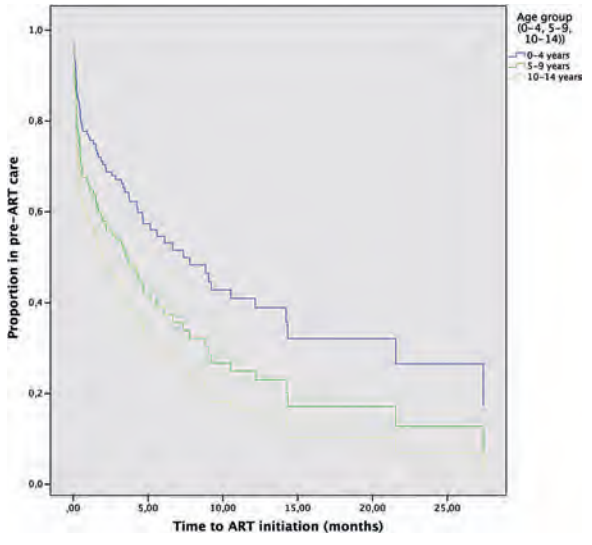

Figure 2 Time to ART for different age groups. Survival curves according to Cox regression analysis showing time to ART initiation for different age groups controlling for sex, place of residence, enrolment phase and WHO clinical stage upon presentation. Survival times for patients not reaching the event during the time of their observation (censored data) are also accounted for in the figure.

TB is the leading cause of death for people living with HIV and ART has been shown to substantially reduce the incidence of TB [22,26]. Therefore it is important to note the high rates of previous and current TB infection among the children presenting to care. Sadly, these findings are not that surprising, seeing that high rates have been reported in other child cohorts from low-income countries [11,25,27]. In any event, the findings underline the importance of earlier initiation of ART and generally improving collaborative TB-HIV care.

The main limitation of this study is the small sample size. Due to this fact, changes in presenting stage and mortality after the rapid scale-up of ART could not be analysed properly. This is unfortunate since these and other factors may have improved as a result of the scale-up, as has been shown for the adult cohort. On some instances when analyses were made on sub-groups of the entire cohort the sample size was even smaller. Therefore the finding that older girls present later than boys should be interpreted with caution. The large number of tests performed on this rather small sample also increases the risk of finding false significance and this should be taken into consideration.

Another limitation of this study was that the circumstances of data collection did not allow for a separate

Table 5 Sex difference in presenting stage of HIV/AIDS

		Less advanced (%)	Advanced (%)	Total	Significance
All ages	**Girls**	24 (40.6)	35 (59.3)	59	
	Boys	44 (55.6)	35 (44.3)	79	
0-4 years	**Girls**	11 (47.8)	12 (53.2)	23	$P > 0.05$[a]
	Boys	22 (59.5)	15 (40.5)	37	
5-9 years	**Girls**	13 (54.2)	11 (45.8)	24	$P > 0.05$[a]
	Boys	16 (57.1)	12 (42.9)	28	
10-14 years	**Girls**	0 (0.0)	12 (100.0)	12	$P = 0.02$[b]
	Boys	6 (42.9)	8 (57.1)	14	

[a]Chi-square significance test.
[b]Fisher's exact test.
Less advanced = Stage I & II combined.
Advanced = Stage III & IV combined.
Sex difference in presenting stage of HIV/AIDS stratified by age group in a cohort of 138 children who initiated pre-ART care during the period 2003–2008.

set of variables to be recorded for the child cohort. Information on parents' infections and social status, measures of prevention during pregnancy, mode of delivery and nutritional status of the child would have been valuable supplements for the analyses.

The range of problems seen in the provision of ART and retention in care all point to the same basic conclusion: reducing the rate of mother-to-child transmission is key to improving the paediatric HIV situation in Ethiopia. More research is needed to assess how perinatal care for infected women as well as testing of and prophylaxis for infants can be improved upon.

Nonetheless in addition to this, as long as there are still children infected with HIV, the detection of and care for these children need improvement as well. More research should explore the factors associated with loss to follow-up, late presentation, not presenting to care at all and possible interventions to solve these problems. Although likely candidates have been suggested in this discussion for the most immediate causative factors, there are likely also more general social factors such as poverty that put children at risk for lower access to care, lower adherence and unfavourable disease outcome. For this reason, more social research in addition to purely medical research would be welcome. To determine changes over time in pre-ART and on-ART loss to follow-up, mortality and presenting stage among children, research on larger Ethiopian cohorts of children is of crucial importance in the future.

Table 6 Presenting stage during the different phases of ART scale-up

	Less advanced (%)	Advanced (%)	Total
Early phase	17 (41.5)	24 (58.5)	41
Rapid scale-up phase	16 (42.1)	22 (57.9)	38
Recent phase	35 (59.3)	24 (40.7)	59

Less advanced = Stage I & II combined.
Advanced = Stage III & IV combined.
Presenting stage during the different phases of ART scale-up in a cohort of 138 children who initiated pre-ART care during the period 2003–2008.

Some inequalities between patient groups described in this study may still be prevalent despite the general improvement after the ART scale-up. Thus, even though our data are by now a few years old the results are nonetheless relevant in this respect and hopefully our findings will also serve a purpose for comparison with the contemporary adult cohort, as well as with future studies of this kind.

Conclusions

Although the sample size in this study was too small to make some important analyses on how the situation has developed over time, a number of problems have been identified concerning HIV-infected children presenting to care. The main ones are high pre-ART loss to follow-up rate, high TB prevalence and late presentation. Reasons for the higher loss to follow-up and longer waiting time to initiate treatment among the youngest children need to be further investigated. So do potential reasons for older girls presenting later than older boys and also general social factors that could be associated with several of these problems.

Additional file

Additional file 1: STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies.

Abbreviations

AIDS: Aquired Immunodeficiancy Syndrome; ART: Antiretroviral therapy; ARV: Antiretroviral drug; CI: Confidence interval; HIV: Human immunodeficiancy virus; HR: Hazard ratio; MOH: Ministry of Health (Ethiopia); TLC: Total lymphocyte count; SNNPR: Southern Nations Nationalities and Peoples' Region; SPSS: IBM SPSS statistics software; TB: Tuberculosis; WHO: World Health Organisation.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

DJ and BL established the Arba Minch Hospital HIV treatment cohort and later collaborated with ZM to update the cohort database in 2009. BL and ZM supervised the cohort data updating process. EW analyzed the paediatric cohort data for this manuscript and wrote the first draft of the manuscript. IH commented on the initial and subsequent drafts of the manuscript. DJ assisted with data analysis and commented on the initial and subsequent drafts of the manuscript. All authors have read and approved the final manuscript.

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The yield of a tuberculosis household contact investigation in two regions of Ethiopia

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SUMMARY

SETTING: Amhara and Oromia regions, Ethiopia.

OBJECTIVE: To determine the yield of a household contact investigation for tuberculosis (TB) under routine programme conditions.

DESIGN: Between April 2013 and March 2014, TB clinic officers conducted symptom-based screening for household contacts (HHCs) of 6015 smear-positive TB (SS+ TB) index cases. Based on quarterly reported programme data, we calculated the yield in terms of number needed to screen (NNS) and number needed to test (NNT).

RESULTS: Of 15 527 HHCs screened, 6.1% had presumptive TB (8.5% in Oromia vs. 3.9% in Amhara). All forms of TB and SS+ TB were diagnosed in respectively 2.5% (Oromia 3.9% vs. Amhara 1.2%) and 0.76% (Oromia 0.98% vs. Amhara 0.55%) of contacts. The NNS to detect a TB case all forms and SS+ TB was respectively 40 and 132. The NNT to diagnose a TB case all forms and SS+ TB was respectively 2.4 and 8. Of 1687 eligible children aged <5 years, 323 were started on isoniazid preventive therapy.

CONCLUSIONS: The yield of the household contact investigation was over 10 times higher than the estimated prevalence in the general population; household contact investigations can serve as an entry point for childhood TB care.

KEY WORDS: index case; systematic screening; active case finding

PROGRESS HAS BEEN MADE WORLDWIDE in reducing the incidence of tuberculosis (TB) and associated deaths, mainly through passive case finding.[1] Active case finding is needed as an additional strategy to identify and treat the many missed cases of TB, which accounted for an estimated one third of all TB cases reported in 2012.[2] About 75% of these are concentrated in 12 countries, including Ethiopia.[2] Systematic screening for TB among close contacts of index cases is one of the strategies recommended to identify these cases.[3,4] Experience with household contact investigation is limited, but screening other high-risk groups contributed 1–9% of adult cases in five studies.[3–5]

Two systematic reviews of studies on household contact investigations in low- and middle-income settings showed that respectively about 4.5% and 3.1% of contacts were found to have active TB.[6,7] The median number of household contacts evaluated to find one case of active TB was 19 (range 14–300). The median proportion of contacts found to have latent tuberculous infection (LTBI) was just over 50% in both studies. The median number of contacts evaluated to find one person with LTBI was 2 (range 1–14). In the review by Fox et al., longer-term follow-up showed that TB incidence remained above the background rate for at least 5 years.[7] Evidence from these reviews and other studies suggests that contact investigation in high-incidence settings is a high-yield strategy for case finding.[8–10] Based on the available evidence, the World Health Organization (WHO) has developed guidance on contact investigation which extends to high-risk groups other than children aged <5 years and people living with the human immunodeficiency virus (PLHIV).[11] Other key international guidelines also recommend contact investigations.[12,13]

Operationalising this guidance requires experience in low-income, high TB burden settings. A few studies from sub-Saharan African countries have looked at the yield of contact investigation, and experience of nationwide implementation was reported from Morocco.[14,15]

Ethiopia's national TB guidelines provide a policy framework for contact investigation; however, these have not been adequately implemented.[16] Earlier reports from Ethiopia were limited to specific population groups and some geographic areas.[17,18]

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In the present paper, we present data on the yield of contact investigation in a large TB project in two regions of Ethiopia. Our objective was to report on the yield of contact investigation under routine programme conditions in a low-income, high TB burden setting.

METHODS

Study setting

With a population of almost 88 million, Ethiopia is the second most populous country in Africa; more than half of the Ethiopian population lives in the two regions of Amhara and Oromia, where this study was carried out.[19] As one of the 22 high TB burden countries, Ethiopia has an estimated TB prevalence rate of 247 per 100 000 population. The proportion of multidrug-resistant TB (MDR-TB) among new and previously treated cases was respectively 2.7% and 17.8% (unpublished data, Ministry of Health, 2014). Table 1 summarises key health and TB data for Ethiopia.

Donor-funded projects contribute a significant share of Ethiopia's health care financing.[25] The Federal Ministry of Health and the Regional Health Bureaux of Amhara and Oromia regions, in partnership with the Help Ethiopia Address the Low TB Performance (HEAL TB) Project, have been implementing a comprehensive TB prevention and control programme that includes contact investigation in the two regions since July 2011. All services were free and available in 2186 health centres and 64 hospitals in HEAL TB-supported regions.

Contact investigation procedure

In each zone of the two regions, HEAL TB assigned a clinical officer and laboratory expert who provided technical guidance and support to zonal and *woreda* (equivalent to district) TB officers on all aspects of TB care, including contact investigation. The team developed and disseminated standard operating procedures for contact investigation to participating health facilities; oriented zonal, woreda and health facility TB focal persons on contact investigation; and supplied the health facilities with registers and job aids. Woreda TB focal persons then conducted supportive supervision and monitored progress by instituting a quarterly reporting mechanism for contact investigation. Participating facilities attended quarterly and semi-annual review meetings at the zonal and subnational levels to review programme performance, identify gaps and develop corresponding action plans.

After obtaining informed verbal consent, TB clinic officers asked each newly diagnosed smear-positive TB (SS+ TB) patient to provide the names and contact details of each household member and recorded the information in the health facility contact register. On registration with the TB clinic, each index case was counselled to bring family members to the health facility for screening. At the clinic, the TB clinic officer screened family members for symptoms using the following criteria for presumptive TB: any household contact with a history of cough for $\geqslant 2$ weeks or with two or more constitutional symptoms suggestive of TB was considered to have presumptive TB. Presumptive TB cases with productive cough were referred for sputum examination by laboratory technicians using Ziehl-Neelsen or fluorescent light-emitting diode microscopy. Patients presumed to have smear-negative (SS–) TB, with persistent respiratory symptoms or extra-pulmonary TB, underwent additional investigations, including chest radiography and pathology, mainly in a hospital setting.

We defined an index case as the initially identified case of new or recurrent SS+ TB around whom a contact investigation was carried out. A household contact was a person who shared the same enclosed living space for $\geqslant 1$ nights or for frequent or extended periods during the day with the index case during the 3 months before the current treatment episode began.[11,26]

Data collection and analysis

Data were collected through the routine programme monitoring system using the contact register. The following variables were recorded: health facility and index cases, type of TB and treatment initiation date, age, household contacts, diagnostic results of close contacts, and treatment and prophylaxis status of contacts. The woreda TB focal person compiled all contact investigation data quarterly and submitted them to the zonal TB focal person. We aggregated the data at the regional and project levels using Excel (MicroSoft, Redmond, WA, USA). We calculated the yield of contact investigation in terms of number needed to screen (NNS) and number needed to test (NNT). NNS is the number of contacts required to be screened to detect a single case of active TB; NNT is the number of persons with presumptive TB required to be evaluated to detect a single case of active TB. We calculated the values with a 95% confidence interval (CI) using OpenEpi software (www.OpenEpi.com). $P < 0.05$ was considered statistically significant.

Ethical considerations

As routine programme data were used for this analysis, no ethics approval was sought. Contact screening was performed with full verbal consent of the patients, and information was handled confidentially. All contacts with confirmed TB received the standard anti-tuberculosis treatment regimen at health facilities. Contacts who failed to visit health facilities were encouraged to visit the nearby health facility or see a community health worker.

Table 1 Sociodemographic, health and TB data, Ethiopia, 2013–2014

Characteristic	Ethiopia	Amhara	Oromia
Estimated population, millions[19]	87 952 991	20 018 988	32 815 995
Estimated annual per capita income, $US[20]	470	—	—
Number of TB cases notified[21]	131 677	29 003	49 886
CNR for all forms of TB/100 000 population[21]	171	172	159
TB prevalence/100 000 population[22]	211		
Estimated HIV prevalence in adults[23]	1.3	1.3	0.8
MDR-TB among new cases, % (95%CI)[24]	2.3 (1.5–3.1)	—	—
MDR-TB among retreatment cases, % (95%CI)[24]	17.8 (13.3–22.4)	—	—

TB = tuberculosis; CNR = case notification rate; HIV = human immunodeficiency virus; MDR-TB = multidrug-resistant TB; CI = confidence interval.

RESULTS

Basic characteristics of study participants

Between 1 April 2013 and 30 March 2014, health facilities screened the household contacts of 6015 SS+ index cases in 627 health facilities across 21 zones in the Amhara and Oromia regions of Ethiopia. Of the 16 512 registered household contacts, 15 527 were screened (Figure). The ratio of household contacts screened to index cases was 2.5. Children aged <5 years constituted 11.2% of all screened household contacts. Only 19.2% of eligible children received isoniazid preventive therapy (IPT) (Table 2).

The yield of household contact investigation

We identified 949 presumptive TB cases, of whom respectively 389 and 118 were confirmed to have all forms TB and SS+ TB. The prevalence of presumptive TB was 6.1% (95%CI 5.7–6.5), with a higher rate in Oromia than in Amhara (8.5%, 95%CI 7.9–9.1 vs. 3.9%, 95%CI 3.5–4.4, χ^2 145, $P < 0.0001$). TB (all forms) was detected in 2.5% (95%CI 2.3–2.8) of all contacts screened; the yield was higher in Oromia (3.9%, 95%CI 3.5–4.4 vs. 1.2%, 95%CI 1.0–1.5, $P < 0.0001$). SS+ TB prevalence was 0.76% (95%CI 0.63–0.91); the rate was higher in Oromia (0.98%, 95%CI 0.8–1.2 vs. 0.55%, 95%CI 0.41–0.74; $P < 0.01$). SS+ TB constituted 30.3% of all forms of TB diagnosed; the rate was higher in Amhara than in Oromia (45.5%, 95%CI 36–55.2 vs. 25.2%, 95%CI 20.51–30.48, $P < 0.001$). However, the proportion of SS+ TB among those with presumptive TB did not differ significantly between the two regions: 14.1%, 95%CI 10.7–18.4 in Amhara vs. 11.6%, 95%CI 9.31–14.33 in Oromia (12.4% overall, $P > 0.1$).

The NNS values for presumptive TB, all forms of TB and SS+ TB were respectively 16 (95%CI 16–17), 40 (95%CI 39–41) and 132 (95%CI 131–134). The corresponding NNT values for all forms and SS+ TB were respectively 2.4 (95%CI 2.3–2.6) and 8 (95%CI 7–9) (Table 2). The yield of presumptive and all forms of TB was higher in children aged <5 years (14.1% vs. 5.1% and 3.5% vs. 2.4%, respectively); however, those aged ⩾5 years had a higher prevalence of SS+ TB (Table 3).

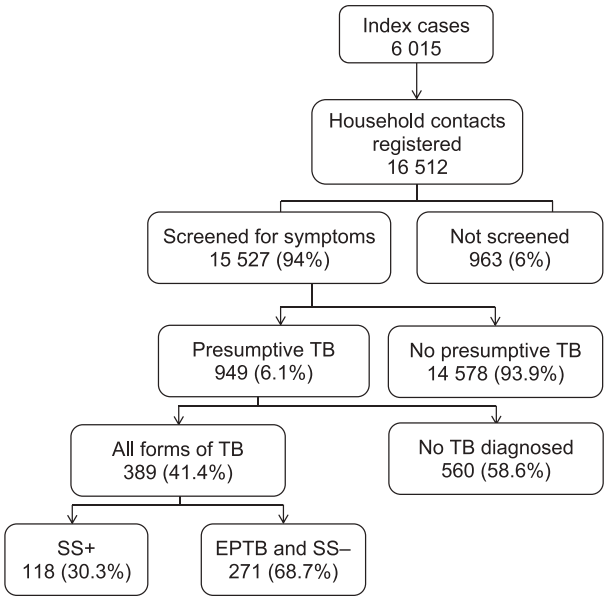

Figure Profile of contacts registered, screened and evaluated, Ethiopia, September 2014. TB = tuberculosis; SS = sputum smear; + = positive; EPTB = extra-pulmonary TB; – = negative.

DISCUSSION

In this study, we found a prevalence rate of all forms of TB among household contacts of SS+ TB index cases to be over 10 times higher than the prevalence estimate of 211/100 000 in the general population. The prevalence rate was about 18 times higher in the Oromia Region and 6 times higher in Amhara Region. The prevalence of SS+ TB, 0.76%, was about seven times higher than the prevalence estimate for SS+ TB of 0.108% in the national TB prevalence survey.[27] About six persons in every 100 household contacts had presumptive TB, with over one third of these eventually confirmed to have TB. The NNS to find a TB case was 40 and the NNT to diagnose a single case of TB was less than 3. Household contact investigations should therefore be prioritised as a high-yield strategy to improve TB case finding. Household contact investigation can also serve as an entry point for achieving high case-finding levels in children aged <15 years and high IPT coverage for children aged <5 years.

The TB prevalence of 2.5% among household

Table 2 Variations in the yield of household contact investigations by administrative region, Ethiopia, April 2013–March 2014

Characteristic	Amhara *n* (%)	Oromia *n* (%)	Total *n* (%)	*P* value
SS+ TB index cases	2 956	3 059	6 015	
Contacts screened	8 141	7 415	15 527	
Age <5 years	604 (7.4)	1 144 (15.4)	1 748 (11.2)	
Eligible for IPT	592 (98.0)	1 092 (95.5)	1 684 (96.3)	
Receiving IPT (95%CI)	133 (22.4) (19.3–26)	190 (17.4) (15.3–19.8)	323 (19.2) (17.4–21.1)	<0.01
Presumptive TB cases				
Total	319	630	949	
Contacts, % (95%CI)	3.9 (3.5–4.4)	8.5 (7.9–9.1)	6.1 (5.7–6.5)	<0.0001
NNS, *n* (95%CI)	26 (25–26)	12 (11–12)	16 (16–17)	<0.0001
All forms of TB cases diagnosed, *n* (95%CI)				
Total	99	290	389	
Contacts, % (95%CI)	1.2 (1.0–1.5)	3.9 (3.5–4.4)	2.5 (2.3–2.8)	<0.0001
Presumptive cases	31 (26–36)	46 (42–50)	41 (38–44)	<0.0001
NNS	82 (80–84)	26 (25–26)	40 (39–41)	<0.0001
NNT	3.2 (2.9–3.6)	2.2 (2–2.4)	2.4 (2.3–2.6)	<0.0001
SS+ TB cases diagnosed				
Total	45	73	118	
Contacts, % (95%CI)	0.55 (0.41–0.74)	0.98 (.8–1.2)	0.76 (0.63–0.91)	<0.01
Presumptive TB, % (95%CI)	14.1 (10.7–18.4)	11.59 (9.31–14.33)	12.4 (10.5–14.7)	>0.1
All forms, % (95%CI)	45.5 (36–55.2)	25.17 (20.51–30.48)	30.3 (26–35.1)	<0.0001
NNS, *n* (95%CI)	181 (177–185)	102 (99–104)	132 (130–134)	<0.01
NNT, *n* (95%CI)	7.08 (6.33–7.91)	8.63 (7.96–9.33)	8.04 (7.54–8.57)	<0.01

CI = confidence interval, SS+ = sputum smear-positive; TB = tuberculosis; IPT = isoniazid preventive therapy; NNS = number needed to screen; NNT = number needed to test.

contacts in our study is slightly lower than that reported (3.1%) in a recent systematic review.[7] The overall lower prevalence in our study could be attributed to the way in which the screening was organised. We did not perform house-to-house visits to identify TB among household contacts. In a high TB-HIV burden district in South Africa, for example, community-based targeted screening resulted in a TB prevalence of 6%, and most of the culture-confirmed TB cases were found among asymptomatic household contacts.[28] Moreover, as we used less sensitive diagnostic tools in our programme, the lower TB prevalence among household contacts in our study could be an underestimate, highlighting the need for more aggressive screening strategies using improved diagnostic tools. We screened 69% of the expected 3.6 family members (index cases excluded), assuming an average family size of 4.6. As the remaining family members are likely to be asymptomatic, there was a possibility of overestimating the TB yield. This might have led to some balancing effect on the above-mentioned underestimation.

Table 3 The yield of TB household contact investigation by age category, Ethiopia, April 2013–March 14

Characteristics	Age category			*P* value
	⩾5 years % (95%CI)	<5 years % (95%CI)	Total % (95%CI)	
Contacts screened, *n*				
Total	13 779	1 748	15 527	
Presumptive TB cases				
Total, *n*	702	247	949	
All screened	5.1 (4.7–5.5)	14.1 (12.6–15.8)	6.1 (5.7–6.5)	<0.0001
NNS, *n* (95%CI)	19.6 (19.3–19.9)	7.1 (6.7–7.4)	16.4 (16.1–16.6)	<0.0001
All forms of TB				
Total, *n*	325	64	389	
All screened	2.4 (2.2–2.6)	3.7 (2.9–4.6)	2.5 (2.3–2.8)	<0.001
Presumptive cases	46.3 (42.6–50.0)	25.9 (20.8–31.7)	41.0 (37.9–44.1)	<0.0001
NNS, *n* (95%CI)	42.4 (41.7–43.1)	27.3 (26.1–28.6)	39.9 (39.3–40.5)	<0.0001
NNT, *n* (95%CI)	2.2 (2–2.3)	3.9 (3.4–4.4)	2.4 (2.3–2.6)	<0.0001
SS+ TB				
Total, *n*	113	5	118	
All screened	0.82 (0.68–0.98)	0.29 (0.10–0.69)	0.76 (0.63–0.91)	<0.01
Presumptive cases	16.1 (13.6–19)	2.0 (0.73–4.8)	12.4 (10.5–14.7)	<0.0001
All forms	34.8 (29.8–40.1)	7.8 (3–17.4)	30.3 (26–35.1)	<0.0001
NNS, *n* (95%CI)	121.9 (119.9–124)	349.6 (333.4–366.4)	131.6 (129.5–133.7)	<0.0001
NNT, *n* (95%CI)	6.2 (5.8–6.7)	49.4 (43.4–55.9)	8 (7.5–8.6)	<0.0001

CI = confidence interval, TB = tuberculosis; NNS = number needed to screen; NNT = number needed to test; SS+ = sputum smear-positive.

NNS and NNT have been suggested as useful metrics for measuring the efficiency of TB screening programmes.[29] Some researchers have suggested measuring the efficiency of TB screening approaches in terms of resource allocation.[30] We used the NNS and NNT, as we did not capture the parameters suggested in the latter approach. In an active community-based screening study in an urban setting in Uganda, the NNS was 131.[29] Although the NNS in contact-screening studies can vary widely, the median is 45,[31] comparable to the NNS of 40 in our study. Similarly, the NNT of 2.4 in our study is better than the recommended value of 7.[32] However, both the NNS and the NNT varied significantly between the two regions, with Oromia having a smaller NNS and NNT than Amhara.

The reasons for the regional variations in the yield of contact investigation are not clear. In studies with populations with mixed or unknown HIV status, the population-level prevalence of TB and HIV, the screening strategy and the availability of culture services were not associated with yield of active TB case finding.[31] Our data were not disaggregated by HIV status; however, the HIV prevalence rate in Amhara Region is higher in both the general population and among TB patients.[23,33] On the other hand, as antiretroviral treatment (ART) coverage is higher in Amhara than in Oromia,[34] some population-level protective effect might have been conferred by ART, which is known to reduce TB incidence in PLHIV.[35] A more in-depth review of factors contributing to regional variations using data from different sources is needed.

The low IPT coverage in under-5 children is another area that needs to be addressed; however, published data on this population are limited. Among PLHIV, the IPT coverage rate was 18% in 2012.[21] Frequent stockouts of isoniazid and provider-related factors, such as fear of drug resistance, are cited as factors contributing to low IPT coverage rates among PLHIV in Ethiopia.[36] Lack of standardised monitoring tools and low level of awareness among health care providers appear to be the main challenges in our project zones.

The study has certain limitations: the data are not disaggregated by HIV status, sex or MDR-TB status; as sputum microscopy was the main diagnostic tool used in the study, generalising the results to settings that use culture or Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) is difficult; and lack of credible local evidence made comparisons with other studies difficult, necessitating comparisons with population-based surveys and WHO estimates. The study also has a number of strengths: this is the first large-scale experience of implementation of household contact investigation in Ethiopia, and one of few in low-income settings; the experience of IPT among children aged <5 years is also one of few in this setting.

CONCLUSIONS

The yield of household contact investigation was more than 10 times higher than the prevalence estimate in the general population, and served as an entry point for childhood TB care in two large regions of Ethiopia. It should therefore be scaled up to similar settings. However, more effort is needed to optimise its yield by using more sensitive diagnostic techniques, and to improve IPT coverage among under-5 children. Future studies should look into factors contributing to regional variations in the yield of contact investigation, underlying reasons for the low IPT coverage among children, cost and cost-effectiveness of various contact investigation approaches, and the performance of the Xpert assay for TB diagnosis in contacts.

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RESUME

CONTEXTE : Régions d'Amhara et d'Oromia, Ethiopie.
OBJECTIF : Déterminer le rendement de l'investigation des contacts domestiques pour la tuberculose (TB) dans des conditions de routine de programme en Ethiopie.
SCHÉMA : Entre avril 2013 et mars 2014, le personnel des dispensaires antituberculeux a réalisé un dépistage basé sur les symptômes auprès des contacts domestiques de 6015 cas index de TB à frottis positif (SS+ TB). En nous basant sur les données des rapports trimestriels du programme, nous avons calculé le rendement en termes de nombre de personnes à dépister (NNS) et de nombre de personnes à tester (NNT).
RÉSULTATS : Sur 15 527 contacts domestiques dépistés, 6,1% ont été présumés d'avoir la TB (8,5% à Oromia contre 3,9% à Amhara). Toutes les formes de TB et de SS+ TB ont été diagnostiquées chez 2,5% des contacts (Oromia 3,9% contre Amhara 1,2%) et 0,76% des contacts (Oromia 0,98% contre Amhara 0,55%), respectivement. Le NNS requis pour détecter un cas d'une forme quelconque de TB et de SS+ TB a été de 40 et 132, respectivement. Le NNT requis pour diagnostiquer un cas d'une forme quelconque de TB et de SS+ TB a été de 2,4 et 8, respectivement. Sur 1687 enfants éligibles âgés de moins de 5 ans, 323 ont débuté un traitement préventif par isoniazide.
CONCLUSIONS : Le rendement de l'investigation des contacts domestiques a été plus de 10 fois la prévalence estimée dans la population générale. Cette recherche peut constituer un point d'entrée pour la prise en charge de la TB de l'enfant.

RESUMEN

MARCO DE REFERENCIA: Las regiones de Amhara y Oromia en Etiopía.
OBJETIVO: Determinar el rendimiento diagnóstico de la investigación de los contactos domiciliarios de los casos de tuberculosis (TB) en el marco de las condiciones de un programa ordinario en Etiopía.
MÉTODO: Entre abril del 2013 y marzo del 2014, los funcionarios de los consultorios de TB llevaron a cabo un cribado sistemático basado en los síntomas de los contactos domiciliarios de 6015 casos iniciales de TB con baciloscopia positiva (SS+ TB). A partir de los datos programáticos trimestrales, se calculó el rendimiento según el número de personas cribadas (NNS) y el número de personas examinadas (NNT) que fueron necesarios con el fin de detectar un caso de TB activa.
RESULTADOS: En el 6,1% de los 15 527 contactos domiciliarios que participaron en el cribado se estableció una presunción diagnóstica de TB (8,5% en Oromia contra 3,9% en Amhara). Se estableció el diagnóstico de cualquier forma de TB en 2,5% de los contactos (el 3,9% en Oromia contra el 1,2% en Amhara) y de SS+ TB en el 0,76% (0,98% en Oromia contra 0,55% en Amhara). El NNS con el fin de detectar un caso de cualquier forma de TB fue 40 y la detección de un caso de SS+ TB necesitó el cribado de 132 personas. El NNT con el fin de detectar un caso de cualquier forma de TB fue 2,4 y un caso de SS+ TB necesitó el examen de ocho personas. De los 1687 niños menos de 5 años de edad que cumplían con los requisitos, 323 iniciaron el tratamiento preventivo con isoniazida.
CONCLUSIÓN: El rendimiento diagnóstico de la investigación de contactos domiciliarios de los casos de TB fue más de 10 veces superior a la prevalencia estimada en la población general. Esta medida ofreció una puerta de entrada a la atención de la TB de los niños.

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RESEARCH ARTICLE Open Access

Variation and risk factors of drug resistant tuberculosis in sub-Saharan Africa: a systematic review and meta-analysis

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Abstract

Background: Prevalence of multidrug resistant tuberculosis (MDR-TB), defined as in vitro resistance to both rifampicin and isoniazid with or without resistance to other TB drugs, in sub-Saharan Africa (SSA) is reportedly low compared to other regions. These estimates are based on data reported to the World Health Organization (WHO) on drug resistance surveys, which may suffer from a reporting bias. We set out to evaluate the variation in prevalence of drug resistant tuberculosis (DR-TB) and its determinants across SSA countries among new and previously treated TB patients.

Methods: The aim was to perform a systematic review and meta-analysis of DR-TB prevalence and associated risk factors in SSA. PubMed, EMBASE, Cochrane and bibliographies of DR-TB studies were searched. Surveys at national or sub-national level, with reported DR-TB prevalence (or sufficient data to calculate a prevalence) to isoniazid (INH), rifampicin (RMP), ethambutol (EMB), and streptomycin (SM) conducted in SSA excluding the Republic of South Africa, published between 2003 and 2013 with no language restriction were considered. Two authors searched and reviewed the studies for eligibility and extracted the data in pre-defined forms. Forest plots of all prevalence estimates by resistance outcome were performed. Summary estimates were calculated using random effects models, when appropriate. Associations between any DR-TB and MDR-TB with potential risk factors were examined through subgroup analyses stratified by new and previously treated patients.

Results: A total of 726 studies were identified, of which 27 articles fulfilled the inclusion criteria. Studies reported drug susceptibility testing (DST) results for a total of 13,465 new and 1,776 previously treated TB patients. Pooled estimate of any DR-TB prevalence among the new cases was 12.6% (95% CI 10.6-15.0) while for MDR-TB this was 1.5% (95% CI 1.0-2.3). Among previously treated patients, these were 27.2% (95% CI 21.4-33.8) and 10.3% (95% CI 5.8-17.4%), respectively. DR-TB (any and MDR-TB) did not vary significantly with respect to study characteristics.

Conclusions: The reported prevalence of DR-TB in SSA is low compared to WHO estimates. MDR-TB in this region does not seem to be driven by the high HIV prevalence rates.

Keywords: Sub-Saharan Africa, Drug resistant tuberculosis, Risk factors, HIV, Survey

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Background

Globally, the World Health Organization (WHO) reports an estimated prevalence of 3.6% and 20.2% among notified TB cases for primary and acquired multidrug resistant tuberculosis (MDR-TB), respectively, with significant country and regional variations [1]. Despite the high burden of TB in sub-Saharan Africa (SSA) fuelled by HIV [1], drug resistance surveillance has not been widely done, with only 22 of the 46 countries reporting drug resistance data by 2005. These studies have been designed to establish a nationwide MDR-TB prevalence only, and most of them had small sample sizes to assess variations between subpopulations or identify potential risk factors of the prevalence of drug resistance [2]. Yet, the use of inferior TB drug regimens, high HIV infection rates, and a wide roll-out of ART may predispose countries in this region to high levels of drug resistant tuberculosis (DR-TB) [3]. In particular, previous exposure to anti-TB treatment is a well-established risk factor for DR-TB [4]. By 2010, a number of TB programs in SSA were still using the eight-months regimen of two months of ethambutol (EMB), isoniazid (INH), rifampicin (RMP), and pyrazinamide (PZA), followed by six months of EMB and INH. This regimen has been associated with lower cure rates and higher rates of relapse than the currently recommended six-months regimen in which rifampicin is given throughout treatment (two months of EMB,INH,RMP,PZA followed by four months of RMP and INH) [4]. Conversely, duration of RMP treatment beyond four months has been associated with increased risk of acquiring drug resistance in initially drug sensitive strains [5]. Additionally, there have been concerns that, in SSA, six months of directly observed therapy are often unfeasible, and RMP throughout would increase the incidence of MDR-TB, in particular in the context of high HIV prevalence and pre-existing INH resistance [6]. While some drug resistance studies have shown an association between HIV and DR-TB/MDR, data showing HIV as an independent risk factor for MDR-TB in individuals have been limited to particular settings [7]. Nevertheless, high mortality among HIV patients suffering from MDR or extensively drug-resistant tuberculosis (XDR: defined as resistance to any of the fluoroquinolones (such as ofloxacin or moxifloxacin) and to any of the three injectable second-line anti-TB drugs (amikacin, capreomycin, or kanamycin) in addition to MDR) [8] are major concerns to TB control programs in SSA. Finally, the association between RMP mono-resistance and HIV infection has also been documented [9]. Therefore, understanding the role of potential 'drivers' of DR-TB in SSA is important to guide intervention policies and future drug resistance monitoring in the region. We did a systematic review and meta-analysis of published and unpublished studies to establish the variation of DR-TB across SSA countries and its determinants.

Methods

Data sources

We searched PubMed, EMBASE, and Cochrane for original publications from 2003 to 2013 without language limitations. Search terms used included *anti-TB drug resistance, drug resistant tuberculosis, M/DR/XDR-TB, and (isoniazid or rifampicin or ethambutol or streptomycin or ofloxacin or fluoroquinolone or kanamycin or amikacin) resistance* for each country in SAA, excluding the Republic of South Africa (RSA). Each term was searched separately with a text string ending with the specific name of the country. We excluded RSA because drivers of DR-TB in this country are likely to be different and prevalence has been reported to be substantially higher than the rest of SSA countries [10]. We also searched bibliographies of other reviews and citations of the original articles identified. Reviewers obtained unpublished DR-TB studies through personal communication with experts and authors of papers identified.

Study selection

We included surveys carried out both at national or sub-national level reporting M/DR-TB prevalence or sufficient data to calculate a prevalence of resistance to isoniazid (INH), rifampicin (RMP), ethambutol (EMB), streptomycin (SM), and/or MDR (INH and RMP). Conference proceedings, chapters of books, and correspondences were excluded. Studies were considered of sufficient quality for inclusion if participants were classified as new or previously treated based on the WHO definition [11], the study covered a large geographical area (district, region, or entire country), and recommended laboratory procedures for culture and drug susceptibility testing (DST) were followed [12]. Studies conducted in a single health unit e.g. a referral hospital or a TB center, or those where fewer than 50 participants had DST were excluded to minimize bias of including non-representative samples of the population. Where cluster sampling was used, adjustment for the cluster design was a requirement for inclusion in this review.

Two authors conducted the electronic searches independently; the last search was conducted in June 2014. Selection of articles was done by both reviewers independently. Disagreements on articles to be included were resolved by consensus among the two authors.

Data extraction

We extracted data using pre-defined forms on: country of the study; sampling method; description of the facilities where the study was done; total number of patients enrolled in the study as per treatment category; number of patients with DST results; number of patients with a positive result for resistance to INH, RMP, EMB, SM, or

MDR-TB; and HIV prevalence among the participants (if available). HIV prevalence at national level for each country of interest was collected from the UNAIDS report 2013 [13]. Two authors extracted data independently and any discrepancies in the data extracted were resolved through discussions.

Data synthesis and analysis

According to WHO, resistance among new cases is defined as resistance to one or more anti-tuberculosis drugs in patients that have never been treated for TB. Resistance among previously treated TB patients, on the other hand, is defined as resistance to one or more anti-tuberculosis drugs in patients that have been treated for TB. It can be transmitted from another patient with DR-TB or acquired in patients diagnosed with pan-sensitive TB who have started TB treatment and subsequently develop resistance to one or more of the drugs used during the treatment. To generate data stratified for the resistance among the new and previously treated TB patients, we calculated pooled resistance prevalence along with the 95% confidence interval through meta-analysis using random effects models for MDR-TB and any DR-TB to the first line drugs (INH, RMP, EMB, and SM). We assessed the heterogeneity among reported prevalence using the I^2 statistic.

To explore the variation observed in the prevalence estimates, we did a subgroup analysis by stratifying studies by predefined variables. In particular, we categorized variables as follows: 1) by sub-region (Eastern sub-region included Burundi, Ethiopia, Kenya, Rwanda, Somalia, Uganda, and Tanzania; West Africa sub-region included Benin, Burkina Faso, Cameroon, Equatorial Guinea, Gambia, Ghana, Ivory Coast, and Nigeria; Southern sub-region: Botswana, Zambia, Mozambique, Madagascar, Swaziland, and Zambia; and Central Africa sub-region: Central African Republic and Chad); 2) HIV prevalence at a national level (countries with a prevalence of less than 5% compared to those with a prevalence of more than 5% in the general population); 3) type of survey (national or sub-national); 4) sampling method (random sampling or cluster sampling); 5) sample size (studies of less than 100 patients or more than 100 patients); and HIV prevalence among study participants (less than 40% compared to, equal to or more than 40%).

We avoided use of acquired resistance for these categories of patients due to limitations of this definition for acquired resistance as it does not put into consideration possibilities of re-infection with resistant forms and initial infection with resistant strains contributing to treatment failure, since capacity to ascertain resistance patterns prior to treatment initiation is rarely available under routine settings.

Results

We identified 725 citations through electronic data searches and one completed study with unpublished data. Out of these, 47 articles were selected for full text review, of which 20 articles were excluded for various reasons (Figure 1). Characteristics of the 27 articles included are summarized in Table 1. Of these 27 studies, 19 (70%) reported DR-TB data on both new and previously treated patients. Seven studies reported resistance among new cases only, while one study assessed DR-TB among the previously treated. Sixteen (59%) studies reported HIV testing, and HIV prevalence estimates at country level were available for more than 90% of the studies. Thirteen (48.1%) studies in total reported data at national level. Compared to other regions, the eastern region contributed the highest number of articles, five of which were from national surveys.

DR-TB data was reported for a total of 15,462 sputum smear-positive TB patients in the 27 articles included from 2003 to 2013. Of these, 13,645 (88.4%) and 1,776 (11.6%) were new and previously treated patients, respectively. All reported estimates for any resistance and MDR-TB among new and previously treated patients are presented separately by study in Figure 2. In Figure 3, we then present pooled estimates for all resistance patterns, including MDR-TB among new and previously treated patients. Prevalence of any DR-TB and of MDR-TB were higher among patients who had been previously treated for TB (Figures 2 and 3). Overall, the pooled prevalence of any DR-TB among new and previously treated patients was 12.6% (95% CI 10.6-15.0%) and 27.2% (95% CI 21.4-33.8), respectively; while MDR-TB among the new and previously treated patients was 1.5% (95% CI 1.0-2.3) and 10.3% (95% CI 5.8-17.4), respectively. Summary estimates for any DR-TB among new and previously treated TB cases were highest for INH [7.8% (95% CI 6.5-9.4) and 23.1% (95% CI 15.9-32.2)] and lowest for EMB [1.9% (95% CI 1.3-2.8) and 8.7% (95% CI 4.7-15.3)] (Figure 3). Resistance to RMP in new cases, 2.0% (1.5-2.8) was also very low (Figure 3).

Variation of DR-TB with key study characteristics

In Figures 4 and 5, we present the subgroup analyses for the prevalence of any DR-TB and MDR-TB by study characteristics. Overall, we observed larger variations in the pooled estimates by subgroup with respect to any DR-TB, compared to MDR estimates.

Regional variations

Prevalence of any DR-TB among new cases varied from 10.4% (95% CI 8.2- 13.1, n = 6) in the Southern region to 17.0% (12.4-23.0, n = 2) in the Central region. Any DR-TB among previously treated TB patients was highest in East Africa with levels of 29.2% (95% CI 21.4-38.6,

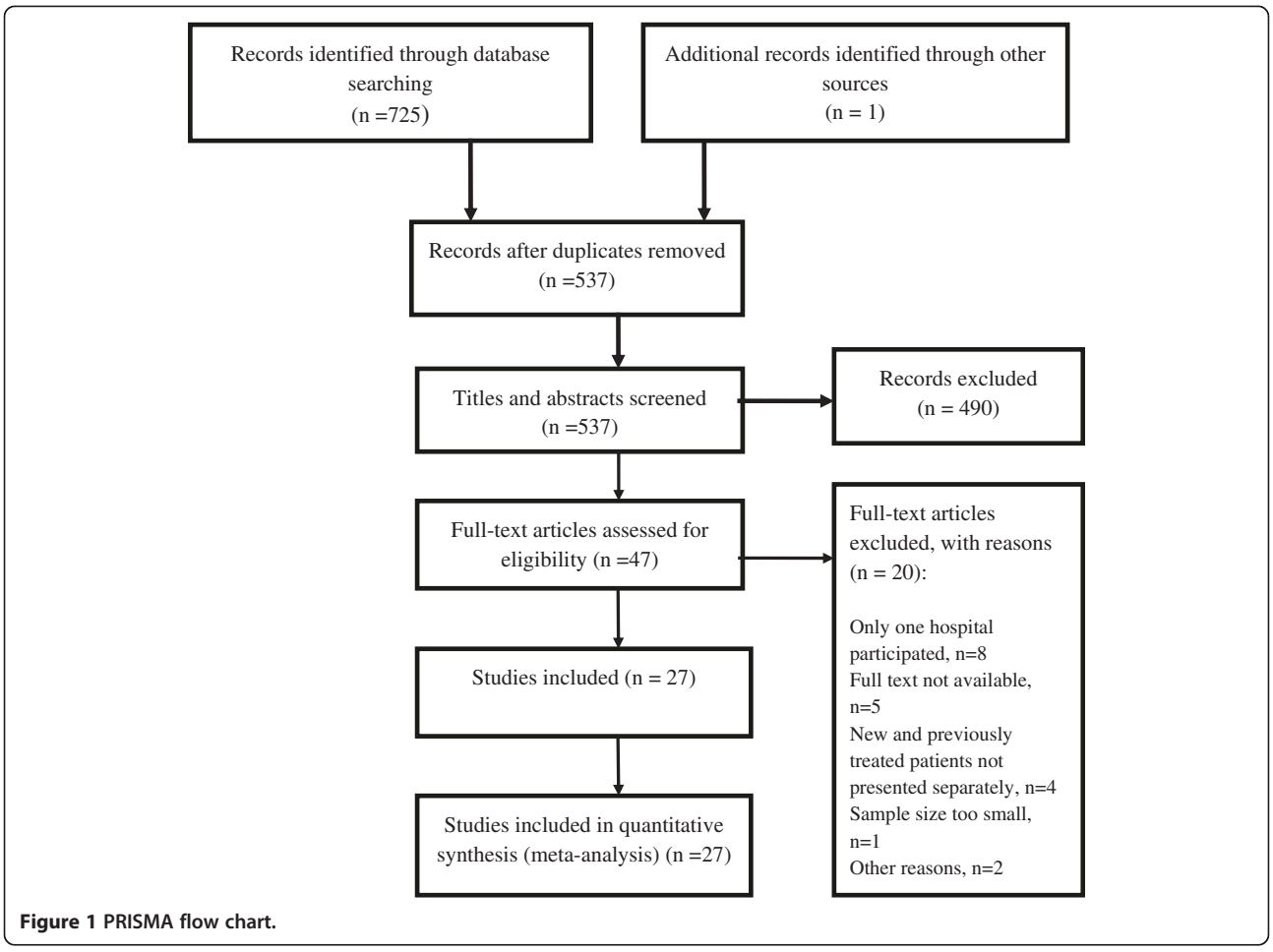

Figure 1 PRISMA flow chart.

n = 8) and lowest in the Southern African countries, 24.0% (95% CI 13.0-40.0, n = 6). MDR TB among new patients was lowest in Central Africa at 1.2% (95% CI 0.3-5.5, n = 2) and highest in Western Africa, 2.3% (95% CI 1.0-4.8, n = 3), while MDR-TB among previously treated was highest in Southern region, 11.7% (95% CI 5.0-25.0, n = 6) and lowest in Eastern region, 9.6% (95% CI 4.7-18.4, n = 9). We did not observe significant variations in pooled estimates of any DR-TB or MDR-TB in the sub-regions as shown by the overlap in the 95% CIs of our estimates (Figures 4 and 5).

Country-level HIV prevalence

Analysis of any DR-TB among new cases in relation to HIV infection rates (Figure 4) showed somewhat higher resistance rates of 13.9% (95% CI 10.5-18.2, n = 12) in countries where HIV prevalence was lower than 5%, compared to countries where the prevalence was equal to or higher than 5%, [11.2% (95% CI 8.7-14.2, n = 12)], while DR-TB among the previously treated was almost the same among settings with these different HIV prevalence rates (26.1%, n = 8 vs 25.4%, n = 9). Primary MDR-TB in settings with less than 5% HIV prevalence was 1.9% (95% CI 1.1-3.2 n = 9) as compared to 1.5% (95% CI 0.8-2.8 n = 12) in settings where the HIV prevalence equal to or higher than 5%. MDR-TB among previously treated patients in countries with lower than 5% HIV prevalence was 8.3% (95% CI 3.4-18.8, n = 11) compared to 11.0 (95% CI 5.8-19.9, n = 9) in countries with HIV prevalence of equal to or higher than 5%. However, differences were small with largely overlapping 95% confidence intervals.

TB/HIV co-infection

Where HIV testing was done as part of the survey (Figure 4), we observe a higher prevalence of DR-TB among new cases in studies where HIV was lower than 40% among the study participants [16.1% (95% CI 12.5-20.6, n = 11)] as compared to 9.6% (95% CI 6.8-13.6, n = 4) in studies where HIV prevalence among participants was equal to or higher than 40%. Analysis of DR-TB among previously treated cases in relation to these HIV co-infection rates shows the same rates in these two settings, those studies with lower than 40% HIV co-infection and

Table 1 Characteristics of studies included in the review of variation of M/DR-TB in SSA; 2003–2013

Author	Study year	Country	Study description	Patient category	Sample size (included in DST)	HIV prevalence in the study (%)	Country HIV prevalence (%)	DST method	Type of resistance tested
Minime-Lingoupou F *et al.* [21]	2009	Central African Republic	Sub-national survey. TB health facilities in Bangui and Bimbo.	New patients	233	26	N/A	LJ	INH, RMP, SM, EMB
Asmamaw D. *et al.* [22]	2004	Ethiopia	Sub-national survey. Twenty-four TB health facilities in Addis Ababa.	New patients	231	29.6	2.9	LJ	INH, RMP, SM, EMB
Abdelhadi O. *et al.* [23]	2009-2010	Chad	Sub-national survey. Number of TB facilities not provided.	New patients	135	25	3	LJ	INH, RMP, SM, EMB
Yimer S.A. *et al.* [24]	2008	Ethiopia	Sub-national survey. Number of TB facilities in Amhara not provided.	New patients	112	26.9	1.9	MGIT	INH, RMP, SM, EMB
Urassa W. *et al.* [25]	2001-2004	Tanzania	Sub-national survey. Five TB health facilities in Dar es Salaam.	New patients	887	53	5.7	LJ	INH, RMP, SM, EMB
Ndungu PW. *et al.* [26]	2010	Kenya	Sub-national survey. Five TB health facilities in and around Nairobi.	New patients	356	26.3	6.6	MGIT/LJ	INH, RMP, SM, EMB
Matee M. *et al.* [27]	2005-2006	Tanzania	Sub-national survey: Thirty-seven TB facilities of Temeke district.	New patients	226	N/A	5.8	LJ	INH, RMP, SM, EMB
Lukoye D. *et al.* (a) [28]	2008	Uganda	Sub-national survey. Twenty-two TB health facilities in Kampala.	New and PT patients	557	30.9	6.7	LJ	INH, RMP, SM, EMB. Km and O
Sanders M. *et al.* [29]	2008	Burundi	Sub-national survey. Seven TB health facilities in Bujumbura.	New and PT patients	859	N/A	2.2	LJ	INH, RMP, SM, EMB, PABA
Lukoye D. *et al.* (b) [30]	2009-2011	Uganda	National survey.	New and PT patients	1537	30.7	7.3	LJ	INH, RMP, SM, EMB, KM and OFX
Umubyeyi A. N. *et al.* [31]	2004-2005	Rwanda	National survey.	New and PT patients	701	N/A	3.3	LJ	INH, RMP, SM, EMB
Irenious S. *et al.* [15]	2011	Somalia	National survey.	New and PT patients	946	N/A	N/A	Hain	INH, RMP only
Chonde TM *et al.* [32]	2006-2007	Tanzania	National survey.	New and PT patients	1,167	N/A	5.8	LJ	INH, RMP, SM, EMB
Tessema B. *et al.* [33]	2009	Ethiopia	Sub-national survey. Five TB health facilities in north west Ethiopia.	New and PT patients	260	25.4	1.7	LJ	INH, RMP, SM, EMB, CPM, OFX, AM, MFX, Amino Salicylic Acid
Chanda M. *et al.* [34]	2006	Zambia	Sub-national survey. Six TB health facilities in Ndola district.	New and PT patients	361	N/A	13.2	LJ	INH, RMP, SM, EMB

Table 1 Characteristics of studies included in the review of variation of M/DR-TB in SSA; 2003–2013 *(Continued)*

Nunes E.A. *et al.* [35]	2002-2003	Mozambique	Sub-national survey. Number of TB health facilities not provided.	New and PT patients	111	N/A	9.8	LJ	INH, RMP, SM, EMB
Nelson L.J. *et al.* [36]	2002	Botswana	National survey.	New and PT patients	2,425	60	25.7	LJ	INH, RMP, SM, EMB
Ramarokoto H. *et al.* [37]	2005-2007	Madagascar	National survey.	New and PT patients	1,275	N/A	0.6	LJ	INH, RMP, SM, EMB
Samo Gudo P. *et al.* [38]	2007-2008	Mozambique	National survey.	New and PT patients	1,200	N/A	11.5	LJ	INH, RMP, SM, EMB
Sanchez-Padilla E. *et al.*	2009	Swaziland	National survey	New and PT patients	633	79.9	25.8	MGIT or LJ	INH, RMP, SM, EMB
Edgbola R.A. *et al.* [39]	1999	Gambia	National survey.	New and PT patients	225	N/A	2.1	LJ	INH, RMP, SM, EMB
Affolabi D. *et al.* [40]	2002-2004	Benin	Sub-national survey. National Pneumo-Phthisiology hospita receiving patients from Benin and surrounding countries	New and PT patients	470	10.2	2.3	LJ	INH, RMP, SM, EMB
Tudo G. *et al.* [41]	2004	Equatorial Guinea	Sub-national survey. Number of TB health facilities not provided.	New and PT patients	236	13.5	3.6	LJ	INH, RMP, SM, EMB
N'guesesan K. *et al.* [42]	2005	Ivory Coast	National survey.	New patients	320	N/A	4.9	LJ	INH, RMP, SM, EMB
Sangare L. *et al.* [43]	2010	Bukina Furso	National survey.	New and PT patients	416	28.7	1.3	LJ	INH, RMP, SM, EMB
Ellis Awusu-Dabo *et al.* [44]	2001-2004	Ghana	National survey.	New and PT patients	216	25.9	4.7		INH, RMP, SM, EMB, Thiacetazone
Jurgen Noesk *et al.* [45]	2012	Cameroon	Sub-national. Twenty-nine TB health facilities in Litoral region.	PT patients	233	26	N/A	LJ	INH, RMP, SM, EMB, Km and GFX
Mbulo G.M.K. *et al.* Results of the national drug resistance survey in Zambia. (in preparation)	2008	Zambia	National survey.	New and PT patients	883	47.6	13.3	LJ	INH, RMP, SM, EMB

Abbreviations: *DST* drug susceptibility testing, *INH* isoniazid, *RMP* rifampicin, *EMB* ethambutol, *SM* streptomycin, *Km* kanamycin, *GFX* gatifloxacin, *CPM* capreomycin, *OFX* ofloxacin, *AM* amikacin, N/A, not available, *LJ* Löwenstein Jensen, *MGIT* mycobacteria growth indicator tube, *PT* previously treated patient.

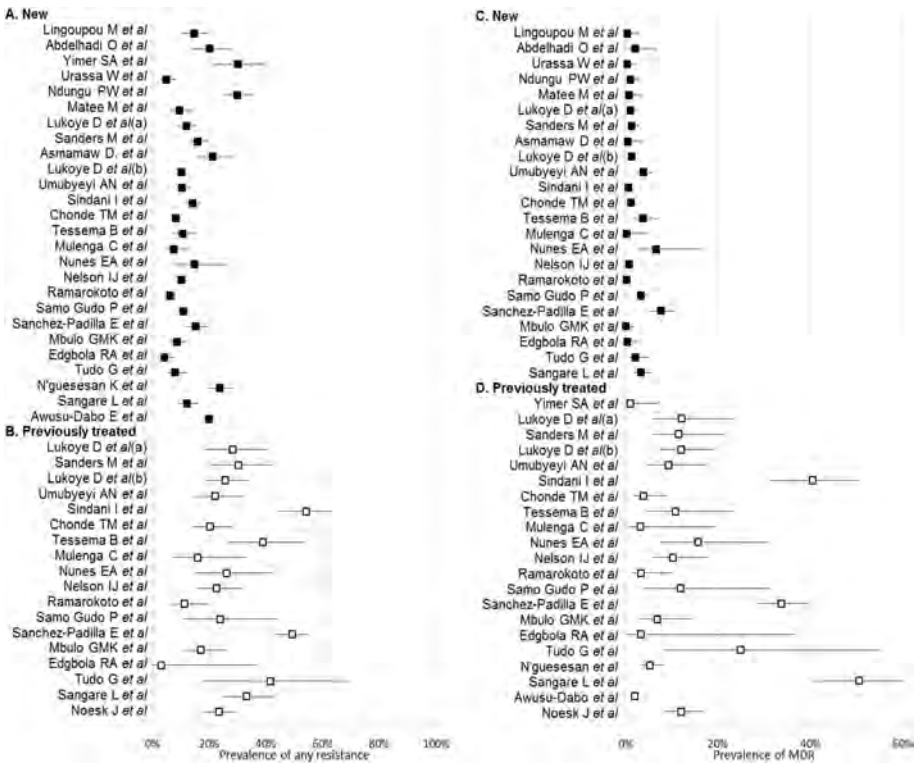

Figure 2 Forest plot of prevalence of any resistance and MDR among new and previously treated patients.

equal to or more than 40% of HIV co-infection, [29.1%, 95% CI = 24.3-34.4 n = 6 and 28.5% 95% CI 12.4-53.0 n = 3]. MDR among new cases in studies where TB/HIV co-infection rates were lower than <40% was 1.8% (1.2-2.7, n = 9); and 1.0% (0.2-5.7; n = 4); in studies with equal to or higher than 40% TB/HIV co-infection. MDR-TB among previously treated patients where TB/HIV co-infection was lower than 40% among the participants was 10.6% (95% CI = 3.6-27.8, n = 8) and 14.6% (95% CI 4.4-38.6, n = 3) where equal to or higher than 40% of the

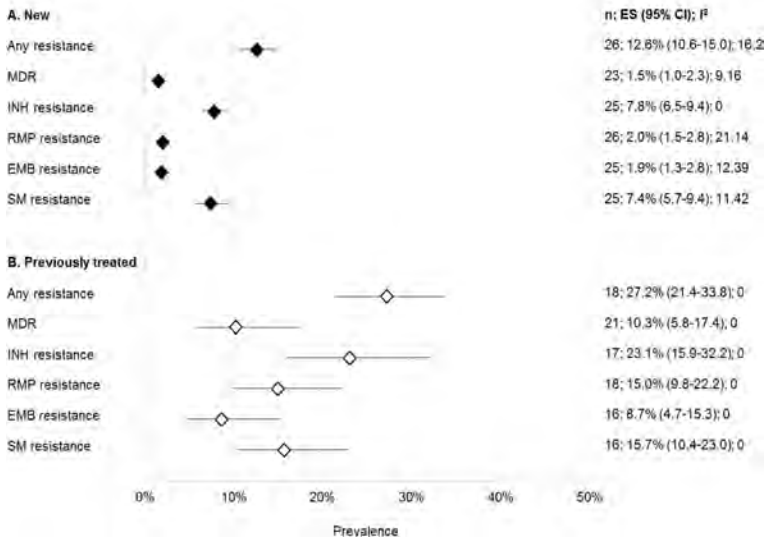

Figure 3 Pooled estimates for all resistance patterns among new and previously treated patients. Abbreviations: n, number of studies; ES, estimate; INH, isoniazid; RMP, rifampicin; EMB, ethambutol; SM, streptomycin.

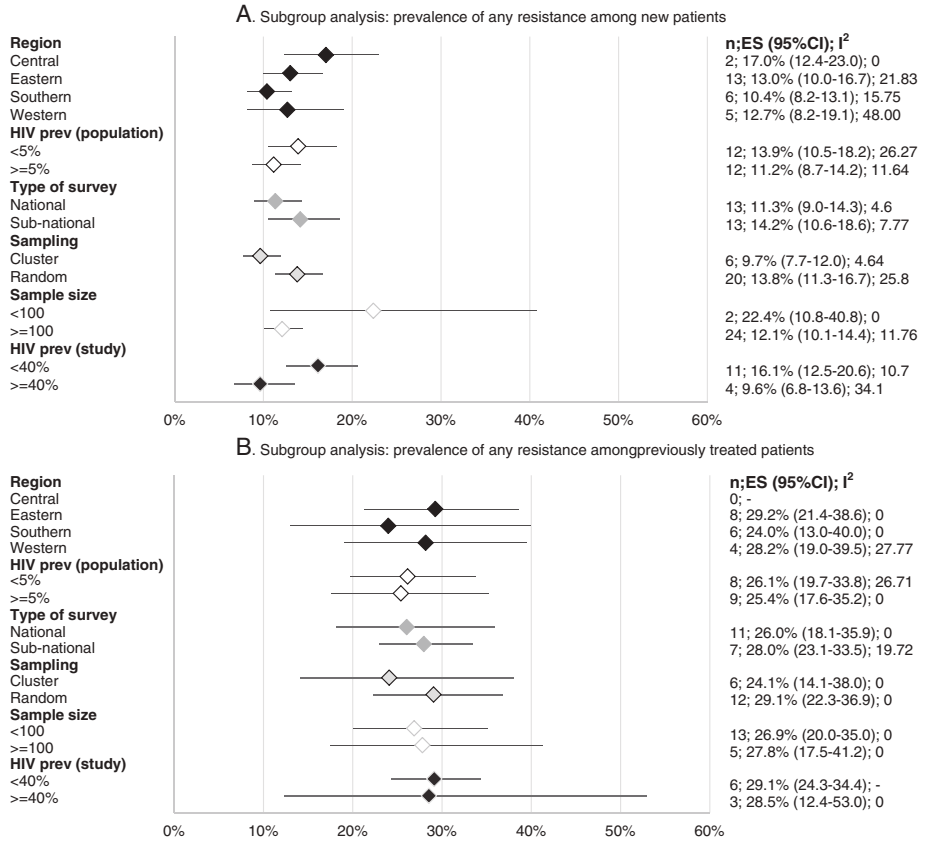

Figure 4 Subgroup analysis: prevalence of any drug resistance. Abbreviations: n, number of studies; ES, estimate. Where data is missing, it means that such a region did not have any study fitting that classification for inclusion in the analysis.

participants were HIV co-infected, although this difference was also not significant (Figure 5).

Study geographical coverage

Generally, articles reporting national surveys estimated lower rates of any DR-TB among new cases 11.3% (95% CI = 9.0-14.3, n = 13) as compared to sub-national reports 14.2% (95% CI 10.6-18.6, n = 13). Any acquired DR-TB was similar in the national (26.0%; 95% CI 18.1-35.9, n = 11) and sub-national surveys (28%; 95% CI-23.1-33.5, n = 7) (Figure 4). MDR estimates among new cases were the same in both national and sub-national studies at 1.6% (95% CI 0.9- 2.8, n = 11) and 1.6% (95% CI 1.0-2.5, n = 12) respectively, as were MDR rates among the previously treated: 10.5% (95% CI 4.7-21.7, n = 13) versus 11.0% (95% CI 5.8-19.9, n = 8), respectively (Figure 5).

Sampling design

Studies that applied a cluster sampling design reported lower rates of any DR-TB 9.7% (7.7-12.0; n = 6) in new cases than studies where random sampling was used 13.8% (11.3-16.7; n = 20); DR-TB rates among previously treated patients in these two study designs were 24.1% (14.1-38.0; n = 6) and 29.1% (22.3-36.9 n = 12) respectively. Rates of MDR-TB followed a similar trend with MDR-TB among the new patients in studies that used cluster and random sampling designs reporting MDR-TB rates of 1.0% (0.5-2.1; n = 6) and 1.8% (1.1-2.9; n = 17), respectively. MDR-TB among the previously treated category in studies that used cluster design was 9.9% (3.7-24.3; n = 6), similar to that in studies where random sampling was used [10.3% (5.1-19.9; n = 15)]. All the differences in these measurements did not show statistical significance (Figures 4 and 5).

Sample size

Studies with sample sizes of less than 100 participants reported significantly higher rates of any DR-TB among new cases, 22.4% (95% CI 10.8-40.0, n = 2) compared to studies where 100 or more participants were recruited, 12.1% (95% CI 10.1-14.4, n = 24). Levels of DR-TB among the previously treated were almost the same in both categories of sample size, 26.9% (95% CI 20.0-35.0, n = 13) and 27.8% (95% CI 17.5-42.1, n = 5). For either category of study size, MDR levels amongst new cases followed similar trends, significantly higher 6.7% (95% CI 2.5-16, n = 1)

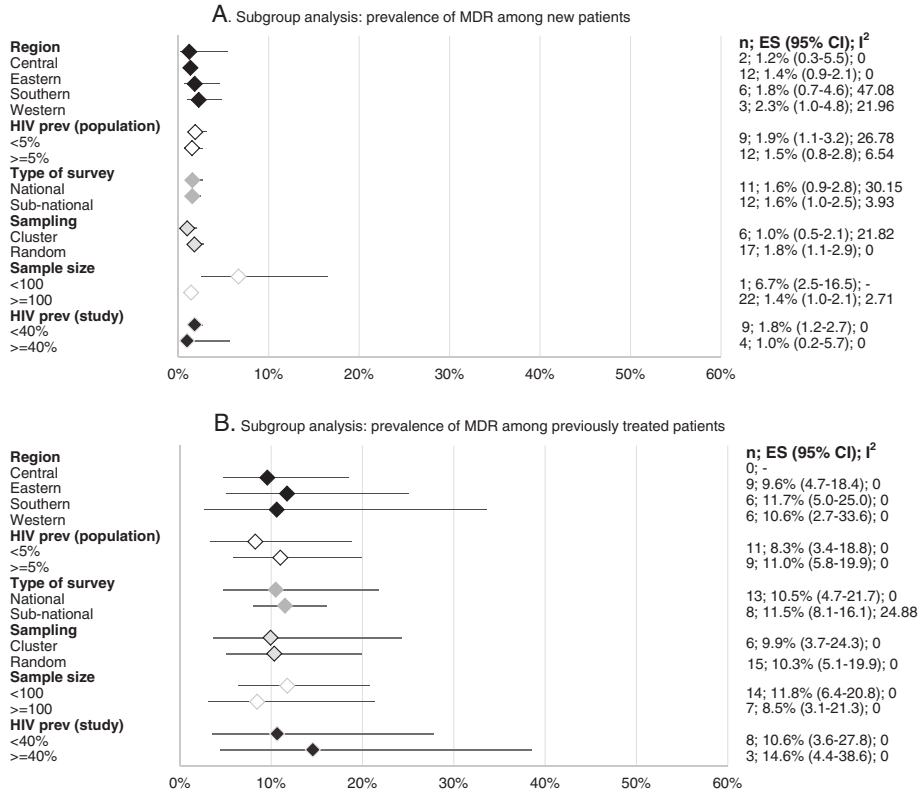

Figure 5 Subgroup analysis: prevalence of MDR-TB. Abbreviations: n, number of studies; ES, estimate, MDR- TB, Multi-drug resistant tuberculosis. Where data is missing, it means that such a region did not have any study fitting that classification for inclusion in the analysis.

in studies with less than 100 participants as compared to 1.4% (95% CI 1.0-2.1, n = 22) in studies with larger sample sizes. Although slightly higher, levels of MDR-TB among previously treated patients in studies with less than 100 participants, 11.8% (6.4%-20.8%, n = 14), this difference was not statistically significant as compared to studies with 100 participants or more, 8.5% (95% CI 3.1%-21.3%, n = 7).

Publication bias

Finally, in Figure 6, we explored graphically the possibility of a publication bias. We did not observe an indication of such a bias in the studies included.

Discussion

In our study, we reviewed variations and risk factors of DR-TB in SSA. We found that levels of any DR-TB and MDR-TB are lower in SSA than reported globally [1]. In particular, our results show MDR-TB prevalence estimates as almost half as compared to the global average reported by WHO for both new (1.5% vs 3.6%) and previously treated TB patients (10.3% vs 20.2%) [2]. These consistent low levels occur in settings with high rates of HIV, largely attributed, among other factors, to the late introduction of RMP and limited availability of TB drugs on the open market outside national TB programs [14] in this region. According to the subgroup analyses, rates of (M)DR-TB remain generally low regardless of the study geographical coverage, sample size, HIV co-infection rates, and sub-region where the study was conducted. This finding happens at a time when more information on rates and factors associated with of DR-TB in this region is emerging, as more countries conduct surveys at national and sub-national level [14], although data on DR-TB from SSA is still limited [10]. The observed low levels of (M)DR-TB may also reflect the functionality of TB control programs in this region. Previous studies have shown that countries where standardized regimens are available and properly implemented, where quality drugs are regularly supplied, and where systems are in place to ensure patients' adherence are less likely to report high rates of (M)DR-TB. From our findings, such explanation can be supported by the high rates of MDR-TB from the Horn of Africa included in our review, which could have resulted from a break down in the public health system and therefore in the functionality of the TB program due to civil strife also observed elsewhere in the world [16,17]. Therefore, regional variations in MDR-TB rates might be considered a proxy measure for functionality of national TB programs which should alert national governments

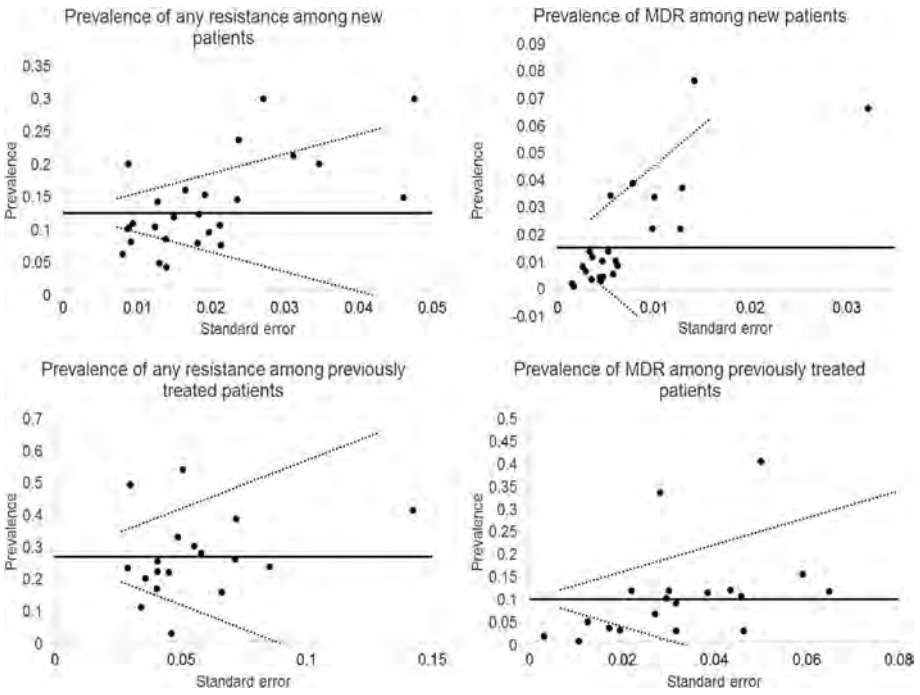

Figure 6 Funnel plot exploring publication bias. The horizontal line represents the summary prevalence and guidelines are given to indicate the 95% confidence interval for this estimate.

and donor communities for timely interventions. The role of *Mycobacterium tuberculosis* (MTB) strains in transmissibility and its potential to develop DR in this region should not be ignored. As observed in some settings, particular MTB strains predominant in specific localities have been associated with varying rates of MDR-TB [18]. Hence, more molecular studies are required to examine and explain possible associations of the predominant MTB strains with the observed prevalence of DR-TB in SSA. Our findings seem to imply that transmission-related factors such as late diagnosis, nosocomial spread, and delay in initiation of second-line treatment as observed in most settings of this region have not led to increase in (M)DR-TB above the minimum WHO estimates. However we observe higher rates of resistance to INH and SM than other drugs in our analysis, also documented earlier, attributed to the long history of INH and SM use in management of TB and to the stepwise acquisition of DR by MTB to these two drugs [19].

Lower levels of MDR-TB (1.5%) in settings with higher HIV prevalence at population level, also observed where HIV testing was included in the study design, could result from less participation rates of (M)DR-TB/HIV co-infected patients in surveys due to either severe illness or higher risk of death [8]. Where collection of individual HIV data was included in the study design, we found higher rates of MDR-TB (25%) among previously treated patients in studies where HIV prevalence was lower, possibly due to the same explanation and the possibility of suspected high MDR-TB rates in such populations.

We observed levels of any RMP resistance among new cases (1.5%) in the analysis close to the reported prevalence of MDR-TB (2.0%). This finding is of significant relevance in the current global and regional efforts to accurately and timely diagnose MDR-TB with the scale-up of molecular technology like GeneXpert MTB/RIF, providing quick results of RMP resistance as a proxy to MDR-TB. In fact, in many SSA countries, access to culture and DST facilities is limited and molecular technologies might ease access to MDR-TB diagnosis and reduce the time spent between diagnosis and initiation of the patient on treatment. High levels of INH and SM resistance found in our review, also documented elsewhere, need to be monitored closely in relation to the potential increase in treatment failure and relapse rates with the current first-line drugs [20]. In light of the recommended roll-out of the RMP-through regimen by WHO, especially in high HIV burden settings such as SSA, TB programs need to ensure correct use of RMP in drug -susceptible cases to avoid adding RMP resistance to the already high levels of INH resistance, likely to lead to high MDR-TB rates.

Finally, we observe higher rates of MDR-TB in smaller studies as compared to larger ones possibly arising from the difference in the core objectives of the studies. Studies with small sample sizes are usually done to explore

possibilities of high MDR-TB rates in specific populations. Similarly, DR-TB rates in sub-national studies are higher than in the national surveys since, in most cases, sample sizes in such studies tend to be smaller, non-representative of the population, and sometimes do not apply standardized methodologies, although we aimed to exclude such studies from our analysis. The lower (M)DR levels observed in cluster surveys as compared to surveys where random sampling was applied may have a similar explanation. Cluster sampling designs are usually applied where the study population is large and covering a wider geographical area for optimal use of resources without compromising the quality of the data. Consequently, lower (M)DR rates in cluster surveys could have been a proxy to the large sample sizes involved.

As demonstrated by the publication bias sub-analysis, we observed no tendency from authors to publish papers showing more or less resistance more frequently that could distort our findings.

Limitations

Our review had some limitations. Of 44 countries in SSA (excluding the Republic of South Africa), only 20 countries had done studies that fulfilled our inclusion criteria, of which studies from five countries were not on a national scale. Many of the DR-TB surveys identified during our searches were excluded because they took place at a single health facility or had not stratified patients according to their treatment history.

Although the association between HIV infection and DR-TB is still controversial and deserves further exploration, ten of the 27 studies analyzed did not include HIV testing. It was, therefore, difficult to draw meaningful conclusions. Similarly, we did not review data on national ART coverage due to challenges associated with accessing accurate data to examine a possible relationship between ART roll-out and levels of MDR-TB. Finally, results on second-line DST were not reported for the majority of studies. This could be a reflection that most countries in SSA had not initiated MDR-TB treatment at the time of the study and the possibilities of finding XDR-TB were limited, although this analysis would be important especially in settings where some fluoroquinolones (a cornerstone of second-line drug regimens) are widely used for treatment of other bacterial infections.

We excluded the republic of South Africa on the basis of high levels of MDR-TB and XDR-TB rates in comparison to other countries of SSA [1,8], possibly fuelled by high nosocomial transmission rates in the context of very high rates of TB/HIV co-infection reported in this country. We assumed that including such studies could potentially skew our results towards higher DR-TB or MDR-TB estimates.

Conclusions

Our analysis showed low levels of MDR-TB in sub-Saharan Africa compared to WHO estimates, with higher resistance to INH and SM as reported elsewhere in the world. There are no major variations in MDR-TB burden by sub-region and evidence of association between MDR-TB and HIV infection rates did not show statistical significance. We attribute these low levels to the limited existence of anti-TB drugs outside the national programs, late introduction of RMP in SSA, and wide use of fixed drug combinations. Since these factors may apply to other settings where rates of MDR-TB are higher, more studies are required to explore other possible explanations for the low levels of MDR-TB in SSA, such as the role of predominant MTB strains in generation and transmission of DR-TB in this region

Abbreviations

ART: Anti-retroviral therapy; DR-TB: Drug resistant tuberculosis; DST: Drug susceptibility testing; EMB: Ethambutol; INH: Isoniazid; MDR-TB: Multi Drug Resistant Tuberculosis; RMP: Rifampicin; RSA: Republic of South Africa; SM: Streptomycin; SSA: Sub-Saharan Africa; TB: Tuberculosis; WHO: World Health Organization; XDR- TB: Extensively drug resistant tuberculosis; PZA: Pyrazinamide.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

DL, FGJC, WS, GBG ad MLJ conceived the idea. DL and WS did literature search, identified and agreed on studies for inclusion and, extracted the data. GBG, DL, FGJ did data synthesis and analysis, DL and GBG wrote the initial draft. All co-authors reviewed the final draft before submission. All authors read and approved the final manuscript.

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Reducing the price of treatment for multidrug-resistant tuberculosis through the Global Drug Facility

Kaspars Lunte,[a] Thierry Cordier-Lassalle[b] & Joel Keravec[a]

Problem Many countries have limited experience of securing the best prices for drugs and have little negotiating power. This is particularly true for the complex, lengthy and expensive regimens used to treat multidrug-resistant tuberculosis.

Approach The Stop TB Partnership's Global Drug Facility is dedicated to improving worldwide access to antituberculosis medicines and diagnostic techniques that meet international quality standards.

Local setting The Global Drug Facility is able to secure price reductions through competitive tendering among prequalified drug manufacturers and by consolidating orders to achieve large purchase volumes. Consolidating the market in this way increases the incentives for suppliers of quality-assured medicines.

Relevant changes In 2013 the Global Drug Facility reduced the price of the second-line drugs it supplies for multidrug-resistant tuberculosis: the overall cost of the longest and most expensive treatment regimen for a patient decreased by 26% – from 7890 United States dollars (US$) in 2011 to US$ 5822 in 2013.

Lessons learnt The price of treatment for multidrug-resistant tuberculosis supplied by the Global Drug Facility was reduced by consolidating orders to achieve large purchase volumes, by international, competitive bidding and by the existence of donor-funded medicine stockpiles. The rise in the number of suppliers of internationally quality-assured drugs was also important. The savings achieved from lower drug costs could be used to increase the number of patients on high-quality treatment.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

Tuberculosis remains a major global public health problem. According to a 2014 report from the World Health Organization (WHO), only 97 000 patients of the estimated 300 000 patients with multidrug-resistant tuberculosis worldwide were receiving treatment.[1] Access to quality medicines for patients in need is restricted by the limited availability of funding, which is often compounded by poor knowledge of drug management (e.g. storage and distribution) and a lack of staff and facilities. To increase cure rates, it is important that antituberculosis medicines are affordable and that systems are in place for providing proper care at all levels.

Many countries have limited experience in securing the best possible prices for drugs and have little negotiating power since they are not able to consolidate purchases into large volumes. This is especially true of the medicines needed for multidrug-resistant tuberculosis, where treatment is complex and can last two years or more. Moreover, these medicines are much more expensive than those for drug-sensitive tuberculosis.[2,3]

The Global Plan to Stop Tuberculosis, which was launched by the Stop TB Partnership, identified universal access to high-quality care for all people with the disease as one of its central objectives.[4] Today, access to quality-assured drugs is promoted by key stakeholders such as the WHO Prequalification Programme,[5] the Global Fund to Fight AIDS, Tuberculosis and Malaria, UNITAID and the Global Drug Facility, which was established by the Stop TB Partnership.

Global Drug Facility

The Global Drug Facility is dedicated to improving access worldwide to tuberculosis medicines and diagnostic techniques that meet international quality standards. In practice, the facility provides only internationally quality-assured medicines that are manufactured under stringent conditions so that countries and their governments can be confident they will always receive high-quality medicines. This stringency ensures that risk of developing drug-resistance is minimized. Recent studies show that the substandard and falsified drugs readily available on the private market have probably contributed to the development of antituberculosis drug-resistance in low- and middle-income countries.[6,7]

Today a growing number of antituberculosis medicines are able to meet international quality standards, as verified by the WHO Prequalification Programme or other stringent drug regulatory authorities. In this context, the Global Drug Facility has contributed significantly to drug volume consolidation and has, over the years, consistently secured lower prices for quality-assured antituberculosis medicines.[8]

Price reductions

In 2013, as in previous years, the Global Drug Facility reduced the price of the second-line drugs it supplies for the treatment of multidrug-resistant tuberculosis. This has resulted in a significant decrease in the overall cost of treatment. Fig. 1 illustrates the change between 2011 and 2013 in the cost of the longest and most expensive regimen for treating multidrug-resistant tuberculosis, one of many regimens available worldwide. For a 24-month treatment course, the cost of

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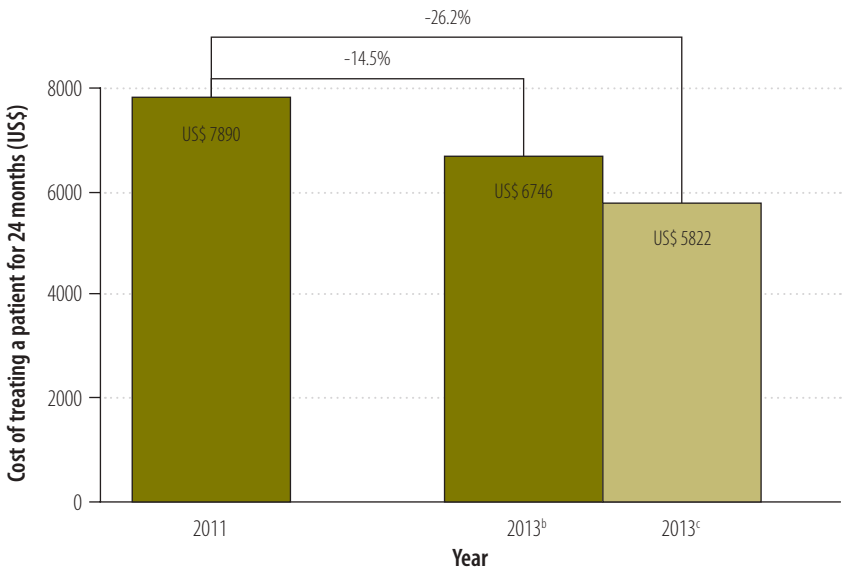
Fig. 1. **Cost of selected treatment[a] for multidrug-resistant tuberculosis from the Global Drug Facility, 2011–2013**



US$; United States dollars.

[a] The selected treatment was the longest and most expensive regimen for multidrug-resistant tuberculosis: 12 months of capreomycin, protionamide, cycloserine, moxifloxacin and *para*-aminosalicylic acid sodium salt, followed by 12 months of protionamide, cycloserine, moxifloxacin and *para*-aminosalicylic acid sodium salt.

[b] Cost of treatment from the same suppliers as in 2011.

[c] The lowest-cost treatment in 2013.

Box 1. **Summary of main lessons learnt**

- The increase in the number of suppliers of internationally quality-assured, second-line drugs for multidrug-resistant tuberculosis provided the competition needed for the Global Drug Facility to secure consistently low prices.
- The price of drugs supplied by the Global Drug Facility was reduced by: (i) consolidating orders to achieve large purchase volumes; (ii) transparent, international, competitive bidding; and (iii) medicine stockpiles funded by donors.
- The savings achieved from the lower cost of high-quality medicines can be used to increase the number of patients treated.

treating one patient decreased by up to 26% – from 7890 United States dollars (US$) to US$ 5822 – over this period. In calculating costs, we used nominal prices obtained from the Global Drug Facility and did not adjust for either inflation or exchange rates.

The price reductions obtained by the Global Drug Facility were secured through a competitive and transparent tendering process among the manufacturers of prequalified, antituberculosis drugs and by the facility's continuing efforts to consolidate orders. During this time, the number of suppliers of quality-assured drugs for multidrug-resistant tuberculosis has increased. In 2012, a capacity assessment carried out by the Global Drug Facility found that a greater number of manufacturers were now able to supply internationally quality-assured, second-line drugs for multidrug-resistant tuberculosis and that, as a result, production capacity could, if required, be rapidly expanded to satisfy twice the current demand.

The actions of the Global Drug Facility have also led to an increase in the number of courses of treatment for multidrug-resistant tuberculosis delivered. In 2013, the facility delivered a sufficient quantity of various drug combinations to provide 32 000 courses of treatment, compared with 19 600 courses in 2011.

Discussion

A summary of the main lessons learnt from the operation of the Global Drug Facility is given in Box 1. First, the expansion of the supplier base for internationally quality-assured, second-line drugs for multidrug-resistant tuberculosis ensures competition in the drug market that enabled the Global Drug Facility to consistently secure low prices. Second, the ability of the Global Drug Facility to increase the volume of drug purchases by consolidating orders from different purchasers also contributed to lower costs, as did the system of competitive bidding involving long-term agreements and the existence of the donor-funded rotating stockpile. The stockpile also helped decrease delivery times. Third, the resulting drug cost savings led to an increase in the number of courses of treatment delivered. In the future, these savings could be used by governments and donors to further increase the number of patients treated, which could, in turn, contribute to even greater consolidation of orders and, hence, to additional reductions in the cost of quality-assured drugs. ■

Competing interests: None declared.

ملخص

خفض أسعار علاج السل المقاوم للأدوية المتعددة من خلال مرفق الأدوية العالمي

المشكلة تعاني بلدان عديدة من محدودية خبرات تأمين أفضل الأسعار للأدوية وليس لديها سوى صلاحيات تفاوض قليلة. وينطبق هذا بوجه خاص على نظم العلاج المعقدة والطويلة وباهظة الثمن التي تستخدم لعلاج السل المقاوم للأدوية المتعددة.

الأسلوب يتخصص مرفق الأدوية العالمي التابع لشراكة دحر السل في تحسين الوصول على الصعيد العالمي إلى الأدوية المضادة للسل وتقنيات التشخيص التي تلبي معايير الجودة الدولية.

المواقع المحلية يستطيع مرفق الأدوية العالمي تأمين انخفاضات في الأسعار من خلال إجراء مناقصات تنافسية بين صانعي الأدوية المؤهلين مسبقاً وعن طريق تعزيز الطلبات لتحقيق أحجام شراء

ضخمة. ويزيد دمج السوق بهذه الطريقة الحوافز لموردي الأدوية مضمونة الجودة.

التغيّرات ذات الصلة في عام 2013، قام مرفق الأدوية العالمي بخفض أسعار أدوية الخط الثاني التي يقوم بتوريدها لمكافحة السل المقاوم للأدوية المتعددة: وانخفضت التكلفة الإجمالية لأطول نظم العلاج وأبهظها ثمناً للمريض بمقدار 26 ٪ – أي من 7890 دولاراً أمريكياً في عام 2011 إلى 5822 دولاراً أمريكياً في عام 2013.

الدروس المستفادة تم خفض أسعار علاج السل المقاوم للأدوية المتعددة الذي يقوم بتوريده مرفق الأدوية العالمي عن طريق دمج الطلبات لتحقيق أحجام شراء ضخمة، عن طريق إجراء مناقصات دولية تنافسية وعن طريق إنشاء مخزونات احتياطية من الأدوية الممولة من المانحين. وكان الارتفاع في عدد موردي الأدوية مضمونة الجودة على الصعيد الدولي مهماً كذلك. ويمكن استخدام الوفورات الناتجة عن خفض تكاليف الأدوية لزيادة عدد المرضى الذين يتلقون العلاج عالي الجودة.

摘要

通过全球药物机构降低多耐药性肺结核的治疗费

问题 许多国家在制定最佳药物价格上经验有限，几乎没有谈判权。对于复杂、漫长且昂贵的多耐药性肺结核疗程来说尤其如此。

方法 遏制结核病合作关系全球药物机构（The Stop TB Partnership’s Global Drug Facility）致力于改善全球对符合国际质量标准的抗痨药物和诊断技术的使用。

当地状况 全球药物机构能够通过在具有资格的药物制造商间竞标并借助合并订单实现大量购买来确保药物降价。以这种方法整合市场提高了优质药物供应商们的积极性。

相关变化 2013 年，全球药物机构降低了供应给多耐药性肺结核病的二线药物价格。肺结核病人耗时最长、最昂贵的治疗总费用降低了 26%，从 2011 年的 7890 美元降至 2013 年的 5822 美元。

经验教训 通过合并订单实现的大量购买、国际竞标以及捐助者资助的药物库存，全球药物机构降低了其供应的多耐药性肺结核药物的价格。国际优质药物供应商数量的增加也起了重要作用。药物成本降低节省下来的资金有助于让更多病人获得高质量的治疗。

Résumé

Réduction du prix du traitement pour soigner la tuberculose multirésistante aux médicaments par le biais du Dispositif mondial d’approvisionnement en médicaments

Problème De nombreux pays ont peu d’expérience dans l’obtention des meilleurs prix pour les médicaments et sont en position de faiblesse pour négocier. Cela est particulièrement vrai pour les traitements complexes, longs et coûteux qui sont utilisés pour traiter la tuberculose multirésistante aux médicaments.

Approche Le Dispositif mondial d’approvisionnement en médicaments du partenariat Stop TB est dédié à l’amélioration dans le monde de l’accès aux médicaments antituberculeux et aux techniques de diagnostic qui répondent aux normes de qualité internationales.

Environnement local Le Dispositif mondial d’approvisionnement en médicaments est capable de garantir des réductions de prix via des appels d’offre compétitifs lancés auprès des fabricants de médicaments pré-qualifiés et via le regroupement des commandes pour arriver à de grands volumes d’achat. Cette manière de procéder à des achats groupés augmente les incitations aux fournisseurs pour qu’ils produisent des médicaments de qualité garantie.

Changements significatifs En 2013, le Dispositif mondial d’approvisionnement en médicaments a réduit le prix des médicaments de deuxième intention qu’il fournit pour la tuberculose multirésistante aux médicaments: le coût global du protocole thérapeutique le plus long et le plus coûteux a diminué de 26% – de 7890 dollars des États-Unis d’Amérique (US$) en 2011 à 5822 US$ en 2013.

Leçons tirées Le prix du traitement pour la tuberculose multirésistante aux médicaments fourni par le Dispositif mondial d’approvisionnement en médicaments a été réduit par les achats groupés pour parvenir à de grand volumes d’achats, par les appels d’offre internationaux et compétitifs, et par l’existence de réserves de médicaments financés par les donateurs. La hausse du nombre de fournisseurs de médicaments de qualité garantie dans le monde a également été importante. Les économies réalisées grâce à la baisse des coûts des médicaments pourraient être utilisées pour augmenter le nombre de patients bénéficiant de traitement de qualité élevée.

Резюме

Снижение стоимости лечения туберкулеза с множественной лекарственной устойчивостью при помощи Глобального механизма по обеспечению лекарственными средствами

Проблема Многие страны имеют небольшой опыт обеспечения минимальных цен на лекарственные препараты и ограниченные возможности ведения переговоров. Это особенно верно, когда речь идет о сложных, продолжительных и дорогостоящих схемах приема лекарств, применяющихся при туберкулезе с множественной лекарственной устойчивостью.

Подход Глобальный механизм по обеспечению лекарственными средствами Партнерства «Остановить туберкулез» предназначается для расширения доступа к противотуберкулезным лекарственным препаратам и соответствующим международным стандартам качества методам диагностики во всем мире.

Местные условия Глобальный механизм по обеспечению лекарственными средствами позволяет обеспечить снижение цен за счет конкурсных закупок у прошедших предварительную проверку производителей лекарственных препаратов и объединенных заказов, увеличивающих объемы закупок. Такое консолидирование рынка более эффективно стимулирует

поставщиков лекарственных средств гарантированного качества.
Осуществленные перемены В 2013 г. Глобальный механизм по обеспечению лекарственными средствами позволил снизить стоимость лекарственных препаратов второй линии, поставляемых для лечения туберкулеза с множественной лекарственной устойчивостью: общая стоимость наиболее продолжительной и дорогостоящей схемы приема лекарств для одного пациента снизилась на 26% — с 7 890 долларов США в 2011 г. до 5 822 долларов США в 2013 г.
Выводы Стоимость препаратов для лечения туберкулеза с множественной лекарственной устойчивостью, поставляемых при помощи Глобального механизма по обеспечению лекарственными средствами, снизилась за счет составления объединенных заказов, увеличивающих объемы закупок, проведения международных конкурсных торгов и наличия запасов лекарственных препаратов, приобретенных благодаря спонсорскому финансированию. Кроме того, важную роль сыграл рост количества проверенных поставщиков лекарственных препаратов, соответствующих международным стандартам качества. Средства, сэкономленные благодаря снижению стоимости лекарственных препаратов, могут быть использованы для увеличения количества пациентов, получающих высококачественное лечение.

Resumen

Reducir el precio del tratamiento para la tuberculosis multirresistente mediante el Servicio Farmacéutico Mundial

Situación Muchos países tienen una experiencia limitada en garantizar los mejores precios de medicamentos y poco poder de negociación, lo cual es particularmente cierto en el caso de los regímenes complejos, largos y costosos utilizados para tratar la tuberculosis multirresistente.
Enfoque La asociación Stop TB del Servicio Farmacéutico Mundial se dedica a mejorar el acceso a nivel mundial a los medicamentos antituberculosos y las técnicas de diagnóstico que cumplen con los estándares internacionales de calidad.
Marco regional El Servicio Farmacéutico Mundial es capaz de lograr reducciones de precios mediante la licitación competitiva entre fabricantes de medicamentos precalificados y la consolidación de pedidos para lograr grandes volúmenes de compra. Consolidar el mercado de esta manera aumenta los incentivos para los proveedores de medicamentos con garantía de calidad.
Cambios importantes En 2013, el Servicio Farmacéutico Mundial redujo el precio de los medicamentos de segunda línea que suministra para la tuberculosis multirresistente: el coste total del régimen de tratamiento más largo y más caro para un paciente disminuyó un 26 % – de 7890 dólares de Estados Unidos (US$) en el 2011 a US$ 5822 en 2013.
Lecciones aprendidas El precio del tratamiento para la tuberculosis multirresistente suministrado por el Servicio Farmacéutico Mundial se redujo mediante la consolidación de pedidos a fin de comprar grandes volúmenes, la licitación internacional competitiva y la existencia de arsenales de medicina financiados por donantes. También fue importante el aumento del número de proveedores de medicamentos con garantía de calidad internacional. Los ahorros obtenidos al disminuir los costes de medicamentos podrían aprovecharse para aumentar el número de pacientes que reciben un tratamiento de alta calidad.

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From availability to uptake: planning for the introduction of new, child-friendly anti-tuberculosis formulations

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SUMMARY

BACKGROUND: Assessing the state of country readiness for the introduction of new, child-friendly anti-tuberculosis formulations can highlight potential bottlenecks, facilitate early planning, and accelerate access to appropriate treatment for children with tuberculosis (TB).

METHODS: To understand pathways and potential obstacles to the introduction of new pediatric formulations, we performed a desk review of key policy documents and conducted 146 stakeholder interviews in 19 high-burden countries.

RESULTS: Issuance of World Health Organization (WHO) guidance serves as the trigger for considering adoption in most countries; however, the degree of alignment with WHO recommendations and duration of introduction processes vary. Endorsement by experts and availability of local evidence are leading criteria for adoption in upper-middle- and high-income countries. Ease of administration, decreased pill burden, and reduced treatment costs are prioritized in low- and lower-middle-income settings. Countries report an average of 10 steps on the path to new treatment introduction, with core steps taking between 18 and 71 months.

CONCLUSIONS: The process of new treatment introduction is complicated by diverse country processes, adoption criteria, and evidence requirements. Challenges differ between low- and middle-to-high-income countries. Responsiveness to the unique hurdles faced across settings is important in ensuring a sustainable market for improved pediatric anti-tuberculosis treatment.

KEY WORDS: introduction; adoption; timelines; access; pathways

IN RECENT YEARS, there has been a call to action to mobilize political will and resources for the neglected epidemic of childhood tuberculosis (TB). The need for improved, child-friendly treatment for both drug-susceptible and drug-resistant TB has been identified as a cornerstone of this agenda.[1] Real and perceived concerns about the size of, and fragmentation in, the pediatric TB market, however, have engendered commercial inertia. These factors have contributed to the current access crisis, whereby even 5 years after World Health Organization (WHO) issuance of guidance on optimal dosing for the treatment of TB in children, there are no quality-assured, correctly dosed, child-friendly TB formulations on the global market.[2,3]

In the absence of child-friendly treatment options, providers and parents have been forced to crush adult pills or use existing, inappropriately dosed pediatric formulations to treat children with TB, options that have been shown to increase the risk of poor treatment outcomes, non-adherence, and loss to follow-up among children.[4–6]

Since 2013, a new initiative spearheaded by the Global Alliance for TB Drug Development and the WHO has brought together commercial partners, policy makers, donors, national TB programs (NTPs), and child health stakeholders to catalyze the market for child-friendly anti-tuberculosis treatment. Through this effort, it is expected that appropriately dosed, dispersible, fixed-dose combinations (FDCs) for the treatment of drug-susceptible TB will be available through the Global Drug Facility (GDF) by late 2015.

Before improved treatments can translate into better outcomes in children with TB, they must be made available to pediatric patients in high-burden countries (HBCs) throughout the world.[7] Lessons learned from previous treatment introductions suggest that the process of country introduction and scale-up is often poorly defined, and associated timelines are protracted.[6] Suppliers report that slow country uptake, erratic procurement, and fragmented demand for pediatric TB products contribute to manufacturing inefficiencies and wastage, deterring

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Table 1 Interview affiliations

	Organization							
Country	NTP	Health Ministry	Procurement	Regulatory	WHO	Expert	NGO	Total
Afghanistan	1	1		1		1	1	5
Bangladesh	1		1	2	1			5
Brazil	2	1	1	1	1	1		7
Cambodia	5			4	1		2	12
China	1		1	1	1	5		9
Democratic Republic of Congo	1			1	1	1	2	6
Ethiopia	1	3	1	2	1			8
India	2				1	3		6
Kenya	2	1	1	1	1	2		8
Myanmar	1	2	1		1			5
Nigeria	2	1	2		1	1	1	8
Pakistan	1		1	1	1	1		5
Philippines	5	1	2	1	1	1		11
Russia	2		2	1	1	1		7
South Africa		1	1			5	1	8
Tanzania	4	1	1	1	1			8
Thailand	4		3	1	1	3		12
Uganda	1	1	1	1		1		5
Viet Nam	6	1			2	1	1	11
Total	42	14	19	19	17	27	8	146

NTP = National Tuberculosis Program; WHO = World Health Organization; NGO = non-governmental organization.

further investment in the childhood TB treatment market.

This article assesses the state of country readiness for the introduction of new pediatric TB formulations and identifies potential bottlenecks on the road to introduction, implementation, and scale-up of new anti-tuberculosis formulations. Clarifying adoption and introduction pathways can facilitate efforts to navigate hurdles, supporting a healthy market for life-saving therapies for children with TB.

METHODS

To understand pathways and potential obstacles to the introduction of new treatments for childhood TB, we conducted qualitative research in 19 of 22 HBCs (Table 1). Three HBCs—Indonesia, Mozambique, and Zimbabwe—were excluded from the study due to time and capacity constraints.

An initial literature review of key policy documents, including national TB strategic plans, TB treatment guidelines, essential medicines lists (EMLs), procurement manuals, regulatory guidelines, budgets, grant plans, and program reviews, was performed. Findings were entered into a standardized data form. Informant interviews were then conducted to validate and expand upon findings from the desktop review. Interviewees were identified through a combination of purposive and snowball sampling. Predetermined criteria included selection of representatives from the NTP, WHO country office, national regulatory authority, procurement office, and the essential medicines committee of each country. Representatives were then asked to identify additional individuals and organizations involved in TB program decision making, such as TB technical working group members, professional societies, development partners, non-governmental organizations, civil society, and 'experts'.

Interview tools were developed and refined by the research team. Interviewers were then trained in the administration of the study tool, a structured questionnaire covering topics such as policy change processes, evidence requirements, decision-making criteria and influencers, procurement and regulatory requirements, and planning sequences and timelines.

In all, 146 interviews were conducted between December 2014 and April 2015 (see Table 1 for affiliations). Interviews were conducted in person in all countries, with the exception of China, Russia, and a subset of interviews in Myanmar. Informed consent was obtained verbally using a standard script. Ethics committee involvement was not required, as the scope of inquiry was institutional processes rather than individuals. Data from interviews were entered directly into an Excel template (MicroSoft, Redmond, WA, USA), cleaned, and validated. Data were then aggregated, coded, and analyzed by the core study team. Results were compared and discrepancies were discussed and resolved by the team.

Study limitations include the potential for recall error or personal bias in the data, given the relatively small sample size per country. These risks were mitigated through triangulation of findings with data from the published literature, and by purposively sampling diverse institutional representatives to

enable multiple perspectives. Limitations also include the study's almost exclusive focus on the public sector TB market, given its disproportionate relevance for TB control efforts (Table 1).

RESULTS

Treatment introduction processes

Stakeholders were asked to describe the steps involved in introducing new TB treatments in their respective countries. The average number of procedural steps reported by participants was 10 (range 7–13), with introduction processes in most countries commencing upon issuance of WHO guidance on new treatments (Table 2). Updates to national treatment guidelines, guideline dissemination, forecasting, procurement transition, and training are core elements of the introduction process across all HBCs; WHO EML inclusion and GDF product availability are less central to the introduction processes in most countries (Table 2).[8]

Timelines associated with introduction vary significantly across HBCs. Reported transition times for a few key steps—including registration, national guideline change, forecasting, and procurement—range from <2 years in countries such as Afghanistan, Bangladesh, and the Democratic Republic of Congo (DRC) to >5 years in countries such as China and South Africa, with a median time across HBCs of 24 months (2 years) (Figure 1).

Of 19 countries participating in the study, 18 reported provisions in place that potentially shorten regulatory timelines. This included 8 countries with fast track registration procedures, 3 that allow regulatory exemptions, and 7 with both fast track and waiver provisions. On the other hand, additional procedural and planning processes across all countries, and requirements for local clinical, cost-benefit, or pilot studies in a subset of countries—including Russia, India, China, South Africa, Uganda, and Viet Nam—serve to further prolong introduction timelines.

Policy adoption criteria

The WHO consistently serves as a catalyst for considering treatment adoption across HBCs. While WHO guidance serves as a trigger for consideration of new treatments in 15 of the 19 countries surveyed, the degree to which countries accept WHO endorsement as a proxy for local review processes differs between low- and middle-to-high-income countries (Figure 2). Although important, WHO recommendation alone is insufficient to trigger guideline change among upper-middle-income and high-income countries (UMICs and HICs), such as South Africa, Thailand, Russia, and China and in India, where endorsement by experts and availability of local evidence on new treatments are seen as priority criteria for adoption (see Appendix for a full listing of countries by World Bank income classification).

Among most low- and lower-middle-income countries (LIC/LMIC), limited capacity to independently execute additional studies and the cascade of influence through funding agencies, such as the Global Fund to Fight AIDS, TB, and Malaria (The Global Fund), drive close alignment with WHO guidelines. Practical considerations, such as decreased pill burden, ease of administration, and reduced costs of treatment, are reported to be leading influencers of treatment adoption in these settings (Figure 2).

Of 19 HBCs participating in the study, 15 (79%) have adopted into national treatment guidelines either the WHO's 2010 'Rapid Advice' or its 2014 dosing recommendations for treatment of drug-susceptible TB in children;[3,9] however, the four countries that have not as yet officially adopted WHO dosing recommendations—Brazil, China, DRC, and India—represent 47% of the estimated burden of pediatric TB across the HBCs and 49% of the burden among countries participating in the study (Figure 3).[10]

Market readiness for new pediatric TB formulations

Existing preferences for treatment of drug-susceptible TB in children may have a bearing on country receptiveness to new pediatric TB formulations. Country practices are currently divided between those that use pediatric FDCs (63%), those that use loose pediatric drug formulations (16%), those that split or crush adult tablets (11%), and those that use a mixture of product types (11%) to treat childhood TB (Figure 4). While there are signs that attitudes may be shifting, experts in countries such as Russia, China, and India have historically been reluctant to implement FDC formats, given either providers' preferences for individually tailored dosing approaches or the lack of locally generated evidence on FDC effectiveness. The majority of countries (84%), however, report an eagerness to switch to pediatric FDCs, once appropriately dosed treatments are available (Figure 4).

Procurement channels for first-line drugs (FLDs) for children and adults are currently divided between quality-assured and non-quality-assured, locally and globally supplied networks. Of the 19 countries surveyed, seven (37%) report exclusively securing quality-assured FLDs through the GDF. A recent study suggests that procurement volumes of FLDs for children through the GDF platform reflect approximately 12% of notified pediatric TB cases in the HBCs.[11] The remaining countries report procuring FLDs through national or international competitive bidding, or a mixture of approaches (Figure 5). Among nine countries procuring some or all FLDs locally, seven report regulatory or procedural provisions prioritizing locally sourced drugs (Figure 5).

Table 2 Reported steps from new treatment availability to introduction

Countries	Steps*												
	WHO recommends	WHO adds to EML	National treatment guidelines updated	Dissemination of new guidelines	Addition to national EML	Product registration	Training	Product quality surveillance	Pharmacovigilance	Product available through GDF	Forecasting/ procurement	Other steps†	Total number of steps
Afghanistan	√	√	√	√	√	√	√			√	√		9
Bangladesh	√	√	√	√	√	√	√	√	√	√	√	√ √	13
Brazil	√		√	√	√	√	√	√	√		√	√	10
Cambodia	√		√	√	√		√	√	√	√	√		9
China			√	√	√	√	√				√	√	7
Democratic Republic of Congo	√	√	√	√	√	√	√	√	√	√	√		11
Ethiopia	√	√	√	√	√	√	√	√	√	√	√		11
India			√	√		√	√	√	√		√	√	8
Kenya	√	√	√	√	√	√	√	√	√		√	√ √	12
Myanmar	√		√	√			√				√	√ √ √	8
Nigeria	√	√	√	√	√	√	√	√	√	√	√		11
Pakistan	√	√	√	√	√	√	√	√	√	√	√		11
Philippines	√		√	√	√	√	√	√	√		√	√	10
Russia			√	√	√	√	√				√	√ √	8
S Africa	√	√	√	√	√	√	√	√	√		√	√	11
Tanzania	√	√	√	√	√	√	√	√	√	√	√	√	12
Thailand	√		√	√	√	√	√	√	√		√	√	10
Uganda	√	√	√	√	√	√	√	√	√	√	√		11
Viet Nam	√	√	√	√	√	√	√	√	√	√	√	√ √	13
Total countries	16	11	19	19	17	17	19	15	15	10	19	18	

* The sequence of 'steps' represented in the table is not indicative of the order of processes in specific countries.
† Each √ represents one step. Potential steps mentioned include technical committee review, import license, local clinical trial, budget approval, approval by the Global Fund to Fight AIDS, Tuberculosis and Malaria, among others.
WHO = World Health Organization; EML = Essential Medicines List; GDF = Global Drug Facility.

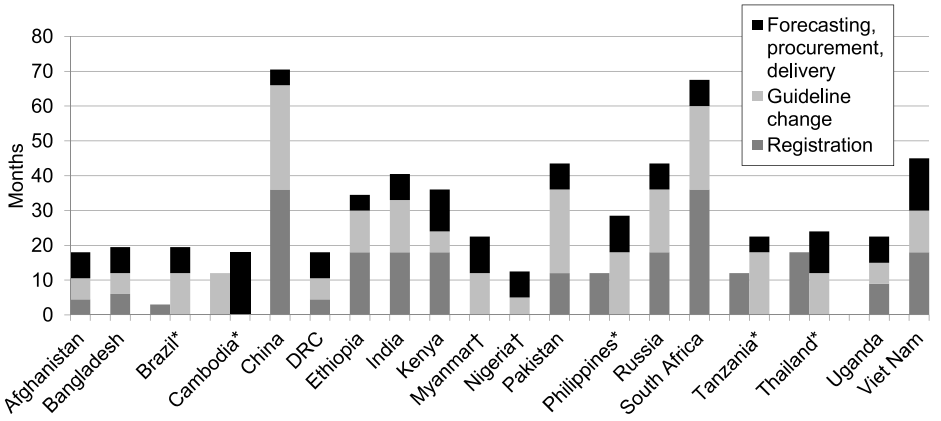

Figure 1 Estimated median time for key steps toward product availability. *Indicates that more than one of these processes may occur in parallel. †Stakeholders report that registration is not required as a condition for introduction of new anti-tuberculosis drugs. DRC = Democratic Republic of Congo.

DISCUSSION

Readiness for the introduction of new pediatric TB formulations is marked by country-level demand, the presence of a receptive policy environment, and the existence of a pathway for the rapid introduction of new treatment formulations. The criteria for the adoption of new treatments differ across low- and middle-to-high-income countries. While WHO guidance serves as the primary trigger for considering the adoption of new anti-tuberculosis treatment formulations across settings, the degree of alignment around WHO recommendations and the duration of national policy adoption processes vary significantly. Among UMICs and HICs, such as South Africa, Thailand, Russia, and China, and in India, both treatment endorsement by experts and the availability of local evidence on new treatments are seen as critically influencing adoption. Donor requirements in most LIC and LMIC settings, on the other hand, drive convergence around WHO-recommended treatments.

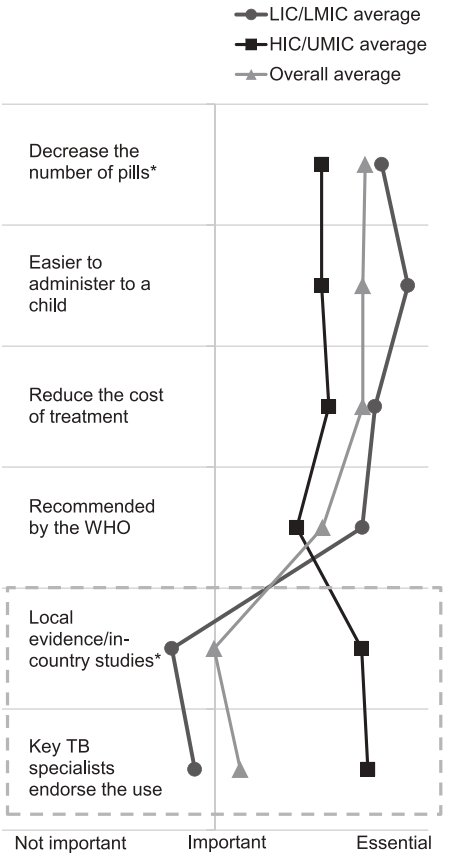

Figure 2 Key criteria for treatment adoption. *Myanmar data on the number of pills and Brazil data on local evidence not available. WHO = World Health Organization; LIC = low-income country; LMIC = low-middle-income country; HIC = high-income country; UMIC = upper-middle-income country.

Interview participants reported standard timelines for drug registration, guideline change, forecasting, procurement, and delivery of new treatments as ranging from 18 to 71 months across the HBCs. Strong expressions of interest in the new FDCs (84% of countries) and expedited regulatory provisions for treatments of public health priority (95% of countries) highlight the potential to accelerate time-to-market for forthcoming child-friendly anti-tuberculosis formulations in some settings; however, additional country-specific procedures in other settings — such as requirements for EML inclusion, product quality testing, pharmacovigilance, and generation of local clinical and non-clinical evidence—further prolong introduction timelines.

Procurement practices for pediatric TB treatments currently remain fragmented across formulation types and procurement channels, and while most countries have adopted WHO dosing guidance, those countries that have not represent approximately half of pediatric TB cases. For small treatment markets, such as the market for first-line pediatric TB formulations, convergence of procurement practice around WHO-recommended treatments and quality-

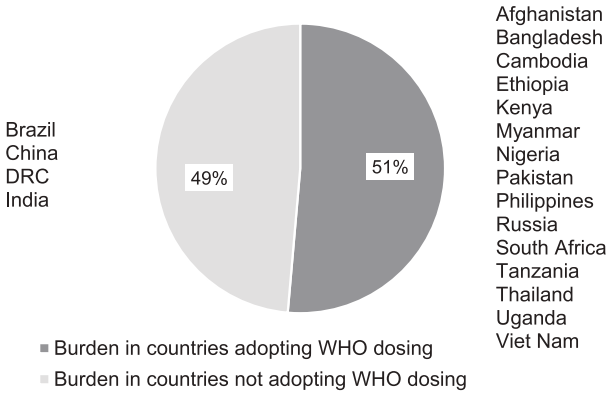

Figure 3 Burden in countries per WHO guideline adoption status. WHO = World Health Organization; DRC = Democratic Republic of Congo.

assured supply through platforms such as the GDF can drive affordability by facilitating demand consolidation to foster manufacturing economies of scale. As home to almost half of all new adult and pediatric TB cases in the 22 HBCs, middle-to-high-income HBCs, such as the BRICS countries (Brazil, Russia, India, China, and South Africa), are also critical in driving solutions to the childhood TB problem.[10] The current non-alignment of some middle- and high-income countries with WHO treatment recommendations and hurdles to introduction—related to slow policy change processes, localized evidence requirements, trade protections, and arduous regulatory provisions—hinder the rapid integration of new treatments in these settings. Failure to capture such a significant portion of the treatment population poses a fundamental threat to both affordability and market sustainability, and can deter further commercial investment in this and other small but essential public health markets.

Identifying opportunities to promote harmonization of treatment practices and requirements across high-, middle-, and low-income TB-endemic settings—including greater mutual recognition of strin-

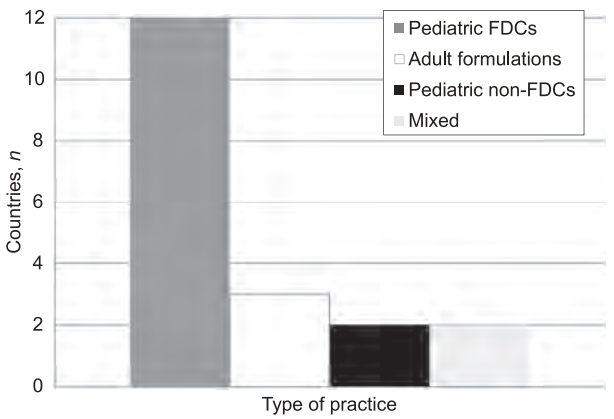

Figure 4 Formulation practices. FDC = fixed-dose combination.

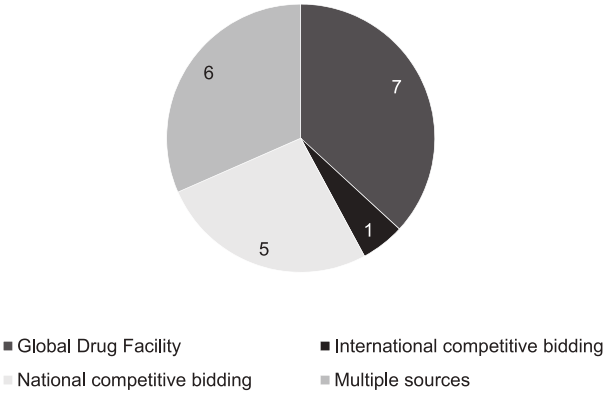

Figure 5 Source of country first line drug supply.

gent regulatory authority or WHO prequalification standards and alignment around normative treatment recommendations—could help accelerate access to life-saving treatments for childhood TB. The recent agreement of BRICS Health Ministers to collaborate in scaling up research on, and access to, new TB treatments represents an important step in the right direction; however, continued political will and resources will be needed.[12]

CONCLUSIONS

Before improved treatments can translate into better outcomes for children with TB, they must be made available to pediatric patients across the TB-endemic world. The process of treatment introduction and scale-up is complicated by a variety of country-specific introduction processes, adoption criteria, and administrative and evidence requirements. The challenges faced differ significantly between low- and middle-to-high-income countries. Clarifying adoption and introduction pathways can facilitate efforts to navigate hurdles and support a healthy market for life-saving therapies for children with TB. In addition, the development of strategies that are responsive to the unique hurdles faced across settings is important in accelerating access to, and ensuring a sustainable market for, new pediatric TB treatments.

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Conflicts of interest: SM is employed by the Global Alliance for TB Drug Development, whose activities are aimed at developing and making available improved therapies for TB. RG, PP, and MS are employed by Management Sciences for Health (Arlington, VA, USA), which provides technical assistance with drug management

in many of the high-burden countries. Other authors declare no conflicts of interest.

The financial sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of this report.

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APPENDIX

World Bank Country and Lending Group Classifications, 2015[1]

Low-income economies	Afghanistan, Bangladesh, Cambodia, Democratic Republic of Congo, Ethiopia, Kenya, Myanmar, Tanzania, Uganda, Zimbabwe
Lower-middle-income economies	India, Nigeria, Pakistan, Philippines, Vietnam
Upper-middle-income economies	South Africa, Brazil, Thailand, China
High-income economies	Russian Federation

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RESUME

CONTEXTE : Evaluer le niveau de préparation du pays à l'introduction de nouvelles formulations pour la tuberculose (TB) acceptables par les enfants peut mettre en lumière des goulots d'étranglement potentiels, faciliter une planification précoce et accélérer l'accès à des traitements appropriés pour les enfants atteints de TB.

MÉTHODE : Pour comprendre le cheminement et les obstacles potentiels à l'introduction de formulations TB pédiatriques correctement dosées, nous avons réalisé une revue approfondie des principaux documents de politique et conduit 146 entretiens avec des parties prenantes dans 19 des 22 pays les plus touchés (HBC).

RÉSULTATS : La publication de la guidance de l'Organisation Mondiale de la Santé (OMS) sert de premier déclencheur pour envisager l'adoption dans la majorité des HBC ; cependant, le degré d'alignement avec les recommandations de l'OMS et la durée des procédures d'introduction dans le pays varient. L'approbation par des experts et la disponibilité de preuves locales relatives aux nouveaux traitements sont les critères principaux d'adoption dans les HBC à revenu moyen supérieur et élevé. La facilité d'administration, la réduction du nombre de comprimés et la réduction du coût du traitement sont les priorités des pays à revenu faible ou intermédiaire. Les pays font état d'une moyenne de 10 étapes dans la procédure d'introduction de nouveaux traitements, les étapes principales prenant entre 18 et 71 mois.

CONCLUSION : Le processus d'introduction de nouveaux traitements et leur expansion sont compliqués par un ensemble de procédures d'introduction spécifiques à chaque pays, par les critères d'adoption, et les besoins de preuves. Les défis diffèrent entre les pays à revenu faible et moyen et ceux à revenu élevé. Les stratégies qui répondent aux obstacles particuliers affrontés dans différents contextes sont importantes pour assurer un marché durable afin d'améliorer le traitement anti-tuberculeux de l'enfant.

RESUMEN

MARCO DE REFERENCIA: La evaluación del grado de preparación de un país para la introducción de nuevas formulaciones de medicamentos antituberculosos adaptados a los niños pone de manifiesto los eventuales cuellos de botella del procedimiento, facilita una planificación temprana y acelera el acceso a los tratamientos apropiados para los niños con diagnóstico de tuberculosis (TB).

MÉTODOS: Con el propósito de comprender los mecanismos de introducción de las formulaciones pediátricas con dosis apropiadas y los posibles obstáculos que pueden surgir, se llevó a cabo una revisión exhaustiva de los principales documentos normativos y se realizaron entrevistas a 146 interesados directos en 19 países con alta carga de morbilidad (HBC) por TB.

RESULTADOS: La publicación de las directrices de la Organización Mundial de la Salud (OMS) constituye el principal incentivo de la adopción de nuevos tratamientos en la mayoría de los HBC; sin embargo, el grado de cumplimiento de estas recomendaciones y la duración de los mecanismos de introducción en los países varía en los diferentes entornos. La aprobación por los expertos y la existencia de datos fidedignos locales sobre los nuevos tratamientos son los criterios fundamentales de la adopción en los países con alta morbilidad e ingresos medios altos y altos. En los países con ingresos medios bajos y bajos se da prioridad a las consideraciones prácticas como la facilidad de administración, una baja cantidad de comprimidos y el bajo costo del tratamiento. Los países notifican un promedio de 10 etapas en el procedimiento de introducción de los nuevos tratamientos y las etapas básicas duran 18–71 meses.

CONCLUSIÓN: La introducción y la ampliación de escala de los nuevos tratamientos se dificultan por la diversidad de mecanismos, criterios de adopción y la exigencia de datos fidedignos en cada país. Los obstáculos difieren de manera significativa en los países de ingresos bajos e ingresos medios a altos. Las estrategias sensibles a las dificultades específicas encontradas en los diferentes entornos son importantes para garantizar un mercado sostenible para mejorar el tratamiento contra la TB pediátrica.

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RESEARCH ARTICLE Open Access

Multidrug resistant tuberculosis: prevalence and risk factors in districts of metema and west armachiho, Northwest Ethiopia

Feleke Mekonnen[1], Belay Tessema[2], Feleke Moges[2], Aschalew Gelaw[2], Setegn Eshetie[2*] and Gemechu Kumera[3]

Abstract

Background: Multi drug resistant tuberculosis (MDR-TB) is an emerging challenge for TB control programs globally. According to World health organization, 2012 report Ethiopia stands 15th out of the 27 high priority countries in the world and 3rd in Africa. Updated knowledge of the magnitude of MDR-TB is so substantial to allocate resources, and to address prevention and control measures. Therefore, the aim of this study was to assess the prevalence of MDR-TB and associated risk factors in West Armachiho and Metema districts of North Gondar.

Methods: A cross-sectional study was conducted in West Armachiho and Metema districts between February 01 and June 25, 2014. A total of 124 consecutive smear positive pulmonary tuberculosis patients were included in the study. Socio-demographic and possible risk factor data were collected using a semi-structured questionnaire. Drug susceptibility testing was first performed for rifampicin using GeneXpert MTB/RIF. For those rifampicin resistant strains, drug susceptibility testing was performed for both isoniazid and rifampicin to identify MDR-TB using the proportional method on LJ media. Data were analyzed using statistical Package SPSS version 20; binary logistic regression was used to assess the association. *P*-values < 0.05 were considered as statistically significant.

Results: Of 124 smear-positive pulmonary TB patients, 117 (94.4 %) were susceptible to Rifampicin, while 7 (5.7 %) were confirmed to be resistant to Rifampicin and Isoniazid. The overall prevalence of MDR-TB was 5.7 % (2.3 % among new cases and 13.9 % among previously treated cases). History of previous treatment (OR = 7, *P* = 0.025) was significantly associated risk factor for MDR-TB.

Conclusion: The overall prevalence of MDR-TB was 5.7 % among cases at five health centers and a history of previous treatment was found to be a risk factor for being infected by an MDR-TB strain. Therefore, maximizing early case detection and treatment, strengthening TB infection control activities and proper implementation of DOTS are recommended to reduce the burden of MDR-TB.

Keywords: Tuberculosis, MDR-TB, Risk factors

Background

Tuberculosis (TB) remains a major global health problem. In 2012, World health organization (WHO) estimated 8.6 million people developed TB and 1.3 million died from the disease [1]. Even more, according WHO 2014 report, the morbidity and mortality rate were increased by 400,000 and 200,000 cases, respectively, with reference to the previous WHO report [2]. Besides both reports presented that the mortality of the disease was predominantly observed in human immunodeficiency virus (HIV) co-infection, thus 320,000 (2012) and 360,000 (2013) patients were died due to HIV co-infection. Tuberculosis compound by the spread of multidrug resistant (MDR) strains becomes a prime global concern, 450,000 and 480,000 multidrug resistant tuberculosis (MDR-TB) cases were reported in 2012 and 2013 respectively. Based on WHO 2014 report, the prevalence of MDR-TB among new and previously treated cases was 3.5 % and 20.5 % respectively. These estimates are essentially unchanged from 2012 [1, 2].

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Emerging and spread of drug resistance TB has encountered as a great challenge in Africa region, Sub-Saharan Africa in particular. Information on the extent of MDR-TB from Africa region is very limited, probably due to poor laboratory facilities, poor surveillance mechanisms and reporting procedures, outdated databases and sub-optimal coverage of the infrequent surveys. Sub-Saharan Africa stands the burden of both very high TB incidence and the highest HIV prevalence rates in the world, and represents 14 % of the global burden of new MDR-TB cases [3].

Moreover, on the basis of WHO 2012 report, Ethiopia stands 15th out of the 27 high priority countries in the world and 3rd in Africa following South Africa and Nigeria with (1600 and 480) among new and retreatment cases respectively were MDR-TB cases [4]. According to the drug resistance survey conducted nationwide, the prevalence of MDR-TB was; 1.6 % in newly diagnosed TB and 11.8 % among previously treated TB cases. The country's burden of MDR-TB in 2009 was estimated to be 1500 (870–2600) and 420 (230–740) among new and re-treatment cases respectively. Despite being a huge global threat, access to treatment is very limited with only 10 % of the estimated MDR-TB cases among notified TB cases in 2009 in the high MDR-TB countries and 11 % globally were enrolled in treatment [5, 6].

In West Armachiho and Metema districts, information regarding TB treatment interrupters, relapses, and failure cases were not well documented. According to the national comprehensive TB/HIV and Tuberculosis & Leprosy guideline these are criteria for suspicion of MDR-TB. Moreover, as to our knowledge, there are only limited data regarding MDR-TB in this particular study area. Therefore, current knowledge on the prevalence of MDR is so substantial to provide useful information on the implementation of standard chemotherapy regimens designed and recommended by WHO for tuberculosis patients who have or have not been treated previously.

Moreover, drug resistance rate can also serve as a useful parameter in the evaluation of the quality of current and past chemotherapy program i.e. direct observed treatment, short course (DOTS). Therefore, understanding the drug susceptibility patterns of *M. tuberculosis* (MTB) is very crucial to treat patients, to decide health priorities, to allocate resources, to monitor the emergency of resistance for planning effective use of anti-TB drugs, to generate knowledge for health workers working in the study area as well as will serve as a preliminary information for health programmers to give special attention and design a package in the national TB control program that addresses such areas where hundred to two hundred thousands of people are employed in huge farms for the production of crops.

Methods

Study area, study design, participants and data collection

A cross-sectional study was conducted in West Armachiho and Metema districts from Feburary 01 to June 25, 2014. A total of 124 smear positive patients were consecutively enrolled through convenient sampling technique. From those patients we gathered; socio-demographic characteristics (gender, age, residence, religion, occupation, marital status, income, ethnicity and education status) and possible risk factors (HIV, smoking, TB contact history, diabetes, fasting, history of prison, BCG vaccination status). Besides from each patient, standard volumes of sputum sample were collected after patients had given instructions accordingly.

Sputum decontamination, isolation, identification & drug susceptibility testing

Smear positive sputum samples were re-confirmed using Gene X-pert and decontamination and further homogenization were done according to Petroff's method. Isolates were identified by using typical colony characteristics on Lowenstein-Jensen (LJ) media and standard biochemical tests. Gene x-pert machine was used to assess rifampicin (RIF) resistant strains, after a while RIF resistant MTB isolates were tested for isoniazid (INH) and RIF using the indirect proportional method on LJ medium. The proportion method calculates the proportion of resistant bacilli present in a strain. Two appropriate dilution of the bacilli, 10^{-2} and 10^{-4}dilutions (undiluted = 10^{6} to 10^{8} CFU/ml), were inoculated on drug-containing and drug-free media. Below a proportion (critical proportion = 1 %), the strain was classified as sensitive; otherwise classified as resistant. Patient's HIV status was collected from the TB unit register at TB clinic of respective health facilities. Quality control was done for gene x-pert (sample processing and probe check) and LJ medium (standard strains of MTB H37Rv-ATCC27294).

Data analysis

Data were entered and analyzed using SPSS version 20.0. Bivariate logistic regression analysis was used to assess the association. *P*-values < 0.05 were considered as statistically significant.

Ethical consideration

Ethical clearance was obtained from the School of Biomedical and Laboratory sciences, University of Gondar. Written permission was obtained from North Gondar Zone Health Department to West Armachiho and Metema Woreda Health Offices and respective health centers. Study participants were recruited after getting written consent.

Results

A total of 124 smear positive tuberculosis patients were included from five different heath centers in West Armachiho and Metema districts. The health centers were Abderafi, Abirihajira, Metema Yohannes, Gendewuha and Metema Hospital.

A majority, 80 (64.5 %) of the study participants were males, the mean and median age of the study subjects were 32 and 29 years respectively. Their age ranges from16–75 years. Nearly half, 46 (48.1 %) were in the age range of 26–35 year, while 37 (29.8 %) were below 25 years old. Of the 124 study subjects, 66 (53.2 %) were urban inhabitants and 59 (47.6 %) were farmers/day laborers. The majority, 116 (93.5 %) of the study subjects were Christians by religion while the rest 8 (6.5 %) were Muslims. More than half, 64 (51.6 %) were illiterate. More than half of new and previously treated cases were males (Table 1).

The proportion of smear positive tuberculosis cases in each health facilities were as follows: Abderafi 49 (39.5 %), Metema Hospital, 34 (29.8 %), Abirihajira 21 (12.9 %), Metema Yohannes 16 (12.9 %) and Gendewuha 4 (3.2 %).

Prevalence of Multi- drug resistant tuberculosis (MDR-TB)

Sputum samples of the 124 smear positive tuberculosis patients were tested for MDR-TB by using Gene-Xpert MTB/RIF technique and conventional solid culture, The overall prevalence of MDR-TB was 7 (5.6 %, 95 % CI; 2.4–10.5 %) and prevalence of MDR-TB among new smear positive TB cases was 2 (2.3 %, 95 % CI; 0–5.9 %) and among previously treated smear positive TB cases 5 (13.9 %, 95 % CI; 2.9–25.7 %). Of the 26 who were reported to have been cured with prior treatment, 1 (3.8 %) and from10 who were reported to have failed or defaulted from prior treatment, 4 (40 %) were relapsed MDR-TB cases. Among 41 patients whose occupation was farmer/daily laborer, 2 (4.9 %) had primary MDR-TB; of 47 whose occupation was other than farmer/day laborer none (0.0 %) had primary MDR-TB. The majority of confirmed MDR-TB subjects were males 6 (85.7 %) and two of the confirmed MDR cases were co-infected with HIV (28.6 %) while, the other five were sero-negative.

Among the five health facilities, MDR-TB cases were obtained from Abderafi health center and Metema District Hospital. Three MDR-TB cases (one from new smear positive study subjects and two from retreatment cases) were identified from Abderafi health center. The other four MDR-TB cases (one from new smear positive study subjects and three from retreatment cases) were identified from Metema hospital.

Table 1 Socio-demographic characteristics of TB patients West Armachiho and Metema districts, Northwest Ethiopia February 01 to June 25, 2014

Variable	Total TB cases (*N* = 124)	New active TB cases (*N* = 88)	Retreatment TB cases (*N* = 36)
Age group in years			
≤25	37 (29.8 %)	31 (35.2)	6 (16.7)
26–35	57 (46 %)	38 (43.2)	19 (52.8)
36–45	16 (12.9)	11 (12.5)	5 (13.9)
≥46	14 (11.3)	8 (9.1)	6 (16.7)
Gender			
Male	80 (64.5)	53 (60.2)	27 (75)
Female	44 (35.5)	35 (39.8)	9 (25)
Resident			
Urban	66 (53.2)	47 (53.4)	19 (52.8)
Rural	58 (46.2)	41 (46.6)	17 (47.2)
Occupation:			
Farmers and day laborers	59 (47.6)	41 (46.6)	18 (50)
House wife	28 (22.6)	21 (23.9)	7 (19.4)
Government employee	8 (6.5)	8 (9.1)	0
Merchant	16 (12.9)	13 (14.8)	3 (8.3)
Driver	5 (4)	1 (1.1)	4 (11.1)
Student	8 (6.5)	4 (4.5)	4 (11.1)
Income/month:			
<500 birr	39 (31.5)	29 (33)	10 (27.8)
500 birr - 999 birr	55 (44.4)	39 (44.3)	16 (44.4)
≥1000 birr	25 (20.2)	16 (18.2)	9 (25)
No means of income	5 (4)	4 (4.5)	1 (2.8)
Religion:			
Christian	116 (93.5)	82 (93.2)	34 (94.4)
Muslim	8 (6.5)	6 (6.8)	2 (5.6)
Ethnicity:			
Amhara	102 (82.3)	77 (87.5)	25 (69.4)
Tigre	22 (17.7)	11 (12.5)	11 (30.6)
Educational status:			
Illiterate	64 (51.6)	42 (47.7)	22 (61.1)
Primary school	36 (29.0)	26 (29.5)	10 (27.8)
Secondary school	17 (13.7)	14 (15.9)	3 (8.3)
Diploma and above	7 (5.6)	6 (6.8)	1 (2.8)
Marital status:			
Married	62 (50)	44 (50)	18 (50)
Un married	45 (36.3)	35 (39.8)	10 (27.8)
Widowed	5 (4)	4 (4.5 %)	1 (2.8)
Divorced	12 (9.7)	5 (5.7)	7 (19.4)

Rifampicin resistant Non-MDR-TB

Sputum samples of 124 smear positive pulmonary TB cases were processed using Gene-X pert MTB/RIF for detection of MTB and identification of RIF resistant strain. Of these only seven smears positive cases were found to be RIF resistant. Sputum samples of RIF resistant cases were further diagnosed with LJ medium for growth of MTB and detection of INH resistance as well as confirmation of RIF resistant strain. The result showed RIF resistant non-MDR-TB isolates were not observed from all RIF resistant isolates that were detected by Gene-X pert MTB/RIF for drug susceptibility testing. All seven RIF resistant isolates were found to be MDR-TB cases.

Risk factors for MDR-TB

The relationship between individual exposure variables and MDR-TB status is shown in Table 2. Association between potential exposure variables and MDR-TB were analyzed. Socio-demographic determinants such as age, sex, residence, occupation, income, religion, fasting, ethnicity, educational status, marital status, and factors such as contact history, history of imprisonment, number of rooms in the house, family number in the household, rooms for sleeping, number of windows and use of substances like cigarette smoking and other clinical characteristics such as, diabetes, history of previous anti-TB treatment, outcome of previous treatment, BCG vaccination, HIV status, history of taking illegal anti-TB treatment were assessed.

All the variables that were considered important were entered into the binary logistic regression models and analysis showed there were significant association between MDR-TB and history of previous anti-TB treatment (OR: 7, 95 % CI = 1. 2–37.6, $P = 0.025$). However, there were no significant association between other variables and MDR-TB. After adjustment for interactions among the independent variables with the binary regression model; analysis also showed there were no significant association between independent variables and prevalence of MDR-TB ($P > 0.05$) with each factor other than previous treatment history.

Discussion

The burden of MDR-TB becomes increasing in alarming pace with function of time particularly in the poorest countries. Before 20 years ago, reports showed that the prevalence of MDR-TB was almost nil or 1 % in different parts of Ethiopia [7–9]. Though, nowadays high proportion of MDR-TB were notified within the country [10, 11]. It is well understood that bacterial and environmental factors play a great role in the spread of MDR-TB. Within the population MTB, spontaneous mutation in genes responsible for drug resistance for all first line and

Table 2 Factors associated with the MDR-TB status among Pulmonary TB cases, West Armachiho and Metema districts, Northwest Ethiopia, February 01 to June 25, 2014

Variable	MDR-TB		Crude OR	*P*-value
	Positive (*N* = 7)	Negative (*N* = 117)		
Age group				
≤25	1	36	2.77 (0.16, 47.56)	0.483
26–35	4	53	1.02 (0.11,9.90)	0.987
36–45	1	15	1.15 (0.07,20.34)	0.922
≥46	1	13	1	
Gender				
Male	6	79	3.49 (0.41, 29.9 4)	0.255
Female	1	43	1	
Resident				
Rural	4	54	1.56 (0.33, 7.26)	0.574
Urban	3	63	1	
Occupation:				
Farmer and day laborers	4	55	1.50 (0.32, 7.01)	0.604
Other	3	62	1	
Ethnicity:				
Tigre	3	19	3.87 (0.80,18.70)	0.092
Amhara	4	98	1	
Educational status:				
Illiterate	2	62	5.17 (0.41, 65.68)	0.206
Primary school	3	33	1.83 (0.16,20.71)	0.624
Secondary school	1	16	2.67 (0.14,49.76)	0.511
Diploma and above	1	6	1	
Fasting				
Yes	3	73	0.45 (0.10, 2.12)	0.313
No	4	44	1	
History of smoking				
Yes	2	33	1.02 (0.19, 5.51)	0.983
No	5	84	1	
BCG vaccination				
Yes	1	27	0.71 (0.13, 3.89)	0.698
No	6	90	1	
History of previous treatment				
Yes	5	31	6.94 (1.28, 37.60)	0.025
No	2	86	1	
HIV status				
Yes	2	26	1.40 (0.25, 7.64)	0.698
No	5	91	1	
History of prison				
Yes	1	17	0.98 (0.11, 8.66)	0.986
No	6	100	1	

Note that: *N* number of subjects, *OR* Odds Ratio

some second line drugs, thus scenarios are highly pronounced by misuse of drugs results in rapid selection of drug resistant mutants [12].

The present study demonstrated MDR-TB is a serious issue of concern in the study area; hence the overall prevalence of MDR-TB was 5.6 % (95 % CI, 2.4–10.5 %). Which is comparable with previous reports from northwestern Ethiopia and national wide survey in Ethiopia [6, 13, 14]. On the other hand, it is lower than finding from Jimma and Bahirdar [10, 15]. The possible explanation for this difference could be due the fact that this study was conducted at the site where TB patients less likely served for medical attention and presumably they have accustomed to visit nearby and relatively advanced health institutions. Besides in previous reports the study population was presumptive MDR-TB patients, whereas in this study only smear positive TB cases were included.

Furthermore, in this finding the prevalence of MDR-TB among new and previously treated cases was respectively 2.3 % and 13.9 %. Which is consistent with previous documented data [13, 14, 16]. Many of the research findings advocated that MDR-TB are frequently identified in patients with history of TB treatment [6, 13, 14], which is also evidenced in this study. In fact, prior treatment creates opportunity for resistance MTB mutant to dominant and results challenging in the management of cases [12]. Emergence of new cases with MDR-TB has frequently related with close contact with known cases, facilitated by overcrowding [17]. Likewise, the present study showed that all of new MDR-TB cases were farmers and day laborers. The truth is a large number of people share the same house or camp for sheltering for the production of crops in the study area, which could be aggravate the issue of concern.

Moreover, this study was aimed to assess associated risk factors of acquisition of MDR-TB. History of previous treatment was the only significantly associated risk factor with MDR-TB (OR: 7, 95 % CI = 1.28–37.6, $P = 0.02$), which shows agreement with previous published reports [12, 14, 17]. This is due to the fact that prior anti-TB exposure provides only to suppress the growth of susceptible bacilli, but on the other side, it could permit suitable circumstances for the multiplication of pre-existing drug resistant mutants [12].

Even though, this study explored that history of treatment is the only risk factors for acquisition of MDR strains, however, several evidences claimed that factors including HIV/AIDS, overcrowding, smoking, opportunistic infection, lack of compliance with DOTS program, are also the potential risk factors attributes MDR-TB infection [15, 18–20]. In the recent time, global MDR-TB control programs have planned by considering the above factors, along with the highest level of compliance with guidelines (early case detection, complete treatment, administrative, environmental, or engineering controls and personal respiratory protection) [3, 12]. It is well acknowledged that DOTS strategy is the best weapon to dismantle the spread of MDR-TB [3]. Despite the fact that we have observed poor implementation of DOTS in the study area, hence it requires political commitment, sustainable budget allocation, effective drug supply and management system, and continuous monitoring and evaluation system.

Conclusion

We report an overall prevalence of MDR-TB of 5.7 % among all cases, with the prevalence of MDR-TB among previously treated cases being 13.9 % and among new cases only 2.3 %. History of previous anti TB treatment was the only statistically significant risk factor for MDR-TB. Therefore, actions should be directed to improve the DOTS program and to maximize diagnostic laboratory facilities.

Abbreviations

BCG: *Bacillus Calmette–Guérin*; DOTS: Directly Observed Treatment, Short-course; HIV: Human Immunodeficiency Virus; INH: Isoniazid; LJ: Lowenstein-Jensen; MDR: Multi-drug resistant; MDR-TB: Multidrug resistant tuberculosis; MTB: *M. tuberculosis*; RIF: Rifampicin; TB: Tuberculosis; WHO: World Health Organization.

Competing interests

The authors declare that they have no competing interest.

Authors' contributions

FM: conception of research idea, study design, data collection, analysis and interpretation. BT, FMo and AG conception of research idea and supervision. SE: data collection, analysis, interpretation and the drafting of manuscript. GK: data collection and analysis. All authors read and approved the final manuscript.

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RESEARCH ARTICLE Open Access

Tuberculosis retreatment 'others' in comparison with classical retreatment cases; a retrospective cohort review

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Abstract

Background: Many of the countries in sub-Saharan Africa are still largely dependent on microscopy as the mainstay for diagnosis of tuberculosis (TB) including patients with previous history of TB treatment. The available guidance in management of TB retreatment cases is focused on bacteriologically confirmed TB retreatment cases leaving out those classified as retreatment 'others'. Retreatment 'others' refer to all TB cases who were previously treated but with unknown outcome of that previous treatment or who have returned to treatment with bacteriologically negative pulmonary or extra-pulmonary TB. This study was conducted in 11 regional referral hospitals (RRHs) serving high burden TB districts in Uganda to determine the profile and treatment success of TB retreatment 'others' in comparison with the classical retreatment cases.

Methods: A retrospective cohort review of routinely collected National TB and Leprosy Program (NTLP) facility data from 1 January to 31 December 2010. This study uses the term classical retreatment cases to refer to a combined group of bacteriologically confirmed relapse, return after failure and return after loss to follow-up cases as a distinct group from retreatment 'others'. Distribution of categorical characteristics were compared using Chi-squared test for difference between proportions. The log likelihood ratio test was used to assess the independent contribution of type of retreatment, human immunodeficiency virus (HIV) status, age group and sex to the models.

Results: Of the 6244 TB cases registered at the study sites, 733 (11.7 %) were retreatment cases. Retreatment 'others' constituted 45.5 % of retreatment cases. Co-infection with HIV was higher among retreatment 'others' (70.9 %) than classical retreatment cases (53.5 %). Treatment was successful in 410 (56.2 %) retreatment cases. Retreatment 'others' were associated with reduced odds of success (AOR = 0.44, 95 % CI 0.22,0.88) compared to classical cases. Lost to follow up was the commonest adverse outcome (38 % of adverse outcomes) in all retreatment cases. Type of retreatment case, HIV status, and age were independently associated with treatment success.

Conclusion: TB retreatment 'others' constitute a significant proportion of retreatment cases, with higher HIV prevalence and worse treatment success. There is need to review the diagnosis and management of retreatment 'others'.

Background

The World Health Organization (WHO) treatment guidelines recommend that all previously-treated TB patients should be managed according the TB retreatment category, while their sputum is cultured and tested for drug susceptibility (DST) [1]. However, few countries have the required laboratory capacity to improve access to DST services to all TB retreatment patients. Therefore, many countries remain unclear on the best management of TB retreatment cases. Of particular concern is the category of TB patients classified as retreatment 'others'. These refer to all TB cases, previously treated but with unknown outcome of that previous treatment or who return for treatment with bacteriologically negative pulmonary or extra-pulmonary TB. This study uses the term classical retreatment cases to refer to all bacteriologically confirmed relapse, return after failure and return after lost to

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follow-up (LTFU) cases as a distinct group from retreatment 'others'.

Uganda has limited capacity to conduct culture and DST investigations in TB retreatment patients. A study conducted in three regional referral hospitals (RRHs) in Uganda showed that only 13 % of 114 registered relapse smear-positive or treatment after failure cases had their sputum samples sent to National TB Reference Laboratory for culture and DST [2]. Since 2002, Uganda has notified an increasing number of TB retreatment cases from 1500 to about 4000 cases per year [3]. Of the 47,650 total TB cases Uganda notified to the WHO in 2013, 4028 (8.5 %) were TB retreatment cases [4]. TB retreatment 'others' constituted a third of the total retreatment cases notified in 2012 [3].

An important step in understanding how to manage retreatment 'others' is to better understand their outcomes. Previous studies in other settings have observed different treatment outcomes, HIV status and management approaches between classical TB retreatment cases and retreatment 'others' [5–7]. A study in India found that retreatment 'others' significantly had better treatment outcomes than classical retreatment cases [7]. Another study in Zimbabwe found that retreatment 'others' constituted 40 % of recurrent TB with no difference in treatment outcomes by HIV status [6]. 65 % of retreatment cases in Malawi were retreatment 'others' with over half of them treated with standard TB regimen for new cases [5]. This study seeks to add this emerging evidence base on how this group of patients differs by setting, to answer the following research question: what is the profile and treatment success of TB retreatment 'others' compared to the classical retreatment cases in Uganda?

Methods

A retrospective hospital-based review of routinely collected TB data on TB retreatment patients started on TB treatment from 1st January to 31st December 2010. The data were extracted between May and June 2012.

Study setting

This study was conducted in 11 RRHs of Uganda serving mostly districts with high TB burden. In 2009, it was observed that districts with RRHs notified an average of 114 retreatment cases each compared to an average of 32 retreatment cases notified by districts without RRHs (unpublished NTLP reports). The study thus systematically selected 11 high burden RRHs based on the burden of TB. The study sites were: Arua, Fort-Portal, Gulu, Hoima, Jinja, Kabale, Lira, Masaka, Mbarara, Mbale and Soroti RRHs.

Case definitions and treatment of retreatment TB patients

In Uganda, a TB retreatment case is defined as a person previously treated with anti-TB drugs for a month or more and is being treated again, in line with WHO definitions [1, 8]. The retreatment category is further classified either as 'relapse', 'treatment after failure', 'return after LTFU' or 'others'. Relapses are patients who become bacteriologically positive after having been treated for TB and declared cured or treatment completed. Treatment after failure are patients who, while on first line anti-TB treatment are bacteriologically positive at 5 months or later during the course of treatment. Return after LTFU patients are those who return to treatment and are bacteriologically positive after having interrupted treatment for more than 2 months. Retreatment 'others' refer to all TB cases that do not fit the above definitions such as patients with history of TB treatment for a month or more but with no bacteriological confirmation of TB for the current episode.

In line with WHO definitions, Ugandan NTLP classifies treatment outcomes as; cured, treatment completed, treatment failure, died, LTFU and transferred-out. Treatment success refers to a combination of cured and treatment completed. In this study, adverse outcome refers to a combination of LTFU, died, treatment failure and transferred-out.

The retreatment regimen in Uganda consists of two (2) months streptomycin (S), rifampicin (R), isoniazid (H), pyrazinamide (Z), and ethambutol (E). This is followed by one (1) month RHZE and five (5) months RHE. The retreatment regimen(2SRHZE/1RHZE/5RHE) is recommended for all bacteriologically positive TB retreatment cases [1, 8]. Both NTLP and WHO guidelines are silent on the management of TB retreatment 'others' in settings with limited TB DST capacity. In Uganda, it is at the discretion of the clinician to decide the TB treatment regimen to use in the management of retreatment 'others'. At the time of the study, routine culture and DST for retreatment cases had been rolled out to the study sites with varying levels of implementation [2].

Study variables, source of information and data collection

Records of routinely collected variables within the hospitals' unit TB registers that were analyzed included: patient demographic (age and sex); clinical (disease classification, pre-treatment smear status and HIV status); treatment-related (type of retreatment and treatment regimen) characteristics and treatment outcomes. In Uganda, each TB patient is registered in the unit TB register by the health facility staff at the start of treatment and individual patient records updated at every visit during the course of treatment. The district TB and Leprosy supervisor (DTLS) enters TB patients registered on treatment from all TB diagnostic and treatment

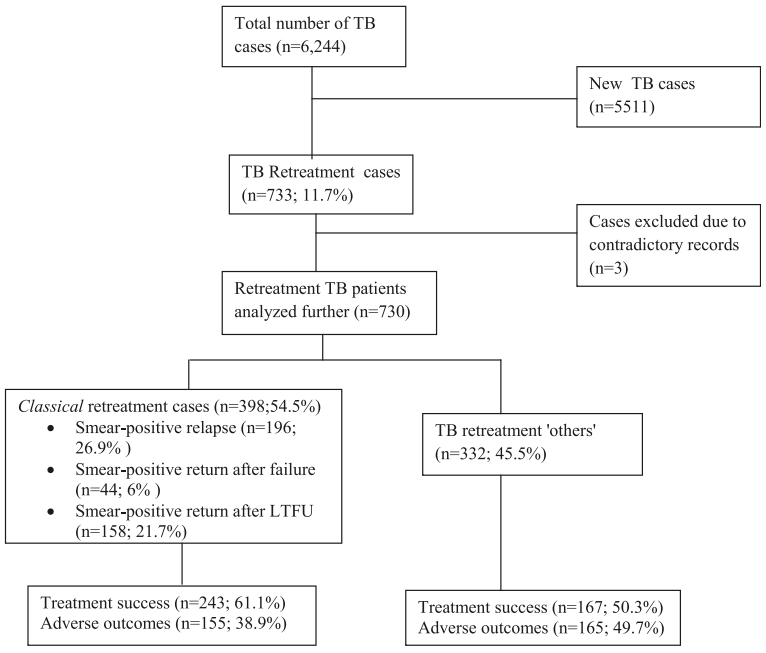

Fig. 1 Proportion of TB retreatment cases and outcomes at eleven regional referral hospitals, Uganda

health facilities within that particular district into the district TB register. Information on patients that transferred to other facilities within the same district is captured by the DTLS and conveyed back to the registering facility. More information on patients transfers between districts in the same zone is exchanged during quarterly zonal performance reviews attended by DTLSs before compiling quarterly district TB and Leprosy reports on notification and treatment outcomes. At the time of the study, the reporting unit at the NTLP central unit was the district. Using an anonymous standardized data collection tool, study variables were extracted from the hospital' TB unit registers by one trained research assistant and all entries were verified by the first author. The respective district TB registers were used to ascertain definitive patient treatment outcomes that were missing in the unit registers.

Data entry and analysis

Data was entered into EpiData version 3.1 (The EpiData Association, Odense, Denmark)and analyzed in STATA version 11.2 (Stata Corp, College Station, TX, USA).

HIV status was categorized into positive, negative and unknown. Age was categorized using cut offs that made meaningful differences between the categories. Descriptive analysis of patient characteristics was computed. Distribution of patient characteristics by type of retreatment cases (classical vs. retreatment 'others') was computed. The differences in distribution of categorical characteristics were compared using Chi-square test for difference between proportions at a significance level of *P*-value equal to 0.05.

Treatment outcome was analyzed as a binary variable of success versus all other outcomes. Odds ratio was the measure of association. Logistic regression was used to identify patient characteristics that were independently associated with treatment success. Characteristics that had *P*-value equal or less than 0.05 at bivariate level were assessed further in a multivariate model. In the multivariate analysis, characteristics that were not significant at *p*-value equal or less than 0.05 were dropped. The multivariable model was determined using forward regression with a two-sided *P*-value equal or less than 0.05. Sex was included as a priori in the final model. The log likelihood ratio test was used to assess the independent contribution of explanatory variables to the models.

Ethical approval

As this study was a review of routinely collected NTLP data at RRHs, approval was obtained from Ministry of Health and Joint Clinical Research Centre Institutional Review Board as the local ethical body. The protocol was also approved by London School of Hygiene Tropical Medicine ethics review committee.

Results

Of the 6244 TB cases registered at the 11 RRHs, 733 (11.7 %) were retreatment cases (Fig. 1). Three retreatment cases were excluded from subsequent analyzes due to contradictory records. Table 1 shows that majority of

Table 1 Frequency of retreatment TB patients' characteristics and their distribution by type of retreatment cases registered at the eleven RRHs, 2010 ($n = 730$ cases)

Characteristic	All retreatment cases	Type of retreatment cases		*P*-value*
		Classical TB retreatment cases;	TB retreatment 'others';	
	n (%)	$n = 398$ (%)	$n = 332$ (%)	
Sex				
Male	523 (71.6)	308 (77.4)	215 (64.8)	<0.001
Female	207 (28.4)	90 (22.6)	117 (35.2)	
Age (years)[a]				
<15	39 (5.4)	3 (0.8)	36 (10.8)	<0.001
15-44	509 (69.8)	293 (73.8)	216 (65.1)	
>44	181 (24.8)	101 (25.4)	80 (24.1)	
Anatomical site				
Pulmonary	689 (94.4)	398 (100.0)	291 (87.7)	<0.001
Extrapulmonary	41 (5.6)	0 (0.0)	41 (12.3)	
Disease classification				
Sputum smear-positive	400 (54.8)	398 (100.0)	2 (0.6)	<0.001
Sputum smear-negative	267 (36.6)	0 (0.0)	267 (80.4)	
No smear done	22 (3.0)	0 (0.0)	22 (6.6)	
Extrapulmonary	41 (5.6)	0 (0.0)	41 (12.4)	
HIV status				
Negative	266 (36.4)	174 (43.7)	92 (27.7)	<0.001
Positive	424 (58.1)	200 (50.3)	224 (67.5)	
Unknown	40 (5.5)	24 (6.0)	16 (4.8)	
Retreatment sub-category				
Sputum smear-positive relapse	196 (26.9)	196 (49.3)	0 (0.0)	<0.001
Sputum smear-positive failure	44 (6.0)	44 (11.1)	0 (0.0)	
Sputum smear-positive return after LTFU	158 (21.6)	158 (39.7)	0 (0.0)	
Retreatment 'others'	332 (45.5)	0 (0.0)	332 (100.0)	
Treatment regimen				
Retreatment: 2SRHZE/1RHZE/5RHE	582 (79.7)	378 (95.0)	204 (61.5)	<0.001
New: 2RHZE/6EH or 2RHZ/4RH	116 (15.9)	19 (4.8)	97 (29.2)	
Other regimen[b]	32 (4.4)	1 (0.2)	31 (9.3)	

**P*-values are from Pearson's chi-squared test or Fisher's exact test for the difference in the distribution of the categorical characteristics across the types of retreatment cases

[a]1 patient had missing data

[b]Other regimen included: 3RHZE/5RHE = 13; 2SRHZ/4-12RH = 14; 2SRHZE/6EH = 2; 3SRH/6RH = 1; unknown = 2

retreatment cases were males (71.6 %) and in age group 15–44 years (70 %). Overall, 690 (94.5 %) retreatment cases had a documented HIV test result.

Retreatment 'others' constituted 45.5 % of retreatment cases. Like the classical retreatment cases, retreatment 'others' were mostly males (65 %), and in the age group 15–44 years (65 %). Significantly, lesser (62 %) of retreatment 'others' were treated with the standard retreatment regimen (2SRHZE/1RHZE/5RHE) compared to 95 % of classical retreatment cases. About a third of the retreatment 'others' were treated with the standard regimen for new TB patients.

Table 2 shows that HIV prevalence was higher among retreatment 'others' (70.9 %) than classical retreatment cases (53.5 %). HIV co-infection was 61.5 % among 690 retreatment patients that had a documented HIV test result. Females had a higher HIV prevalence (70.7 %) than males (57.8 %). Of the 424 patients with an HIV-positive test result, 385 (91 %) and 221 (52 %) were provided with Cotrimoxazole preventive therapy (CPT) and antiretroviral therapy (ART) respectively.

Table 3 shows that treatment was successful in 410 (56.2 %) of the 730 retreatment cases. Adverse outcomes were; 16.4 % LTFU, 9.9 % died, 2.6 % failed on treatment

Table 2 Prevalence of HIV by patient characteristics, retreatment type among retreatment TB patients with known HIV test results at eleven RRHs, Uganda ($n = 690$)

Characteristic	Total		Classical retreatment cases		'Others' retreatment cases		*P*-value*
		HIV Positive		HIV Positive		HIV Positive	
		n (%)		*n* (%)		*n* (%)	
Overall	690	424[b] (61.4)	374	200 (53.5)	316	224 (70.9)	<0.001**
Sex							
Male	492	284 (57.8)	289	145 (50.2)	203	139 (68.5)	0.022
Female	198	140 (70.7)	85	55 (64.7)	113	85 (75.2)	
Age group, years[a]							
<15	35	24 (68.6)	3	2 (66.7)	32	22 (68.8)	<0.001
15-44	488	316 (64.8)	277	157 (56.7)	211	159 (75.4)	
>44	166	83 (50.0)	94	40 (42.6)	73	43 (58.9)	
Anatomical site							
Pulmonary	650	391 (60.2)	374	200 (53.5)	276	191 (69.2)	<0.001
Extrapulmonary	40	33 (82.5)	0	0 (0.0)	40	33 (82.5)	
Treatment regimen							
Retreatment: 2SRHZE/1RHZE/5RHE	553	329 (59.5)	357	192 (53.8)	196	137 (69.9)	<0.001
New:2RHZE/6EH or 2RHZ/4RH	106	73 (68.9)	16	8 (50.0)	90	65 (72.2)	
Other regimen	31	22 (71.0)	1	0 (0.0)	30	22 (73.3)	

**P*-values are from either Pearson's chi-squared test of Fischer's exact tests for the difference between given characteristics and the type of retreatment among only HIV positive patients
***P*-value from Z-test for two proportions
[a]1 patient had missing data on this variable
[b]Cotrimoxazole preventive therapy and antiretroviral treatment were documented among 385 (91 %) and 221 (52 %) of all HIV positive TB retreatment patients respectively

while 5.1 % transferred-out and 9.9 % were not-evaluated. Table 4 shows that retreatment 'others' were associated with reduced odds of treatment success [odds ratio (OR) =0.65, 95 % CI 0.48, 0.87] compared to the classical retreatment cases. Anatomical site and treatment regimen were not associated with treatment success. Using multivariable analysis, odds of treatment success remained lower among retreatment 'others' compared to the classical retreatment cases after adjusting for age group, HIV status and sex (Adjusted OR (AOR)) = 0.60, 95% CI 0.44, 0.82). Unknown HIV status was significantly associated with lower odds of treatment success compared to known HIV status (AOR = 0.44, 95% CI 0.22, 0.88). Together with type of retreatment case, age group (less than 15 years) became significantly associated with treatment success (AOR = 2.32, 95% CI 1.12, 4.81).

Discussion

Retreatment 'others' constitute almost half of the retreatment cases in the RRHs of Uganda. Compared to the classical retreatment cases, more cases of retreatment 'others' were HIV positive. And more than a third of retreatment 'others' were not managed with the standard retreatment regimen. Fewer (half) retreatment 'others' succeeded on treatment (50.3 %) compared to six in ten of the classical retreatment cases (61.1 %). Lost to follow

Table 3 Outcomes of retreatment cases by WHO retreatment category

Type of retreatment	Treatment outcome		Adverse outcomes				
	Successful	Adverse	Failure	Died	LTFU	Transfer-out	Not -evaluated
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Smear-positive relapse: $n = 196$	134 (68.4)	62 (31.6)	9 (4.6)	9 (4.6)	23 (11.7)	7 (3.6)	14 (7.0)
Smear-positive return after failure: $n = 44$	30 (68.2)	14 (31.8)	4 (9.1)	3 (6.9)	5 (11.4)	0 (0.0)	2 (4.5)
Smear-positive return after LTFU: $n = 158$	79 (50)	79 (50.0)	3 (1.9)	19 (12)	26 (16.4)	12 (7.6)	19 (12.0)
Retreatment 'others': $n = 332$	167 (50.3)	165 (49.7)	3 (0.9)	41 (12.3)	66 (19.9)	18 (5.4)	37 (11.0)
Total; $n = 730$	410 (56.2)	320 (43.8)	19 (2.6)	72 (9.9)	120 (16.4)	37 (5)	72 (9.9)

$P < 0.001$ for the difference between the type of retreatment and treatment outcome using Pearson's chi-squared test

Table 4 Patient characteristics associated with binary treatment success among TB retreatment cases registered in eleven RRHs of Uganda ($n = 730$)

Characteristics	Total	Treatment Success n (%)	Unadjusted OR (95 % CI)	*P*-value*	Adjusted[b] OR (95 % CI)	*P*-value*
Overall	730	410 (56.2)				
Type of retreatment case						
Classical retreatment cases	398	243 (61.1)	1.00		1.00	
Retreatment 'others'	332	167 (50.3)	0.65 (0.48, 0.87)	0.004**	0.60 (0.44, 0.82)	0.001**
HIV status						
Positive	424	236 (55.7)	1.00		1.00	
Negative	266	159 (59.8)	1.18 (0.87, 1.62)	0.288	1.13 (0.82, 1.56)	0.452
Unknown	40	15 (37.5)	0.48 (0.24, 0.93)	0.030**	0.44 (0.22, 0.88)	0.020**
Age group[a]						
15-44	509	292 (57.4)	1.00		1.00	
<15	39	27 (69.2)	1.67 (0.83, 3.37)	0.143	2.32 (1.12, 4.81)	0.024**
≥45	181	90 (49.7)	0.73 (0.52, 1.03)	0.073	0.75 (0.53, 1.06)	0.102
Sex						
Male	523	296 (56.6)	1.00		1.00	
Female	207	114 (55.1)	0.94 (0.68, 1.30)	0.708	0.97 (0.69, 1.35)	0.844
Anatomical site						
Pulmonary	689	388 (56.3)	1.00			
Extrapulmonary	41	22 (53.7)	0.90 (0.48, 1.69)	0.739		
Treatment regimen						
Retreatment: 2SRHZE/1RHZE/5RHE	582	322 (55.3)	1.00			
New: 2RHZE/6EH or 2RHZ/4RH	116	66 (56.9)	1.07 (0.71, 1.59)	0.756		
Other regimen	32	22 (68.8)	1.78 (0.83, 3.82)	0.137		

*Wald P-value
**Significant at $P = 0.05$
[a]1 patient had missing data
[b]Adjusted for HIV status, age, and sex

up was the commonest adverse outcome for both retreatment groups.

Nearly half of the retreatment cases in this study were retreatment 'others' compared to one in three cases notified nationally [3]. Probably, RRHs receive mostly very sick patients whose sputum is likely to test negative on Ziehl Neelsen (ZN) smear test due to their inability to mount an immune response and/ or produce sufficient sputum for microscopy. In addition, the TB diagnosis in RRHs is likely to be made by relatively highly qualified clinicians with capacity and/or bias to rely on their clinical acumen to diagnose TB even in the absence of a positive AFB sputum result. The presence of high TB-HIV co-infection rates in our study may account for the observed high proportion of retreatment 'others' [9]. The proportion of retreatment 'others' in this study is comparable to those from Zimbabwe and India [6, 7], but less than the proportion observed from a study conducted in a large registration centre of Malawi [5].

Overall, treatment success was low at 50 % in retreatment 'others' and 61 % in classical retreatment cases, compared to 71 % treatment success notified to WHO [3]. This study considered patients in referral hospitals who may be different from other TB patients from lower levels of care on a number of factors. Due to the referral cascade, patients with atypical forms of TB or drug-resistant TB are likely to be managed at RRHs and hence likely to exhibit poor treatment outcomes. However, the observed factors like the weakness in recording and reporting system, inability to track these patients (15 % of participants didn't have definitive outcomes) and the low uptake of ART (52 %) among HIV co-infected patients may also explain the low treatment success. The 52 % ART uptake observed in the study population was higher than the national average of 24 % [10]. The difference between treatment success in this study and that reported to WHO may be because we evaluated all retreatment cases registered and not only classical retreatment cases that are routinely evaluated. Nonetheless, the

results support previous findings from a smaller study conducted in three RRHs in Uganda [2].

The outcomes for retreatment 'others' in this study were worse than those of retreatment 'others' reported in India as compared to the classical retreatment cases [7]. This difference across settings may be influenced by factors such as difference in treatment regimens' [5], drug resistance [11], co-morbidity [12], delay in diagnosis or even misdiagnosis [5, 13], adherence levels or having another pulmonary or extra-pulmonary disease for which they are not adequately treated.

Similar to the results reported in previous studies [5, 6], this study found that a higher proportions of retreatment 'others' were co-infected with HIV compared to the classical retreatment cases. Just like in other studies, we found that patients' knowledge of their HIV status is beneficial [9, 14, 15]. 90 % of study participants that were found to be HIV-positive were started on CPT and half of them started on ART as well. The high uptake of HIV testing coupled with good initiation of CPT in this study could have resulted in observing no difference in treatment success between HIV-positive and negative patients. Age group and unknown HIV status were only significant independent predictors, but did not modify the effect of type of TB retreatment case on treatment outcome.

The findings of this study should be viewed with the following limitations. Firstly, this was a retrospective study utilizing hospital TB registers which could be prone to inaccuracies resulting from poor recording and completeness in the patient data and compromise the validity of the finding. However, this study found that 94.5 % of smear-positive retreatment cases had smear result correctly recorded. In addition, completeness of treatment outcomes was improved by use of the district TB registers whereby 28 % (176/621) of definitive outcomes among study participants were obtained.

We could not establish treatment outcomes in 15 % of the study participants even after reviewing district TB registers. There were no differences in patient characteristics between those who had complete information on the outcomes and those who had missing outcomes. However, the high proportion of missing treatment outcome could have introduced bias in determining treatment success or underreported deaths or LTFU among the study participants.

This study highlights the importance of ensuring appropriate management for retreatment 'others' given the relatively poor outcomes. A first key step is to ensure that this high number of retreatment 'others' is not a result of misdiagnosing drug-resistant TB or a false positive diagnosis of TB. More accurate TB diagnostic tools like the GeneXpert MTB/RIF that are currently available in all the study sites may have a role in providing access to a confirmation of TB in this special group.

Secondly, the continued notification of high proportions of retreatment 'others' to national authorities and Global TB Program calls for clear guidance on the management of retreatment 'others' including further definition of treatment regimen(s) in high HIV prevalence settings and limited TB diagnostic capacity. A future prospective study involving culture and drug-susceptibility testing could be conducted in programmatic settings to further understand the appropriate treatment regimens in such patients.

Thirdly, the observed high LTFU in the retreatment patients especially the retreatment 'others' calls for focused and innovative interventions to ensure treatment adherence in this group of patients. Social incentives and community outreach may have a role to play in reducing the loss to follow-up of these groups.

Fourthly, high HIV prevalence among retreatment cases especially the TB retreatment 'others' calls for better strategies of improving provision of the full range of TB/HIV collaborative services to reduce the burden of HIV in this group of patients.

Finally, further research is recommended at different levels of the TB treatment program to further clarify the importance of patient, health worker and system related factors on treatment success among retreatment cases to complement the findings of this study; and design the most appropriate response to ensure favorable outcomes from this underserved and evaluated group of TB patients.

Abbreviations

AFB: Acid fast bacilli; AOR: Adjusted odds ratio; ART: Antiretroviral therapy; CI: Confidence interval; CPT: Cotrimoxazole preventive therapy; DST: Drug susceptibility testing; DTLS: District TB and Leprosy supervisor; E: Ethambutol; H: Isoniazid; HIV: Human immunodeficiency virus; LFTU: Lost to follow up; LSHTM: London School Of Hygiene and Tropical Medicine; MTB/RIF: Mycobacterium tuberculosis and rifampicin-resistance mutations; NTLP: National Tuberculosis and Leprosy Programme; OR: Odds ratio; R: Rifampicin; RRHs: Regional referral hospitals; S: Streptomycin; TB: Tuberculosis; WHO: World Health Organization; Z: Pyrazinamide; ZN: Ziehl Neelsen.

Competing interests

The authors declare no conflict of interest.

Authors contributions

Substantial contributions to conception and design, acquisition of data or analysis and interpretation of data (MGN, HJK, PM, AV). Manuscript writing and revising for intellectual content and approval for journal submission (MGN, HJK, MB, PM, AV). All authors read and approved the final manuscript.

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Research

Performance of LED fluorescence microscopy for the detection of tuberculosis in Rwanda using Zeiss Primo Star

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Abstract

Introduction: Ziehl-Neelsen (ZN) bright-field microscopy is time-consuming, with poor sensitivity, even under optimal conditions. Introduction of Primo Star iLED fluorescent microscopy (FM) may improve TB case finding at referral hospitals in Rwanda. The study aimed to determine the acceptability and effectiveness of iLED in a low resource setting. **Methods:** Between June 2009 and May 2010, the Rwandan TB Program and National Reference Laboratory carried out demonstration studies with iLED at a referral hospital in the capital, Kigali, and a rural district hospital in Nyamata, taking conventional FM as Gold Standard. **Results:** Agreement between the iLED and rechecking at the Reference Laboratory were deemed "almost perfect" (kappa = 0.81-1.00) across three of four site-phase combinations. The exception was Nyamata District Hospital during the validation phase, which was deemed "substantial" agreement (kappa = 0.61-0.80). However, the 100% concordance at both demonstration sites during the continuation phase shows technicians' rapid command of the new iLED microscope in a relatively short time. The lower overall positivity rate obtained in the rural clinic is not related to the performance of the microscope (or technicians), but is attributable to a significant increase in total number of patients and samples screened through active case finding. **Conclusion:** Laboratory technicians demonstrated high acceptance of iLED. Additionally, fluorescent microscopy reduces the time necessary for examination by more than half. The high level of agreement between iLED and FM during implementation in both sites provides initial evidence for iLED to replace current methods.

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Introduction

Sputum smear microscopy for acid-fast bacilli (AFB) using Ziehl-Neelsen (ZN) staining remains the most cost-efficient tool available to diagnose tuberculosis (TB) in low-resource countries. This method is rapid, inexpensive, and highly specific for detecting AFB in high-burden settings. However, the main limitation is its low and variable sensitivity, exacerbated in high HIV prevalence settings [1]. High TB-HIV co-infection rates and low TB case detection impede disease control in many TB endemic settings, notably sub-Saharan Africa [2]. Furthermore, where workloads are high, the amount of time spent examining smears compromises sensitivity [3]. A recent systematic review demonstrated that fluorescence microscopy (FM) is, on average, 10% more sensitive than conventional bright-field microscopy in detecting AFB in clinical specimens, with comparable specificity, and takes significantly less time [4]. However, widespread implementation of FM in disease-endemic settings remains limited due to several factors, including the short life and high cost of mercury vapor lamps; difficulty in maintaining machines; the need for a darkroom; and strict requirements for electrical power supply. Light-emitting diodes (LEDs) for FM have been identified as an alternative to conventional FM for screening of AFB [5, 6]. LED lamps do not have the disadvantages of mercury vapor lamps, with life expectancy averaging around 50,000-100,000 hours (10-20 years) of use [5]. They can also run on batteries [5, 7, 8]. Several commercial LED systems are now available, either as stand-alone microscopes or as add-on adapters to conventional microscopes [9]. Data published so far on LED microscopy for TB show that results in terms of sensitivity and specificity are comparable or better with LED than mercury vapor lamps [6, 7, 10-13]. **Study objectives**: This demonstration project evaluated the effectiveness of employing the Primo Star iLED fluorescence microscope (subsequently referred to as iLED) for case finding of TB under routine conditions in one referral and one rural setting in Rwanda. Microscopists without prior experience in FM were solicited in order to determine operational and clinical performance, as well as acceptability of the technology to laboratory staff. **Study design**: This project was conducted at two sites: Nyamata district hospital (DH) in Bugesera district and the Centre Hospitalier Universitaire de Kigali (CHUK) in Kigali. Nyamata DH is a 100-bed hospital with a catchment area of about 300,000 people. CHUK is a 509-bed national referral hospital (RH) serving the capital city, Kigali, with a catchment area of approximately 1 million people. The implementation of iLED was carried out in five phases: (1) ZN baseline; (2) iLED training and appraisal (five days); (3) validation (one month); (4) implementation (three months); and (5) continuation (six months).

Methods

Ethics statement: The evaluation was approved by the Ethical Review Committee of the Ministry of Health (Kigali, Rwanda) under Protocol Number 58/RNEC/2009 and by the Institutional Review Board of Columbia University IRB-AAAC6248 (New York, NY, USA). Written consent was not obtained because microscopy for AFB smears is the standard of care in Rwanda as part of regular clinic monitoring and evaluation of Tuberculosis. During validation, all sputum results obtained though iLED were rechecked systematically by the National Reference Laboratory before results were provided to patients for management. The implementation phase was only allowed once iLED was validated as a replacement for light microscopy with similar or better sensitivity, therefore not placing patients at risk of misdiagnosis. Written consent to participate in the study was not sought from the microscopists or their supervisors because the introduction of the iLED only minimally increased the workload and only for a short duration (1 month) during the whole study. Participants were informed about the purpose and impact of the study, and microscopists readily participated enthusiastically. The need for collecting documented informed consent was waived by the IRB. **Phase 1: ZN Baseline**: The aim of this one-month phase was to establish a baseline, under study conditions, of false positivity and negativity rates for ZN. TB treatment decisions were based on ZN results. All incoming sputum smears were stained for ZN examination under routine conditions. Slides were read using the available conventional bright-field microscope (1000x). After reading, all slides were kept in slide boxes, which were labeled to specify the study phase, study site, box number, and slide ID. Once every two weeks, the National Reference Laboratory (NRL) study supervisor collected all boxes. NRL study technicians rechecked all slides using conventional bright-field microscopes. Discrepant slides, if any, were sent to the Supra National Reference Laboratory (SNRL) in Germany for rereading. **Phase 2: Training and Appraisal**: A standardized five-day training course for microscopists and supervisors participating in the study was conducted. All eight participants had skills in ZN microscopy but not conventional FM. Participants after learning the purpose and impact of the study, participated readily. Following the training, all technicians involved

in the project filled out a questionnaire about several features of the iLED, including installation and first use, training, and optics and handling. **Phase 3: validation**: The validation phase lasted one month. Each sputum sample at the study sites was stained using Auramine O and examined by the iLED at 400x magnification. Patient management was based solely on the rechecking results carried out by the NRL. Staining solutions were prepared by NRL using Merck staining reagents (Catalogue 41000, Auramine O, item number 1013010050, lot number ZC 253201532) and provided to the study sites once per month, taking into consideration the limited shelf life of Auramine O. All readings (including rechecking) were done within 48 hours of staining. Results were quantified according to the scale presented in **Table 1**. NRL rechecked all slides using conventional FM. Rechecked results were provided to study sites the next day for timely patient management. The semi-quantitative scale for rechecking by NRL was different than the one used by study sites (**Table 2**). Discordant slides, if any, were sent to the SNRL for final discussion. The study sites were allowed to proceed to phase four only if the following performance targets were met: (1) 95% accordance between validation results of microscopy center and supervisory site; (2) quality of Auramine O stains acceptable in 100% of slides examined; and (3) fewer than two false results in a proficiency testing panel of 10 pre-defined slides.

Phase 4: implementation phase: The procedures were the same as during the validation phase. The duration of this phase was three months, and patient management was now based on iLED results. Supervision and rechecking by the NRL study supervisor were carried out using Lot Quality Assurance Sampling (LQAS). The sample size was calculated by NTP/NRL based on the positivity and number of negative smears, but the frequency of rechecking was decreased from daily to once every two weeks. Rereading by NRL was done using conventional FM at 400x magnification. Discordant slides, if any, were sent to the SNRL in Germany for umpire reading. Rechecked results were provided to study sites. **Phase 5: continuation and expansion**: The continuation phase lasted six months, and patient management was based on iLED results. Supervision and rechecking by NRL supervisors was carried out according to national Rwandan External Quality Assurance guidelines. Fifteen slides were collected quarterly and rechecked by NRL using conventional FM at 400 x magnification. Discordant slides, if any, were sent to the SNRL in Germany for umpire reading. Rechecked results were provided to study sites. After the six-month continuation phase, and following the availability of the compiled results of the previous phase, the demonstration project coordinator allowed all sites to use the iLED method routinely under program conditions. **Data entry and analysis**: All data and results were recorded in phase-specific forms and sent to NRL and NTP. An electronic database was completed on-site. Positivity agreement between methods at the study laboratories (DH or CHUK) and the National Reference Laboratory was assessed using Cohen's Kappa, which corrects for agreement by chance. Strength of agreement was evaluated using guidelines from Land is and Koch [14]: <0 = poor; 0-0.20 = slight; 0.21-0.40 = fair; 0.41-0.60 = moderate; 0.61-0.80 = substantial; 0.81-1.00 = almost perfect.

Results

Baseline: At the DH in Nyamata, all incoming sputum samples (100) from 37 patients, using the Spot-Morning-Spot criteria, were examined using ZN staining during the baseline phase. The positivity rate of the slides was 11% (11/100 -**Table 3**) with only one low false positive (LFP) as determined following rechecking. The LFP result had no negative public health consequence on the accurate diagnosis of the patient. There were no poorly stained slides reported by the NRL. At CHUK in Kigali, all incoming sputum samples (205) from 94 patients (Spot-Morning-Spot) were analyzed. The positivity rate for the samples was 7.3% (15/205 - **Table 4**) and two quantification errors (QEs) were reported following rechecking at NRL. The two QEs, corresponding to two samples from two different patients, had no negative public health consequence. There were no poorly stained slides reported by the NRL for CHUK during the rechecking of the baseline. For the comparison between results obtained by the DH in Nyamata and the NRL, Kappa was 0.947 [95% CI: 0.84, 1.00], which indicates an almost perfect agreement between the two laboratories (see results in **Table 5**). For the comparison between CHUK and NRL, Kappa was 1.000 due to full agreement (**Table 5**).

Validation phase: In Nyamata, all incoming samples (100) from 39 patients were screened. The positivity rate decreased to 4% (4/100 - see Table 3) and there were 1 low false positive and 1 low false negative (LFN) errors reported. Additionally, 15 samples were reported as having poor stains. The LFN and LFP errors, corresponding to two samples from the same patient, would not have a negative public health consequence and were probably due to administrative errors. However, as per protocol, diagnosis was made solely on the basis of the rechecking by the NRL. Kappa was

0.740 [95% CI: 0.38, 1.00], which indicates substantial agreement between the laboratories (**Table 5**). In CHUK, all incoming samples (202) from 87 patients were screened. The positivity rate significantly increased from baseline to 22.3% (45/202 - see Table 4) and there was one LFN reported. Since only one sample was collected for that particular patient, the LFN error would have had a negative public health consequence on the accurate diagnosis of the patient. The patient was adequately treated following rechecking by NRL. Nine samples were reported as having poor stains by the NRL. Kappa was 0.986 [95% CI: 0.96, 1.00'> 1.00], which indicates an almost perfect agreement between laboratories (**Table 5**). No errors were detected at the proficiency panel test. Both sites were allowed to proceed to the implementation phase.

Implementation phase: In Nyamata, following LQAS, 44 samples (corresponding to 44 patients) were rechecked by the NRL study supervisor. The positivity rate for samples increased from validation to 9.1% (4/44) but remained lower than in the baseline phase (**Table 3**). No reading/diagnosis errors were reported by the NRL. However, there were six poorly stained samples. Kappa was 1.000 due to full agreement (**Table 5**). In CHUK, following LQAS, 45 samples from 45 patients were rechecked. The positivity rate for samples increased further from baseline and validation to 31.1% (14/45), as shown in Table 4. Only one LFN and three poor stains were reported by the NRL. It is not possible to say whether the LFN error had a negative public health consequence, since the other two samples from this particular patient were not rechecked and could have been positive. Kappa was 0.949 [95% CI: 0.85; 1.00], which indicates an almost perfect agreement between laboratories (**Table 5**).

Continuation phase: In Nyamata, 16 samples were read from January through March by iLED at the site and conventional FM at NRL, and 100% concordance was observed. From April through June, an additional 11 samples were rechecked and all results concurred. At CHUK, there were 15 samples screened from January through March and 100% concordance was observed. Sixteen additional samples were screened from April through June and 100% concordance was also observed. **Technicians' appraisal**: the appraisal took place after training of the technicians. ***Installation and first use:*** All technicians felt that installation of the iLED was easy and that the manual was comprehensive and easy to read and understand. ***Training:*** The technicians participating in the iLED project felt that for technicians already trained in ZN microscopy (such as themselves), an iLED training of 1-5 days was suitable. However, for technicians not familiar with ZN microscopy, an iLED training of 3-20 days was suitable. Technicians also felt that NTPs can readily use the current manual developed by the manufacturer for implementation of LED microscopy without major changes.

Optics and handling: All technicians were satisfied with the contrast, color, intensity, and signal-to-noise ratio of the iLED. All technicians were very satisfied with the resolution and depth of focus of the iLED. All technicians also felt that the field of view of the iLED is more homogenously illuminated compared to the standard view. All of them were very satisfied with the overall handling features of the microscope. All technicians also felt that it was convenient or very convenient to switch between bright field and fluorescence. Only one technician surveyed felt that the toggle field was not robust. All technicians felt that no darkroom was needed when using iLED, a really convenient feature of iLED compared to regular FM. All technicians also agreed that the dazzling protection for the eyepieces was useful. None of the technicians surveyed reported any technical problems with the microscope overall.

Discussion

Compared to classical FM with mercury vapor lamp, LED FM is more user-friendly and benefits from a high acceptability by technicians. Microscopes do not require warm-up and cool-down time, a considerable advantage when power supply is erratic, and the LED light source is considered safer than the mercury vapor lamp. LED systems developed for AFB smears consist either of modules that can be fitted to a conventional microscope, or a complete microscope with built-in LED as the light source, such as the iLED. While Partech (Münster, Germany) and Cytoscience (Fontaines, Switzerland) have both developed complete LED FM microscopes, these microscopes are less appropriate for TB than iLED since they are monocular. Using a camera and monitor might be an appropriate solution, but not in less-developed countries. iLED, a binocular FM microscope with built-in LED lamp for epi-fluorescence has produced very good results in reference laboratories [13]. So far, very few reports on these systems exist. These rare reports, however, show excellent performance compared to ZN microscopy [15, 16]. Our study is the first direct evaluation of iLED in Rwanda. LED add-on kits have been designed for different common types of

bright field microscopes. The complete installation is not difficult, but it requires slightly more time and care, which could be a disadvantage from the end-user perspective. As difficulty in acceptance by inexperienced microscopists seems to be the main obstacle to the use of FM outside referral laboratories, this may prove to be a major advantage of transmitted LED light FM, as reported earlier from Tanzania [8]. It also remains to be seen whether complete binocular LED microscopes using epi-fluorescence, rather than transmitted light, will meet the same acceptance level with the progressive decentralization of FM to peripheral hospitals and health centers. Our study shows that the acceptability amongst the staff using iLED was extremely high and proficiency in adequate usage was rapid. Compared to traditional bright-field methods, LED fluorescence methods using Auramine O staining allows up to four times faster screening. The detection rate is also estimated to be at least 10% higher. While we did not directly compare the positivity rates between ZN and iLED, we monitored the positivity rate over time during our study.

In Nyamata, the positivity rate surprisingly decreased during the validation phase (Table 5). This result compares with previously established data from the National TB Programme, which has shown that in the last quarter of 2009 and first quarter of 2010, during which our study took place, there was an overall decrease in positivity rate that is not related to the performance of the microscope (or the technicians) but is rather attributable to a significant increase in total number of patients and samples screened. Indeed, the positivity rate dropped to 7.7% during our study, compared to 9.2% the year before. This increase in the total number of patients screened may be the result of the impact of Community Health Workers (CHWs) in Bugesera District (where Nyamata DH is located), who have been involved in active case finding, therefore casting a wider net for overall screening of TB suspects and decreasing the positivity rate at the Nyamata Center. One of the expected issues associated with the change from ZN to Auramine staining for the purpose of our study was a difficulty in preparing and then subsequently reading the slides adequately using the Auramine protocol. Indeed, a few of the smears in the various phases were reported as having poor stains. We believe these could be explained by the fact that some laboratory technicians were not completely proficient in staining the slides appropriately, as can also sometimes be the case for ZN. However, this was not an issue throughout the study as the number of slides poorly stained gradually decreased at both sites. Agreement between the iLED and rechecking at the Reference Laboratory were deemed "almost perfect" (kappa = 0.81-1.00) across three of four site-phase combinations. The exception was Nyamata District Hospital during the validation phase, which was deemed "substantial" agreement (kappa = 0.61-0.80). However, the 100% concordance at both demonstration sites during the continuation phase shows technicians' rapid command of the new iLED microscope in a relatively short time. Technicians can therefore be easily trained to switch from ZN microscopy to LED FM with a high success rate. This should be of interest to national TB control programs that are interested in improving their overall case detection rate but cannot yet invest in the newer, molecular-based technologies currently being rolled out.

Conclusion

In our study, the use of iLED FM module in both a referral hospital and rural clinic setting was associated with a high concordance rate as compared to a Reference Laboratory using conventional FM. The high level of agreement between iLED and FM during our study in multiple sites, combined to the fact that fluorescent microscopy reduces the time necessary for examination by more than half, provides initial evidence for the iLED to replace current standard methods. The iLED microscope also excelled in terms of user-friendliness and acceptance by users.

Competing interests

The authors declare no competing interests.

Authors' contributions

AUN, MG, and YBA conceived the study and participated in its design and coordination. MT and GV participated in the design and coordination of the study. BN performed all statistical analysis. All authors helped to draft the manuscript and read and approved the final manuscript.

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Tables

Table 1: Semi-quantitative scale used for reading with Iled

Table 2: Semi-quantitative scale for rechecking with conventional FM

Table 3: Distribution of slides by outcome at different phases of the study evaluation at Nyamata Hospital

Table 4: Distribution of slides by outcome at different phases of the study evaluation at CHUK

Table 5: Statistical analysis of diagnostic outcomes by site at Nyamata District Hospital (DH) and at the Centre Hospitalier Universitaire de Kigali (CHUK) by either LM or iLED

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Table 1: Semi-quantitative scale used for reading with iLED

IUATLD Scale (1000field =HPF) Result	**iLED** (400x magnification: 1 length =40 fields = 200HPF
Negative	Zero AFB /1 length
Scanty	1–19 AFB/1 length
1+	20–199 AFB/1 length
2+	5–50 AFB/1 field on average
3+	>50 AFB/1 field on average

Table 2: Semi-quantitative scale for rechecking with conventional FM

IUATLD Scale (1000field =HPF) Result	**Conventional FM** (200-250x magnification: 1 length =30 fields = 300HPF
Negative	Zero AFB /1 length
Scanty	1–9 AFB/1 length
1+	30–299 AFB/1 length
2+	10–100 AFB/1 field on average
3+	>100 AFB/1 field on average

Table 3: Distribution of slides by outcome at different phases of the study evaluation at Nyamata Hospital

Quantification	**Negative**	**Positive**	**Scanty**	**Total**	**%Positive**
Baseline	89	8	3	100	11.0%
Validation	96	1	3	100	4.0%
Implementation	40	3	1	44	9.1%
Continuation	0	23	4	27	100.0%

Table 4: Distribution of slides by outcome at different phases of the study evaluation at CHUK

Quantification	Negative	Positive	Scanty	Total	%Positive
Baseline	190	14	1	205	7.3%
Validation	157	25	20	202	22.3%
Implementation	31	12	2	45	31.1%
Continuation	2	22	7	31	93.5%

Table 5: Statistical analysis of diagnostic outcomes by site at Nyamata District Hospital (DH) and at the Centre Hospitalier Universitaire de Kigali (CHUK) by either LM or iLED

Site	Phase	Method	N	Sens.	Spec.	Cohen's Kappa	Kappa 95% CI
DH	Baseline	LM	100	1.000	0.989	0.947	[0.84, 1.00]
CHUK	Baseline	LM	205	1.000	1.000	1.000	[1.00, 1.00]
DH	Validation	iLED	100	0.750	0.990	0.740	[0.38, 1.00]
CHUK	Validation	iLED	202	0.978	1.000	0.986	[0.96, 1.00]
DH	Implementation	iLED	44	1.000	1.000	1.000	[1.00, 1.00]
CHUK	Implementation	iLED	45	0.933	1.000	0.949	[0.85, 1.00]

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RESEARCH ARTICLE

Addressing tuberculosis control in fragile states: Urban DOTS experience in Kabul, Afghanistan, 2009-2015

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Abstract

Tuberculosis (TB) is a major public health problem in Afghanistan, but experience in implementing effective strategies to prevent and control TB in urban areas and conflict zones is limited. This study shares programmatic experience in implementing DOTS in the large city of Kabul. We analyzed data from the 2009±2015 reports of the National TB Program (NTP) for Kabul City and calculated treatment outcomes and progress in case notification using rates, ratios, and confidence interval. Urban DOTS was implemented by the NTP in partnership with United States Agency for International Development (USAID)-funded TB projects, the World Health Organization (WHO), and the private sector. Between 2009 and 2015, the number of DOTS-providing centers in Kabul increased from 22 to 85. In total, 24,619 TB patients were enrolled in TB treatment during this period. The case notification rate for all forms of TB increased from 59 per 100,000 population to 125 per 100,000. The case notification rate per 100,000 population for sputum-smear-positive TB increased from 25 to 33. The treatment success rate for all forms of TB increased from 31% to 67% and from 47% to 77% for sputum-smear-positive TB cases. The treatment success rate for private health facilities increased from 52% in 2010 to 80% in 2015. In 2013, contact screening was introduced, and the TB yield was 723 per 100,000Đmo re than two times higher than the estimated national prevalence of 340 per 100,000. Contact screening contributed to identifying 2,509 child contacts of people with TB, and 76% of those children received isoniazid preventive therapy. The comprehensive urban DOTS program significantly improved service accessibility, TB case finding, and treatment outcomes in Kabul. Public- and private-sector involvement also improved treatment outcomes; however, the treatment success rate remains higher in private health facilities. While the treatment success rate increased significantly, it remains lower than the national average, and more efforts are needed to improve treatment outcomes in Kabul. We recommend that the urban DOTS approach be replicated in other countries and cities in Afghanistan with settings similar to Kabul.

Introduction

Tuberculosis (TB) is a global public health challenge. In 2015, the largest number of new TB cases was in the Southeast Asia and Western Pacific Regions, accounting for 58% of new cases globally [1]. Rapid urbanization and overcrowded housing in high-density slums contribute to the high TB incidence rates in those regions [2, 3]. The United Nations estimates that about 3.9 billion people live in urban areas, a number that is expected to increase in the less urbanized areas of Asia and Africa [4]. The same trend affects the capital city of Afghanistan. Kabul has experienced a high rate of urbanization caused by internal migration of those seeking jobs or fleeing from conflict. Other studies have shown that the TB burden is high in urban areas but is not related to informal settlements [5]. In Brazil, high TB prevalence rates are reported in dense urban areas but are not necessarily related to income level [6].

Of Afghanistan's estimated 33 million people approximately 4.4 million live in Kabul City. According to the Ministry of Public Health (MOPH), conflict in Afghanistan has weakened the health care system and led to overcrowded living conditions and a poor quality of life that facilitates TB transmission (Urban DOTS Strategic Plan for five cities [Kabul, Mazar-i-Sharif, Herat, Kandahar, Jalalabad]±Afghanistan, 2015±2019; 2015). The estimated incidence of all forms of TB in Afghanistan is 189 per 100,000 population [1], the prevalence of all forms of TB is 340 per 100,000 [7], and the TB death rate is 37 per 100,000 [1]. Annually, there are an estimated 62,370 cases of all forms of TB in the country, but only 37,001 new TB cases were notified in Afghanistan in 2015. The treatment success rate (TSR) for all forms of new and relapse TB nationwide is 87% [1].

In 2009, only 22 health facilities in Kabul provided partial TB services. As a result, Kabul had poor TB indicators in comparison with national levels. For instance, in 2009 the TB case notification rate was only 59 per 100,000, the TSR for all forms of TB was 31%, and the cure rate for sputum-smear-positive (SS+) TB was 47%. Few private-sector providers had been trained on national TB clinical guidelines, resulting in misdiagnosis, misclassification, improper treatment combinations, and incorrect treatment (MOPH Urban DOTS Strategic Plan 2015).

To address this disparity, the Afghanistan National TB Program (NTP), with assistance from the US Agency from International Development (USAID) and the World Health Organization (WHO), developed an urban DOTS approach in Kabul. This paper describes our experiences in improving DOTS services in Kabul from 2009 to 2015.

Methods

The setting

Administrative. In 2009, Kabul was home to 3.27 million people. Kabul is the primary referral center for the neighboring 16 districts and is the highest referral point for TB services in the country. In 2015, the total population living in Kabul reached 4.37 million and there were 25 sub-districts.

Health system structure. In 2009, there were 137 public and private health facilities of which 106 (77%) provided laboratory services. Twenty-two were public health facilities (16% of the health facilities in Kabul) and provided DOTS. Of those, most provided partial TB services with poor diagnostic and treatment quality and weak infrastructure (MOPH, National Report, 2015). This distribution was not regular. Fourteen of 22 sub-districts were covered, and 54% (12) of DOTS centers were located in four sub-districts; none of the private facilities were covered by DOTS. Per the 2015 National Health Management Information System (HMIS) report, Kabul has 282 public and private health facilities. Of those, 132 (76 public and 56 private) provided laboratory services. DOTS coverage reached 85 (33%) health facilities

(69 public and 16 private). Ninety percent of public facilities and 28% of private facilities were covered by DOTS.

The city's health infrastructure is among the poorest in the country, with 65% of Kabul's primary health facilities located in rented houses (MOPH, National Surveillance Report, 2009).

The urban DOTS program approach

The urban DOTS model in Kabul focuses on four major intervention areas: (1) building the capacity of the NTP and health care providers; (2) expanding DOTS coverage in public and private health facilities; (3) improving management and drug supply at health facilities; and (4) improving surveillance, supervision, and monitoring.

In July 2009, the NTP, TB Control Assistance Program (TB CAP) of USAID, and WHO assigned a team to implement and support an urban DOTS program in Kabul City and simultaneously established an urban DOTS taskforce to assist the NTP with developing implementation guidelines and standard operating procedures and creating coordinated and collaborative approaches among sectors including the private sector. The team conducted an assessment, shared the results with senior staff of the MOPH/NTP, private sectors, other non-MOPH sectors, and other stakeholders and partners to obtain political and technical support for the expansion of DOTS in Kabul. During the same year, the NTP presented the urban DOTS program to stakeholders through an orientation workshop. Through this consultative process, the NTP and TB CAP developed an integrated package of standard operating procedures for case detection, TB treatment monitoring for adults and children, TB infection control, community-based DOTS, and surveillance. Following the development of these procedures, from 2009 to 2015, 681 health workers (physicians, laboratory technicians, and nurses) were trained to apply them.

Between 2009 and 2015, the multisectoral urban DOTS program was scaled up to 85 health facilities from various sectors, such as the public and private sectors, ministries of interior, defense, and justice, and the Afghan Red Crescent Society (ARCS). Urban DOTS was implemented in the following phases.

During the scale-up process, the health facilities were assessed to ensure that they met the standards for becoming a DOTS facility The selection criteria were facilities that served large populations, had a high patient volume, covered a diverse population, and were willing to participate voluntarily. The NTP and partners selected health facilities for DOTS implementation and prepared an implementation plan for each facility. The implementation process started and was monitored through routine supervision and monitoring visits. Lastly, the performance of each facility was monitored during quarterly review workshops.

After the selection of health facilities, an action plan was developed and implementation began. Through this process, the MOPH/NTP issued unique identification codes to the selected facilities to provide free TB diagnostic and TB treatment services. At the same time, the MOPH/NTP signed a memorandum of understanding with the private health facilities to delineate the roles and responsibilities in the urban DOTS program.

Public and private health care providers were trained together and the same training curricula, presentations, and standard operating procedures for TB case finding and treatment were applied. Sputum laboratory microscopy was performed in public health facilities and 20 private facilities performed it as well. A similar number of private health facilities were referring presumptive TB patients for diagnosis to public facilities. The NTP provided drugs, supplies, and standard TB recording and reporting forms to private facilities to ensure that they provided quality TB services.

The NTP team was then tasked with ensuring the regular supply of free reagents, anti-TB drugs, and other consumables to the public and private health facilities. The private health facilities were also provided with furniture, and their laboratory rooms and sputum collection points were renovated. The staffs at health facilities selected for DOTS were trained on recording and reporting as well as on the use of data for program improvement. Additionally, selected DOTS health facilities were renovated to enable TB infection control measures.

The diagnostic capacity of the health facilities was strengthened through the implementation of TB microscopy in each facility with laboratory capacity and through the design of a decentralized external quality assurance system. The support included training laboratory personnel, providing standard registers, supplying reagents, and providing quarterly supportive supervision and on-site technical support.

The NTP also introduced the contact investigation strategy in 2013, which was implemented in Kabul under urban DOTS. The household contacts of index cases were screened for symptoms of TB and tested through chest X-ray and sputum examination. The NTP defines an index case as a bacteriologically confirmed pulmonary TB case that results in infection or disease among contacts. The households of index cases defined as close contacts (a person living in the same household with the index case [e.g., the caregiver of the child] or in frequent contact with the index case) are verbally screened for the signs and symptoms of TB. If symptomatic, they are tested for TB (sputum examination and chest X-ray) and the health care workers apply standard procedures for TB case finding and treatment.

Children under the age of five were screened with chest X-ray and the Mantoux test to diagnose TB. Children who were symptom-free and were not diagnosed with TB received preventive therapy with isoniazid 10 mg/kg (administered daily for six months to prevent the risk of developing TB illness) (NTP, Guidelines for National TB Control, 2015). The health workers conduct symptomatic screening of all family members for TB signs and symptoms with the following actions: They identify the children under the age of five, both sick and healthy. If the children are not symptomatic, they apply isoniazid preventive therapy for six months. If they are symptomatic, the standard operating procedure for TB case finding among children is applied (Fig 1).

The NTP also instituted a quarterly monitoring mechanism to monitor the stock of drugs and reagents at the facility and national levels. Regular supervision and monitoring visits were conducted to verify the clinical quality of diagnosis and treatment. The facilities' performance was compared to pre-set targets and reviewed during quarterly workshops. During the workshops, the facilities received feedback on their performance, and recommendations were followed up through regular visits to health facilities.

Finally, after a performance review of facilities covered by DOTS, they were moved to the next step of development. As per guidelines for TB control in Afghanistan and standard operating procedure for TB diagnosis and treatment, TB patients are followed by either health care providers or treatment supporters from the community. This includes ensuring follow-up examination at the end of month two or three and month five and the end of treatment and contact with TB patients who are in isoniazid preventive therapy to promote adherence to treatment. Also, if a TB patient moves to another city or facility during treatment, the referring facility reports the treatment outcomes to the refer-out facility.

The MOPH provided overall leadership of health service delivery in DOTS implementation in Kabul and authorized the public and private facilities to implement DOTS by signing a memorandum of understanding with each of the facilities, registering each facility with the HMIS, and issuing a unique code. The NTP's role was to ensure that these facilities

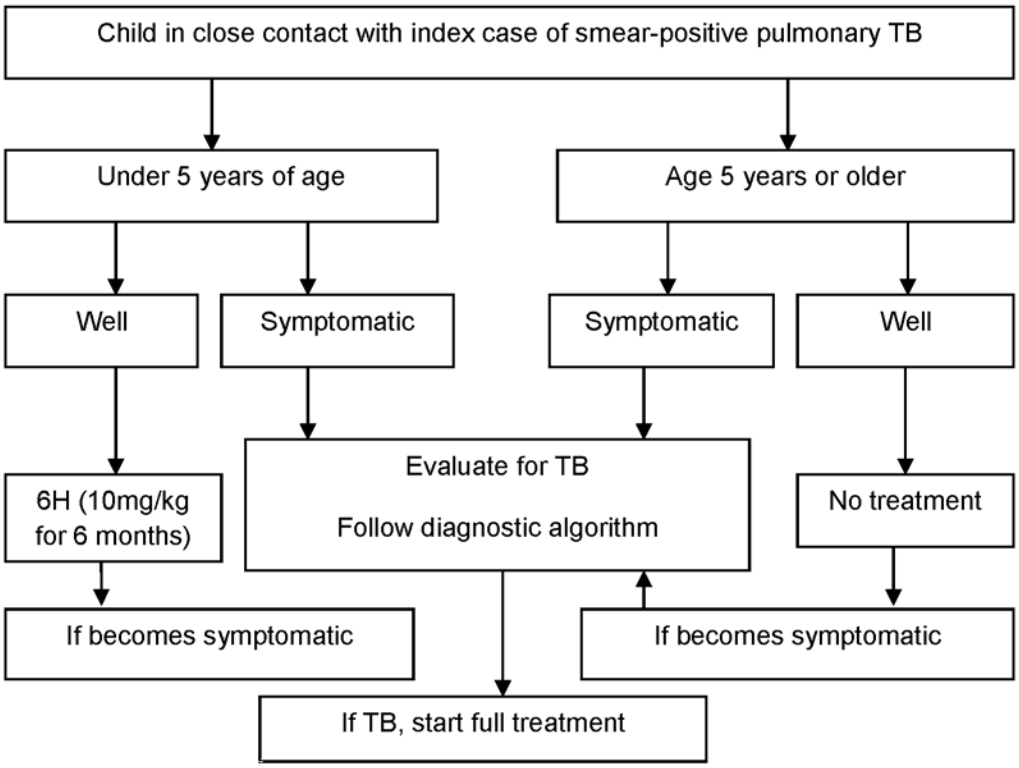

Fig 1. Algorithm for screening children in contact with an index case.

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implement the national TB guidelines and standard operating procedures for TB case finding and treatment. The NTP also ensured the supply of drugs, reagents, and other consumable to these facilities through the provision of supportive supervision and monitoring of TB activities. The USAID-funded TB projects provided technical assistance to the NTP and public and private facilities to ensure that activities are implemented as planned and that the facilities had sufficient technical and diagnostic capacity. The role of the private and public sectors was to provide free TB services and apply the NTP standards and guidelines for diagnosis and treatment, contact investigation, TB infection control, and the TB information system, procure manuals, and identify and refer drug-resistant TB cases to the NTP for further investigation.

Data collection and analysis

The data used in this analysis were collected from health facilities by using standard NTP recording and reporting forms. Frequencies, proportions, ratios, rates, and 95% confidence intervals were used to describe treatment outcomes and case notifications. Case notification rates (CNRs) were computed using the projected population for each year. Given that Afghanistan has very low HIV prevalence, HIV patients were not included in our calculations.

Ethics statement

We used routine programmatic data for this analysis and thus no ethical approval was sought. The urban DOTS implementation was planned and implemented with the leadership of the

NTP. The NTP reviewed and approved the manuscript for publication in a peer-reviewed journal.

Results

Building the capacity of health workers and expanding DOTS

Using the new NTP guidelines and standard operating procedures, 681 physicians, laboratory technicians, and nurses from health centers and private and public hospitals were trained on DOTS. Between 2009 and the end of 2015, the number of DOTS health facilities increased from 22 to 85 facilities owned by the MOPH, other governmental agencies, the private sector, and the Afghan Red Crescent Society. The initiation of DOTS in 85 health facilities in Kabul decreased the population covered by each DOTS facility from 1 facility per 148,636 population in 2009 to 1 per 51,411 population in 2015. A TB patient referral system from community volunteers and lower-level health facilities to the DOTS centers was established. The lower-level health facilities identify presumptive TB cases and refer them to upper-level health facilities (diagnostic centers). After diagnosis, people with TB are referred back to their locality to begin treatment. Another accomplishment between 2009 and 2015 was an increased number of laboratories providing microscopy services, from 106 to 132 (Table 1). Finally, all visitors to health facility outpatient departments were screened for TB using the NTP's standard operating procedures for case detection.

Case notification rate of new TB cases and treatment outcomes

A total of 24,619 of all forms of TB cases were detected in Kabul from 2009 to 2015. Among the detected cases, 8,025 (32.4%) were SS+ TB (Fig 2). The CNR for all forms of TB improved from 59 cases per 100,000 population to 125 cases per 100,000 population between 2009 and 2015 respectively. The CNR for SS+ TB also increased from 25 cases per 100,000 population to 33 cases per 100,000 population for the same period (Fig 3).

The TSR for all forms of TB increased from 31% in 2009 to 67% in 2015. Likewise, the TSR for SS+ TB cases improved from 47% in 2009 to 77% by the end of 2015. The SS+ TB cure rate also improved, from 47% to 68%. The not-evaluated rate for 2009±2015 remained high, but it decreased from 62% to 24%. The not-evaluated rate for SS+ TB decreased from 44% in 2009 to 16% in 2015. During the seven-year period, the death rate was constant at 2%, and the lost-to-follow-up rate was consistently between 4% and 6%. The treatment failure rate remained low (1%) (Table 1, Fig 4).

In 2009 there were no reports of TB diagnosis and treatment in private health facilities. In 2010, among the 40 private health facilities, 10 (25%) were willing to start DOTS. By 2015, 26 (46%) of the 56 private health facilities were implementing a full DOTS program. Among the diagnosed cases of all forms of TB during the seven-year period, 1,797 (7.2%) came from the private sector. Interestingly, the TSR for all forms of TB was better in private health facilitiesÐ at 52% at 2010, 89% in 2014, and 80% in 2015Ðas compared to 67% in public health facilities in 2015 (Tables 1 and 2).

Contact screening. Contact screening of SS+ TB index cases was introduced in the urban TB program in 2013. A total of 14,935 contacts were screened for TB, and 1,377 (9.2%) had presumptive TB. Of these presumptive TB cases, 108 (7.8%) were diagnosed with TB. This makes the yield of TB among contacts 723 per 100,000 population. The private sector registered 707 household contacts and identified 38 as presumptive TB; of those, 37 were tested for TB and 2 new SS+ TB cases were diagnosed. The private sector's overall contribution to contact investigation is 5% for households registered and 2% in TB case notification among contacts screened for TB during 2013±2015.

Table 1. Contribution of urban DOTS to TB service delivery in Kabul city, 2009±2015.

	2009 N (%)	2010 N (%)	2011 N (%)	2012 N (%)	2013 N (%)	2014 N (%)	2015 N (%)
Characteristics							
DOTS coverage							
Total population, Kabul	3.27 M	3.57 M	3.82 M	3.95 M	4.09 M	4.23 M	4.37 M
No. of health facilities	137	145	182	189	192	216	282
Facilities with lab services	106 (77)	111 (77)	111 (61)	112 (59)	120 (63)	131 (61)	132 (47)
Health facilities providing DOTS	22 (16)	48 (33)	53 (29)	68 (36)	73 (38)	80 (37)	85 (30)
No. of private health facilities	NA	40	49	49	50	53	56
Private health facilities providing DOTS	NA	10 (25)	14 (29)	17 (35)	21 (42)	22 (42)	26 (46)
Population per DOTS facility	148,636	74,375	72,075	58,088	56,027	52,875	51,411
Case noti®cation							
Outpatient attendance	232,367	340,394	374,866	412,352	474,205	545,536	627,136
Presumptive TB patients identi®ed/examined	2,856 (0.13)	10,150 (3)	11,900 (3)	13,644 (3.3)	14,181 (3)	17,061 (3)	17,525 (3)
TB cases noti®ed(all forms)	1,934 (31) (SD = 38.7, CI = 16.2)	2,738 (41)	2,728 (38)	3,215 (43)	3,548 (46)	5,007 (63)	5,449 (66) (SD = 23.4, CI = 4.9)
New SS+ TB cases noti®ed	871 (32) (SD = 16.1, CI = 6.7)	1,022 (36)	1,082 (36)	1,174 (38)	1,204 (37)	1,280 (38)	1,449 (42) (SD = 9, CI = 1.9)
Case noti®cationrate per 100,000 population (all forms)	59	77	71	81	87	118	125
Case noti®cationrate per 100,000 population (SS+)	25	29	28	30	29	30	33
Treatment outcomes (all forms TB)							
Treatment success rate	601 (31)	1,305 (48)	1,695 (62)	2,069 (64)	2,369 (67)	3,186 (64)	3,651 (67)
Not evaluated	1,206 (62)	1,184 (62)	791 (29)	889 (28)	893 (25)	1,418 (28)	1,308 (24)
Lost to follow-up	86 (5)	158 (12)	166 (6)	169 (5)	194 (5)	313 (6)	327 (6)
Treatment failed	7	38 (1)	14 (1)	30 (1)	25 (1)	23 (1)	54 (1)
Died	34 (2)	53 (2)	62 (2)	58 (2)	67 (2)	67 (1)	109 (2)
Treatment outcomes (new SS+ TB)							
New SS+ TB started on treatment	814 (94)	1,022 (100)	1,082 (100)	1,174 (100)	1,204 (100)	1,280 (100)	1,449 (100)
Cured	382 (47)	531 (52)	682 (63)	740 (63)	783 (65)	845 (66)	985 (68)
Treatment success rate	382 (47)	634 (62)	736 (68)	821 (70)	879 (73)	947 (74)	1,116 (77)
Not evaluated	358 (44)	297 (29)	248 (23)	258 (22)	229 (19)	230 (18)	233 (16)
Lost to follow-up	50 (6)	61 (6)	65 (6)	59 (5)	60 (5)	77 (6)	72 (5)
Treatment failed	8(1)	10 (1)	11 (1)	12 (1)	12 (1)	13 (1)	14 (1)
Died	16 (2)	20 (2)	22 (2)	24 (2)	24 (2)	13 (2)	14 (1)
***TB cases diagnosed among children* < 15**	180 (9)	235 (9)	198 (7)	238 (7)	383 (10)	1,317 (26)	1,080 (120)
Contact investigation							
Index cases (BC) investigated	NA	NA	NA	399	571	809	1,208
Contacts (symptomatic) screened for TB	NA	NA	NA	1,994	2,855	4,046	6,040
Contacts presumed to have TB	NA	NA	NA	195 (10)	219 (8)	318 (8)	645 (11)
TB cases noti®edamong contacts	NA	NA	NA	18 (1)	14 (0.5)	23 (0.6)	53 (1)
Children < 5 among contacts	NA	NA	NA	415 (42)	580 (100)	678 (84)	836 (69)
Children < 5 put on IPT	NA	NA	NA	119 (29)	495 (85)	519 (77)	767 (92)

SD, standard deviation; CI = con®dence interval.

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Childhood TB. A total of 2,509 (67%) children under the age of five were registered as contacts and 2,004 (80%) were screened for TB. Of those found to be negative for TB, 1,900 (76%) were put on isoniazid preventive therapy (Table 1).

A total of 3,631 children under the age of 15 were notified in seven years. The number of children diagnosed as compared to the rest of the age groups was 180 (9.3%) in 2009; in 2015 the number increased to 1,080 (19.4%) (Table 1).

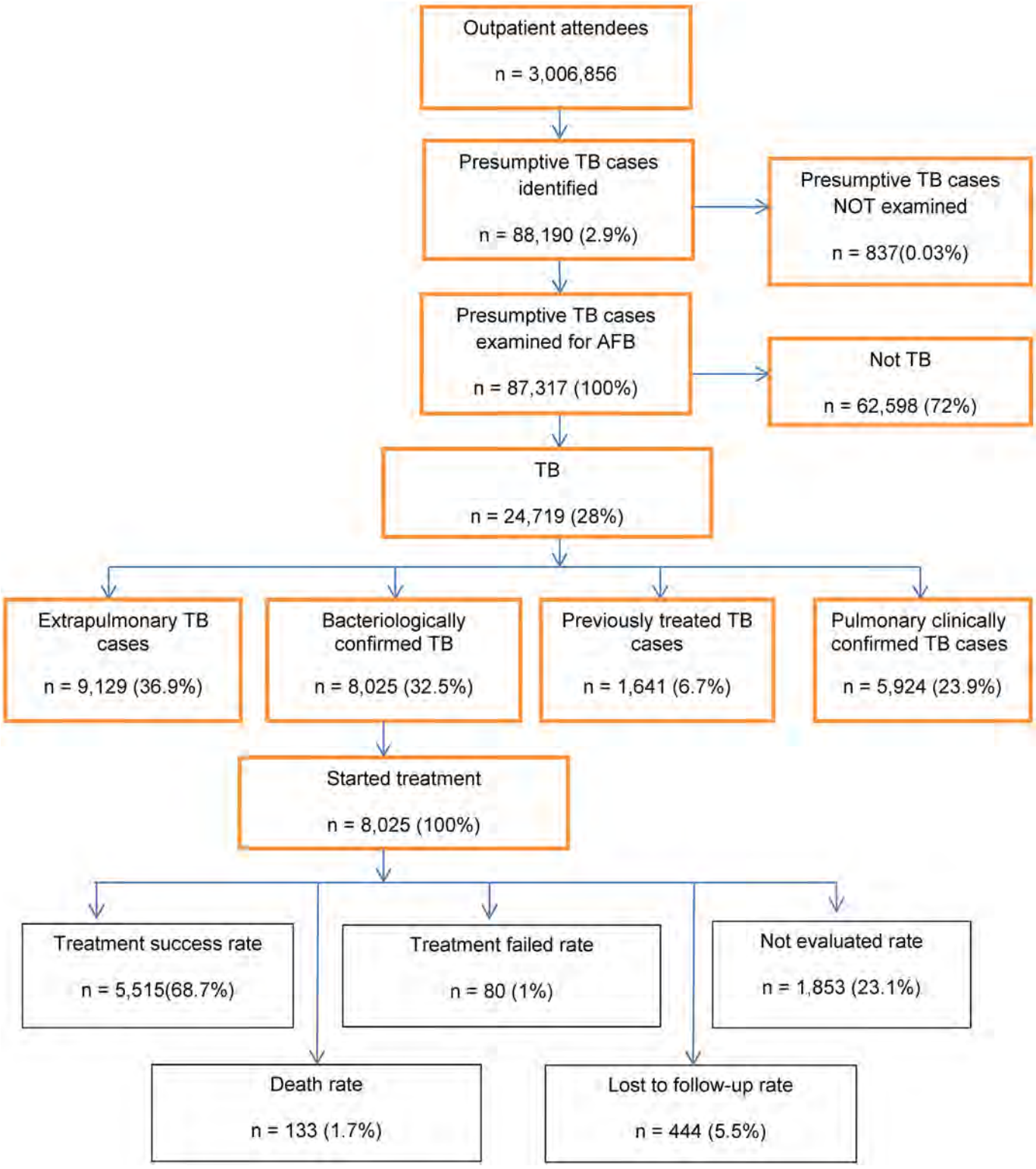

Fig 2. Flow chart of TB case notification and treatment outcomes in Kabul, 2009±2015.

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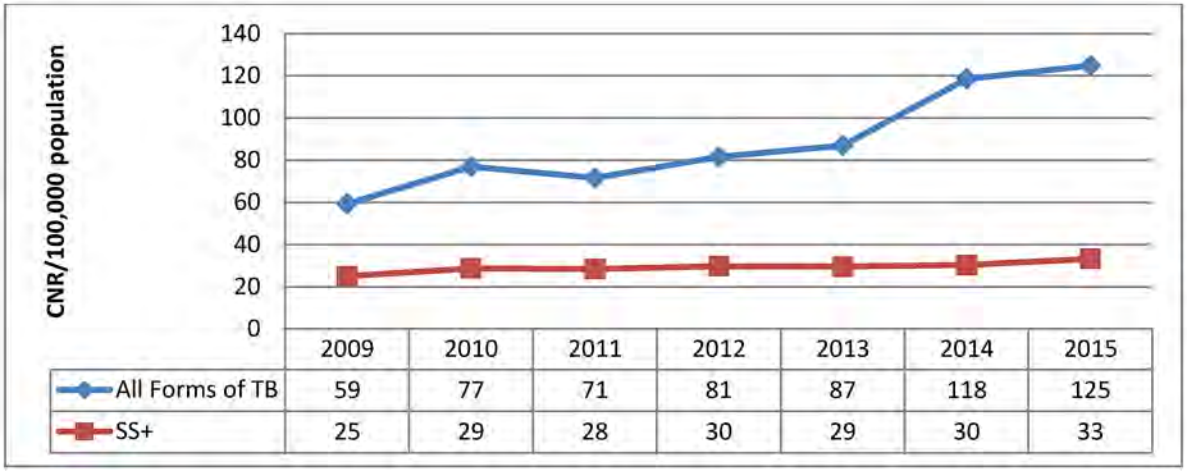

Fig 3. Case notification rate per 100,000 population in Kabul, 2009±2015.

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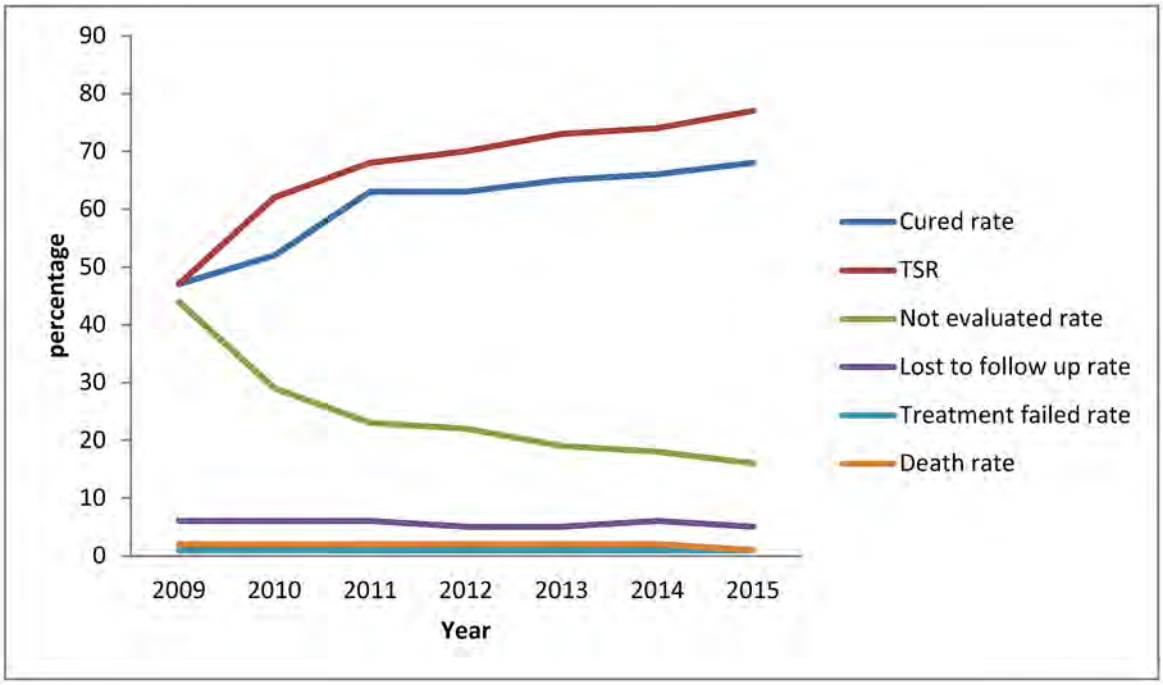

Fig 4. Treatment outcomes for SS+ TB, Kabul, 2009±2015.

https://doi.org/10.1371/journal.pone.0178053.g004

Table 2. Treatment outcomes in private facilities, 2009±2015.

	2009 N (%)	2010 N (%)	2011 N (%)	2012 N (%)	2013 N (%)	2014 N (%)	2015 N (%)
Characteristics	0						
All forms TB cases noti®ed	NA	120	182	267	213	410	605
Treatment success rate	NA	63 (52)	166 (91)	175 (66)	147 (69)	363 (89)	482 (80)
Not evaluated rate	NA	31 (26)	1 (0.5)	69 (26)	38 (18)	0 (0)	21 (4)
Lost to follow-up rate	NA	2 (1.5)	9 (5)	9 (3)	7 (3)	29 (7)	48 (8)
Treatment failure rate	NA	1 (1)	0 (0)	1 (0.5)	1 (0.5)	0 (0)	0 (0)
Death rate	NA	2 (1.5)	1 (0.5)	5 (2)	1 (1)	10 (2.5)	16 (3)

https://doi.org/10.1371/journal.pone.0178053.t002

Discussion

The data from Kabul provide operational and epidemiological evidence that implementation of the urban DOTS program between 2009 and 2015 resulted in significant improvements in TB service expansion, case finding, and treatment outcomes in a country experiencing ongoing conflict. The data show that the NTP and partners such as USAID, Japanese International Cooperation Agency, Global Fund to Fight AIDS, Tuberculosis and Malaria, and WHO were able to more than double the number of DOTS-providing health facilities in Afghanistan, leading to an improvement (decline) in the population-to-DOTS facility ratio of more than 50%. At the same time, the CNR for all forms of TB increased from 59 cases per 100,000 population in 2009 to 125 cases per 100,000 population in 2015, and the number of SS+ TB cases per 100,000 population rose from 25 to 33. The program also led to significant improvement in the CNR for both all forms of TB and SS+ TB. Improvements can be attributed to integrated urban community-based TB screening, health facility±level screening of all outpatient department visitors, contact screening strategies, and better diagnostic capacity because of strengthening of the TB laboratory network in Kabul.

It should also be noted that many patients from adjacent provinces and throughout the country prefer to travel to Kabul to see more qualified health professionals and receive better diagnostic services. It is evident from the data that the transfer-out rate within the not-evaluated rate is very high even though it gradually decreased because patients were referred back to their localities before they started treatment. Regardless, the number of patients travelling to Kabul was high and this may have inflated the CNR (since the denominator to calculate the CNR is only the Kabul population).

The significant increase in the number of pediatric TB cases from 383 cases in 2013 to 1,317 in 2014 (a threefold increase in one year) could be attributed to the implementation of a project for pediatric TB in select children's hospitals in Kabul. Additional analysis is required to confirm if the data reflect the real pediatric TB situation in Kabul.

Per the 2015 WHO estimates, TB prevalence in Afghanistan was 340 cases per 100,000 population [7] and if we assume the urban prevalence is the same as that of the national level, more than half of the TB patients in Afghanistan are missed. Interventions to increase case detection should be prioritized to address the large number of estimated missed TB cases every year. Case detection should be prioritized through a multi-level approach, starting with increasing strategic investments for TB control; scaling up the use of new technology (digital X-ray machines and GeneXpert), with an emphasis on TB hot spots and high-risk populations (contacts, children, prisoners, health workers, diabetics, and people in congregate settings and slums); and addressing barriers to health-seeking behaviors within the community. The country currently relies heavily on smear microscopy. This approach limits the capacity to diagnose smear-negative patients and multidrug-resistant TB cases.

Another significant achievement of the urban DOTS program in Kabul is an increase in the TSR for all forms of TB from 31% in 2009 to 67% in 2015. In 2015 the national TSR was 87% [1], a rate that is higher than that of Kabul City. The improved TSR resulted from increased access to TB services, free treatment, and improvements in the delivery of directly observed treatment (DOT) services provided by nursing staff in DOT-specific areas in health facilities, with the involvement of patients' families. The TSR in Kabul remains lower than the national rate due to the large number of patients not evaluated. In reality, many of these patients could have transferred out of the health facility, returned to their homes (outside the city) and continued treatment elsewhere. The TSR also reflects the 2015 death rate (2%), which is higher than the 37 deaths per 100,000 population reported by the WHO [1]. Since the TB services and medical professionals are better in Kabul, many of the patients who come to receive services

are in a critical state. Death rates among critical patients are higher than those of patients diagnosed and treated at early stages of the disease. This fact might have inflated the TB death rate in Kabul City.

In major urban centers in Asia and Africa, different TSRs have been reported. In the urban DOTS expansion in Abia State of Nigeria, the TSR for TB patients in slum areas was 88.5% [8]. It was 88% in Latvia [9] and reported to be more than 90% in Nepal [10]. In another study in urban Pakistan and one in Thailand, TSRs of 64% and 62%, respectively, have been reported [11, 12]. Loss to follow-up is a major challenge in urban areas because many patients start their treatment in urban areas but return to their home areas to continue treatment. In our patients the lost-to-follow-up rate was 5±6% during the seven years, which is lower than the rates reported in Kolkata, India (9.4%) [13] and in a slum area of Nairobi, Kenya (13%) [14].

The proportion of patients not evaluated for all forms of TB decreased from 62% to 24%, while the decrease in the proportion of patients not evaluated for SS+ TB dropped from 44% to 16% between 2009 and 2015. The proportion of patients not evaluated is still high and is the main cause of the lowered treatment success and cure rates. Zhuben et al. reported a higher transfer-out rate of 52.6% in selected health facilities in Kabul [15]. In a different setting in Ethiopia, the transfer-out rate declined from 4% to 1% over the course of five years [16]. The situation in Kabul is different from the other country situations described above because progress has been made in a country experiencing conflict and a high influx of internally displaced people, with the health care system functioning suboptimally.

The yield of TB among contacts was 1%, which is lower than the 2.3% reported in Ethiopia [17]. Two systematic reviews reported 4.5% and 3.1% TB yields in low-income and middle-income countries, respectively [18, 19]. In one study in Pakistan, the yield of TB among contacts was 22.7% [20], which is the highest rate reported.

The introduction of TB index contact screening has also contributed to pediatric TB diagnosis, treatment, and prevention. Contact screening, which was nonexistent at baseline, became fully operational during the project period, leading to the screening of 2,509 children under the age of five, with 67% of them receiving isoniazid preventive therapy. The high yield of TB among contacts in Kabul illustrates the magnitude of the TB epidemic within the general population and within the families of index cases in Kabul. The high yield of TB among contacts further demonstrates the importance of scaling up and sustaining the urban DOTS program.

Our study has several limitations. There has been no TB prevalence survey in Afghanistan that could provide accurate estimates of the burden of TB in the country. For this paper the estimates of the TB burden in Kabul were based on WHO estimations and do not accurately reflect the burden of the disease in the country. The level of uncertainty was great; therefore, an accurate estimate of the burden of TB is required for future studies. Although data from the NTP lack the deductive power required for a formal experiment, they do cover a large population and provide information about numerous indicators. There was no disaggregated data about some of the high-risk populations (e.g., prisoners, nomads), given the operational limitations to access to information about these groups.

Although Afghanistan is affected by continuing conflict, the positive results highlighted in this paper demonstrate the importance of NTP-led urban DOTS interventions supported by multiple stakeholders in improving access to and quality of TB services in a challenging environment. The lead role of the NTP in providing robust technical assistance through externally supported mechanisms, and the engagement of broader health-sector componentsÐincluding other government agencies and the private sectorÐhave been essential success factors. Continued efforts are needed to further improve TB indicators and sustain the achievements of the urban DOTS program in Kabul.

In addition, implementation of the public-private mix has contributed 7.2% of patients notified among all TB cases in Kabul. The urban DOTS program covered private health facilities, whose coverage reached 46% in 2015. Similarly, notified TB cases in the private sector increased from 120 in 2010 to 605 in 2015. The TSR increased from 52% in 2010 to 80% in 2015 and the not-evaluated rate decreased from 26% in 2010 to 4% in 2015. The results in private health facilities are better than in public health facilities. Intrinsic and extrinsic factors motivate the private sector to perform well. Intrinsic motivators could include managing a positive relationship with and receiving recognition from the MOPH, as well as the private sector's ability to attract and retain clients because of the broader (and better-quality) services the private sector provides. Staff in private facilities generally counsel patients better and are sensitive to their needs. In the public health facilities there are no personal gains related to the quality of services. Another reason might be that more educated and wealthier patients are more likely to choose private-sector services. Private health facilities may cater to more Kabul residents because they are more likely to be able to afford private services. The poor who come from the rural areas may have to resort to public health facilities. Extrinsic motivating factors could include support for renovations; trainings; and free reagents and drugs. In Nigeria, however, the contributions of private for-profit health facilities to TB care were lower than those of public facilities [21]. The major reasons for the difference in contributions were that private practitioners are not trained on the national TB guidelines, which was the case in Kabul in 2009 when we started the urban DOTS program. Similar treatment outcomes were observed in private health facilities in Pakistan, where 84% of patients completed treatment [22].

Furthermore, evidence from Dhaka, Bangladesh, suggests that engagement of private practitioners and institutions such as clinics and hospitals contributed to 36% of all forms of TB case finding [23]. The participatory approach used in the current implementation model appears to have made it possible to promote better coordination and collaboration between the public and private health sectors in Kabul. This has led to the private sector applying public health approaches to identify and diagnose TB cases and refer them to health facilities for treatment and follow-up examinations. Furthermore, the private sector has understood the importance of recording and reporting health events and started implementing a TB surveillance system as a routine practice. It also assisted the NTP to use the private sector's significant opportunity to identify and diagnose TB according to NTP and MOPH strategies and guidelines.

Conclusions

Implementation of the urban DOTS model in the densely populated city of Kabul contributed to the institutionalization of TB service delivery within the public and private health sectors. Health facilities in these sectors provided sustainable TB care to their clients, which ultimately improved access to high-quality free TB services. Furthermore, it led to improvements in TB case notification and the TSR in a challenging setting. Based on these successes, it is strongly recommended that DOTS implementation be expanded to other countries and cities in Afghanistan with conditions similar to those of Kabul. The yield of contact screening is also high, and we recommend that it be implemented nationwide. More effort is needed to further improve the treatment success and cure rates in Kabul, which remain lower than the national averages.

Supporting information

S1 File. Case notification Afghanistan 2006±2016.
(RAR)

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The yield of screening symptomatic contacts of multidrug-resistant tuberculosis cases at a tertiary hospital in Addis Ababa, Ethiopia

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Abstract

Background: Early detection and treatment of multidrug-resistant tuberculosis (MDR-TB, resistant to isoniazid and rifampicin) is an urgent global priority. Identifying and tracing close contacts of patients with MDR-TB could be a feasible strategy to achieve this goal. However, there is limited experience with contact tracing among patients with drug-resistant tuberculosis both globally and in Ethiopia. Here we present our findings on the extent of screening symptomatic contacts and its yield in a tertiary hospital in a major urban setting in Ethiopia.

Results: Symptomatic household contacts were identified in 29 (5.7 %) of 508 index cases treated at the hospital. There were a total of 155 family members in the households traced of whom 16 (10 %) had confirmed MDR-TB. At least one confirmed MDR-TB cases was identified in 15 (51.7 %) of the 29 traced households.

Conclusions: Tracing symptomatic contacts of MDR-TB cases could be a high yield strategy for early detection and treatment of MDR-TB cases in the community. The approach should be promoted for wider adoption and dissemination. Larger scale studies should be done to determine its effectiveness and sustainability in similar settings.

Keywords: Contact tracing, MDR-TB, Ethiopia

Background

Multidrug-resistant tuberculosis (MDR-TB, resistant to isoniazid and refampicin) like drug-sensitive tuberculosis (TB) is transmitted through air droplets from infected person and they have a high potential to spread within people who have close contact with infected persons. Close contacts of MDR-TB patients are defined as people living in the same household, or spending long hours a day together with the patient in the same indoor living space. According to the World Health Organization (WHO), the International Union Against Tuberculosis and Lung Disease (IUATLD) and the International Standards of TB Care (ISTC), contacts of patients with multi or extensively drug-resistant TB (MDR/XDR-TB, XDR-TB is MDR-TB and have additional resistance to one of fluoroquinolones and any of the second-line injectables which include kanamycin, amikacin and capreomycin) should be closely followed up to prevent further spread of the bacteria [1, 2]. Close contacts of tuberculosis cases, such as household members, are the most likely to become infected due to intense and/or prolonged exposure to index cases in the weeks to months before diagnosis and treatment initiation [3].

In the absence of molecular epidemiologic data, secondary cases of MDR-TB within a household in an area with increasing incidence of MDR-TB are generally assumed to be the result of within-household transmission [4]. The spread of tuberculosis occurs mainly in settings where prolonged contact between people promotes the transmission from an infectious 'index case' with TB disease to one or several 'contacts'. Contact tracing in general is believed to serve two functions: (1)

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identifies contacts with TB disease so that treatment can be initiated early when disease is more limited—this also serves to reduce transmission and (2) identifies high risk infected contacts who might benefit from either preventive therapy or close observation [5].

As is in many high MDR-TB burden countries, there is little experience with contact tracing of MDR-TB patients in Ethiopia. The main objective of this study was to assess the extent of screening symptomatic contacts in specialized tuberculosis treatment center in Addis Ababa. In this report, we present data on screening symptomatic contacts and its yield at a tertiary TB care center in Addis Ababa. The findings from this study are believed to inform the national MDR-TB treatment implementation plan as well as other similar countries in their effort to roll out MDR-TB treatment services.

Methods

Setting and study design

We conducted this study at St. Peter Tuberculosis Specialized Hospital (SPTSH) from February 2013 to April 2013 in Addis Ababa, Ethiopia. SPTSH was the first hospital to start MDR-TB treatment in 2009. The program was initiated as part of a pilot program with the Green Light Committee (GLC) approval to treat 45 patients. As of November 2012 there were over 508 patients enrolled in the MDR-TB care unit of the hospital [6]. Considering the total treatment period and to see the treatment out-come, we carried out retrospective chart and register review of patients enrolled and treated at SPTSH during the period February 2009–December 2012 to determine the yield and extent of household contact investigation.

Screening contact practice at the hospital

In the hospital, it was a routine work practice to ask all index cases if any household member had respiratory symptoms suggestive of TB. If any symptomatic household members were identified, the index case was encouraged to bring the household member for further evaluation at the hospital. The clinic staff did thorough clinical evaluation of the symptomatic household member including detailed history, physical examination, and laboratory work up as per the national algorithm. Close contacts with no active TB disease were monitored carefully for at least 2 years. In particular, careful and close follow-up was encouraged for infants and children under 5 years of age. Those contacts with no signs and symptoms suggestive of active TB were educated about the signs and symptoms of TB, about their contact with an MDR-TB index case and about the importance of seeking treatment urgently if they develop signs and symptoms of TB disease. Follow up monitoring was done every 1–2 months. For contacts from Addis Ababa and nearby towns, community team members composed of a health officer and a nurse did 1–2 monthly home visits. Those contacts who came from outside Addis Ababa were encouraged to visit the clinic every 1–2 months.

Data collection

We used secondary data abstraction form for data collection. We did data collection at two stages—first for the index cases and then for the contacts. For each index case we used the MDR-TB register as data source. The register contained the following variables: age, gender, marital status, employment status, whether the patient had MDR or XDR-TB, vital status within the last 24 months (as alive or dead), HIV status, and whether contacts were traced/screened. For contacts who were screened, detailed information was recorded in a separate Contact Tracing Form. Data recorded in the Contact Tracing Form included a list of all household members and their age, sex, symptoms, physical findings, HIV status, sputum microscopy, chest X-ray, and actions taken. Two health officers and four nurses who were working at the MDR-TB care unit collected the data by reviewing each patient's chart and register of patient files at the MDR-TB centers. A two-day training was given for all data collectors. Data quality was controlled through continuous supervision by one of the authors (AT) during data collection. All completed data collection forms were examined for completeness and consistency during data management, storage and analysis.

Data entry and analysis

We used EPI-INFO version 3.3.1 and SPSS version 16.0 for data entry and analysis respectively. A descriptive analysis was performed by calculating proportions. The median and inter-quartile- range were calculated to measure variability of quantitative variables. Results were analyzed with the outcome being whether contact tracing was performed. Categorical variables were compared using the χ^2 test. *Odds ratios* (OR) and confidence intervals to 95 % (CI) were calculated as a measure of association. The variables found to have a p value ≤ 0.2 on a bivariate analyses were further analyzed using the logistic regression, step wise technique. A p-value of <0.05 was considered statistically significant.

Ethical considerations

The study was approved by the Institutional Review Board (IRB) of the College of Health Sciences, Addis Ababa University. Following the approval, official letter of co-operation was written to St. Peter TB specialized hospital by the School of Public Health. The ethical committee of St. Peter TB specialized Hospital reviewed the protocol and agreed on the study. Since the study was

conducted through review of medical records, no invasive procedures were involved. To preserve the confidentiality, nurses and health officers working in MDR-TB clinic of the hospital extracted the data from the medical records. Moreover, no personal identifiers were used on data collection form. The recorded data was not accessed by a third person.

Operational definitions

Index case—the initially identified case of MDR-TB.

Contact case—a person who shared the same enclosed living space.

Results

Baseline information

We reviewed the records of 508 index cases. Their median age (interquartile range, IQR) was 27 years (23–35). Over a half (52 %) were men, 54 % were married and 41 % had secondary level of education. Only four (0.8 %) out of 508 index cases had history of previous exposure to confirmed MDR-TB or TB patient and majority of index cases were retreatment patients that received treatment either of first line anti TB drugs of WHO treatment category regimen previously. In the study population, 410 (80.7 %) were HIV negative, ninety eight (19.3 %) of confirmed MDR-TB index cases were also HIV positive, 87 (88.8 %) of whom started ART including four on second line ART regimens (Table 1).

Table 1 Baseline and socio demographic characteristics of index cases, St. Peter TB Specialized Hospital, 2013

Characteristics	Number (n = 508)	%
Age group		
<15	10	2
15–24	162	31.9
25–34	198	39
35–44	70	15.6
45+	59	11.7
Sex		
Female	244	48
Male	264	52
Marital status		
Single	287	56.5
Married	200	39.4
Undocumented	21	4.1
Educational level		
No formal education	44	8.7
Formal education	380	84.7
Undocumented	34	6.7
Exposure to MDR-TB patient		
Yes	4	0.8
No	504	99.2
Events		
Cured	93	18.3
On follow up	321	63.2
Drop	20	3.9
Died	53	10.4
Undocumented	21	4.1
HIV status		
Positive	98	19.3
Negative	410	80.7
Index cases traced		
Yes	29	5.7
No	479	94.3

Characteristics and yield of contacts screened in the household

A symptomatic household contact was identified in 29 of 508 (5.7 %) index cases. Household screening and follow up was undertaken in these 29 symptomatic contacts. At least one confirmed MDR-TB case was identified in 15 of the 29 symptomatic contact traced households. The household contacts of the index cases were identified via the medical records of the index cases and through interviews; symptomatic contacts or family members identified on the screening form and attached with the respective index case file. Of 155 household contacts screened, 16 (10.3 %) were found to have MDR-TB. Of the 16 confirmed cases, 15 had already been started on treatment at the time of chart review; eight have shown improvement, three died, two of them were HIV positive and the outcome of five patients were not documented. The family size in the traced households ranged from 2 to 14. Nine (6 %) of the screened household contacts had previous history of TB treatment and four of the sixteen confirmed MDR-TB contact cases had previous history of TB treatment. From the sixteen confirmed MDR-TB contact cases, 13 (81.25 %) were also diagnosed for pulmonary TB (Table 2).

Factors associated with developing MDR-TB

The number of contacts traced for MDR-TB was too small to identify associated factors. However, we identified some degree of associations on univariate analyses. The odds of developing MDR-TB was five times [OR: 5, 95 % CI: 1.03, 24.279], higher among contacts from Addis Ababa as compared to the odds of contacts from other regional towns. Similarly the odds of developing MDR-TB was five times higher among contacts that received previous TB treatment [OR: 5.3, 95 % CI: 0.86, 32.02] as compared to those who didn't receive previous TB treatment. From the confirmed contacts of MDR-TB, the odds of developing MDR-TB was 0.33 less likely among HIV positive contacts as compared to HIV negative [OR: 0.33,

Table 2 Characteristics of index cases for whom contacts were identified, St. Peter TB Specialized Hospital, 2013

Characteristic	Number (n = 29)	%
Age group		
14–24	16	55.2
25–34	9	31
35–44	3	10.3
45+	1	3.4
Sex		
Female	20	69
Male	9	31
Familial position of the index case		
Mother/father	2	6.9
Sister/brother	12	41.4
Wife/husband	7	24.1
Child	4	13.8
Cousin	4	13.8
Place of living		
Addis Ababa	14	48.3
Out of Addis Ababa	15	51.7
Number of MDR-TB cases per household		
One	14	48.3
Two	12	41.4
Three	3	10.3
Number of symptomatic contacts who developed MDR-TB per household		
One	14	44.8
Two	1	3.4
None	14	44.8

95 % CI: 0.06, 1.74]. Sex of contacts compared on bi varate among contacts confirmed MDR-TB and the odds of female was three times higher compared to the odds of male [OR:3, 95 % CI: 0.58, 15.61].

On multivariate analyses none of the variables found to be statistically significant.

Discussion

In this study, we found a high rate of confirmed MDR-TB cases among symptomatic household contacts of MDR-TB index cases. ONE IN TEN of the family members in the traced households had MDR-TB. The overall rate of contact tracing, however, was low and it focused on the symptomatic ones only. The study suggests that active tracing of symptomatic contacts of index MDR-TB cases could contribute to prompt identification and treatment of MDR-TB cases. This could be a highly effective strategy in saving more lives as well as in cutting the chain of the transmission in the community. Many risk factors for the development of MDR-TB have been reported among contacts. In our study, we considered variables such as place of living, previous history of TB treatment, HIV status, sex, age, number of confirmed MDR-TB in the house, and number of family traced.

As genetic studies were not performed, this study could not ascertain whether or not the source of infection was the index case. However, there is considerable evidence to support human-to-human MDR-TB strain transmission. Indeed over half of global MDR-TB cases are thought to result from primary transmission [7]. Moreover, our finding is similar to findings from a cross sectional study conducted in India among contacts of MDR-TB patients which showed high proportion of MDR-TB cases among contacts of MDR-TB index cases [8].

Although studies have shown that household contacts with TB are likely to have acquired infection independently in high-incidence settings, there are no published estimates of the probability that two household members with multidrug-resistant TB share a similar genotype and are members of the same transmission chain. Molecular epidemiologic data from households with more than one MDR-TB case can help shed light on the transmissibility of highly drug-resistant disease and also help guide public health policy. For example, international guidelines for the management of known contacts of MDR-TB patients recommend an empirical drug regimen based either on the drug-resistance profile of an isolate from the suspected index MDR-TB case-patient or on the most common drug-resistance pattern in the community while drug sensitivity tests are pending [9, 10]. Since this is the first report of the yield of MDR-TB contact investigation from Ethiopia and among few from the developing world, it provides useful information that can serve us input for planning contact investigation at larger scale.

The high rate of MDR-TB cases among traced household contacts suggests the need for improved TB control measures. The data calls for improved infection control measures, implementation of rapid diagnostics, and enhanced active screening strategies. This was suggested by others as well. A cross sectional study conducted in India among contacts of MDR-TB patients, for examples, showed from the total 302 contacts of 58 index MDR-TB patients traced 16 (5.29 %) developed TB and two (0.66 %) had MDR-TB. The study concluded that evaluation of contacts of MDR-TB case may lead to early diagnosis and prevention of tuberculosis [11].

Few studies have examined the burden of active disease in close contacts of MDR-TB patients [12–14]. A Brazilian study reported that the prevalence of TB infection and progression to active TB was comparable in close contacts of MDR-TB and drug-susceptible TB patients, despite the longer duration of exposure of contacts in patients with MDR-TB. Another study by Ottmani S et al. showed high proportion of index case contacts developed

tuberculosis and the authors concluded that performing contact investigation as a routine activity of the national TB programme was feasible and useful in low–middle-income countries [15].

Whether only symptomatic contacts could be screened as a first stage in scaling up contact tracing in low and middle income countries is an possible consideration arising from our study. This would make contact tracing more feasible in resource limited settings given the burden of disease. In the systematic review by Shah et al. 8 % of household MDR-TB contacts were found to have MDR-TB. In our study 10 % of symptomatic contacts had MDR-TB. These figures are comparable but have different entry points as most of the studies included in the systematic review/meta analysis included screening of all MDR-TB contacts, not just those with symptoms. It may be that it is only necessary to screen symptomatic contacts [16].

Earlier diagnosis of MDR-TB remains a significant programmatic objective because of in this setting where close contacts of MDR-TB cases, such as household members, are the most likely to become infected, due to intense and/or prolonged exposure to index cases in the weeks to months before diagnosis and treatment initiation. Our study highlights the high proportion of MDR-TB in household contacts of MDR-TB cases. Dhingra et al. reported a 53.5 % prevalence of TB infection of disease in household contacts in their study group compared to 44 % in the general population [17]. A better understanding of the relative importance of intra household or community transmission may help to inform the choice of empirical regimens [18].

There are several limitations in the study. First, the small sample size of drug-resistant contact cases available for analysis of associated factors and contacts with active TB (only with cough symptom) did not allow for making valid conclusions as to factors associated with MDR-TB among household contacts. Second, data on several determinants for MDR-TB disease were absent from analysis because they were not in the routine registers and charts of the patients. Third, we considered only household contacts and not other casual or close contacts. Fourth, the investigation considered only recorded household contacts, were not able to find each household contact. Finally, the lack of molecular typing data which could help determine whether the drug susceptibility profiles between index and contact cases were from strains with the same genotype or not.

Conclusions

Tracing symptomatic close contacts of MDR-TB cases could be a high yield strategy for early detection and treatment of MDR-TB cases in the community. The approach should be promoted for wider adoption and dissemination. Larger scale studies should be done to determine its effectiveness and sustainability in similar settings.

Authors' contributions

AT carried out the conception and design, or acquisition of data, or analysis and interpretation of data and also drafting the manuscript. DJ reviewed the manuscript for important intellectual content, participated in the design of the study and helped to draft the manuscript. FE reviewed the manuscript for important intellectual content, participated in the design of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical guidelines

Competing interests

The authors declare that they have no competing interest.

Financial competing interests

In the past 5 years there are no received reimbursements, fees, funding, or salary from an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future. There is no organization financing this manuscript (including the article-processing charge). The authors do not hold stocks or shares in an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future. Currently we are not applying for any patents relating to the content of the manuscript. There are no any other financial competing interests.

Non-financial competing interests

There are no any non-financial competing interests (political, personal, religious, ideological, academic, intellectual, commercial or any other) to declare in relation to this manuscript.

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Epidemiology of tuberculosis in children in Kampala district, Uganda, 2009–2010; a retrospective cross-sectional study

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Abstract

Background: The global tuberculosis (TB) estimate in 2011 was 500,000 cases among children under 15 years representing 5.7 % of all cases and 64, 000 deaths among HIV negative children representing 6.5 % of the total deaths. In Uganda, the child TB cases reported in 2012 made up less than 3 % of the total cases while recent modelling estimates it at 15–20 % of adult cases. Mapping of these cases in Kampala district most especially for the children under five years would reflect recent transmission in the various communities in the district. We therefore conducted a retrospective study of reported child TB cases in Kampala district Uganda for 2009–2010 to provide an estimate of child TB incidence and map the cases.

Methods: This was a retrospective cross-sectional study on data collected from the health unit TB registers in the five divisions of Kampala district, Uganda. The data was a starting point in preparation for a TB Vaccine study in children. The extracted data spanned a period from 1st January 2009 to 31st December 2010. The projected population of children below 15 years was 637,922 in 2009 and 744,750 in 2010 for Kampala district. We based our projections on the National Bureau of Statistics most recent census report of 2002 before the study duration while assuming a population growth rate of 3.7 % each year. We captured the data into EPI DATA 3.1 and analysed it using STATA version 12.

Results: We accessed 15,499 records and analysed 1167 records that were of children below 15 years old. The child TB cases represented 7.5 % (7.3 in 2009 & 7.6 % in 2010) of all the registered cases in Kampala district. The females were 47 % and the median age was 4 years (IQR 1, 10). The percent of children less than 5 years old was 54 %. The percent of pulmonary TB cases was 89 % (1041/1167) with 15 % smear positive. The proportion of extra-pulmonary TB cases was 11 % (126/1167). Among those that tested for HIV, 60 % (359/620) had test results available with an HIV co-infection rate of 47 % (168/359). Antiretroviral treatment uptake was 24 % among the co-infected. The incidence of child TB in Kampala was 56 (95 % CI 50–62) per 100,000 in 2009 and 44 (95 % CI 40–49) per 100,000 in 2010. Most of the TB cases (60 % (410/685)) in Kampala live in slum areas.

Conclusion: There was a higher child TB incidence of 56 per 100,000 in 2009 compared with 44 per 100,000 in 2010. The percentage of child TB cases was much higher at 7.5 % of all the reported TB cases than the WHO reported national average. For the review period, the TB cases clustered in particular slums in Kampala district.

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Background

In 2011, the global TB estimate was 8.7 million incident cases with the African region accounting for 26 % and 1.4 million deaths including 430, 000 deaths among HIV-positive people [1]. The 2011 estimates represented for the first time the expanded inclusion of data in children beyond smear positive cases. In the same report, there were an estimated 500, 000 cases among children under 15 years old representing 5.7 % of all cases and 64, 000 deaths in children 6.5 % of the global deaths [1]. Until the global tuberculosis report of 2012, reported PTB cases were the smear positives and therefore included few children. Children mainly have paucibacillary (low TB germ load) disease so are usually smear negative. Consequent to the paucibacillary nature of TB in children, the true burden of TB disease in children remains uncertain.

A recent mathematical modelling estimated about 650,000 incident TB cases in children under 15 years old in 2010 and about 7.5 Million TB infections [2]. There were however no global estimates for the 2010 incident TB cases in children for comparison. The model further estimated that 4–20 % of global TB cases occurs in children while for Uganda it estimated that 15–20 % the cases should be among children [2]. The challenge of childhood TB diagnosis coupled with misdiagnosis of extra-pulmonary TB contributes to uncertain estimates.

Although TB and HIV epidemics link, the drop of 50 % in HIV infection between 2001 and 2012 [3] does not compare with the 2 % decline in TB incidence between 1990 and 2012 [4]. Most of the TB decline is in South-East Asia specifically China. Uganda has registered a remarkable decline in the prevalence of TB and is on track to meet the Millennium Development Goal (MDG) target [5]. We do not know if the decline is in all communities or a few selected population areas. There is a high risk of TB disease in exposed children most especially those with HIV infection and severe malnutrition [6, 7]. The interplay between TB, poverty and overcrowding [8] leads to varying trends in different populations.

In Uganda, the TB cases reported in children in 2012 made up less than 3 % of the total reported TB cases [4]. There is a high likelihood of TB under-reporting in children because most are diagnosed on clinical basis as opposed to bacteriologically confirmed. We also expect the numbers in children to be a reflection of adult numbers since their TB disease is commonly from adults. Tuberculosis in under fives represents recent transmission reflected in mapping of cases in communities [9]. Until 2012, the World TB reports data for Uganda did not provide information on all forms of childhood TB reported. Age broken down data and TB cases location information is important for targeted interventions and may guide the choice of TB research populations.

The specific objective this cross-sectional retrospective study was to provide an estimate of incidence and distribution of childhood TB in Kampala district, Uganda.

Methods

Study design

This was retrospective study on data collected from health unit TB registers as starting data in preparation for a TB vaccine study in children.

Setting

We collected data from the five administrative divisions of Kampala district. Kampala city, the capital city of Uganda is located in Kampala district. It has an estimated population of 1.5 million by night and much higher by day due to large numbers that come to work. Kampala district is surrounded by Wakiso district from where many people travel to work in the capital city. The district has 62 informal settlements referred to as slums. The district had a projected population of children below 15 years of 637,922 in 2009 and 744,750 in 2010. The projection was from the National Bureau of Statistics 2002 population census report (which was the most recent before the study period) assuming a constant annual population growth rate of 3.7 % [10]. During the study period, TB surveillance in most of the health unit was mainly passive. In the passive surveillance patients present to the health unit for TB related symptoms. In active TB surveillance patients presenting to the health unit for any reason are screened for TB. Active TB surveillance or screening was limited to HIV clinics. There are 52 TB diagnostic and treatment units (DTU) in the Kampala district. Each of the DTUs registers TB cases in the Unit TB registers.

Data source

We reviewed all extracted routine NTLP data from 1st January 2009 to 31st December 2010 from the health unit TB registers in Kampala district, Uganda. Following the clinician's diagnosis, unit TB focal person or TB staff record patient data in paper based unit TB registers. We used the national guideline definitions as adapted from WHO TB guidance of 2006 for case classification during the review period [11]. A case of TB was one with bacteriological confirmation (sputum smear positive or culture) or where a clinician decided to treat for TB. Each TB case is reported as pulmonary TB (smear positive or smear negative or smear not done) or extra pulmonary TB. Since not all children had sputum collected, we included PTB smear not done as a category for intervention purposes. All the TB cases are offered an opportunity to test for HIV as part of the routine tests.

Data management and statistical analysis

We captured the data in EPI DATA 3.1 and analysed using the STATA version 12. We described continuous data using medians with inter-quartile ranges while categorical data as proportions. We present the data in tables and graphs. We only included cases of children residing in Kampala district at registration time to calculate incidence rates for Kampala district.

Ethical considerations

The study received ethical approval from Mulago Hospital Research and Ethics committee and consent obtained from the NTLP of the Ministry of Health. We only extracted non-identifying data.

Results

We accessed 15,499 patient TB records and extracted 1167 records of children less than 15 years for analysis.

Descriptive data

Children accounted for 7.5 % (7.3 in 2009 & 7.6 % in 2010) of all the reported TB cases in Kampala. The median age was 4 years (IQR 1, 10) and the majority (54 %) were under 5 years old with 47 % (548/1167) being females. See Table 1 for other demographic characteristics. Most of the children were 0–4 years making up 54 %, those 5–9 years made up 21 % and the 10–14 years were 25 %. The TB cases residing in Kampala were 59 % while those residing outside Kampala district were 41 % (Wakiso –20 %, elsewhere– 21 %).

Table 1 Demographic characteristics of the children with TB notified in Kampala district, Uganda 2009–2010 ($N = 1167$)

Characteristic		Frequency of TB cases	Percentage
Age group in years	0–4	629	54 %
	5–9	246	21 %
	10–14	292	25 %
District	Kampala	685	59 %
	Wakiso	238	20 %
	Others	244	21 %
Division	Kawempe	172	25 %
	Makindye	139	20 %
	Central	38	5.6 %
	Nakawa	120	17 %
	Rubaga	216	31 %
Sex	Female	548	47 %
	Male	619	53 %
TB type	PTB	1041	89 %
	EPTB	126	11 %
Sputum collected	Yes	456	39 %
	No	711	61 %

Seventy five percent (874/1167) had HIV test counselling, 71 % (620/874) were tested and results were available for 60 % (359/620). More children under five had unknown HIV status than other age groups (57 % vs 48 %). Table 2 shows some other characteristics of children with known and unknown HIV status. Of those children with available results, 47 % (168/359) were HIV-positive. Twenty four percent (40/168) of the children with HIV co-infection were on antiretroviral therapy (ART) while 84 % (141/168) were on cotrimoxazole prophylaxis therapy (CPT).

There were 89 % (1041/1167) PTB cases and 10 % (126/1167) EPTB cases. Among the children with pulmonary TB (PTB), 30 % (308/1041) had HIV test results of which 47 % (144/308) were positive. Among extrapulmonary TB (EPTB) cases, 40 % (51/126) had HIV test results of which 47 % (24/51) were positive. The HIV positivity rate by age groups was; 47 % in 0–4, 59 % in 5–9 and 26 % in 10–14 years. The differences were statistically significant (see Table 3).

Of the PTB cases, 15 % (160/1041) were sputum acid-fast bacilli smear positive, 16 % (170/1041) were sputum acid-fast bacilli smear negative and 68 % (711/1041) had no smear done (no sputum collected). Among those with smear not done, most (68 %) were below 5 years old. There was a higher number of PTB cases with smear not done in 2010 (69 %) compared with 53 % in 2009 as shown in Fig. 1. The smear positive and smear

Table 2 Characteristics of children with known and unknown HIV status notified as TB in Kampala district, Uganda 2009–2010 ($N = 1167$)

Characteristic		HIV test result		
		Known *n* (%)	Unknown *n* (%)	*P* value
Age group in years	0–4	172 (48)	457 (57)	0.023
	5–9	84 (23)	162 (20)	
	10–14	103 (29)	189 (23)	
District	Kampala	210 (59)	475 (59))	0.049
	Wakiso	86 (24)	152 (19)	
	Others	63 (18)	181 (22)	
Division of Kampala district	Central	10 (5)	28 (6)	0.044
	Kawempe	43 (20)	129 (27)	
	Rubaga	74 (35)	142 (30)	
	Makindye	36 (17)	103 (22)	
	Nakawa	47 (22)	73 (15)	
Sex	Female	190 (53)	358 (44)	0.006
	Male	169 (47)	450 (56)	
TB type	PTB	307 (86)	733 (91)	0.011
	EPTB	51 (14)	75 (9)	
Sputum collected	Yes	207 (58)	249 (31)	<0.001
	No	151 (42)	560 (69)	

Table 3 General characteristics of HIV positive and negative children with TB notified in Kampala district, Uganda, 2009–2010 ($N = 359$)

Characteristic		HIV test result		
		Positive *n* (%)	Negative *n* (%)	*P* value
Age group in years	0–4	81 (48)	91 (48)	<0.002
	5–9	51 (30)	33 (17)	
	10–14	36 (21)	67 (35)	
District	Kampala	98 (58.33	112 (58.64	0.989
	Wakiso	40 (23.81	46 (24.08	
	Others	30 (17.86	33 (17.28	
Division	Kawempe	15 (15.31	28 (25.00	0.158
	Makindye	19 (19.39	17 (15.18	
	Central	4 (4.08	6 (5.36	
	Nakawa			
	Rubaga	32 (32.65	42 (37.50	
Sex	Female	88 (52.38	102 (53.40	0.846
	Male	80 (47.62	89 (46.60	
TB type	PTB	144 (85.7	163 (85.8)	0.983
	EPTB	24 (14.29)	27 (14.21)	
Sputum collected	Yes	103 (61.3)	104 (54.7	0.208
	No	65 (38.69)	86 (45.26)	

negative PTB cases as well as EPTB cases decreased between 2009 and 2010 (see Fig. 1). Distribution of the smear positive cases by age group was; 73 % (116/160) among 10–14, 15 % (24/160) among 5–9 and 13 % (20/160) among 0–4 years. Distribution of the EPTB cases by age group was: 36 % (45/126) among 10–14, 37 % (46/126) among 0–4 and 28 % (35/126) among 5–9 years old.

Main study results

The proportion of TB cases in the 0–4 years age group was 52 in 2009 and 56 % in 2010. In the 10–14 years age group the percent was 27 in 2009 and 24 % in 2010 while in the 5–9 years age group it was 21 in 2009 and 20 % in 2010.

The overall child TB incidence in Kampala was 56 (95 % CI 50–62) per 100,000 in 2009 and 44 (95 % CI 40–49) per 100,000 in 2010. The child TB incidences by age group and division also decreased over the study period as shown in Fig. 2.

Most of the TB cases, 60 % (410/685), in Kampala lived in slum areas. The Fig. 3 shows distribution of TB cases by area and division.

Discussion

Main findings

Our findings showed a general decrease in TB incidence with most cases of PTB having no smear done and majority of EPTB cases occurring among adolescents. We found a high rate of smear positive cases of up to 15 %. Our study highlights low HIV test uptake, high absence of HIV test results and large percentage TB cases residing in slum areas in the Kampala district.

Relation to literature

Our findings showed that many cases registered in Kampala district live outside the Kampala administrative borders. The incident cases registered in Kampala district may therefore not represent the true picture of TB burden within the various communities in Kampala district.

We noted a decrease in TB incidence over the review period similar to that in the World TB report 2011 [12]. The report shows a declining trend in TB incidence in adults. This trend should reflect in children as we know that TB cases in children especially those below 5 years represents recent transmission in the community [13, 14]. Previous work showed that up to 30 % of the children with TB will have an identifiable household source case

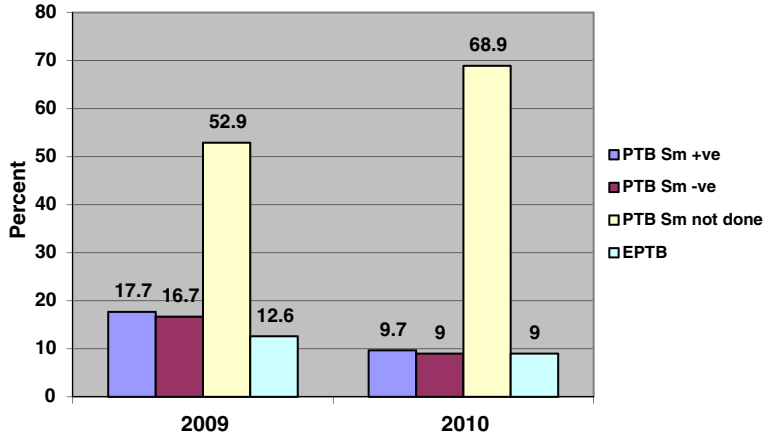

Fig. 1 Distribution of TB types in children in Kampala district, Uganda 2009, 2010 ($N = 1167$)

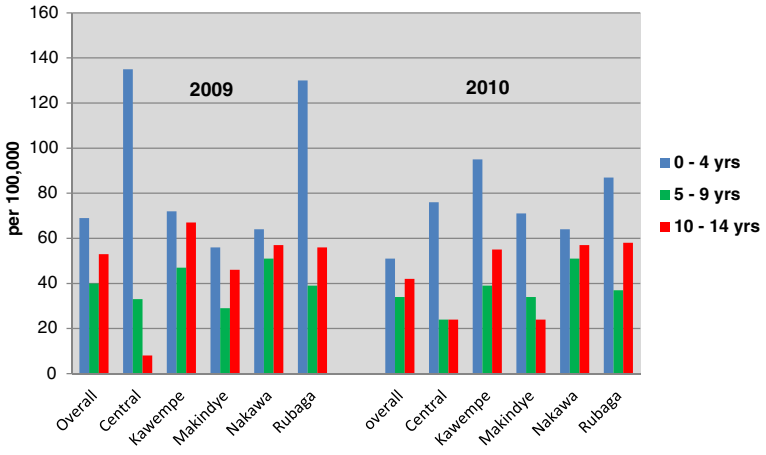

Fig. 2 Childhood TB incidence by age group and division in Kampala district, Uganda 2009, 2010

[15]. Similar to previous reports, our data shows a bimodal distribution with more cases in under five and 10–14 years age groups compared with the 5–9 year olds [16, 17].

Our study found the total number of TB cases had not substantially reduced (the reported TB cases decreased by 8 %) over the review period. The reported decreased incidence may be due to high population growth rate without the proportionate increase in the number of new TB cases. We however report an increased TB incidence in the under fives that we suppose is attributable to improved diagnosis and reporting rather than increasing burden of TB in children. Our report shows that 7.5 % of the TB cases registered in Kampala district were among children. This is much higher than the national average of 1.5 % reported in the world TB report 2013 but less than the estimated expected burden of 15–20 % in the high burden countries [2]. The World TB report 2014 still documented that childhood TB represents 1.5 % of the total cases with no decline in the total number of new cases [18]. We suppose that this discrepancy is due not reporting PTB cases in children with smear negative disease or smear not done. The increased child TB case detection in the under fives is an encouraging finding during this review period. This finding may be a spill over from Tuberculosis control assistance program (TB CAP) activities that included health worker training and provision of tools for TB care [19]. There is evidence that training health workers and provision of the relevant job aids in the diagnosis of children TB increases childhood TB detection rates [20]. Finding more children with no sputum examinations done on the background of several efforts to increase TB detection in children needs innovative ways to cause routine sputum collection from children. The high number of smear not done cases in children is likely due to limited health worker confidence and skills to collect sputum from children. This means most children are diagnosed on

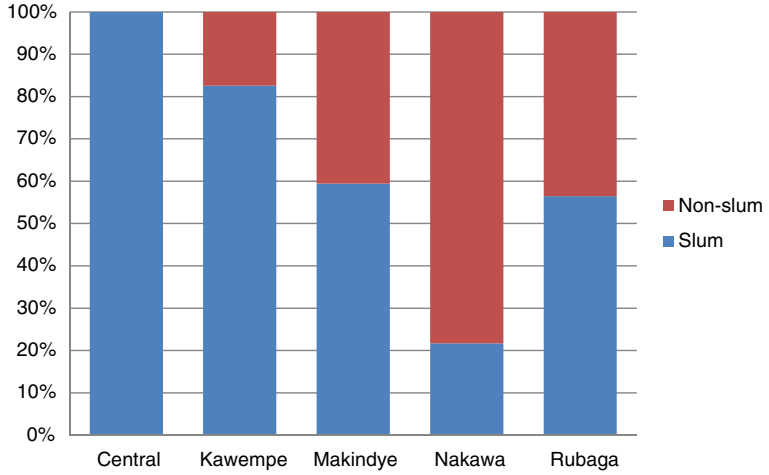

Fig. 3 Distribution of residence of TB cases residing in Kampala District, Uganda 2009–2010 ($N = 685$)

clinical basis with no sputum collection. The reality of multi-drug resistant (MDR) TB makes it even more pressing to build capacity for sputum collection from children.

The lowest TB incidence was in the 5–9 year age group, a safer age group as reported in literature [16]. Most of the childhood TB cases (56 %) were in children below 5 years old. This age group has the highest risk of developing TB disease because of low immunity and other reasons such as malnutrition and HIV [8, 21]. This age group is more likely to get exposure for longer periods to infectious adults within their households [22].

We found most TB cases were pulmonary, a finding reported by other studies [23, 24]. A TB report from Zambia showed that about 72 % of childhood TB cases were pulmonary [25]. Even for the children less than five years old we report more PTB cases than EPTB. Literature reports children are more prone to EPTB most especially if HIV positive [26]. However, we report more cases of PTB than EPTB even when the HIV prevalence was high among the tested patients. We found equal proportions of children with HIV among the PTB and EPTB cases. We expect a higher proportion with EPTB in a population of children with high HIV co-infection and low ART uptake at 24 % on the premise that children are prone to disseminated disease if HIV infected. This finding also reported in other settings [23–25] may be related to training of health workers that mainly focuses on PTB. It is possible the EPTB cases are largely missed. Finding about forty per cent EPTB cases among adolescents is unexpected since at this age there is more TB containment outside the lungs. The available data neither included the sites of EPTB nor provided an explanation for this observation. A study of incident TB cases among adolescents in South Africa found only 3 % had EPTB [27]. The total child TB cases reported in the 2010 and 2011 Global TB reports is 1291 for Uganda while we report 1167 child TB cases for Kampala district alone during the same time period. Our report underpins the reality of child TB under-reporting because of the emphasis on reporting smear positive cases only.

We report an overall smear positivity rate of 15 % among those tested and most of these (72 %) were adolescents 10–14 years. We report a high positive smear rate ranging from 13 % in 0–4 years to 15 % among children 10–14 years. The smear positivity rate among adolescents is similar to the adult smear positivity rate of 20 % reported in Uganda in 2007 [28]. This is not surprising since adolescents get adult type pulmonary disease. We report a smear positivity rate of 13 % among those below 5 years. This suggests that routine use of Xpert® MTB/RIF as recommended in this age group would yield many more bacteriologically confirmed cases in the under fives. The Xpert® MTB/RIF is a hands-free sample real-time PCR analysis system, developed under Cepheid (a molecular diagnostics company), that simultaneously detects mycobacterium tuberculosis (MTB) and resistance to rifampicin (RIF). In our previous study in a research setting, Xpert® MTB/RIF identified twice as many cases as microscopy [29].

The low HIV testing and results availability reported in this paper suggests gaps in integration of TB and HIV services. A similar finding was reported in non-integrated TB and HIV services in South Africa where only 26 % of the TB patients knew their HIV status. In the same report, the number tested for HIV was low at diagnosis compared to at 2 or 6 months while on TB treatment [30].

There were many TB cases residing outside Kampala district but registered and treatment in Kampala. This finding may reflect limited confidence and capacity of health workers outside Kampala district to diagnose TB in children. The likely implication is potential increase in TB transmission by caregivers (who are the likely source of TB) during their travel by public transport to access services in Kampala district. This exposure may vary from as short as 10 min to as long as one hour depending on the traffic flow and distance to the health units in Kampala. We found TB cases clustered in particular areas especially slum areas. Most of TB cases originate from slum areas. This observation may represent ongoing transmission in these areas. A study in high TB incidence urban setting in South Africa found 72 % of the cases were clustered within slum communities [31]. We found similar TB case notifications in the same slum areas over the two years of our report. This suggests the transmission cycle in those particular slum areas is uninterrupted.

Strengths and limitations

This is the first report to document the burden of TB in Kampala from the routine programmatic data. We collected all the data reported in Kampala district during the review period for at least two years. At the minimum this would provide insight on TB epidemiology in children in Kampala district. We conducted this work before availability of Xpert® MTB/RIF in Kampala provides important comparative data in assessing the impact of Xpert® MTB/RIF wide use on TB detection in children.

We acknowledge some limitations to this work. We had two data points (2009 and 2010) which are not enough to show a trend in TB epidemiology constituting a selection bias. There is no comparative published childhood TB data for Kampala district to affirm our the observation as part of a national downward trend of TB incidence in Uganda [18]. We could not confirm the accuracy of the TB diagnoses. We report the bacteriologically confirmed cases based on only sputum smears

which is an under estimate. Work done in South Africa found 22 % of the children with TB were smear negative but culture positive [27]. We used programmatic data that did not capture important aspects of paediatric TB epidemiology such as TB contact history, those on isoniazid preventive therapy and BCG vaccination status. The population projections we used depend on birth rates but for urban settings in Uganda population growth is mainly because in-migrations. Also population projects beyond 10 years become increasingly inaccurate. This is a reasonable explanation for the wide confidence intervals around our incidence estimates. We believe this is the best estimate within our limitations.

Implication for practise, policy and research

This paper highlights the reality of under-reporting of childhood TB where documenting all childhood TB cases would improve the estimates. The sputum collection for TB detection in children was low and there is need to understand the underlying reasons. Assuming limited skills and knowledge of health workers as the explanation for low sputum collection in children may only be part of a larger problem. The finding that many children reside outside Kampala district but are diagnosed and treated in Kampala district requires further study. Contacts of smear positive cases were not captured in the unit TB registers representing missed opportunities for control of TB. The reality of large number of TB cases arising from the same slum areas means that targeted TB control interventions would break this cycle. In this study we noted the TB cases remained clustered in the same slum areas over the review period. The finding that 100 % of TB cases in the central division of Kampala resided in slum areas requires specific TB control interventions at household level. Using private health units in the slum areas to detect and treat TB has proved an effective intervention that is worthy strengthening. The Slum Partnerships to Actively Respond to Tuberculosis in Kampala (SPARK-TB) project showed impact of this approach by being able to identify an extra 1267 smear positive cases [32].

Conclusions

There was a reduction in child TB incidence in Kampala district over the review period. The incidence was 56 per 100,000 in 2009 and 44 per 100,000 in 2010. The number of child TB cases was much higher at 7.5 % of all cases during the review period compared to the national average of 2.5 % in the world TB reports 2010, 2011. There was a high HIV co-infection rate and low antiretroviral uptake over the review period. Pulmonary TB remains the commonest form of TB in children with children below five years bearing the biggest burden. For the review period, the TB cases clustered in particular Kampala district slum areas.

Competing interest

The authors declare that they have no competing interests.

Authors' contributions

EW conceived the research idea, developed the proposal, interpreted the data and wrote the manuscript draft. DL helped to develop the research proposal, collected the data, analysed, interpreted the data and contributed to the manuscript writing. IL helped in developing the research proposal, data interpretation and contributed the manuscript. FM contributed to interpreting and writing of the manuscript. MS contributed to interpreting and writing of the manuscript. PM contributed to interpreting and writing of the manuscript. All the authors read and approved the manuscript.

Authors' information

Not applicable.

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Connectivity of diagnostic technologies: improving surveillance and accelerating tuberculosis elimination

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SUMMARY

In regard to tuberculosis (TB) and other major global epidemics, the use of new diagnostic tests is increasing dramatically, including in resource-limited countries. Although there has never been as much digital information generated, this data source has not been exploited to its full potential. In this opinion paper, we discuss lessons learned from the global scale-up of these laboratory devices and the pathway to tapping the potential of laboratory-generated information in the field of TB by using connectivity. Responding to the demand for connectivity, innovative third-party players have proposed solutions that have been widely adopted by field users of the Xpert® MTB/RIF assay. The experience associated with the utilisation of these systems, which facilitate the monitoring of wide laboratory networks, stressed the need for a more global and comprehensive approach to diagnostic connectivity. In addition to facilitating the reporting of test results, the mobility of digital information allows the sharing of information generated in programme settings. When they become easily accessible, these data can be used to improve patient care, disease surveillance and drug discovery. They should therefore be considered as a public health good. We list several examples of concrete initiatives that should allow data sources to be combined to improve the understanding of the epidemic, support the operational response and, finally, accelerate TB elimination. With the many opportunities that the pooling of data associated with the TB epidemic can provide, pooling of this information at an international level has become an absolute priority.

KEY WORDS: laboratory; connectivity; tuberculosis; surveillance; data

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IN THE PAST DECADE, the use of new diagnostic tests has increased dramatically in the laboratories of developing countries and, more recently, in decentralised point-of-care facilities. Self-contained molecular diagnostic devices have been successfully deployed to detect tuberculosis (TB) (e.g., Xpert® MTB/RIF; Cepheid, Sunnyvale, CA, USA[1]) or monitor treatment for the human immunodeficiency virus (HIV) (e.g., Alere Pima™ CD4, Alere, Waltham, MA, USA[2]) in very basic clinical facilities. Despite the accumulating evidence that these tools can be successfully used in the most challenging environments[3,4] and the establishment of distribution and funding channels that should theoretically allow any country to access and scale up these new technologies, the majority of patients that could benefit from these technical evolutions still do not have access to them. It is clear that the introduction of an improved TB diagnostic tool is not sufficient to assure improved outcomes for patients, as the details of implementation within existing health delivery systems have a critical influence on impact.[5]

We suggest that the introduction of new tools such as Xpert offers an important opportunity to better understand, monitor and improve such delivery systems to assure greatest impact. If the scale-up of novel diagnostic devices can be accompanied by the simultaneous introduction of up-to-date quality indicators and technical connectivity solutions, the vast amount of data generated by this new generation of automates could both simplify and potentiate the global response to the TB epidemic.

On a national and global level, as the quantity of information produced following the introduction of new-generation laboratory instruments was not anticipated, no plans were in place on how to manage the information flow or orient it in such a way that it could generate an evolution in the organisation of the epidemic response. In the absence of adequate laboratory information technology infrastructure, complemented by standardised reporting solutions for screening activities and treatment follow-up, many low-resource countries have continued to use slow, error-prone paper-based recording systems. In such systems, editing and transmission of paper reports cause inherent delays and contribute to the cost, complexity and relative inaccuracy of data interpretation.

Diagnostic e-health solutions have the potential to help overcome some of these problems and maximise the patient and public health impact following the introduction of a particular technology. The combination of this unprecedented evolution of the laboratory landscape and the potential of e-health could be leveraged to generate the revolution in national and global health delivery systems that is needed to achieve TB elimination. Pragmatically, this requires device connectivity, whereby secure testing data and results are automatically sent to repositories, translated into useful information and channelled to appropriate parties. Although device connectivity within other industries has been routine for some time, within the health care community it is still largely in its infancy.[6]

In this paper, we discuss lessons learned from the global scale-up of the first generation of easy-to-connect diagnostic tools[7] and the pathway to tapping the potential of connectivity in the field of TB diagnostics.[8]

EXPERIENCE FROM FIRST-GENERATION CONNECTED DIAGNOSTICS: THE EXAMPLE OF XPERT

During the last decade, several diagnostic companies, such as Cepheid Inc and Alere Inc, have begun developing a new generation of tests essential to fight diseases of poverty such as TB and HIV, with significant support from public and philanthropic funders, including the National Institutes of Health (Bethesda, MD, USA) and the Bill & Melinda Gates Foundation (Seattle, WA, USA).

The Xpert assay, which is run on the GeneXpert platform, was the first truly game-changing test to come out of this research, and it has since been widely distributed in health facilities with limited human and infrastructure resources. The coverage of Xpert varies considerably between countries, with some countries still having only a limited number of machines based in reference laboratories, and others, such as South Africa, that realised the advantages of implementing this novel platform as a first-line test fairly rapidly.[9] In the last 5 years, more than 13 million Xpert tests have been procured worldwide. When GeneXpert was rolled out in 2010, the instrument had no built-in connectivity outside basic standards, and the TB community did not have the software tools to connect to GeneXpert machines and use the data being generated to its full capacity. Valuable information housed in the hard drives of local computers was thus never used to inform surveillance efforts or health care providers, and was largely lost.

In the light of this issue, national TB programmes (NTPs) called for tools to reduce loss to follow-up and improve device and laboratory management, including a better ability to maintain cartridge supplies and local redistribution, and evaluate and fulfil the training needs of device operators and laboratory technicians. Likewise, NTPs voiced a need for connectivity systems that could relieve the high overhead costs of data aggregation and analysis, which hamstring the process of collecting raw data and turning it into useful information.

In 2012, responding to this critical gap in the implementation landscape, innovative third-party players developed connectivity solutions. GxAlert

(ABT, Cambridge, MA, USA, and SystmOne, Horsforth, UK), XpertSMS (Interactive Research and Development, Karachi, Pakistan, and TB REACH, Geneva, Switzerland) and GenXchange (Université Catholique de Louvain, Louvain, Belgium, and the NTP, Kinshasa, Democratic Republic of Congo) were devised to respond to the needs of low-resource countries, where internet is often unavailable or unreliable and laboratory information systems or electronic medical records are not widely used. These tools offered immediate solutions and, in response to national requests, hundreds of local laboratories have since become interconnected on implementing these systems. The scaling of these connectivity solutions has been taken back by dedicated companies (Global Connectivity. Somerville, MA, USA. http://www.globalconnectivity.co/; and Savics. Brussels, Belgium. http://www.savics.org).

Cepheid, the manufacturer of GeneXpert, also worked to enable remote monitoring of their devices in response to expressed national needs and requests from the TB community. Like many developers, Cepheid lacked comprehensive information about what use-cases needed to be supported, and for ethical and regulatory reasons they prioritised data security and confidentiality. As a result, the company launched an initial software tool that was a step forward but was unable to fulfil all NTP needs.

In response, an alliance of key implementation partners, such as USAID (Washington DC, USA), MSF (Paris, France), Clinton Health Access Initiative (Boston, MA, USA) and Foundation for Innovative New Diagnostics (FIND) (Geneva, Switzerland) and donors, such as UNITAID (Geneva, Switzerland) and the Global Fund (Geneva, Switzerland), was formed, led by the World Health Organization (WHO), to work with Cepheid in ensuring secure, open access to critical data and finding a broader, holistic approach to connectivity and data management. An immediate solution was found, and both Cepheid and the alliance remain interested in the creation of a non-proprietary, long-term connectivity platform or a series of integrated and inter-operational platforms. This highlights how the global TB community can collectively define priority needs and work with manufacturers to negotiate and realise solutions for accessing and utilising key data.

Another important lesson from the implementation of first-generation connected diagnostics is the importance of a well-tailored delivery pathway for connectivity software that supports sustainable uptake in a given country. For example, Alere, the manufacturer of Pima™ CD4, devised a country-based public-private partnership model to ensure appropriate training and support for their connectivity software. Without this support and engagement of key stakeholders, many countries would have struggled to make use of the influx of data. While the tool itself has limited wider applicability because of the proprietary nature of the software, the partnership model offers a valuable example of how non-proprietary, interoperable systems could be disseminated and nurtured in the future.

CONNECTIVITY OF DIAGNOSTICS: A SHARED RESPONSIBILITY AND PUBLIC HEALTH NECESSITY

The WHO and research funding agencies have been advocating for, and implementing, data-sharing policies for some time. While these efforts have increased access to synthesised research data, efforts to make NTP data available are in their infancy. The use of new-generation diagnostic platforms has triggered thinking about the potential utility of real-time analysis of national data, and how diagnostic connectivity could further improve epidemiological surveillance and guide targeted public health responses. Accelerated TB elimination, for example, as called for in the WHO End TB strategy,[10] can only be realised if case detection, individual patient management and epidemiological surveillance are intensified simultaneously, and if these efforts are closely monitored and validated. Data generated by Xpert testing can be used both to improve patient management and treatment efforts and to provide important population-level information on average infectiousness as a predictor for TB burden[11] and spread of new mutations. This requires optimised programmatic data management, pooling, sharing, analysis and use. To realise improvements in surveillance and public health demands, the information generated by diagnostic technologies in programme conditions should be easily accessible and usable for national programmes. Ultimately, data access, enabled by diagnostic connectivity, should be seen as a public health good. Countries, international organisations, test developers and civil society organisations have a collective responsibility to work together to ensure sustainable use of information and communications technology to improve health care. In doing so, important questions regarding ethical obligations and data ownership and stakeholder interests, such as market competitiveness, need to be acknowledged and addressed. International collaborative efforts must furthermore address the issue of personal unique identifiers in a context of continuous human migration and data mobility.

THE WAY FORWARD: REALISING THE POTENTIAL OF CONNECTED DIAGNOSTICS

Built-in connectivity has become an evident prerequisite for upcoming diagnostic platforms.[12] Tests that until recently were un-connectable, such as rapid diagnostic tests for, for example, HIV and malaria,

can now be connected to digital readers, with collection of results, storage and transfer (e.g., Fio Corp, Toronto, ON, Canada).

In the field of TB diagnostics, a wide range of complementary laboratory tests are used. This includes rapid diagnostic tests and more conventional approaches such as microscopy, culture, drug susceptibility testing and sequencing.[13] Inter-connecting these diagnostic devices and further integrating this information with clinical indicators is the upcoming challenge for the TB community.

The Connected Diagnostics Initiative (CDx), coordinated by FIND, is an example of a potential solution for accelerating the connectivity and interoperability of diagnostic devices. CDx is providing an open-source software platform that allows centralised aggregation of data from diagnostics, regardless of the manufacturer. For this new effort to succeed, wide buy-in from implementers, policy makers and developers will be essential. In parallel, FIND is working with the WHO towards guidelines for standardised result reporting for diagnostic devices and assisting developers to be compliant with these standards. These efforts go hand in hand with further deployment of local laboratory information systems and electronic medical records.[14]

Alongside this initiative, various groups are creating global databases with the intention of enhancing research and development applications for data. For example, genTB (Harvard University, Cambridge, MA, USA) is an open-source platform that allows for the pooling, analysis and visualisation of genetic, epidemiological and clinical data. A global partnership, including the WHO, the US Centers for Disease Control and Prevention (Atlanta, GA, USA), the Center for Policy Analysis on Trade and Health (San Francisco, CA, USA), Stop TB (Geneva, Switzerland), the National Institute of Allergy and Infectious Diseases (Bethesda, MD, USA) and FIND, has been established to develop a data platform (ReSeqTB) to store, curate and provide access to globally representative TB data that can inform the development of new diagnostics, facilitate clinical decisions and improve surveillance of drug resistance. While opportunities for sharing information at an international scale must be promoted, countries must also be provided with technical solutions that can support them in efficiently managing with whom, and for what purposes, national data are shared, and to ensure that these database efforts ultimately benefit patients.

Consensus is forming around the central role that connected diagnostics and digitisation can play in tackling health systems weaknesses and diseases of poverty. However, the global health community must also address the complex question of how new tools and practices can be implemented effectively in health systems. Substantial programmatic changes will be required in the countries to absorb the innovation of connectivity and capture its benefits. This demands a holistic approach to cultivating effective development and adoption of new diagnostic tools. In this context, laboratory connectivity may also serve the need for more efficient post-marketing surveillance of newly rolled out diagnostics, for both national stakeholders and their global partners. As the amount of information collected will rapidly increase beyond our conventional capacities of analysis, the global health community will also need to initiate and intensify innovative collaboration to exploit the data collected using big data analysis and self-learning algorithms. Managing, visualising and analysing big data creates challenges beyond the capacities of standard statistical methods, and thus generates an increasing demand for data science and multidisciplinary efforts.

CONCLUSION

Our common goal of TB elimination is longer a dream: it is an achievable objective, with clear milestones.[15,16] The elimination effort will require strengthened collaboration between information technology and big data specialists, social medicine and private companies.[6]

In the future, all diagnostic technologies should be interconnected, allowing data generated by laboratories to be merged in a common repository while safeguarding patient confidentiality. The TB community could use such a repository to monitor progress and identify problems and potential solutions at both patient and global levels. Data pooling will open up opportunities to comprehend the rapid evolution of drug-resistant mutations, which will aid in selecting cost-effective treatment schemes and improving patient management. With the many solutions it can provide, data pooling at an international level is an absolute priority, as it will accelerate progress in critical sectors, including patient care, epidemiological surveillance and operational response. As an international health emergency, the TB epidemic requires optimal international collaboration and unambiguous political commitment for intensifying data-sharing efforts.

Conflicts of interest: none declared.

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RESUME

Dans le domaine de la tuberculose (TB) et d'autres épidémies majeures au niveau international, l'utilisation de nouvelles technologies pour le diagnostic s'est largement répandue, y compris dans les pays à faible ressources. Cependant, malgré la grande quantité de données générées par ces nouveaux outils, la majorité de cette source d'information reste aujourd'hui inexploitée. Dans cet article d'opinion, nous discutons les leçons tirées de l'utilisation de ces nouveaux outils diagnostics et la voie pour mieux mettre à profit les informations générées par les laboratoires TB en utilisant leur potentiel de connectivité. En réponse à l'absence de solutions permettant cette connectivité, des solutions innovantes ont été proposées par des acteurs tiers et ont été largement adoptée par les utilisateurs du test Xpert® MTB/RIF. L'utilisation croissante de ces solutions permettant la surveillance de larges réseaux de laboratoires a porté l'attention sur la nécessité de proposer une approche plus globale et intégrée par rapport à la connectivité des laboratoires diagnostiques. Ces solutions facilitent la transmission des résultats, mais permettent également le partage d'informations générées en situation réelle. Ces données, lorsqu'elles deviennent aisément accesibles, peuvent être utilisées pour améliorer la qualité des soins prodigués aux malades, la surveillance des maladies et la découverte de médicaments. Pour ces raisons, elles devraient être considérées comme un bien de santé publique. Nous dressons une liste d'exemples d'initiatives concrètes qui devraient permettre de faciliter le partage de données de laboratoire dans le but de renforcer notre compréhension de l'épidémie, soutenir les réponses opérationnelles, et accélérer l'élimination de la TB. En raison des nombreuses opportunités associées au partage d'information liées à l'épidémie de TB, la centralisation des données au niveau international est devenu une priorité absolue.

RESUMEN

En el contexto de la tuberculosis (TB), la utilización de nuevas pruebas diagnósticas está aumentando de manera espectacular, especialmente en los países en desarrollo. Pese a que nunca se ha generado tanta cantidad de datos, aún no se aprovechan todas las posibilidades que ofrece esta nueva fuente de información. En el presente artículo de opinión, se examinan las enseñanzas extraídas del uso en todo el mundo de estos nuevos instrumentos diagnósticos y se analiza la hoja de ruta hacia la explotación de las ventajas y el potencial de la conectividad para el diagnóstico de la TB. Respondiendo a la falta de conectividad incorporada a las herramientas de diagnóstico, se han creado soluciones de conectividad, que a su vez han sido adoptadas por usuarios en el terreno con el fin de monitorizar la utilización del test Xpert® MTB/RIF. El uso creciente de estas soluciones ha centrado la atención sobre la necesidad de explorar de manera más general y exhaustiva la conectividad destinada al diagnóstico. Además de facilitar a los laboratorios la tarea de comunicar los resultados, la información digital debería favorecer el intercambio y el acopio de la información recogida en el marco programático. Dado que estos datos pueden mejorar la atención al paciente, la vigilancia de enfermedades y el descubrimiento de nuevos medicamentos, es preciso considerarlos como un bien de salud pública. Aquí, enumeramos varios ejemplos de iniciativas concretas que deberían facilitar la combinación de diferentes fuentes de datos para mejorar la vigilancia de la TB y acelerar su eliminación. Habida cuenta de las múltiples soluciones que ofrece, la combinación de datos a escala internacional constituye una prioridad absoluta, pues agilizará el progreso en sectores primordiales como la atención al paciente, la vigilancia epidemiológica y la respuesta operativa.

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RESEARCH ARTICLE Open Access

Tuberculosis treatment outcomes of six and eight month treatment regimens in districts of Southwestern Ethiopia: a comparative cross-sectional study

Abyot Asres[1,3*], Degu Jerene[2] and Wakgari Deressa[3]

Abstract

Background: A switch of continuation phase tuberculosis (TB) treatment regimen from Ethambutol (E) and Isoniazid (H) combination for 6 months (6EH) to Rifampicin (R) and Isoniazid (H) combination for 4 months (4RH) was recommended. However, the effect of the regimen switch in Ethiopian setting is not known.

Methods: A comparative cross-sectional study among 790 randomly selected new cases of TB (395 each treated with 4RH and 6EH during the continuation phase) was conducted in nine health centers and one hospital in three zones in southwestern Ethiopia. Data were abstracted from the standard unit TB register composed of standard case and treatment outcome definitions. Data were analyzed using STATA version 13 where binary logistic regression was fitted to identify independent predictors of unsuccessful treatment outcomes at 5 % significance level.

Results: Over all, 695 (88 %) of the patients had a successful treatment outcome with statistically significant difference (85.3 % vs 90.6 %, $p = 0.02$) among the 6HE and 4RH regimens, respectively. After adjusting for confounders, 4RH continuation phase treatment regimen adjusted odds ratio (AOR) [(95 % confidence interval (CI)) 0.55 (0.34,0.89)], age [AOR (95 % CI 1.02 (1.001,1.022)], rural residence [AOR (95 % CI) 2.1 (1.18,3.75)] Human Immunodeficiency virus (HIV) positives [AOR (95 % CI) 2.39 (1.12,5.07)] and increased weight at the end of the second month [AOR (95 % CI 0.28 (0.11,0.72)] independently predicted treatment outcome.

Conclusion: The switch of continuation phase TB treatment regimen from 6EH to 4RH has brought better treatment outcomes which imply applicability of the recommendation in high prevalent and resource constrained settings. Therefore, it should be maintained and augmented through further studies on its impact among the older, rural residents and HIV positives.

Keywords: Tuberculosis, Continuation phase, treatment regimen, Treatment outcome, Ethiopia

Background

In the history of tuberculosis (TB) control, discovery of chemotherapy [1] brought about dramatic changes in patient survival. Before the advent of chemotherapy, 30–40 % of TB cases used to die within a year and 50–70 % within 5–7 years after the onset of TB illness [2]. Introduction of chemotherapy resulted in cure and reduction of mortality for majority of TB cases [1, 3]. However, shortly after the therapy, resistance to drug and poor adherence by patients were reported [4]. Consequently, the first standard combination therapy for 12 months comprised of Thiacetazone (T), Isoniazid(H) and streptomycin(S) for the first 2 months (2STH) followed by T and H for 10 months(10TH) was issued [2]. Subsequent to the introduction of rifampicin (R), effective short-course chemotherapy regimens for less than 12 months became standard therapy [2, 5–7]. The short-course regimens comprised of an initial, or bactericidal, phase called intensive that aimed to kill bacilli and make patients non infectious and a continuation or sterilizing

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phase which eliminates persisting mycobacteria to prevent relapse [1, 8]. Thus evidence based combinations of drugs for different categories of cases have been recommended for the two phases across the different regimens [5–7].

Introduction of Rifampicin has shortened TB treatment duration [1, 9]. In 1991, an eight months treatment regimen composed of 2 months intensive with Isoniazid(H), Rifampicin (R), Pyrazinamide(Z) and Ethambutol(E) (2RHZE/S) and 6 months continuation (6HE) phases were recommended for all new cases of TB across the world [6]. To avoid resistance to the most potent drugs, isoniazid and rifampcin and ensure patient adherence, directly observed treatment short course (DOTS) strategy was launched in 1994 [10]. Later in 2003, a directly observed intensive phase treatment followed by two continuation phase regimens, 6 months of isoniazid plus ethambutol (6HE) or 4 months of isoniazid plus rifampicin (4HR) were recommended. The 4HR continuation phase treatment regimen needed to be observed throughout the treatment period whereas the 6EH regimen relied on self administered treatment [5]. As a result, regimens without rifampicin had been considered safer in developing countries owing to irregular treatments and high absentee rates [1, 5]. However, the latest World Health Organization (WHO) guideline recommends 2-month initial phase of (2RHZE) and a 4-month continuation phase (4RH) for the treatment of virtually all forms of new TB cases across the globe [7].

The government of Ethiopia has adopted the switch of 4HR continuation phase TB treatment for all new cases and accommodated in the latest TB treatment guideline [11]. Though global strategies are relevant, investigation of the applicability to the local settings is highly required. A continuation phase treatment with 4HR regimen elsewhere has demonstrated lower unsuccessful treatment outcomes and costs as compared to 6EH continuation phase [12–15]. But well designed studies evaluating effects of the introduction of 4RH for the continuation phase TB treatment in high TB burden and resource limited settings like Ethiopia are limited. Thus, we compared treatment outcomes of TB cases who received 4RH and 6EH continuation phase regimens under routine program condition in high burden and resource limited setting. Our objective was to compare baseline patients' bacteriologic, socio-demographics, clinical characteristics and treatment outcomes among those TB patients treated with the 4RH and 6EH continuation phase treatment regimens.

Methods

Study setting

We conducted this study in ten health facilities (one hospital and nine health centres) in three remote *zones* of Southern Nation Nationalities and Peoples Region (SNNPR), one of the nine regions in Ethiopia with about 18million population [16]. Ethiopia is among the 22 TB High Burden Countries (HBC) where 230,000 incident cases of which 147,592 (64 %) were notified. In the same year, 16100 deaths and 90 % treatment success among the smear positives cases registered in 2011 were reported [17, 18]. The country has adopted and implemented the DOTS strategy for the treatment of all forms of TB. Accordingly new cases of TB had been treated with directly observed RHZE combinations for the first 2 months (2RHZE) followed by self administered EH combinations for six months (6EH) [19]. As of the end of 2011, the continuation phase treatment was switched from 6EH to 4RH. Thus the regimen became directly observed 2RHZE/4RH combinations for all forms of new TB cases throughout the 6 months treatment period [11].

The three study *Zones*, Bench Maji, Kaffa and Sheka are located at the southwestern border of the SNNPR where about 2,064,102 peoples reside [16]. The *zones* (an administrative unit that liaison *weredas* with the region) are organized in to four town administrations and 26 *weredas* (lowest administrative unit closer to the community) those have three hospitals and 65 health centers those provide TB DOTS services for free. However, the three hospitals and only 27 health centers were providing TB/Human Immunodeficeincy Virus (HIV) collaborative activities [20].

Study design and sampling

A comparative cross-sectional study among TB cases treated with 2RHZE/6EH and 2RHZE/4RH regimens was carried out. New cases registered between 2008 and 2014 were eligible of which those aged above 15 years were studied. Sample size was estimated using the Stat Calc program of Epi Info version 7 [21] with 95 % confidence level, 80 % power and ratio of 6EH to 4RH ($r = 1$). Accordingly, 512 cases (256 from each group) was required to detect 7 % difference [12] in the proportion of unsuccessful outcome among the 6EH and 4RH groups. Finally, considering the design effect of 1.5 and 10 % missing records, a total of 846 cases were required. The samples were selected through proportional allocation to the three zones followed by selection of *weredas* and health facilities from the zone using probability proportional to size. The allocation and selection was made based on total number of cases reported from the *weredas* and health facilities during 2008 through 2014. Lastly, cases from the selected health facilities were selected randomly using SPSS statistical software using TB unit number of the cases.

Data were extracted from a standard unit TB register recommended by the WHO [11, 19, 22] using extraction

format prepared for the study. Thus patients' baseline attributes (age, gender, residence, sputum smear, type of TB, HIV status) and follow-up measures (sputum smear, weight, drug regimen and treatment outcomes) were extracted. The following standard case and outcome definitions were adopted and used for the study [11, 19].

- New case of TB a patient who never had treatment for TB, or had been on anti-TB treatment for less than four weeks in the past
- Other cases are those patients who do not fulfill the criteria for new, relapse, and return after default or treatment after failure.
- Cured: a patient whose sputum smear or culture was positive at the beginning of the treatment but who was smear or culture-negative in the last month of treatment and on at least one previous occasion.
- Treatment completed: completed treatment but does not have a negative sputum smear or culture result in the last month of treatment and on at least one previous occasion.
- Treatment failure: a patient whose sputum smear or culture is positive at 5 months or later during treatment or patients found to harbor Multidrug Resistant (MDR) TB strain at any point of time during the treatment, whether they are smear-negative or -positive.
- Died: a patient who dies for any reason during the course of TB treatment.
- Defaulter/loss to follow-up: a patient who has been on treatment for at least 4 weeks and interrupted treatment for eight or more consecutive weeks.
- Successful treatment: a treatment that ends up in cure or treatment completion
- Unsuccessful treatment: a treatment that end up in treatment default or loss to follow up, treatment failure or death.

The extracted data were checked for consistency and completeness and entered in to Epinfo version 7 that later exported to STATA 12 [23] for analysis. Data were described separately for the two groups (6EH and 4RH) using frequencies, mean, standard deviations and tables. Besides, crude comparisons of the baseline and follow up measures among the 6EH and 4RH groups were made using chi square (x^2) or t-tests as appropriate. Subsequently, bivariate and multiple binary logistic regression analysis were made to compute crude and adjusted odds ratios respectively between the explanatory and outcome variables. Multiple logistic regression model was fitted with those variables having $p \leq 0.2$ on bivariate analysis. Finally, statistical significance was judged at $p < 0.05$ and/or 95 % confidence interval (CI) of odds ratio (OR) excluding one.

Ethical considerations

We received ethical approval from the institutional review board of the College of Health Sciences at Addis Ababa University. Accordingly, anonymous patient data were extracted from routine service registry upon permission from the respective institutions.

Results

Demographic and baseline clinical characteristics

We retrieved 846 patient records of which 790 (93.4 %) with complete outcome records [395 each treated with 2RHZE/6HE and 2RHZE/4RHregimens respectively] were described and analyzed. The mean age of the patients was 30.8 (31.5 vs 30.9 years, $p = 0.5$) respectively, for those treated with 6HE and 4HR (Table 1). More than half, 56.6 % and 55.7 % of the patients were male and reside in rural areas, respectively, with no statistically significant difference among the two groups. With regard to the patient profile, 86.8 % and 77%were registered at health center and had pulmonary TB, respectively. Of the patients, 765 (96.8 %) were new cases (378 treated with 6EH vs387 with 4RH regimen) and the rest ((25 (3.2 %) (17 from 6EH vs 8 from 4RH) were transferred in and other cases treated with new case regimen. Human Immunodeficiency virus (HIV) test result was available for 612 (77.5 %) with statistically significant difference among the two groups [283 (71.6 %) from 6EH and 329 (83.3 %) from 4RH, $p < 0.001$]. Among those tested HIV positives, 44 (57.1 %) received either Cotrimoxazole Prophylactic Therapy (CPT) or Antiretroviral Therapy (ART) with no statistically significant difference among the regimens 24 (64.9 %) from 6EH and 20 (50 %), $p = 0.2$.

Patient follow-ups and treatment outcomes

A total of 695 (88 %) of the patients had successful treatment outcomes with statistically significant difference (85.3 % vs 90.6 %, $p = 0.02$) among the 6HE and 4RH groups, respectively (Table 2). A total of, 324 (90.3 %), 208 (85.4 %) and 163 (91.1 %) of pulmonary positive, pulmonary negative and extra pulmonary TB cases respectively had successful outcomes with statistically significant difference, $P = 0.03$. Besides, statistically significant differences in successful outcomes, 64 (83.1 %), 482 (90.1 %) and 149 (83.7 %, $p = 0.005$ were also found among HIV positive, HIV negatives and unknown HIV status TB cases, respectively.

Measurements of patient weight at the end of second, fifth and sixth/seventh months of treatment were available for 504 (63.8 %), 145 (18.4 %) and 141 (17.8 %) respectively. Thus, 368 (46.6 %) or (48.4 % from 6EH and 44.8 % from 4RH, $p = 0.4$) have gained some amount of weight at the end of second month of treatment. On the other hand, of those initially smear positive pulmonary

Table 1 Demographic and clinical characteristics of the tuberculosis patients registered between, 2008–2014, Southwest Ethiopia

Variable		Continuation phase treatment regimen		Total	*P* value
		6EH (*n* = 395) *n* (%)	4RH (*n* = 395) *n* (%)		
Age (years)	Mean ± SD[a]	31.1 ± 12.9	30.5 ± 11.9	30.8 ± 12.4	0.5
Gender	Male	221 (55.9)	226 (57.2)	447 (56.6)	0.7
	Female	174 (44.1)	169 (42.8)	343 (43.4)	
Residence	Urban	175 (44.3)	175 (44.3)	350 (44.3)	1
	Rural	220 (55.7)	220 (55.7)	440 (55.7)	
Zone	Kaffa	106 (26.8)	104 (26.3)	210 (26.6)	0.9
	Bench Maji	206 (52.2)	203 (26.3)	409 (51.8)	
	Sheka	83 (21.0)	88 (22.3)	171 (21.6)	
Treatment center	Hospital	55 (13.9)	49 (12.4)	104 (13.2)	0.5
	Health center	340 (86.1)	346 (87.6)	686 (86.8)	
Baseline weight	Mean ± SD[a]	47.6 ± 8.6	48.4 ± 8.5	48 ± 8.5	0.2
Baseline sputum smear	Positive	186 (47.1)	173 (43.8)	359 (45.4)	0.6
	Negative	151 (38.2)	165 (41.8)	316 (40)	
	Unknown	58 (14.7)	57 (14.4)	115 (14.6)	
Type of TB	Pulmonary	303 (76.7	305 (77.2)	608 (77.0)	0.9
	Positive	186 (47.1)	173 (43.8)	359 (45.4)	
	Negative	117 (30.4)	132 (33.4)	252 (31.9)	
	Extra pulmonary	92 (23.3)	90 (22.8)	179 (23)	
HIV status	Positive	37 (9.4)	40 (10.1)	77 (9.7)	<0.001
	Negative	246 (62.3)	289 (73.2)	535 (67.7)	
	Unknown	112 (28.4)	66 (16.7)	178 (22.5)	
Received CPT[b] (*n* = 77)	Yes	18 (48.6)	17 (42.5)	35 (45.5)	0.6
Received CPT or ART[c] (*n* = 77)	Yes	6 (16.2)	6 (15.0)	12 (15.6)	0.8
Received ART (*n* = 77)	Yes	12 (32.4)	9 (22.5)	21 (27.3)	0.3
Baseline sputum smear	Positive	186 (47.1)	173 (43.8)	359 (45.4)	0.6
	Negative	151 (38.2)	165 (41.8)	316 (40)	
	Unknown	58 (14.7)	57 (14.4)	115 (14.6)	

[a]Standard deviation,[b] *CPT* Cotrimoxazole prophylactic therapy, [c]*ART* antiretroviral therapy

TB cases, 78.6 % had undergone sputum follow up examination at least once after the diagnosis (76.3 % among 6HE and 80.9 % among 4HR, $p = 0.3$). Thus sputum smear results at the end of second, fifth and sixth/seventh months of treatment were available for274 (76.3 %), 184 (51.3 %) and 179 (49.9 %) cases respectively with no statistically significant differences among the 6EH and 4RH regimens. The majority of the smear positives (69.9 % vs 79.8 % respectively from the 6EH and 4RH regimens, $p = 0.4$) converted to negative at the end of second month treatment.

Factors associated with unsuccessful treatment outcomes

In bivariate analysis patient age, residence, zone, weight change at the end of the second month of treatment, sputum smear follow-up and continuation phase regimen are associated with treatment success at $p < 0.05$. But, in multivariate analysis 4RH continuation phase treatment regimen [AOR (95 % CI) 0.55 (0.34,0.89)], patient age [AOR (95 % CI) 1.02 (1.001,1.022)], rural residence [AOR (95 % CI) 2.1 (1.18,3.75)], treated at health center [AOR (95 % CI) 0.37 (0.14,0.97)], HIV positives [AOR (95 % CI 2.38 (1.12,5.07)], gained weight at the end of the second month [AOR (95 % CI) 0.28 (0.11,0.72)] independently predicted unsuccessful treatment outcome (Table 3). The odds of unsuccessful outcome was higher among the older, rural residents, HIV positives and unknown weight change at the end of second month treatment. The odds of having unsuccessful outcome increase by 2 % for every one year increase in age (AOR = 1.02).On the other hand, treated with 4RH continuation phase regimen, being treated at health center and weight gain at the end of

Table 2 Patient follow-up measures and treatment outcomes of TB patients registered during 2008–2014, Southwest Ethiopia

Variables		Continuation phase treatment regimen			
		6EH ($n = 395$) *n* (%)	4RH ($n = 395$) *n* (%)	Total *N* (%)	*P* value
Weight at 2nd month	Mean ± SD	49.9 ± 8.9	50.8 ± 8.2	50.4 ± 8.6	0.2
Weight at 5th month	Mean ± SD	51.4 ± 8.6	51.3 ± 7.3	51.3 ± 7.9	0.9
Weight at 6/7th month	Mean ± SD	51.1 ± 8.9	52.5 ± 6.5	51.7 ± 7.9	0.3
Change in weight at 2nd month	Not increased	49 (12.4)	61 (15.4)	110 (13.9)	0.4
	Increased	191 (48.4)	177 (44.8)	368 (46.6)	
	Unknown	155 (39.2)	157 (39.7)	312 (39.5)	
Sputum smear end of 2nd month ($n = 359$)	Positive	4 (2.2)	2 (1.2)	6 (1.7)	0.09
	Negative	130 (69.9)	138 (79.8)	268 (74.7)	
	Unknown	52 (28)	33 (19.1)	85 (23.7)	
Sputum smear end of 5th month ($n = 359$)	Positive	1 (0.5)	0 (0)	1 (0.3)	0.03
	Negative	83 (44.6)	100 (57.8)	183 (51)	
	Unknown	102 (54.8)	73 (42.2)	175 (48.7)	
Sputum smear end of 6/7th month ($n = 359$)	Positive	0	0	0	0.8
	Negative	94 (50.5)	85 (49.1)	179 (49.9)	
	Unknown	92 (49.5)	88 (50.9)	180 (50.1)	
Sputum smear done during treatment ($n = 359$)	No	44 (23.7)	33 (19.1)	77 (21.4)	0.3
	At least once	142 (76.3)	140 (80.9)	282 (78.6)	
Continuation phase visit	Mean ± SD	5.8 ± 1.1	5.4 ± 3.1		0.09
Treatment outcome	Successful	337 (85.3)	358 (90.6)	695 (88)	0.02
	Cured	77 (19.5)	85 (21.5)	162 (20.5)	
	Completed	260 (65.8)	273 (69.1)	533 (67)	
	Unsuccessful	58 (14.7)	37 (9.4)	95 (12)	
	Died	28 (7.1)	18 (4.6)	46 (5.8)	
	Defaulted	29 (7.3)	19 (4.8)	48 (6.1)	
	Failure	1 (0.3)	0	1 (0.1)	

second month have lower likelihood of unsuccessful outcome. Patients put on 4RH continuation phase of treatment regimen are 45 % less likely to have unsuccessful outcome compared to those put on 6EH regimen. Patients treated at health center have about 63 % lower odds of unsuccessful outcome as compared to those treated at hospitals. HIV co infected TB patients have more than two fold higher risk of unsuccessful outcomes compared to HIV negatives (AOR = 2.38). Those patients gained weight at the end of the second month of treatment have 72 % lower odds of unsuccessful outcomes compared to those with reduced or unchanged weight (AOR = 0.28). A subgroup analysis among smear positive pulmonary cases showed having a sputum checkup at least once during treatment independently predicted 96 % lower odds of unsuccessful outcomes compared to those unchecked (AOR 0.04 (95 % CI, 0.01–0.12), $P < 0.001$) (Additional file 1).

Discussion

Treatment outcomes among TB patients treated with RHZE for the first 2 months, followed by HE for 6 months (2RHZE/6EH) and RH for 4 months (2RHZE/4RH) was compared. Both groups of the cases had no statistically significant difference with respect to socio-demographic, baseline clinical, bacteriologic and follow up measures that depict comparability of the groups. The comparison was made between regimens used during the continuation phase treatment (4RH vs 6EH). Thus a lower rate of unsuccessful outcomes was reported among those treated with 4RH continuation phase regimen.

A statistically significant difference in treatment outcomes where lower unsuccessful treatment outcome (9.4 % vs 14.7 %) was observed among patients treated with 4RH and 6EH regimen respectively. Similarly, a study conducted in Nigeria [14] reported higher odds of unsuccessful outcome among those treated with 6EH.

Table 3 Factors associated with unsuccessful treatment outcomes among TB patients registered during 2008–2014, Southwestern Ethiopia

Variables		Treatment outcomes		Odds ratio (OR)	
		Unsuccessful *n* (%)	Successful *n* (%)	Crude OR 95 % CI[a]	Adjusted OR 95 % CI
Age (years)	Mean(SD)	33.5 (14)	30.4 (12.0)	1.02 (1.002,1.03)	**1.02 (1.001,1.022)**
Gender	Male	60 (13.4)	387 (86.6)	1	1
	Female	35 (10.2)	308 (89.8)	0.73 (0.47.1.14)	0.63 (0.38,1.03)
Residence	Urban	32 (9.1)	318 (90.9)	1	1
	Rural	63 (14.3)	377 (85.7)	1.66 (1.06,2.61)	**2.1 (1.18,3.75)**
Zone	Kaffa	34 (16.2)	176 (83.8)	1	1
	Bench Maji	50 (12.2)	359 (87.8)	0.72 (0.45,1.14)	1.41 (0.73,2.75)
	Sheka	11 (6.4)	160 (93.6)	0.36 (0.17,0.73)	1.2 (0.44,3.32)
Treatment center	Hospital	17 (16.3)	87 (83.7)	1	1
	HC	78 (11.4)	608 (88.6)	0.66 (0.37,1.16)	**0.37 (0.14,0.97)**
Type of TB	Pulmonary	78 (12.8)	530 (87.2)	1	1
	EPTB[b]	17 (9.3)	165 (90.7)	0.70 (0.40,1.22)	0.57 (0.32,1.04)
HIV status	Negative	53 (9.9)	482 (90.1)	1	1
	Positive	13 (16.9)	64 (83.1)	1.85 (0.95,3.57)	**2.39 (1.12,5.07)**
	Unknown	29 (16.3)	178 (83.7)	1.77 (1.08,2.88)	**2.26 (1.23,4.11)**
Weight change end of 2nd month	No increase	11 (8.2)	357 (91.8)	1	1
	Increased	9 (3)	101 (97)	0.35 (0.14,0.86)	**0.28 (0.11,0.72)**
	Unknown	75 (24)	237 (76)	3.55 (1.71,7.37)	**3.48 (1.60,7.54)**
Continuation phase regimen	6EH	58 (14.7)	337 (85.3)	1	1
	4RH	37 (9.4)	358 (90.6)	0.60 (0.39,0.93)	**0.55 (0.34,0.89)**

[a]Confidence interval, [b]Extra pulmonary Tuberculosis, bold figures indicate statisticaly significant at $p<0.05$

This could be due to the differences in length and type of drugs used during the continuation phase treatment those influence adherence and ultimate outcome. Studies reported that reduced continuation phase (from 6EH to 4HR) treatment is associated with lower cost and expected mortality [12] that enhance successful treatment outcome. On the other hand, use of rifampcin for longer period of time during the treatment of TB is associated with better outcomes [13] that might be related with efficacy of the drug. The finding implies the adoption [11] of the latest WHO recommendation [7] in high prevalent and resource constrained settings is working well.

Apart from the treatment regimens, patient attribute like age and residence independently predicted treatment outcomes. We found that age had an inverse relation with unsuccessful outcome where the odds of unsuccessful outcome increase with age. Several studies also reported that older patients were more likely to have unsuccessful outcomes than younger [24–27]. This could be due to higher risk of age related co morbid situations those lead to poor adherence and outcomes [28]. Patients residing in rural areas had higher risk of unsuccessful outcomes which could be attributed to the low access to TB care and unfavorable living conditions. The findings imply need for focused intervention targeted to those older age groups and rural dwellers besides the treatment regimen.

Monitoring of patient weight and sputum are among the recommended follow-up measures required for TB patients on treatment [7]. The results of both weight and sputum monitoring are used to adjust for drug dose and predict outcomes of the treatment. The proportion of smear positive patients converted to negative at the end of the intensive phase has been taken among indicators of TB programme performance [7]. However, only small proportion of patients had documented results of the weight and sputum follow-ups particularly at the later periods of treatment. Consistent to findings from African settings [29] majority of those patients undergone sputum checkup during treatment converted to negative.

Patients gained some amount of weight at the end of second month treatment had lower risk of unsuccessful outcomes which is consistent with other studies [30, 31]. This could be explained by the fact that weight gain marks some level of improvement from the TB illness including reduced appetite. In addition, changes in weight while on treatment might be an indication of appropriateness of the drug dose to treat the illness. On the other hand those with unknown weight change at the end of first two months treatment had higher odds

of unsuccessful outcomes. This might have occurred due to possible misclassification of cases with reduced or remains unchanged to unknown. The weight change might be unknown due to patients' treatment interruption subsequent to treatment default or death those constitute unsuccessful outcome. So that patient's status of weight during treatment might be left undetermined.

Having sputum checkup at least once during treatment among initially smear positives predicted lower risk of unsuccessful outcome. However, reviews showed low sensitivity and modest specificity of sputum results at the end of intensive phase to predict failure and relapse [32]. On the other hand, detection of sputum positive during treatment trigger further patient assessment that influence treatment regimens and ultimate outcome. Hence, the routine sputum monitoring adopted by the country [11] during treatment should be improved as it is an indicator of program performance and trigger for patient assessment.

Consistent with other studies [33, 34], HIV positive TB patients are more likely to have unsuccessful outcomes compared to those negatives. This could be due to multifaceted influences of HIV on TB diagnosis and response to TB treatment those negatively affect the outcomes of TB treatment [35]. Consequently, collaborative services have been recommended in order to curb the influence of HIV on TB and vice versa [36]. Evidences from systematic review in African context supported the recommendation and reported better outcomes among concurrently screened and managed TB and HIV infected patients [37]. Nonetheless, we found no statistically significant difference in treatment success among those infected TB patients provided with CPT and/or ART. The indifference could be explained by the low uptake of integrated TB/HIV collaborative services among the studied patients. In this study, more than three quarter of the patients were offered HIV test which is little higher than the national average of 65 % [18] and 9.7 % TB/HIV co infected patients which is almost similar to the national average of 10 %. However, only few HIV co infected patients (45 % on CPT and 27.3 % on ART) were found to have documented service provision. [18]. The discrepancies could be due to differences in reporting periods where the national average is a single year attainment but that of this study is over a period of six years including the nationally reported year. Over all, the targets set for the TB/HIV service collaboration has not yet met which calls for in depth understanding and focused intervention that suit local settings. On the other hand, unknown HIV status predicted higher odds of unsuccessful outcomes. This could be due to possible misclassification of HIV positive cases those predict worse outcome in to unknown. The study is limited to control for changes in medical resources, polices and quality of care across the study periods. Since only few variables were captured on the register, we could not control for possible confounding effect of socio-economic, lifestyle and co morbid illness. Furthermore resistance pattern of the treatment regimens could not be evaluated which is recommended for the assessment of impact of treatment regimens. On the other hand the random selection of relatively large sample from both groups minimized risk of selection bias. The groups treated with 4RH and 6EH had insignificant differences with regard to baseline and follow-up clinical and bacteriologic attributes that enhanced comparability of the groups. Besides, we extracted data from a standardized routine programme register that reflect operational reality. In general, our study is valid and can apply in similar settings given the limitations.

Conclusion

In conclusion, the switch of continuation phase TB treatment regimen for new cases from 6EH to 4RH has brought better treatment outcomes. The findings verified the applicability of latest WHO recommendation and national adoption to the high prevalent and resource constrained settings. However, the unsuccessful outcome among the older, rural dwellers and HIV positives is higher independent of the treatment regimen that need further investigation and focused intervention. Therefore, the recommended switch of treatment regimen should be maintained and progressively assessed for outcomes, including drug resistance survey or surveillance. Moreover, further studies should be carried out on the impact of treatment regimens among older, rural residents and HIV positives.

Additional file

Additional file 1: Table 4: Factors associated with unsuccessful treatment outcome among smear positive pulmonary TB cases registered during 2008-2014, southwestern Ethiopia (n=359). Table 5: Factors associated with unsuccessful outcome among clinically diagnosed (smear negative 10.1186/s12879-016-1917-0 pulmonary and extra pulmonary) TB cases registered during 2008-2014, Southwestern Ethiopia (n=431). (DOCX 17 kb)

Abbreviations

ART: Antiretroviral therapy; CI: Confidence interval; CPT: Cotrimoxazole prophylactic therapy; DOTS: Directly Observed Treatment Short course; EH: Ethambutol and Isoniazid combination; HIV: Human Immunodeficiency Virus; OR: Odds ratio; RH: Rifampicin and Isoniazid combination; RHZE: Rifampicin, Isoniazid, Pyrazinamide and Ethambutol combination; TB: Tuberculosis; WHO: World Health Organization

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Availability of data and materials
The datasets analyzed during the current study will be available from the corresponding author on reasonable request.

Authors' contributions
AA conceived, designed the study, analyzed data and prepared manuscript. WD and DJ critically reviewed for intellectual content of the study protocol and manuscript as primary and co-supervisors respectively. All authors approved the final version of the manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
The study protocol was approved by the institutional review board of the college of health sciences at Addis Ababa University (protocol number 045/14/sph). Since we did not carry out patient interview or examination, consent of participation was not sought as the patients were not on treatment at the time of study. Accordingly an anonymous patient data from routine service registry (unit TB register) were abstracted upon formal permissions of the health facilities.

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Digital health for the End TB Strategy: developing priority products and making them work

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ABSTRACT In 2014, the World Health Organization (WHO) developed the End TB Strategy in response to a World Health Assembly Resolution requesting Member States to end the worldwide epidemic of tuberculosis (TB) by 2035. For the strategy's objectives to be realised, the next 20 years will need novel solutions to address the challenges posed by TB to health professionals, and to affected people and communities. Information and communication technology presents opportunities for innovative approaches to support TB efforts in patient care, surveillance, programme management and electronic learning. The effective application of digital health products at a large scale and their continued development need the engagement of TB patients and their caregivers, innovators, funders, policy-makers, advocacy groups, and affected communities.

In April 2015, WHO established its Global Task Force on Digital Health for TB to advocate and support the development of digital health innovations in global efforts to improve TB care and prevention. We outline the group's approach to stewarding this process in alignment with the three pillars of the End TB Strategy. The supplementary material of this article includes target product profiles, as developed by early 2016, defining nine priority digital health concepts and products that are strategically positioned to enhance TB action at the country level.

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Introduction

Tuberculosis (TB) remains an urgent public health threat and a leading infectious cause of death worldwide [1]. In 2014, the World Health Assembly resolved to end the global TB epidemic by 2035 [2]. This led to the elaboration of the End TB Strategy by the Global TB Programme of the World Health Organization (WHO) and its partners for the 20 years post-2015 [3, 4]. The End TB Strategy's vision is to make the world free of TB, with no deaths, disease and suffering due to the disease. For the global TB epidemic to be brought to an end by 2035, a drastic reduction in TB incidence and mortality will be needed. The strategy is structured around distinct components and achievement of its goals will depend on action on its three pillars, namely: 1) expanding the scope and reach of interventions for TB care and prevention, with a focus on efficient, high-impact and patient-centred approaches; 2) maximising the benefits of health and development policies and systems, by engaging a broader cross-section of actors across government, communities and the private sector; and 3) pursuing new scientific knowledge and innovations that can dramatically change TB prevention and care. The End TB Strategy is aligned to the broader post-2015 development framework mapped out by the United Nations Sustainable Development Goals (SDGs) [5]. The SDGs seek to build upon the actions catalysed by the Millennium Development Goals (MDGs) until 2015 and to complete what the MDGs did not achieve. The SDGs' vision is to improve the economic, social and environmental dimensions of development. A plan of action to strengthen universal peace and eradicate poverty by 2030 has been formulated, and the 17 SDGs and their 169 targets are geared towards this [6]. TB care and prevention fit primarily under SDG 3, which is devoted to health; however, activities needed to accomplish the End TB Strategy will need to engage other SDG domains, such as supporting infrastructure and innovation (SDG 9), reducing inequalities (SDG 10) and strengthening alliances with partners towards common ends (SDG 17).

Innovative approaches to care and prevention are needed to achieve the ambitious goals of the End TB Strategy and the SDGs. The operationalisation of the End TB Strategy requires that national TB programmes and other stakeholders re-examine how their respective objectives must evolve in order to align with the post-2015 trajectory.

Electronic health (eHealth) and mobile health (mHealth), collectively referred to as "digital health", occupy an increasingly important space in preventive and curative interventions in both affluent and resource-constrained settings. Digital health is destined to play a pivotal role in the implementation of key activities to achieve a number of SDGs and to end the global TB epidemic, be they old or new, or directed at patient care, surveillance, programme management, advocacy, staff development or the engagement of civil society (figure 1) [7]. These interventions will also be needed to implement most of the eight priority action areas to eliminate TB in low-incidence countries [8]. In recent years, TB programmes and technical partners worldwide have initiated several digital health projects in order to enhance the reach and effectiveness of their work. Some of these efforts have shown promise but many have lacked the scale, the end-user ownership and the coordination needed to achieve population-level impact.

The existing state of the art of information and communication technology (ICT) and its "next-generation" enhancements present opportunities to broaden the scale of action and to overcome barriers to programmatic interventions in TB, which appear insurmountable even today. Fresh thinking on how to adopt, implement, market and sustainably support these technologies would, however, be needed.

In April 2015, WHO established a Global Task Force on Digital Health for TB (referred to henceforth in this paper as the Task Force) to promote the integration of digital health into national operational plans to implement the End TB Strategy [9]. This paper expands upon the content of the WHO digital health Agenda for Action created by this enterprise and in collaboration with the European Respiratory Society (ERS) [10]. In addition, it describes the process by which the Task Force and other partners identified digital health products that are strategically positioned to address the challenges faced by TB patients and health professionals. A key outcome of this process is the development of a set of target product profiles (TPPs) by the Task Force: a detailed description of the TPPs can be found in the supplementary material.

Methods and rationale

Process

On February 25–26, 2015, WHO and the ERS held a joint technical consultation on the role of digital health for TB and tobacco control in Geneva, Switzerland [11, 12]. Ahead of this consultation, in early 2015, WHO surveyed public views on the priority products to be focused upon during the discussions using an online questionnaire. The consultation was attended by close to 100 participants and was organised into tracks of work devoted to each of the four functions identified by the WHO conceptual framework for digital health in the TB response, namely patient care, surveillance and monitoring, programme management, and electronic learning (eLearning) [13]. The programme management function was devoted to the strengthening of laboratory information systems, a critical priority for the TB manager. Each of the tracks focused on one or more digital health products selected by its members.

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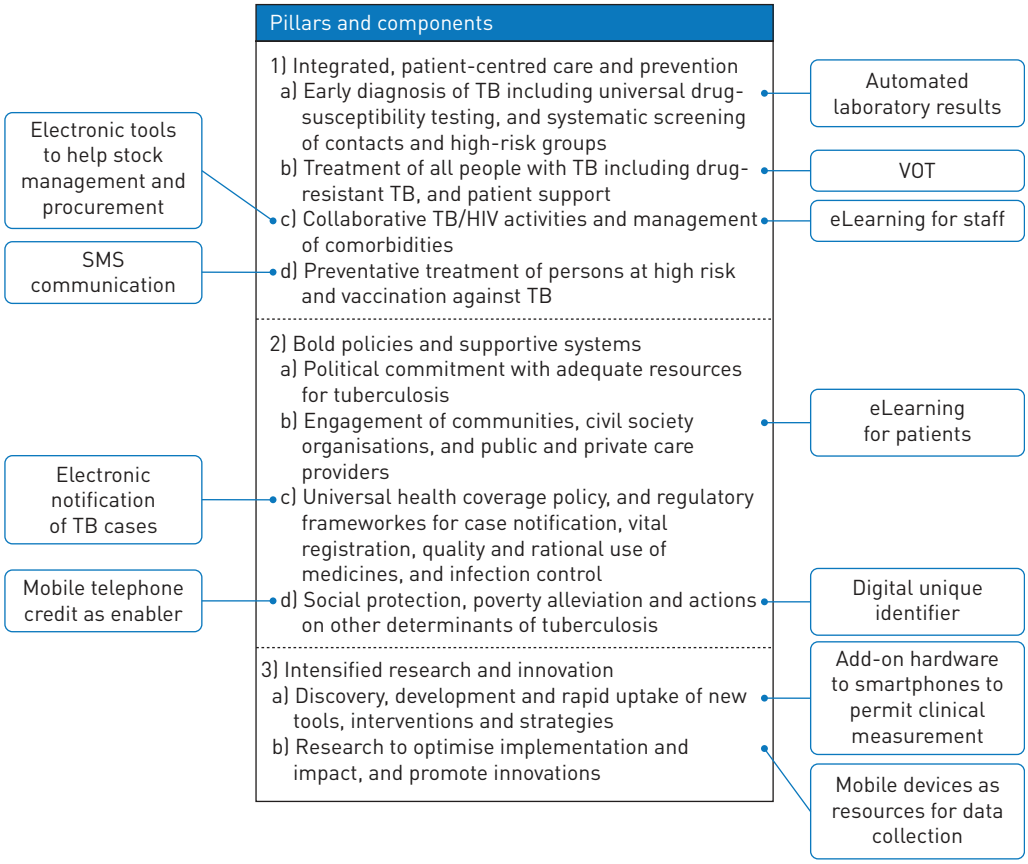

FIGURE 1 Examples of common digital health products and their potential contribution to different components of the End TB Strategy. TB: tuberculosis; VOT: video (virtually) observed therapy; eLearning: electronic learning; SMS: Short Message Service.

The characteristics of the digital health products were described using TPPs. TPPs define the features of the desired solutions in sufficient detail and transparency to stimulate more interest from potential developers [14]. They are dynamic discussion tools that are revised in the development process. Where they apply to the creation of software, the TPP approach shares many characteristics with behaviour-driven development [15]. The TPP approach has recently been used to focus the views of multiple stakeholders and developers on the priority diagnostics required for TB [16, 17]. One of the members of the Task Force was recently involved in finalising a detailed TPP for electronic medication monitors for use in patients on TB medication following positive findings from a trial of its use (Bruce V. Thomas, personal communication) [18]. This product is scheduled for large-scale roll out in high TB burden settings from 2016.

These recent developments motivated the Task Force and other partners who were involved in this initiative to follow a similar approach in their work. The digital health TPPs are expected to serve users at both national and global levels; they will guide developers to come up with solutions tailored to the problems faced by national TB programmes, and to steward the implementation of these new concepts, and ensure a more systematic method of collection and reporting of evidence.

This article presents the TPPs as they were developed until February 2016 as a result of an iterative consultative process, which started during the technical consultation and followed electronically thereafter (table 1 and supplementary material). The description of each of the TPPs is structured in nine identical sections, namely: 1) goals, scope and description; 2) target end-users; 3) value to the target end-user and other beneficiaries; 4) strategic fit; 5) rationale for prioritisation; 6) optimal requirements; 7) minimal requirements; 8) factors for success; and 9) key risks (threats) for its development. At this stage of development, the descriptions do not contain comprehensive details sufficient for a developer to create a product. The TPPs will eventually need to be refined by developers into technical specifications for the design of concrete products. Designing, building and rolling out a digital application needs to embrace a broad cross-section of representative users and policy-makers, one that engages with them and that supports their efforts [19]. This will require additional work to test concepts at the country level and study which processes need to happen alongside to ensure successful adoption, such as human resource

TABLE 1 Summary of target product profiles (TPPs) for the End TB Strategy (as of February 2016)

Function	TPPs
Patient care	1) Video treatment support (VOT) for TB patients *via* mobile telephones 2) eHealth portal to improve TB and tobacco care
Surveillance and monitoring	3) Digital dashboard for TB indicators and epidemiological trends 4) Digital notification of TB cases 5) Digital application for active TB drug safety monitoring
Programme management	6) Diagnostic device connectivity for TB
eLearning	7) Information resources platform for patients on TB and smoking cessation 8) Web-based training for health professionals on TB and smoking cessation 9) Clinical decision support systems for TB treatment and smoking cessation

eLearning: electronic learning; VOT: video (virtually) observed therapy; TB: tuberculosis; eHealth: electronic health.

development and changes to regulations. Moreover, the introduction of new technologies into a setting needs to complement others that are already in place, and to fit within the eHealth framework that a country may already have and within which these technologies are expected to function [20, 21].

TPPs for digital health for the End TB strategy: criteria for selection

The choice of products and associated activities were premised upon the pressing needs and realities of TB programmes, upon existing evidence and knowledge about the effectiveness of certain digital health interventions, and the rapid advances in technologies of which potential users may be unaware. Firstly, there is a need for an articulated and step-wise approach to develop comprehensive digital health solutions to support the End TB Strategy and other associated policies that exist (*e.g.* eliminating TB in low-incidence settings [8, 22, 23]), in particular, to limit fragmentation of efforts leading, for instance, to parallel systems, redundancy and waste of resources. The products and concepts defined by the TPPs were selected to complement each other in a given setting, which would be the desirable approach to implementation in contrast to the creation of independent standalones; they should thus be developed in parallel, ideally at comparable speeds towards completion [10]. Secondly, opportunities should be sought to integrate and seek synergies with promising ICT initiatives, both within healthcare and beyond, so as to increase the efficiency, scalability and sustainability of efforts. Thirdly, managers and other decision-makers may not be well informed about which digital health technologies could be most appropriate to match their needs in TB prevention and care work. Fourthly, on the practical side, the Task Force opted to keep the first batch of TPPs to a manageable set.

Based on these considerations, the members of the work groups selected one to three products deemed to be advantageously placed to secure gains to that particular function at a large scale, in the near future. This choice should not be construed as a recommendation for the immediate, large-scale implementation of these products, which at times represent emerging technologies with incomplete knowledge on their effectiveness. Moreover, the authors acknowledge that several promising concepts deserving of investment would not be captured in the initial wave of TPPs. These include telemedicine interventions, apart from video (virtually) observed therapy (VOT), which is described here, as well as electronic monitoring of the use of medication containers [18, 24–26]; computer-assisted diagnostic tools, particularly in connection with imaging techniques such as digital radiography [27]; aids to planning the supply of medicines and forecasting their consumption [28]; "clip-on" hardware that converts smartphones into clinical measurement devices [29–32]; and others. The Task Force encourages such initiatives and intends to stay abreast of similar developments led by technical or funding agencies to take forward additional TPPs to the nine included at this stage.

Justification for digital health in TB care and prevention

The pace with which ICT has developed and diversified over the years can only be described as revolutionary. By the end of 2015, half of the world's population had a mobile telephone subscription, representing more than a doubling in coverage within the space of 5 years (https://gsmaintelligence.com/). About 40% of the world's population can access the Internet, although coverage and broadband speed differ substantially between and within regions [33]. Smartphones are progressively replacing less sophisticated mobile phones all over the world, a trend primarily driven by uptake in developing countries. Developments such as these could present huge openings for health care, as users become better informed about lifestyles that pose a risk to health and about access to services, while health professionals enjoy

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more efficient means to keep their knowledge up to date and maintain contact with their patients to follow up on their healthcare needs.

New opportunities are created for public health researchers, health system managers, patients and practitioners to explore how the innovative use of these tools can strengthen health systems. Field experience with digital health interventions for TB is growing. The increased deployment of cutting-edge digital health concepts is destined to inject greater power, speed, flexibility and diversity into the same processes that have been helping public health practitioners, managers and clinicians to deliver better TB care to populations and patients for several decades. Improving the knowledge base on these experiences could increase opportunities for more of the successes and failures to be fed into a virtuous cycle of continuous quality improvement of digital interventions.

There is a need for better quality evidence for impact or efficiency from more rigorous studies that are directly relevant to TB programme implementation. Several digital health concepts still need to be tested under different conditions, including broader geographical spread, levels of decentralisation and models of care, and in a larger cross-section of patient subgroups. Certain digital activities are implemented on the basis of indirect evidence or experience imported from outside TB care, such as the monitoring of antiretroviral uptake [34–36] and smoking cessation programmes [37, 38]. Drawing parallels from outside the TB world can add value and is justified on the basis that the challenges of limited resources, such as the problems associated with stock management, supplies and logistics, cut across different disciplines. Inferences on behaviour change drawn from such analogies may, however, at times be obscured by imperfect comparison (such as the duration of treatment, safety profile of medicines used and stigma attached to TB). Conversely, there may be missed opportunities if the adoption and large-scale roll out of technological advances is put on hold until suitable studies have been devised and completed among TB patients. Given the imperative to link effectiveness with value for money, a sound "investment case" based on measured or modelled costs could build convincing arguments for specific interventions. This is particularly relevant for nascent technologies which have yet to attain the recognition needed to become integrated into mainstream activities or others that would need a significant outlay to take off.

One important question is: what type of evidence is required to support the operationalisation of digital health in TB programmes in future? And what kind of evidence would be recognised by implementers before a product is embedded in routine practice, including TB care and prevention [39]? Many trials are under way investigating different elements of mobile health [40]. Certain interventions lend themselves more easily to a prospective cohort study or randomised controlled trial (RCT) design than those for which impact is less straightforward to measure or is influenced by a number of external factors. These include interventions possessing parameters that can be fairly well standardised, for which the collection of quantitative data on both the intervention and the outcome is digitised and relatively discrete, which allow randomisation or where large numbers of study participants as well as comparison groups can be recruited. This may explain why initiatives involving mobile text messaging (Short Messaging Service (SMS)), medication monitors and VOT for adherence support have been studied more frequently under RCT conditions than others such as eLearning or laboratory information systems. Another closely related question relating to evidence is how much research will be needed before users are confident of the effectiveness or efficiency of an intervention? The ease with which data can nowadays be collected and stored during the operation of a digital tool paves the way for the prospect of continuous appraisal and validation, bringing processes such as routine surveillance based on electronic medical records within the reach of more users.

Patient care

Treatment of active TB requires daily administration of medicines for at least 6 months, and up to 2 years or more in the case of multidrug-resistant (MDR)-TB and extensively drug-resistant (XDR)-TB [41]. Erratic treatment adherence may lead to unfavourable outcomes with continued spread of infection, acquisition of drug resistance, disease chronicity, and death. Loss to follow-up could be alleviated if patients are better supported during their treatment [42, 43]. Improved communication between patients and healthcare providers could thus increase patient engagement to adhere to treatment; ICT could facilitate bidirectional exchange. An added advantage is that the same medium of communication for patient–caregiver interaction could address other health risks that predispose to poor patient outcomes, such as smoking [44, 45]. Action on social and behavioural risk factors is very much in line with the objects of pillar 2 (Bold policies and supporting systems) of the End TB Strategy [4]. The potential for digital health tools to deliver and monitor access to social support and, more specifically, social protection schemes like cash transfers, is largely untapped at the moment. The extensive global coverage of standardised TB programmes represents a unique opportunity to deliver other interventions at a time when patients may be particularly attuned to health messaging (*e.g.* smoking cessation to tobacco users). The long-term care of patients with MDR-TB and XDR-TB, some of whom are in need of palliative care,

others of concomitant management of comorbidities such as HIV and diabetes, could benefit from existing and emerging digital health products.

As global connectivity expands, and hardware becomes more widely available and affordable, digital health products are destined to become increasingly present in the daily life of TB patients and practitioners. The potential for mobile phones to influence patient outcomes has been the subject of recent reviews [46, 47], one of which has looked specifically at evidence for the impact of SMS on TB adherence. Both reviews concluded that the evidence for the effectiveness of SMS-based interventions was not always clear: at times, no impact was registered, such as when SMS was used as a reminder. This lack of effect indicates that the design of future studies may need to test digital interventions within a wider range of behaviour-change techniques. High-quality evidence from RCTs is rare in this area and more has been published based on work from observational studies [48–52]. However, results from RCTs of mHealth and TB treatment adherence (including latent TB infection) conducted in very contrasting settings and using different applications, ranging from simple SMS to smartphone and online applications, are expected in the next few years [53–57]. Video interventions using phones have the potential to save resources when used to observe treatment and support patients [58–62]. Their feasibility is set to increase as Internet-enabled phones increasingly come to dominate the mobile phone markets, with low-resource countries expected to drive the incremental trend into the future [63]. Two ongoing RCTs are now investigating the effectiveness of VOT in TB patients using smartphones or other mobile digital devices [64, 65]; more are planned for the near future, including for the treatment of latent TB infection [66].

As various digital health products start to be developed in support of different components of TB programmes, it will be important to optimise their uptake at large scale. Even at the country level, it is becoming difficult, at times, to keep track of all the different initiatives, leading to underuse or wasteful parallel development of tools with a similar purpose. A one-stop Internet hub that links up to different services of relevance to TB care could serve to channel health professionals, patients and the wider public to an appropriate service (*e.g.* http://e-sanatate.md/). The end-product will not replace the triage or counselling roles of healthcare workers but will help them to locate resources better. This product may overlap with other tools being proposed in this report under the eLearning track (see the "eLearning" section later in this report, and TPPs 4.1 and 4.2); however, the primary intent of the Internet portal will be to inform about access rather than to promote learning.

The discussion on the digital health products for the "patient care" function thus focused on two items that were of particular interest at this juncture, namely: 1) VOT using mobile electronic devices to support TB patients on treatment; and 2) a common eHealth portal to inform TB patients and professionals about resources.

Surveillance and monitoring

Public health surveillance involves the continuous and systematic collection, analysis and interpretation of health-related data for planning, implementation and evaluation of public health practices [67]. It is one of the principal pillars of any functional public health system and an important tool for health action [68]. Effective surveillance will be needed to support the End TB strategy in the coming years [3], particularly through: measuring and monitoring the burden of disease and death, and determinants of TB, including risks such as tobacco use; measuring and monitoring the effectiveness of efforts to tackle the TB burden; reducing delays in TB care; monitoring drug safety; detecting and responding to TB outbreaks, including identifying "hot spots" and drug resistance, and interrupting the chain of transmission; planning for and managing resources such as TB medicines; guiding the planning, implementation, and evaluation of programmes and public policy to prevent TB; identifying gaps in knowledge and devising questions for research.

Implementing the core activities for a functional TB surveillance system often remains challenging in many countries due to a variety of factors, including: underdiagnosis or misdiagnosis of TB either through lack of access to health services or through poor diagnostic skills; inaccurate reporting and/or under-reporting of TB cases and inconsistent follow-up by frontline healthcare workers; inadequate use of the WHO standardised TB case definitions and reporting parameters [69]; TB notification may not be mandatory or, if it is, may not be enforced, with little motivation for the individual clinician (public or private) to notify; no coordination between different sources in the management of data useful for surveillance, including public and private sectors, insurance systems, laboratories, and hospital and outpatient facilities (these may have multiple information systems that live in silos and are not interoperable); weak culture of making use of programme data to inform decisions and often few efforts being made to have good quality data (*e.g.* by providing user feedback, updating the information and correcting mistakes); fragile health systems with limited resources, technology, human resources, knowledge, skills and time of frontline health workers due to various factors including competing duties, mismatching of an individual's skills with their job profile, inadequate pay, inefficient and error-prone paper-based processes, lack of feedback on the utilisation of the data, and lack of logistical and expert support.

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While general surveillance of TB often faces challenges in accuracy and completeness, the monitoring of TB drug safety tends to be even less developed globally. Many countries lack a functional drug-safety monitoring framework, as a result of weak health systems and the absence of a culture for routine monitoring of drug toxicity in TB programmes (in contrast for instance to TB drug resistance surveillance, which has been a mainstay for over 20 years [70]). This aspect of surveillance is now gaining importance within TB programmes as new drugs and novel regimens that incorporate repurposed medicines start to become available globally, particularly for MDR-TB and XDR-TB. These new interventions carry fresh hope for improved outcomes for patients. However, the safety profile of new medicines such as bedaquiline and delamanid, which were released on the market ahead of the completion of phase III trials, remains incomplete [71, 72]. The WHO policy on the use of these medicines recommends active monitoring for possible harm related to their use is in place. In 2015, WHO and main technical and financial partners defined the parameters for different levels of active drug-safety monitoring and management as they apply to the particular context of TB programmes [73, 74]. Development of basic but effective digital tools to collect and consolidate TB drug-safety data are thus in high demand at this point in time as countries prepare to expand their programmatic management of drug-resistant TB and avail of initiatives to facilitate access to new drugs (*e.g.* [75, 76]).

For many of the problems related to the collection, management, safe storage and transmission of data, today's state-of-the-art in ICT can already offer transformative solutions [77–80]. However, information systems are tightly knitted to social, cultural, legal and working environments, and the introduction of new digital products may be perceived by people as a challenge and an intrusion into their work. The intended users are more likely to embrace change if they are convinced that it will bear tangible benefits. Thus, for instance, the flexibility for managers to access data securely from wherever they can get online could be an important selling point. As in any other areas of change management, introducing new digital products in surveillance and monitoring needs an enabling environment [81], which includes: support of senior management for change; sufficient resources for key functions such as training, software development, updates, testing and troubleshooting, and data storage; development of guidance and standard operating procedures; health policy changes (*e.g.* mandatory notification of infectious diseases to public health authorities); data policy, such as promotion of data standards and interoperability [82], the adoption of unique patient and provider identifiers to link data sets, and the adoption of standard data dictionaries; and a legal framework for data ownership and privacy to establish trust in information systems.

Streamlining the electronic health record and reducing tedious and time-consuming paperwork could support "eHealth readiness" [83]. The steady transition in the management of medical records and surveillance systems, from paper-based methods, through electronic systems installed on isolated computer terminals, to systems on local area networks and, now, Internet-accessible databases with storage of data on the cloud, is an evolution over a continuum that happened in the space of a few decades. Such processes are not easy to evaluate with efficacy trials. Nonetheless, basic principles that apply under comparable situations, such as how to protect patient confidentiality and ensure that data are valid, safely stored and not corrupted, need to be followed when implementing digital health interventions [19, 84]. There are various measures that can be put in place to achieve this, ranging from automating error logs and crash reports (*e.g.* for electronic surveillance systems), building in user feedback modules (*e.g.* in eLearning packages), and holding regular audit reviews with system users to analyse critical episodes. Users intent upon introducing digital health interventions to facilitate their work would benefit from the description of best practices and lessons learnt narratives [85–87]. The effects described in such experiences could be modelled to illustrate their potential to save resources or to render a process more efficient. Implementation research to document gaps, bottlenecks, workarounds and good practices will be important for continued advancement [88–90].

TPPs for three products were proposed following the discussion in the consultation, namely: 1) an electronic dashboard of indicators and epidemiological trends relevant to TB; 2) digital notification of TB cases detected outside national TB programmes; and 3) digital tools to monitor the safety of TB drugs.

Programme management

Measuring the impact of ICT on programme management and building an evidence base around it pose similar challenges to those encountered in other areas of TB systems, given that the determinants of successful coordination and management are multifactorial. Indicators can nonetheless be identified to characterise the performance of certain elements of management. One such example is the influence of digital laboratory information systems (LISs) on the accuracy and turnaround time of test results [91, 92].

Diagnostic tests are an integral part of many public health interventions, guiding the detection of markers of disease and response to therapy. They have an important role in ensuring proper treatment, and avoiding unnecessary treatment and waste. In selecting the representative target product within the "programme management" function, the technical consultation focused on the performance of TB diagnostics as a domain of particular importance in modern TB care and which is now at a crucial

juncture following the wide roll-out of self-contained systems that employ molecular methods functioning on digital platforms, such as GeneXpert (Cepheid, Sunnyvale, CA, USA) [93]. These units can work with a high accuracy even when operated by staff without formal laboratory training located in decentralised healthcare centres with basic facilities. However, inefficiencies in the management of data are being recognised as a bottleneck in the operation of these new diagnostics. In reaction, software that extracts and transmits data from GeneXpert machines has been developed and successfully implemented in recent years [94–97]. However, up to now, these software programmes have been narrowly focused on a single technology and work in isolation of other diagnostic equipment located at times within the same premises. They thus miss out on larger benefits to be gleaned from a more comprehensive system that manages information from various diagnostic processes and that can also handle rapid roll-out and decentralisation of the diagnostic capacity.

Reliable and timely information is of paramount importance for the proper functioning of several processes in the TB laboratory, ranging from the management of patient results data (*i.e.* emission to the requestor of the tests and their integration within electronic health records to facilitate clinical management), the quality assessment of testing, the monitoring of laboratory activity, and the generation of indicators for surveillance (by avoiding repeated enumeration of same samples from the same patient) [98]. Improving laboratory information also serves the "patient care" function, by reducing time for patients to receive results [99]. Projects aiming to implement LIS in low-resource settings have rarely advanced beyond the pilot or demonstration stages. One reason for this is that the chain of requirements necessary for its proper functioning at the scale of a country or a laboratory network often has weaknesses in one or more elements. The difficulty of sharing data between different diagnostic technologies has been one formidable hurdle, resulting from either insufficient knowledge or willingness by the manufacturers of equipment to render their machine software compliant with accepted standards that facilitate the interoperability of data without additional costs to the user (*e.g.* Health Level Seven (www.hl7.org) and LOINC (http://loinc.org)).

Figure 2 is a schematic representation of three critical stages in information management within a functional TB diagnostic facility. The first step represents the concept of "connected diagnostics", whereby data generated by different diagnostic equipment are routed through a single channel. This stage would be closely followed by the next two components, namely 1) the storage of data and 2) their transmission to the requesting clinician or to the electronic health record. The TPP described in this document relates only to the first step; once the concept has matured, it is planned to develop separate TPPs for the next two components in the logical sequence.

eLearning

eLearning is defined as "an approach to teaching and learning, representing all or part of the educational model applied, that is based on the use of electronic media and devices as tools for improving access to training, communication and interaction and that facilitates the adoption of new ways of understanding and developing learning" [100]. eLearning techniques range from support, to conventional learning (as a "blended" approach), to teaching that is delivered entirely online. Regardless of the technology applied, learning still remains its central element [101].

Innovations in eLearning, such as the application of game techniques to education (gamification), and technologies like augmented reality and three-dimensional learning environments, are challenging the time-honoured fundamentals of how new knowledge is acquired. For instance, some websites now promote

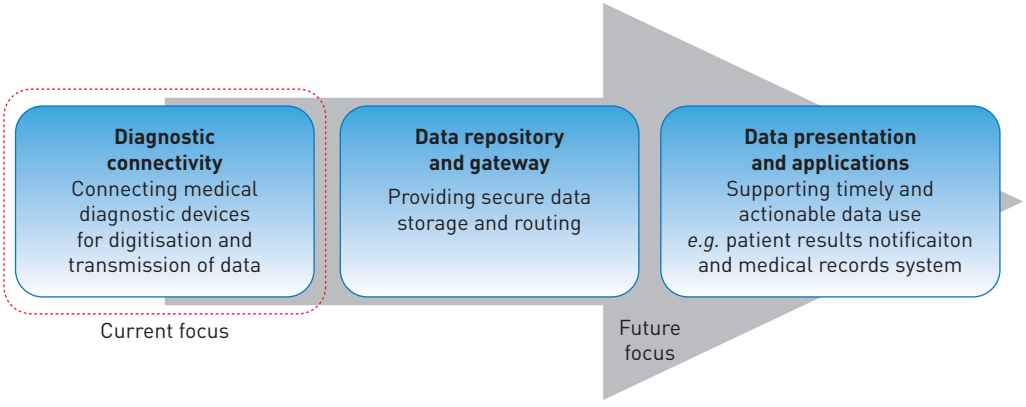

FIGURE 2 Schematic representation of the position of "diagnostic device connectivity" alongside other elements of a comprehensive laboratory information system for tuberculosis.

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the sharing of resources between frontline healthcare workers in peer-to-peer fashion (*e.g.* www.health-orb.org). Beyond eLearning as defined above, other resources, such as clinical decision support tools can assist health professionals to make a diagnosis or find the most suitable intervention in a particular patient interaction [102–104].

Both healthcare workers (formal or lay) and patients could benefit from new developments in learning techniques. In healthcare, the health needs of the population keep outpacing the health workforce availability and expertise, and eLearning presents many opportunities to close this gap. Reliable information about TB and other health risks could help patients and their relatives to cope better with the associated challenges. Clear and easy-to-understand messaging is expected to lead to a better informed decision when considering treatment options. Treatment of active TB involves the concomitant use of multiple medicines that often cause adverse effects that the patient should be aware of. Moreover, much of the evidence-based policy in TB care relies on low or very low quality data, which limits the strength of recommendations: in such a situation, aids would be of help for patients and professionals to make the most advantageous informed decision on care [105]. The combination of rapid access to a vast repertoire of online resources and the computational power of handheld devices now makes it possible to exploit more operational intelligence data when making a decision. This could ultimately improve a clinician's skills, just as eLearning delivers knowledge to a learner.

eLearning has the added advantage that it affords learners the luxury to work at their own pace and to follow their preferred educational pathways. When tutors are involved, these also stand to benefit from greater flexibility when compared to conventional training in organising their schedules and managing their time. eLearning is likely to reduce costs, improve the speed with which training and refresher courses are delivered, and permit access to a vast spread of resources, including novel curricula and experts. By virtue of their availability to a huge number of users across geographical space, eLearning products bear great promise as interventions that can be scaled up rapidly and efficiently.

Various sources for self-directed learning on TB management or smoking cessation are available online [106–114]. However, many such courses usually focus on one particular disease, and fail to capture a fuller spectrum of pulmonary conditions and other noncommunicable disease (NCD) risks that may be pertinent for the learner. The need for maintenance and updates of eLearning course material is often understated, and the quality and state of content of some sites may be poor. eLearning resources available today are still frequently text-heavy and not always customised for the virtual environment and for handheld devices in particular.

Published research comparing the outcomes of eLearning with more traditional methods of acquisition of knowledge in healthcare is still limited. However, there is a growing literature that supports the potential benefits for web-based training and use of multimedia techniques [115, 116], although there are only few reported studies that address synchronous eLearning programmes in medical education [117]. Online tobacco cessation courses have been reported by learners to improve ability and skills to counsel patients on tobacco cessation [118].

One of the risks of eLearning is the tendency for the depersonalisation of teaching and training. In some studies, dropout rates among eLearning students have been associated with feelings of isolation [119–124]. Greater interaction between eLearning participants may avert such situations [125].

Clinical decision support tools have been shown to influence the screening of patients at high risk of latent TB infection [126]. In another study, a clinical scoring system was found to be cost-effective for the diagnosis of smear-negative pulmonary TB [127]. Automating routines such as these could conceivably serve the practicing physician. Given the potential for such tools to improve the technical knowledge of the user, they have been included under the eLearning function.

Discussions during and after the WHO/ERS consultation identified three priority concepts for which TPPs could be usefully developed to support TB programmes. In the eLearning tools directed at both patients and professionals, antitobacco components feature prominently, given the impact that improved knowledge is expected to have on changing the behaviour of TB patients who smoke, alongside economic, environmental and organisational influences, and thus improving their treatment outcome. The TPPs were: 1) an online tool for patients and their relatives to learn about disease, treatment options, risk of transmission and associated health risks such as smoking (linked to TPP 1.2, which focuses on information on access rather than learning); 2) a comprehensive, web-based course on respiratory diseases, optimised for mobile devices and equipped with visual instruction aids aims to help building capacity and skills of health professionals in managing TB and reducing risks of negative outcomes (*e.g.* from smoking); and 3) a clinical decision-support tool to facilitate the daily work of practitioners and reduce the number of patients who receive suboptimal treatment.

Key steps in implementing digital health products for the End TB strategy

As discussed, the introduction of novel digital health technologies into a setting needs to fit within the digital health landscape that exists or is planned for the health services [20]. There needs to be agreement on the nature of the problem to be addressed, its relative priority compared with other pressing needs and the expectations made of the solution being envisaged. These discussions would need to be held through an iterative process with all interested parties.

Several digital health products may contribute to different functions of the digital health framework for TB [13]. Thus, for instance, eLearning is instrumental to staff development and would help caregivers acquire new skills in digital concepts, LISs will contribute not only to "programme management" but also to "patient care" and to "surveillance and monitoring", while digital applications for drug-safety monitoring will be important for "patient care". Likewise, many of the digital health products identified will contribute variably to the different components of the End TB strategy (table 2 and figure 1) [4].

"Thinking digital" needs to become a recurring motif in discussions on how to align national TB strategic plans [128], TB guidelines, budgets, grant proposals and other documents to the concepts of the End TB Strategy. These processes should keep abreast of ICT advances and, mindful of the fast pace with which ICT evolves, ensure that solutions do not lose their edge between the time that they are conceived to when they get deployed. A sequence of key steps is proposed for decision-makers to follow when digital health is operationalised at the country level.

At the country level, influential deciders in the TB programme who have the vision, knowledge, authority and drive will champion the "digital health" cause and steward in the necessary developments. To act as true "agents of change", they need to be willing to address critical issues in the adaptation and uptake of digital health interventions [129]. Different concepts are unified into a single vision for the local context. A group of key stakeholders, representing TB, public health, ICT, mobile and Internet network providers, technical agencies, private caregivers, patients and donors, is required to advise in different areas. Multidisciplinary "consortia" of developers and designers, users, and donors could be assigned to specific tasks, and to develop particular concepts, and ensure their sustainability and, at times, commercial viability.

Pillar 2 components of the End TB Strategy (on "bold policies and supportive systems"), which lie beyond the span of control of TB programmes or even ministries of health, are a particular challenge. Nonetheless, digital health can provide opportunities to make significant inroads in this domain and can have a profound impact on many of the upstream determinants of TB. These include broader issues in lung health and in prevention of NCD, money transfers *via* mobiles to reward health-promoting behaviour and alleviate poverty, universal health care (*e.g.* unique digital identifiers, such as the e-AADHAAR project in India (https://uidai.gov.in)), and other contributors to health system strengthening.

Critical points are identified on the pathway to the successful implementation of the End TB Strategy at the national level. These can then be mapped to complementary digital health interventions that are suited to the problems. The interventions would need to be prioritised based on the dual considerations of 1) knowledge of their effectiveness and 2) programmatic circumstances, including feasibility, time to implementation, resource use, potential benefit, associated opportunities, support structure for particular technologies and "eHealth readiness", *etc*. The TPPs described in this article were identified through a similar process and could be a starting point for similar country-level discussions. The documentation (*e.g.* national strategic plan [128]) and any regulatory instruments (*e.g.* eHealth strategy [20]) that need to be created or updated should be targeted for specific focus.

Resources will be needed for implementation. The interventions can be mapped to various likely sources of funding to create sound "investment cases" for specific interventions. Such investments will be expected to generate dividends beyond TB and health; this needs to be emphasised in messaging and is of particular relevance in the SDG era [130]. Products that are either open source or operated under a model of socially responsible licensing would be preferred [85, 131, 132]. Building capacity and developing human resources necessary for the implementation of the End TB Strategy needs to factor in the additional requirements for the workforce of tomorrow to be conversant with ICT and its uses. Looking for in-country expertise can stimulate innovation and cultivate partnerships that are more likely to be sustainable than those depending heavily on external support.

A realistic timeline for implementation should be developed and new interventions validated in the local setting ahead of scale-up. The notion of feasibility at scale is an important consideration when prioritising products: interventions should not remain stuck in the pilot stage [133].

Operational research should be planned in advance to measure the uptake, utilisation (type and extent) and impact of the intervention on performance, including costs. It is a means to ensure adherence to good

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TABLE 2 Relative importance of digital health products targeted by the target product profiles to individual components of the End TB strategy

End TB strategy pillars and components	1) Patient care		2) Surveillance and monitoring			3) Connected diagnostics for TB	4) eLearning		
	1.1) VOT	1.2) Digital health portal	2.1) Digital notification	2.2) Electronic dashboard	2.3) Drug safety data capture		4.1) Tools for patients	4.2) Tools for healthcare staff	4.3) Aids to decision-making
1) Integrated, patient-centred care and prevention									
a) Early diagnosis of TB including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups		++	++	++		++	++	++	++
b) Treatment of all people with TB including drug-resistant tuberculosis, and patient support	++	++	++	++	++	++	++	++	++
c) Collaborative TB/HIV activities and management of comorbidities	++	++	++	+	++	++	++	++	++
d) Preventive treatment of persons at high risk and vaccination against TB		++					++	++	++
2) Bold policies and supportive systems									
a) Political commitment with adequate resources for TB care and prevention		+	+						
b) Engagement of communities, civil society organisations, and public and private care providers	+	++	++				++	++	++
c) Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control	++		++	+	++		++	++	
d) Social protection, poverty alleviation and actions on other determinants of TB			++	+			++	+	

Continued

TABLE 2 Continued

End TB strategy pillars and components	1) Patient care		2) Surveillance and monitoring			3) Connected diagnostics for TB	4) eLearning		
	1.1) VOT	1.2) Digital health portal	2.1) Digital notification	2.2) Electronic dashboard	2.3) Drug safety data capture		4.1) Tools for patients	4.2) Tools for healthcare staff	4.3) Aids to decision-making
3) Intensified research and innovation									
a) Discovery, development and rapid uptake of new tools, interventions and strategies	+	+				++	++	++	++
b) Research to optimise implementation and impact, and promote innovations			+	++	++	+			

TB: tuberculosis; VOT: video (virtually) observed therapy; +: some relevance; ++: high relevance.

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practice, for instance, in data management and security during implementation [84]. Reporting of findings in a systematic manner would go some way to help strengthen the evidence base [90]. Lessons learnt would contribute to the third pillar of the End TB strategy ("intensified research and innovation"). Communication of findings would be of interest to both local and international workers.

Conclusion and next steps

Digital health interventions can strengthen health systems yet they remain underused [130]. In TB programmes, they need to be applied more consistently to improve patient care (*e.g.* support to adherence and efficient handling of medical records), surveillance and monitoring (*e.g.* improved notification, follow-up and drug-safety monitoring), programme management (*e.g.* laboratory management and drug procurement), and eLearning to enhance patient education and professional development [13]. In its diversity, ICT can contribute to all three pillars and 10 components of the End TB strategy [4]. This is particularly important in the first years of the post-2015 period, when TB programmes need to draw upon their creativity to optimise the effectiveness of currently available interventions to achieve the early targets slated for 2025 [2]. Digital health has far-reaching potential to help address more upstream determinants of TB, such as the large-scale assignment of truly unique personal identifiers (*e.g.* e-AADHAAR), which not only enhances medical record keeping but also facilitates access of vulnerable populations to their social entitlements. Similarly, schemes to reward healthy behaviours can be mediated more readily when records and monetary transfers are automated. ICT will remain an important factor for the large-scale roll-out of new diagnostics and novel medicines; two examples of these applications in the last few years include the software successfully implemented for the transmission of result data from Xpert MTB/RIF and for active drug-safety monitoring for bedaquiline-implementing programmes. However, if not appropriately planned or implemented, digital health interventions could lead to failures, waste and disenchantment. Negative experiences may have long-standing repercussions and prejudice against broader efforts to automate work processes, depriving programmes of potential efficiencies and other benefits.

The application of digital health for TB presents the dual challenges of having to deal with rapidly evolving technologies that can offer new opportunities at every turn, and the need for the decision-makers and implementers to maintain a creative outlook when implementing a new strategy that demands a fundamental departure from previous approaches to TB control. However, in addition to following the rapidly advancing technology closely, the implementer is also in a position to evaluate the technology, and to help inform about when and how it is best applied. Increasing this body of evidence and the documented best practices on digital health will be an important resource for decision-makers, and needs to be enriched by more experience gathered systematically from the field of TB.

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RESEARCH ARTICLE

The Yield of Community-Based "Retrospective" Tuberculosis Contact Investigation in a High Burden Setting in Ethiopia

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Abstract

Objective

To determine the yield and determinants of retrospective TB contact investigation in selected zones in Ethiopia.

Materials and Methods

This was a community-based cross-sectional study conducted during June-October 2014. Trained lay providers performed symptom screening for close contacts of index cases with all types of TB registered for anti-TB treatment within the last three years. We used logistic regression to determine factors associated with TB diagnosis among the contacts.

Results

Of 272,441 close contacts of 47, 021 index cases screened, 13,886 and 2, 091 had presumptive and active TB respectively. The yield of active TB was thus 768/100, 000, contributing 25.4% of the 7,954 TB cases reported from the study zones over the study period. The yield was highest among workplace contacts (12,650/100, 000). Active TB was twice more likely among contacts whose index cases had been registered for TB treatment within the last 12 months compared with those who had been registered 24 or more months earlier (adjusted odds ratio, AOR: 1.77 95% CI 1.42–2.21). Sex or clinical type of TB in index cases was not associated with the yield. Smear negative (SS-) index cases (AOR: 1.74 955 CI 1.13–2.68), having index cases who registered for treatment within <12 months (AOR:

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Contributions:

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Funding acquisition: MM YK YH PS.
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Visualization: ZG DJ DH MM NH.
Writing - original draft: ZG.
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2.41 95% CI 1.51–3.84) and being household contact (AOR: 0.072 95% CI 0.01–0.52) were associated with the occurrence of active TB in children.

Conclusions

The yield of retrospective contact investigation was about six times the case notification in the study zones, contributing a fourth of all TB cases notified over the same period. The yield was highest among workplace contacts and in those with recent past history of contact. Retrospective contact screening can serve as additional strategy to identify high risk groups not addressed through currently recommended screening approaches.

Introduction

Despite improvements in TB prevention and control efforts worldwide, national TB control programs miss a significant proportion of TB patients in many low and middle-income settings [1]. There is also delay in diagnosing TB and initiating treatment [2–5]. About one third of all incident cases of active TB are not properly diagnosed and there is a diagnostic delay in high TB burden settings [1, 6]. This is more pronounced in population groups with poor access to health care [4]. Even when physical access to health services is not a major challenge, people fail to seek health care for TB related complaints as people infected with TB are not symptomatic during early stages of the disease [7, 8]. Therefore, active case finding strategies are needed to detect and treat patients who are not identified through the usual passive approach.

Systematic screening of close contacts of smear positive pulmonary TB (SS+) is one of the globally recommended active case finding strategies [9]. Accordingly, contact investigation is done "prospectively", along the course of treatment of the index case [9, 10]. We previously reported our experience with implementing contact investigation among household contacts in two regions of Ethiopia indicating significant contribution of the intervention to overall TB case finding [11].

However, organizing prospective follow up of all close contacts is not adhered to because of logistical difficulties [12, 13]. Besides, earlier contact investigation studies in Ethiopia used only household contacts of SS+ index cases [11, 14]. While there is some evidence that TB among close contacts of SS-[15–17] and in contacts other than households [18, 19] is high, this has not been demonstrated in routine program settings.

We introduced a "retrospective" contact screening approach whereby all clinical types of TB cases treated in the previous three years were listed and their contacts were traced to determine if they had developed symptoms of TB. Our objective was to determine the yield of "retrospective" community-based TB contact investigation and identify factors associated with occurrence of TB among the contacts in selected six zones in Ethiopia.

Materials and Methods

Design and Setting

We conducted a community based cross-sectional study in six zones with population of over 14 million in Oromia and Amhara regions of Ethiopia between June-October 2014. These zones had a higher case notification rate (CNR) of more than 130 per 100,000 from 2011–2014. The two regions have implemented the DOTS strategy for the last two decades [20, 21]. The regional health bureaus of the two regions led the implementation of the study with support

from the Help Ethiopia Address the Low Performance of TB (HEAL TB), a project funded by the United States Agency for International Development (USAID).

Data Collection

We recruited and trained lay providers to do active tracing and symptomatic screening of contacts of TB index cases. These lay providers also served as data collectors. They were recruited and deployed from the same *Kebeles* (the smallest administrative unit) of their residence, for easy tracing of past TB patients and their contacts. The data collectors were high school graduates. Together with TB focal persons and health extension workers (HEWs), they received a 2-day training on the basics of symptoms of TB including the screening algorithm, data collecting tools and standard operating procedures of the study.

Definitions

We defined an *index case* as PTB or extra-pulmonary TB (EPTB) identified within a household registered at health facilities. A *close contact* is a person who shared the same enclosed living space for one or more nights or for frequent or extended periods during the day with the index case during the 3 months before the diagnosis of TB, such as household family, co-workers sharing same enclosed workplace or neighbors [19]. If close contacts are other than household, co-worker or neighbor they were classified as "other". The approximate dates of contacts' last exposure to the patients were determined using the treatment initiation data of the patients [22].

We used locally-adopted and translated version of standard symptom-based screening criteria developed by the World Health Organization [9, 10]. The criteria used in adult contacts were cough, weight loss, fever and night sweating. In child contacts the criteria were cough, weight loss or failure to gain weight, reduced playfulness, fever or/and night sweating. Presumptive TB case was defined when cough or two or more of the symptoms other than cough persisted for at least two weeks [9, 10].

TB case definition was based on the standard definitions of the National TB and leprosy control program guideline of Ethiopia for the diagnosis and treatment of TB cases [23]. Accordingly, SS+ is a patient with at least two initial sputum smear examinations positive for acid fast bacilli (AFB) by direct microscopy, or one initial smear examination positive for AFB by direct microscopy and culture positive, or one initial smear examination positive for AFB by direct microscope and radiographic abnormalities consistent with active TB as determined by a clinician. SS- is a patient with symptoms suggestive of TB with at least three AFB negative sputum smear examinations, radiographic abnormalities consistent with active pulmonary TB, no response to a course of broad spectrum antibiotics and a decision by a clinician to treat with a full course of anti-TB chemotherapy. EPTB is a patient who has TB in organs other than the lungs, with at least one specimen with M. tuberculosis or histological or strong clinical evidence consistent with active EPTB, followed by a decision by a clinician to treat with a full course of tuberculosis chemotherapy.

The Procedure for Contact Investigation

We listed all TB cases registered for TB treatment from mid-2011 to mid-2014 in the health facility registers. Using the list, data collectors visited the index cases and traced their close contacts. The lay providers used the symptom-based screening criteria to screen the contacts. Thus, contacts that fulfilled the criteria for presumptive TB were documented as screen result positive. Otherwise, they were screen result negative. Screen negative under-five children were referred for Isoniazid preventive therapy (IPT) to health facilities.

The lay providers referred presumptive TB cases to health centers using TB suspect referral slip. At health centers, sputum examination was done using Ziehl-Neelson (ZN) microscopy,

the nationally recommended TB diagnostic method [23]. Presumptive TB cases gave three sputum samples, morning-spot-morning, to diagnose pulmonary TB. EPTB and clinically suspected SS− were referred to hospitals and private clinics for chest radiography and other necessary investigations for TB. Health care workers at the health centers sent back the sputum result of the suspects to the lay providers using the feedback section of the suspect referral slip. The lay providers registered the sputum result on the contact register.

The HEWs closely monitored the work of data collectors and reviewed their performance on a monthly basis. Zonal and district TB focal persons supervised the implementation of these activities as part of their routine work.

Data Management and Analysis

We used contact registers for the registration of traced and symptomatically screened contacts. The register had the following variables: types of index TB cases, age and sex of contacts, number of contacts per index case, type of contacts, contacts screened, screening result, presence or absence of active TB, and type of TB cases identified. The register served as primary data source for the study based on which data entry template was prepared using the Cis-pro software. We exported the data to STATA for analysis. We have uploaded the minimal data set without identifier of the study participants as supporting information (S1 Dataset).

To ensure data quality, randomized blinded quality check was made. Data was also entered to excel based performance monitoring system for consistency check. In addition, each data element was run independently to identify data entry errors. Zonal and district TB focal persons supervised the data collection to ensure completeness of data. Hence, there was only 0.23–0.44% missed data. Average imputation method for age, common-point imputation for period when index cases registered for anti-TB and modal imputation for type of contacts and sex was applied to fill in the missed values [24]. There was no unique pattern in the missing data on these variables.

We used frequency, percentage and mean to describe index cases and their contacts. The yield is described using proportion and per 100, 000 of contacts with 95% confidence interval (95% CI). We used logistic regression analysis to determine factors associated with TB diagnosis among the contacts. The outcome variable, TB diagnosis, was labeled as 1 if TB was detected and 0 if no TB detected. Variables with p-value less than 0.2 in univariate analysis were included in the multivariable analysis. We conducted a subgroup analysis of child contacts $<$15 years to determine factors associated with cases of TB in children.

Ethical Statement

Ethics Review Committees of Oromia and Amhara Regional Health Bureaus approved the study protocol, oral informed consent procedure and the data collection tool. Letters of permission to implement the intervention and access to TB registers were obtained from relevant authorities. Only contacts who gave oral consent to participate in this study were screened for TB. We used oral consent because the study included predominantly rural population who could not read and write. In the contacts of age less than 18 years, their parents or guardian were asked for consent. Contacts with TB diagnosis received care according to the standard practice.

Results

Characteristics of Index Cases and their Contacts

We included 47,021 index cases registered in the 427 health facilities of the study zones during the five month of study period. About 43% of these had been registered for anti-TB treatment

before 24 months during data collection period. The rest (57.3%) initiated the treatment within 24 months of data collection period. Forty-one percent of the index cases were SS+.

Of 272,515 eligible close contacts approached, the lay workers screened 272,441(99.97%) close contacts. The proportion of screened contacts among total population in the study zones was 1.9%. The ratio of contacts to index cases was 5.8. About 43% of the contacts were identified from SS+ index cases whereas the respective 29% and 28% were from SS- and EPTB index cases. Household, neighbor, work place and other contacts constituted 63%, 11.3%, 0.6% and 25.7% respectively. About 52.5% and 64.6% of the contacts were male and adults or adolescents of age greater than 14 years, respectively (Table 1).

The Yield of TB Screening

Of those screened, 13,886 (5.1%) and 2, 091 (0.8%) were found to have presumptive and active TB respectively. The yield of all forms of TB per 100, 000 contacts was thus 768/100, 000. Of

Table 1. Characteristics of index cases registered and contacts with index cases approached for screening in the six study zones, June-October 2014, Ethiopia.

Variables	Number	Percent (%)
Index cases		
By type of TB		
SS+	19235	40.9
SS-	13652	29
EPTB	14134	30.1
Total	47021	100
By the period they registered for treatment		
<12 months	15251	32.4
12–23 months	11678	24.8
> = 24 months	20092	42.7
Contacts with index case registered		
Contacts approached by type of index cases		
SS+	116324	42.7
SS-	78721	28.9
EPTB	77470	28.4
Total	272515	
Type of contacts		
House hold	170136	62.4
Neighbor	30585	11.3
Workplace	1643	0.6
Other	70151	25.7
Contacts by sex		
Male	143143	52.5
Female	129372	47.5
Contacts by Age Category		
<5 years	22655	8.3
05–14 years	73963	27.1
> = 15 years	175897	64.6
Contacts based on the period their index cases registered for treatment		
<12 months	89822	33
12–23 months	66669	24.5
> = 24 months	116024	42.6

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the 2,091 active TB cases diagnosed through contact screening, 77.4% were SS- while 16.5% were SS+ cases. Active TB cases detected through the retrospective screening constituted 25.4% of the 7,954 TB cases reported in the study zones during the study period. The prevalence of SS + among the adult contacts was 106/100,000. The proportion of SS+ among presumptive TB cases was 2.5%. TB cases detected among household contacts were 0.96%. Also, the respective yield per 100, 000 among households, neighbors and workplace contacts was 861, 1053 and 12, 650 (Fig 1). For contacts whose index cases registered for treatment < 12 months, 12–23 months and > = 24 months, the respective yield per 100, 000 contacts were 1106, 600 and 602 (Fig 2).

After adjusting for co-variates, the rate of active TB was 1.77 times higher among contacts whose index cases registered for treatment within the last 12 months than contacts that had been exposed 24 or more months earlier (AOR: 1.77 95% CI 1.42–2.21). The rate of active TB was higher in the age group of 25–34 years (AOR: 1.80 95% CI 1.2–2.62) and 35–44 years (AOR: 2.14 95% CI 1.42–3.22) as compared to under-five children. The odds of active TB cases from neighbor (AOR: 1.35, 95% CI 1.02–1.78) and workplace (AOR: 3.95: 95% CI 2.21–7.03) were significantly higher than active TB cases detected from household contacts. However, the yield from contacts of "other" category was less than the yield from household contacts (AOR: 0.13, 95% CI 0.08–0.20).There was no significant difference in yield between close contacts of SS+ index cases and those of EPTB (AOR: 0.88: 95% CI 0.69–1.13) and SS- index cases (AOR: 1.19: 95% CI 0.95–1.49) (Table 2).

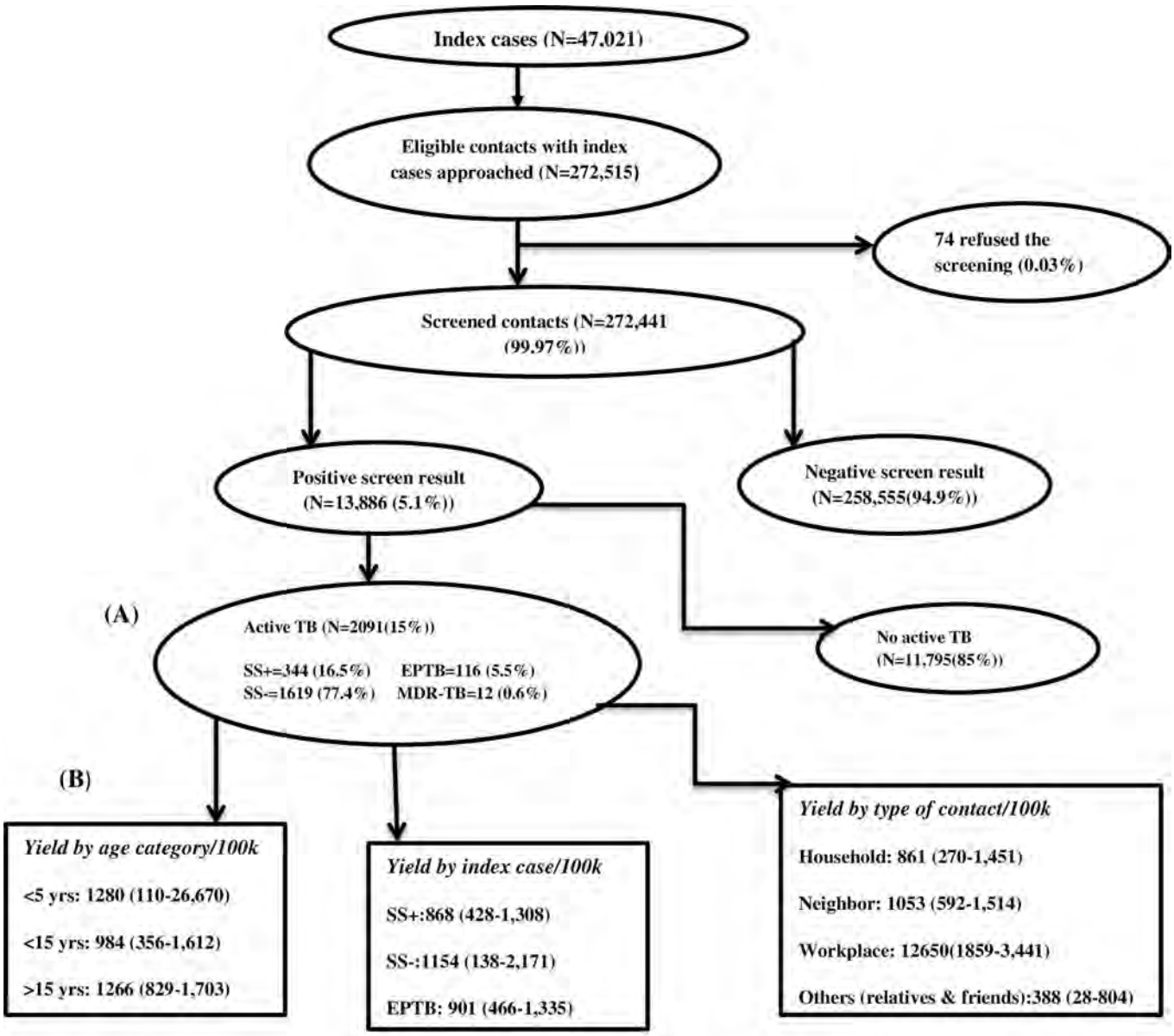
Being contact of SS- index cases (AOR: 1.74 95% CI 1.13–2.68), having index cases who registered for treatment within <12 months (AOR: 2.41 95% CI 1.51–3.84), and being household contact (AOR: 0.072 95% CI 0.01–0.52) were factors that were significantly associated with the occurrence of active TB in children (Table 3).

Discussion

To our knowledge, this is the first report of the yield of retrospective TB contact screening in a community setting in Ethiopia through which we were able to detect over two thousand TB cases. The yield was about six times the case notification rate in the study zones and contributed about a quarter of all notified cases over the same period. Our findings suggest that retrospective contact screening can be considered a useful strategy for identifying additional TB cases not addressed through the routinely implemented case finding strategies.

Earlier studies reported the yield of contact screening among household contacts of SS + index cases using prospective screening approach [11, 14, 25–29]. The yield of 0.96% among household contacts in the current study is comparable with what was reported by Salinas et al [30]. On the contrary, it is lower than the yield by the prospective approaches; 2.5% in similar setting in Ethiopia [11], 6.07% in South Africa [28] and the global average of 3.1% [31]. However, the overall yield in our study is about six times the case notification rate in the study zones during the same time period. The yield among contacts whose index cases registered for TB treatment within 12 months was eight times the TB case notification in the study zones. Thus, our finding clearly highlights the need to include retrospective contact screening, at least for contacts whose index cases registered for treatment within the past one year, as one of the strategies for case detection.

The 2.5% SS+ cases among the presumptive TB cases in this study might be underestimate but still relatively higher than the corresponding rate of 1.2% in the Ethiopian National TB prevalence survey [32]. However, the 106/100,000 prevalence of SS+ among the adult contacts is much higher than the result from the TB prevalence survey in Eritrea [33] and equivalent to the prevalence of 108/100,000 in the national TB prevalence survey in Ethiopia [32].



Ethiopia. **(A)** Contacts that fulfilled the criteria for presumptive TB were documented as screen result positive. Proportion of TB categories (SS+(smear positive TB), SS-(smear negative TB), EPTB (extra-pulmonary TB) & MDR-TB (multi-drug resistance TB)) was from all TB cases identified (2,091). **(B)** Yield of TB for age categories, type of index cases and contacts was computed per 100k (100,000) of their respective contacts. Ranges in parentheses are 95% Confidence Intervals.

Fig 1. Flow diagram of screening and yield of retrospective contact investigation, June-October 2014, Ethiopia.

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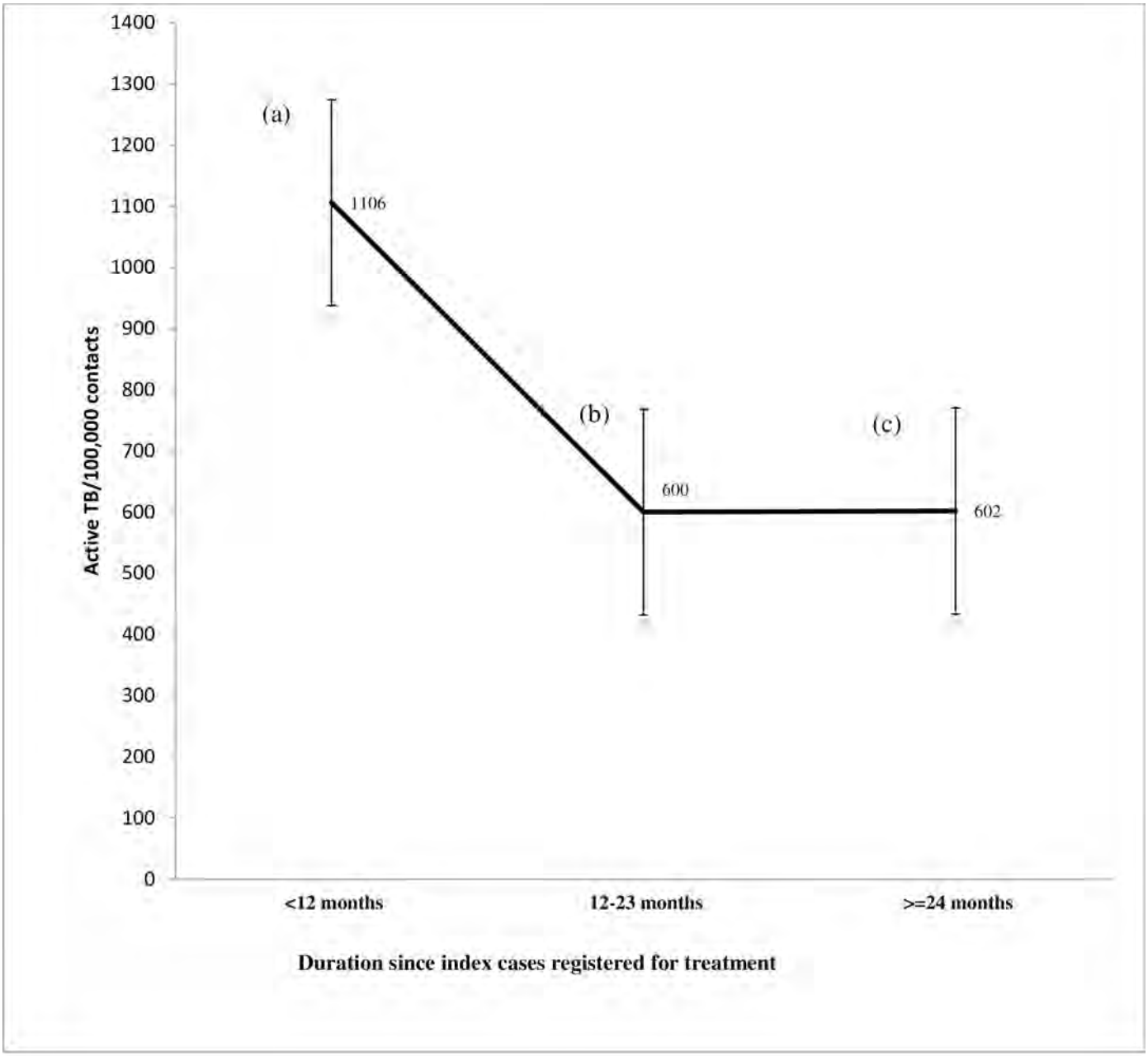

Line bars; (a) (923-1288), (b) (418-754) and (c) (423-749) indicate 95% Confidence Intervals (CIs) for the yield of TB per 100,000 of contacts of index cases registered for TB treatment during <12 moths, 12-23 months & >= 24 moths, respectively. The CI of the yield from contacts whose index case registered within one year during the study period is not overlapping and higher than the CI of the yields from contacts whose index cases registered for treatment during 12-23 months or more.

Fig 2. Yield per 100,000 contacts based on the time since index cases registered for TB treatment.

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Table 2. Factors associated with active TB in retrospective contact investigation, June–October 2014 Ethiopia.

Variables	Active TB case (%)		Active TB [1] versus non-TB[0] cases		
		COR	95% CI	AOR	95% CI
Year index cases registered for TB treatment					
<12 months	993 (1.4)	2.04	1.64–2.54	1.77	1.42–2.21
12-23months	400 (0.7)	0.98	0.74–1.30	0.93	0.7–1.24
> = 24 months	698 (0.7)	1			
Type of Index cases registered					
SS+	854 (0.9)	1			
EPTB	507 (0.7)	0.8	0.63–1.03	0.88	0.69–1.13
SS-	730 (1.1)	1.23	0.98–1.53	1.19	0.95–1.49
Age C**ategory of contacts**					
Children (<15 years)	581 (0.7)	0.68	0.54–0.84	0.55	0.44–0.69
Adult (>15 years)	1510 (1.0)	1			
Sex of Contacts					
Female	951 (0.74)	1			
Male	1140`(0.80)	1.15	0.95–1.40	1.12	0.92–1.37
Type of contacts					
House hold	1627(1.1)	1			
Neighbor	352(1.4)	1.23	0.94–1.62	1.35	1.02–1.78
Workplace	78(4.8)	4.5	2.55–7.94	3.95	2.21–7.03
Other	34(0.2)	0.14	0.09–0.22	0.13	0.08–0.20

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Our study revealed a significantly higher yield of active TB among workplace contacts as compared to other types of contacts. This might be due to the fact that the index cases share the same enclosed space for longer hour and the spaces might be overcrowded and poorly ventilated coupled with the little awareness on TB prevention [34]. A study on contact screening at workplace from Portugal revealed that the yield was 8.4 TB cases per index case [19]. This

Table 3. Determinants of active TB in children <15 years through retrospective contact screening, June-October 2014, Ethiopia.

Variables	Number (%) of active TB	Active TB [1] and no TB [0] in children <15 years of age			
		COR	95% CI	AOR	95% CI
Type of Index cases					
SS+	223 (0.6)	1			
SS-	242 (1.0)	1.85	1.20–2.84	1.78	1.16–2.75
EPTB	116 (0.5)	0.88	0.51–1.50	1.004	0.59–1.72
Time index cases completed treatment					
<12 months	313 (1.1)	2.69	1.69–4.27	2.4	1.50–3.82
12 months—23months	131 (0.6)	1.4	0.78–2.51	1.31	0.73–2.36
> = 24 months	137 (0.4)	1			
Type of Contacts					
Household	542 (0.8)	1			
Neighbor	32 (0.4)	0.47	0.21–1.08	0.51	0.22–1.17
Workplace and Others	7 (2.3)	0.12	0.03–0.51	0.14	0.035–0.58
Sex of contacts					
Female	312 (0.70)	1			
Male	269 (0.73)	0.95	0.64–1.39	Not applicable	Not applicable

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suggests that there is a need to consider contact tracing beyond households especially in congregated workplaces such as schools, mining areas and prisons. Further studies should include detailed work place related variables such as employment status, hours and working conditions so as to generate more evidence on factors associated with increased risk of TB in work place contacts.

We also involved neighbor visitors of the sick index cases for contact investigation. This is because most neighbors in rural Ethiopia are relatives and genetically related to the sick. It is also part of the tradition of Ethiopian society to visit and stay with the sick while they are possibly exposed. The yield was higher at 1.4% among the neighbor contacts. Cheng et al (2015) from Uganda showed that first degree relatives' contacts were more likely to be symptomatic for TB [18]. It was also shown by Lienherdt et al (2003) in Gambia that development of TB cases increased with first degree relatives compared with more distant and non-genetically related households [13]. In fact, it is possible that genetic factors contributed to the susceptibility to TB infection [15]. Also, Classen et al (1999) indicated the need to target contacts outside of households in high incidence TB areas to reduce TB transmission [35]. These studies from elsewhere suggest the need to consider close relatives for contact screening, and the higher yield among the neighbors in the current study suggests that retrospective contact is also a feasible strategy for contacts of neighbor and relatives.

The yield of TB among adult contacts was higher than that of child contacts, which is likely to be related with underdiagnoses among children due to diagnostic difficulties [36]. Most of the TB cases were also identified from close contacts of TB patients with SS+ which is in line with most studies [11, 15, 26, 27, 29, 30, and 37].The greater proportion of childhood TB was detected from the contacts of SS-. It could be due to the selective nature of the prospective contact screening through which contacts of SS+ cases might have already been identified and taken care of. However, it needs further clarification in future studies. The fact that SS- can contribute to TB transmission has been shown in other studies [15–17]. The strategy of screening only those in contact with SS+ cases is likely to miss about one third of infected individuals [38].

Through the retrospective contact screening approach, we also detected TB cases from close contacts of EPTB index cases. Likewise, there are studies which included EPTB as an index case during active case findings [12, 39]. Contacts of patients with EPTB were evaluated because there are possibilities of associated pulmonary TB (PTB) cases [15]. Laryngeal TB and pleural TB are EPTB but can transmit TB as well [15–22]. There is also the opportunity to identify the real index cases of the identified EPTB that failed to be detected through the routine case detection strategy. Thus, in settings where TB is highly prevalent and there is a challenge of delay in the diagnosis there are possibilities of missed TB cases in the community [40]. Seeking for contacts of EPTB could detect the undiagnosed and missed TB cases which could be the real index cases of the EPTB. These could be cases that shared other common index cases but failed to seek health service. Therefore, comprehensive contact tracing should be considered in high burden settings.

The findings in this study should be interpreted cautiously as there were some limitations. We used symptom screening and light microscopy to diagnose SS+. Hence, a chance of missing the SS+ cases cannot be ruled out [41] though our study was done at health facilities that participated in a regular AFB microscopy external quality assessment (EQA) with concordance of 95% on random blinded rechecking [42]. In other studies, using digital X-rays in addition to symptom screening and fluorescent microscopy for diagnosis could not also detect all SS + cases individuals [32, 33]. Also, we included limited number of variables which did not allow thorough evaluation of all the potential determinants of TB among contacts. In addition, only few of the neighbor close contacts were accessed and screened as most of them did not fulfill

the criteria of close contacts. However, this is the first study reporting the yield of retrospective contact screening from Ethiopia and perhaps one of a few globally [43]. The other strength of this study is the large number of contacts screened compared with earlier reports.

Conclusions

The yield of retrospective contact screening through community-based approach was about six times the case notification in the study zones and contributed a significant proportion of all cases notified in the study districts. The risk of TB was high among contacts irrespective of the type of TB in the index case. This highlights that retrospective contact screening can be of high yield strategy among all types of index TB cases especially within one year of the registration of the index case. The yield was highest among work place contacts, suggesting the need to prioritize work place interventions for TB prevention and control. Further implementation and evaluation of retrospective contact screening should be done in similar settings to validate these findings. Such evaluations should include cost and cost-effectiveness studies.

Supporting Information

S1 Dataset. Data set for the retrospective contact investigation study.
(DTA)

S1 Table. The contact investigation register.
(DOCX)

S1 Text. Information sheet and oral informed consent form.
(DOCX)

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The additional yield of GeneXpert MTB/RIF test in the diagnosis of pulmonary tuberculosis among household contacts of smear positive TB cases

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ABSTRACT

Objective: The objective of this study was to compare the diagnostic yield of GeneXpert MTB/RIF with Ziehl-Neelson (ZN) sputum smear microscopy among index TB cases and their household contacts.
Methods: A cross sectional study was conducted among sputum smear positive index TB cases and their household contacts in Northern Ethiopia.
Results: Of 353 contacts screened, 41 (11%) were found to have presumptive TB. GeneXpert test done among 39 presumptive TB cases diagnosed 14 (35.9%) cases of TB (one being rifampicin resistant), whereas the number of TB cases diagnosed by microscopy was only 5 (12.8%): a 64.3% increased positivity rate by GeneXpert versus ZN microscopy. The number needed to screen and number needed to test to diagnose a single case of TB was significantly lower with the use of GeneXpert than ZN microscopy. Of 119 index TB cases, GeneXpert test revealed that 106 (89.1%) and 5 (4.2%) were positive for rifampicin sensitive and rifampicin resistant TB, respectively.
Conclusion: GeneXpert test led to increased TB case detection among household contacts in addition to its advantage in the diagnosis of Rifampicin resistance among contacts and index TB cases. There should be a consideration in using GeneXpert MTB/RIF as a point of care TB testing tool among high risk groups.
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1. Background

Globally, there were an estimated 9.6 million incident cases of TB in 2014. The best estimate of the case detection rate for all forms of TB globally in 2014 was 63%, whereas 3.6 million cases remained undetected[1]. The cases that remained undetected continue to suffer from TB disease and also transmit the disease to their contacts[2]. The regions that contributed for most of the undetected all-forms incident TB cases are south-east Asia and Africa[3]. The passive TB case finding has contributed significantly in the identification and management of TB cases presenting to health facilities[3,4]. There is still the need to exert further efforts geared toward improving TB case findings and possibly identify the undetected TB cases that would have been missed while using the conventional passive TB case finding approaches[5–7].

The World Health Organization (WHO) recommends systematic screening for active TB with the aim of early detection of TB cases and prompt treatment that ensures better treatment outcome and reduced TB transmission to contacts[8]. There is a strong recommendation that household contacts and other close contacts should be systematically screened for active TB[8,9]. The globally recommended initial diagnostic tests for presumptive TB cases identified among contacts were either sputum smear microscopy to identify acid fast bacilli (AFB) or a rapid molecular test like GeneXpert MTB/RIF[8,9].

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A total of 137,081 incident TB cases were diagnosed in Ethiopia in the 2014/15 fiscal year with a case detection rate of 67%[10]. In Ethiopia, TB case finding was mainly focused on passive case finding at health facilities and referrals by community health workers which were able to detect up to two-third of the annually estimated TB cases[11]. To improve the TB case finding, one of the new approaches recommended by the national TB program is TB screening among close and household contacts of infectious TB cases. The first line laboratory test for presumptive TB cases identified in the contact screening is sputum smear microscopy while GeneXpert MTB/RIF test is also recommended if the index TB case is a drug resistant TB patient or is at risk of harboring drug resistant TB[11].

The national GeneXpert MTB/RIF implementation guideline recommends its use among presumptive MDR TB cases that include symptomatic contacts of MDR-TB cases, and presumptive TB cases among HIV positive individuals and children below 14 years of age[12]. Studies have been confirming that GeneXpert MTB/RIF test had significantly higher yield than sputum smear microscopy in different settings including Ethiopia[13–15]. However, the wider decentralization and use of GeneXpert MTB/RIF in low income countries needs to be evaluated in terms of its cost, ongoing supplies, maintenance issues and the need for uninterrupted electric supplies. There is also a need to demonstrate the added advantage of GeneXpert MTB/RIF over conventional sputum smear microscopy in different settings including contacts[16,17]. Studies that compared the yield of GeneXpert MTB/RIF with smear microscopy among contacts of index TB cases are scarce.

In this study, the diagnostic yield of GeneXpert MTB/RIF was compared with that of Ziehl-Neelson (ZN) sputum smear microscopy among index TB cases and their household contacts.

2. Methods

2.1. Study design and setting

A cross sectional study was conducted among sputum smear positive index TB cases and their household contacts. The study was done at eleven TB diagnostic and treatment health centers in North Gondar zone of Amhara region, Ethiopia between May 2013 and April 2015. North Gondar Zone has a total population of 3.6 million with TB case notification rate of 119 per 100,000 population (Unpublished data, Management Sciences for Health, 2015). There are three hospitals and 133 public health centers providing TB prevention and control services in the zone. Health centers are operated by Nurses, Health Officers, Laboratory Technicians, Pharmacy Technicians and administrative staff. The eleven health centers included in the study were selected as they are closer to Gondar University Hospital so that sputum specimens for GeneXpert test could be transported easily. These health centers have been participating in the external quality assurance (EQA) program of the country for ZN microscopy. The false positivity and false negativity rate of AFB slide readings at health facilities against the EQA center readings in the study area were found to be 0.19% and 0.17% respectively (Unpublished data, Management Sciences for Health, 2015).

2.2. Identification of index TB cases and their household contacts

We trained TB focal persons in the eleven health centers on the data collection, symptomatic screening, sputum sample collection and referral. New AFB sputum smear positive patients diagnosed in the 11 health centers during the study period who had at least one household family member were included in the study. Once the patient was diagnosed, the address of the patient was recorded. The contact details of 119 consecutive smear positive index TB cases were noted. All index cases were either asked to bring their household contacts to the health center or visited at home by the study team composed of supervisors and community health workers called health extension workers (HEW) within 2 weeks of diagnosis. Household contact was defined as a person who shared the same enclosed living space for one or more nights or for frequent or extended periods during the day with the index case during the 3 months before commencement of the current treatment episode[9]. TB focal persons and both urban and rural HEWs were involved in registering the household contacts and screening of contacts for symptoms suggestive of TB.

2.3. Data collection and TB symptom screening

A baseline data was filled in a standardized questionnaire for each index smear positive TB case by the TB focal person in the health centers. The major information collected was socio-demographic data, signs and symptoms, duration of illness, contact history and the laboratory results. A family matrix form was used to register all household contacts. A standard questionnaire was administered by the TB focal person or HEWs to each household contact independently that included socio-demographic characteristics and relationship status to the index case. The TB focal person or HEWs registered the household contacts and screened them for the major signs and symptoms of TB. Household contacts with history of cough for two or more weeks or with two or more symptoms suggestive of TB were considered to have presumptive TB[8]. Presumptive TB cases were referred to the health center for further evaluation and laboratory investigation (ZN microscopy and GeneXpert).

2.4. TB diagnosis

Three sputum samples (Spot-Morning-Spot) were collected at the health centers from each household contact with presumptive TB. Morning sputum specimens were also collected from the 119 index TB cases for GeneXpert test. All the 119 index TB cases were already put on first line anti-TB drug treatment based on the ZN microscopy result and continued the treatment even if the GeneXpert test result turned out negative. The TB focal persons in the respective health centers transported the sputum samples to Gondar University hospital following the standard infection control and specimen transportation procedures (using cold box) for GeneXpert test. Trained senior laboratory personnel in the health centers and Gondar University hospital were engaged in conducting the ZN microscopy and GeneXpert tests, respectively. The laboratory personnel doing ZN microscopy and GeneXpert MTB/RIF test were blinded. The three samples from contacts were tested for AFB by ZN sputum smear microscopy and GeneXpert test was also done on the morning sputum sample. In addition, GeneXpert test was done on the morning sputum specimens collected from the index TB cases.

2.5. Data analysis

Data entry and analysis was performed using SPSS, Version 13 (SPSS Inc., Chicago, Illinois). Data was entered by an experienced data clerk under the supervision of the principal investigator. Frequency, percentage and 95% confidence interval of proportions were computed. The number needed to screen (NNS) and number needed to test (NNT) was also computed. NNS is the number of contacts required to be screened to detect a single case of active TB; NNT is the number of contacts with presumptive TB required to be investigated in the laboratory to detect a single case of active TB. The 95% confidence intervals of proportion among different

categories were compared: absence of overlap in 95% confidence intervals is considered as a statistically significant difference.

2.6. Ethical considerations

Ethical approval was obtained from the University of Gondar ethical review board [reference number RCS/P/05/485/2013 dated June 4th 2013]. Each study participant provided a written informed consent and permission was obtained from all health facilities. Written parental consent was also obtained for participants below the age of 18 years. Household contacts with positive TB result were treated in accordance with the national tuberculosis program recommendations[11]. Rifampicin resistant results by GeneXpert test were immediately communicated to each health centers for proper management of patients as per the national tuberculosis program recommendations[11].

3. Result

3.1. Characteristics of index cases

A total of 119 newly diagnosed index TB cases were registered during the study period. They were sputum smear positive by the ZN staining done in the laboratory of the respective health center. The index cases lived in 119 different households. Two-thirds of the index cases were urban residents and the male to female ratio was 1.38. Four-fifths of the index cases were in the age range 15 to 44 years with mean (SD) age of 31.2 (14.1) years (Table 1). Only 6 (5%) had past history of TB. GeneXpert MTB/RIF test was done for all index TB cases. The GeneXpert test among index TB cases revealed that 8/119 (6.7%) were negative for TB while 106/119 (89.1%) and 5/119 (4.2%) were rifampicin sensitive and rifampicin resistant TB, respectively.

3.2. The yield of active TB case finding among household contacts

A total of 393 contacts were identified in 119 households with contact to index TB cases ratio of 3.3. The contacts were between 1 and 94 years of age with Mean (SD) age of 24.6 (18.2). Out of 393 contacts, 353 (89.8%) were screened for symptoms suggestive of tuberculosis. A total of 41 (11%) of the screened contacts were found to have presumptive TB of which all with the exception of two under-five children were checked with ZN microscopy (spot-morning-spot) and GeneXpert MTB/RIF test. Of 39 presumptive TB cases with sputum samples, GeneXpert test diagnosed 14 (35.9%) cases of TB whereas the number of TB cases diagnosed by ZN microscopy was 5 (12.8%): a 64.3% increased positivity rate by GeneXpert versus ZN microscopy. The entire five cases positive by ZN microscopy were also positive for TB in the GeneXpert test. Two under-five children were diagnosed clinically and using X-ray as smear negative pulmonary TB cases (Figure 1). Of the 14 bacteriologically confirmed TB cases, one was found to be rifampicin resistant TB. A total of 108 (90.8%) households did not have any active TB case among the contacts, 8 households (6.7%) had one TB case each, 2 (1.7%) households had 2 TB cases each and 1 (0.8%) household had four TB cases diagnosed among the contacts.

Table 1
Socio-demographic characteristics of smear positive index tuberculosis cases

Characteristics	Frequency (%)
Residence	
Rural	44 (37.0)
Urban	75 (63.0)
Gender	
Male	69 (58.0)
Female	50 (42.0)
Age in years	
12-14	5 (4.2)
15-24	39 (32.8)
25-34	35 (29.4)
35-44	22 (18.5)
45+	18 (15.1)
Educational background	
No formal education	48 (40.3)
Primary education	24 (20.2)
Secondary education	40 (33.6)
Diploma and above	7 (5.9)
Occupation	
Farmer	25 (21.2)
Government employee	7 (5.9)
Domestic work	9 (7.6)
Petty trade	3 (2.5)
Daily laborer	32 (27.1)
Driver	5 (4.2)
Student	29 (24.6)
Other	9 (7.6)

3.3. The prevalence of TB among household contacts

Sixteen cases of tuberculosis were identified (two clinical and X-ray diagnosis; and one rifampicin resistant) through the household TB contact screening with overall prevalence of 4,532.6 per 100,000 contacts: bacteriologically confirmed TB was 3,966 per 100,000, rifampicin sensitive TB was 3,682.7 per 100,000 and rifampicin resistant TB was 283.3 per 100,000. The prevalence of TB in rural and urban residence was 4,458.6 and 4,591.8 per 100,000, respectively ($p>0.05$). The prevalence of TB among male and female contacts was 4,545.5 and 4,522.6 per 100,000, respectively ($p>0.05$). TB prevalence per 100,000 ranged from 2343.8 in the age group 15 to 34 years to 11,111.1 in the age group 60 years and above ($p>0.05$). With regard to relationship status with the index case, the prevalence of TB per 100,000 ranged from 2702.7 among sibling contacts to 6666.7 among other relatives ($p>0.05$) (Table 2).

3.4. Comparison of the performance of GeneXpert MTB/RIF versus ZN microscopy in TB household contact investigation

The prevalence of TB by using the GeneXpert diagnostic test was 3966.0 per 100,000 contacts while it was 1416.4 per 100,000 contacts by ZN microscopy. The number of contacts needed to screen (NNS) to find a single case of TB while using GeneXpert as a diagnostic test was 25 as compared to the 70 while using ZN microscopy. The number of presumptive TB cases needed to test (NNT) to diagnose a single case of TB while using GeneXpert was three and the corresponding number in using ZN microscopy was eight.

4. Discussion

The performance of GeneXpert MTB/RIF in identifying TB among household contacts of index cases was significantly higher as compared with ZN microscopy. Out of 14 bacteriologically confirmed TB cases among household contacts, nine cases (64.3%) would have been missed if we had relied on ZN microscopy alone. The number needed to screen and number needed to test to diagnose a single case of TB was significantly lower with the use of GeneXpert than ZN microscopy indicating the better efficiency of the former laboratory test. ZN microscopy needed three consecutive sputum samples while GeneXpert test was done using a single, morning sputum sample but with additional diagnostic yield.

Studies have shown that smear microscopy is able to detect TB in patients with advanced disease who discharge sufficient number of bacilli[18,19]. In our study, two-thirds of the TB cases among household contacts would have remained undiagnosed if

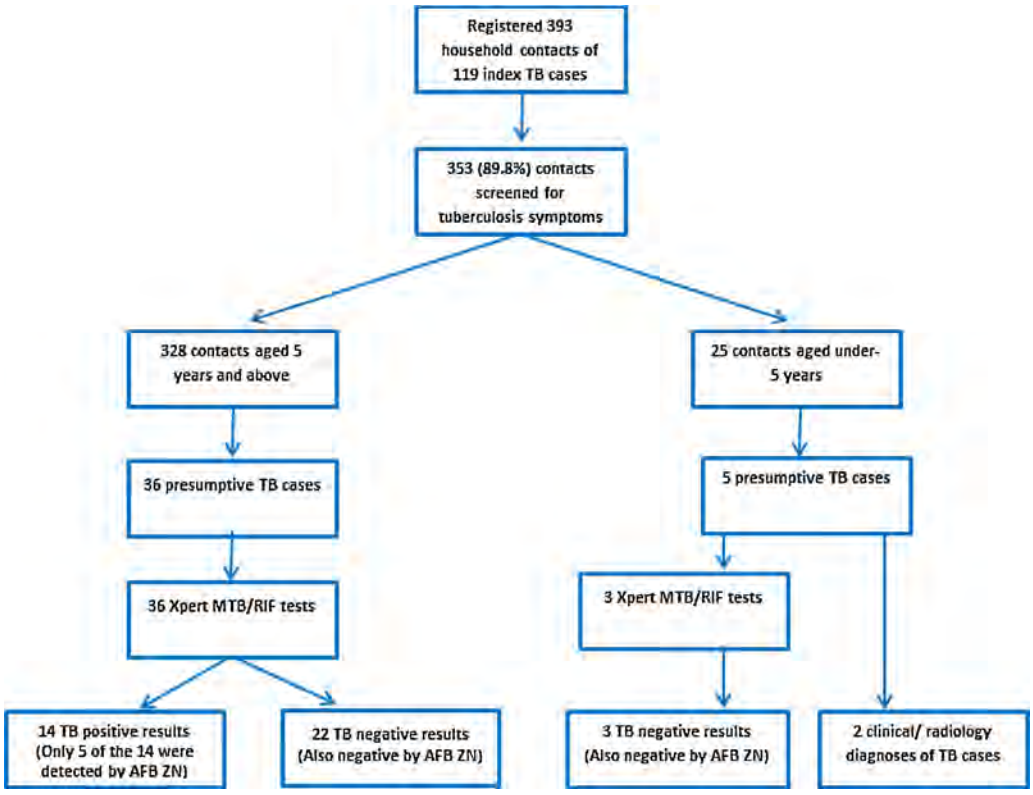

Fig. 1. Active case finding among household contacts of smear positive index TB cases.

GeneXpert test was not done. Hence, the contacts who harbor and discharge TB bacilli but couldn't be detected by the conventional smear microscopy would continue suffering with the disease and transmit the disease to their contacts unless we use a more sensitive test like GeneXpert to enable early identification of cases. Although the use of GeneXpert enabled better case detection among contacts, the wider use of GeneXpert in low income settings needs to be evaluated in terms of its cost-effectiveness, feasibility and the priority group to be targeted by the service[16,17]. Further clinical characterization of subsets of presumptive TB cases among TB contacts who would benefit most from GeneXpert MTB/ RIF testing could help to optimize its use in settings with limited resources.

Significant proportions of smear positive index TB cases by ZN microscopy were also confirmed positive by GeneXpert which signifies the quality of ZN microscopy service in the health centers. Eight (6.7%) of the already smear positive index TB cases (ZN microscopy) were negative for TB in the GeneXpert test. The incongruity can be attributed to either a false positive result by the ZN microscopy even though the EQA false positivity rate in the study area was 0.19% or the bacilli might have been mycobacteria other than tuberculosis as the GeneXpert only detects *Mycobacterium tuberculosis* complex strains. Rifampicin resistant TB, a surrogate marker for MDR-TB, was also diagnosed among 5 (4.2%) index cases who were put on first line anti-TB drugs based on ZN microscopy result alone at the health centers. It would have taken time for the health centers to suspect drug resistance TB in the course of first line treatment and consider drug susceptibility testing (DST). The rifampicin resistant TB burden among index cases in our study is greater than the 2.3% rate of MDR-TB (resistant to at least rifampicin and isoniazid) among new cases of TB and less than the 17.8% rate reported in previously treated TB cases in the national TB drug resistance survey[20]. One of the components of the End TB strategy emphasized on early diagnosis of tuberculosis including universal drug-susceptibility testing which is also supported by the findings of this study[21].

Although GeneXpert test has a cost implication, a single sputum test using GeneXpert would have improved the diagnostic capacity, reduced the number of sputum samples to be collected and enabled the immediate identification of drug resistant TB. A survey done in 24 countries in 2015 revealed that 8 countries, including Swaziland and South Africa from Africa, adopted GeneXpert test as a first line diagnostic test in the diagnosis of TB replacing smear microscopy[22]. It is advisable that countries like Ethiopia learn from the experience of countries that are using GeneXpert as a first line test for possible scale up of the GeneXpert test. There is a critical need for operational research to understand the pros and cons of decentralizing GeneXpert MTB/RIF test at the district level[16].

There were two households with four and two TB cases diagnosed among the contacts. It appears that there were households who had higher risk of transmission with resultant clustering of TB cases in the households. The clustering of TB cases in a household is more likely to be due to shared risk factor rather than individual level risk factor such as nutritional status, ventilation, air pollution or any other factor shared by household members[23–26]. Further analysis on the factors that fueled the TB transmission in those households was not done. There is a need to strengthen community TB care to ensure early diagnosis and treatment of index TB cases and reduce the risk of transmission to household and close contacts. TB infection control at household level is also an area that can be improved by educating community members regarding TB transmission, prevention and earlier health care seeking.

The overall prevalence of tuberculosis among household contacts using GeneXpert was 3,966 per 100,000 which is 20 fold of the estimated national prevalence of TB[1]. There was no significant difference in the diagnosis of TB among household

Table 2
Prevalence of TB among contacts by socio-demographic characteristics

Characteristics	Number of contacts	Number of presumptive TB (Row %)	Prevalence of TB diagnosis per 100,000; N (prevalence: 95% CI)[a]
Overall	353	41 (11.6%)	16 (4.5:2.8, 7.2)[b,c]
Residence			
Rural	157	13 (8.3%)	7 (4.4: 2.2, 8.9)
Urban	196	28 (14.3%)	9 (4.6: 2.4, 8.5)
Gender			
Male	154	15 (9.7%)	7 (4.5: 2.2, 9.1)
Female	199	26 (13.1%)	9 (4.5: 2.4, 8.4)
Age in years			
0-4	25	5 (20.0%)	2 (8.0: 2.2, 2.5)
5-14	106	10 (9.4%)	6 (5.7: 2.6, 1.2)
15-34	128	17 (13.3%)	3 (2.3: 0.8, 6.7)
35-59	67	6 (9.0%)	2 (2.9: 0.8, 10.2)
60 & above	27	3 (11.1%)	3 (11.1: 3.9, 28.1)
Educational background			
No formal education	147	18 (12.2)	12 (8.2: 4.7,13.7)
Primary education	97	13 (13.4)	4 (4.1: 1.6, 10.1)
Secondary education	56	9 (16.1)	-
Diploma and above	11	1 (9.1)	-
Marital status			
Single	217	26 (12.0)	9 (4.1: 2.2, 7.7)
Married	112	11 (9.8)	4 (3.6: 1.4, 8.8)
Divorced	10	1 (10.0)	1 (10.0: 1.8, 40.4)
Separated	2	0	-
Widowed	12	3 (25.0)	2 (16.7: 4.7,44.8)
Relation to index			
Head/ Spouse	93	8 (8.6%)	4 (4.3: 1.7, 10.5)
Son/Daughter	117	14 (12.0%)	7 (5.9: 2.9, 11.8)
Parent	33	4 (12.1%)	1 (3.0: 0.5, 15.3)
Sibling	74	8 (10.8%)	2 (2.7: 0.7, 9.3)
Other relative	30	5 (16.7%)	2 (6.7: 1.8, 21.3)
Non-relative	6	2 (33.3%)	-

[a] prevalence & 95% CI in thousands
[b] One case is RR TB
[c] Two cases are clinical diagnosis of TB

contacts by residence type, age, gender and type of relationship to the index case. However it is worth noting that the diagnosis of TB in the contacts was made largely based on laboratory confirmation except the two Pediatric cases diagnosed clinically and using X-ray. It is likely that more cases of clinical and extra-pulmonary TB might have been diagnosed subsequently from the presumptive TB cases which were not captured here due to the cross sectional nature of this study. It could have led to possible underestimation of the prevalence of all forms of TB among the household contacts.

The study needs to be interpreted with the following limitations in mind. The study did not consider some risk factors like HIV status of study participants and the condition of households, and the associated risk in the development of TB. The study also did not include the gold standard culture test to evaluate the sensitivity and specificity of ZN and GeneXpert test results. The use of standard operating procedures, availability of quality assurance mechanisms in the laboratories and involvement of highly qualified laboratory personnel are amongst the strengths of this study.

Our findings suggest that GeneXpert MTB/RIF test could lead to increased TB case detection among household contacts in addition to its advantage in the diagnosis of rifampicin resistant TB among contacts. The use of GeneXpert also helped in the identification of rifampicin resistant TB among newly diagnosed index TB cases in the health centers. There should be a consideration in using GeneXpert MTB/RIF as a point of care TB testing tool among high risk groups such as contacts especially in settings like Ethiopia where the burden of TB is high. Further study is recommended to analyze the cost-effectiveness and feasibility of scaling up GeneXpert as a first line test.

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Conflicts of interest: None

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Act local, think global: how the Malawi experience of scaling up antiretroviral treatment has informed global policy

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Abstract

The scale-up of antiretroviral therapy (ART) in Malawi was based on a public health approach adapted to its resource-poor setting, with principles and practices borrowed from the successful tuberculosis control framework. From 2004 to 2015, the number of new patients started on ART increased from about 3000 to over 820,000. Despite being a small country, Malawi has made a significant contribution to the 15 million people globally on ART and has also contributed policy and service delivery innovations that have supported international guidelines and scale up in other countries. The first set of global guidelines for scaling up ART released by the World Health Organization (WHO) in 2002 focused on providing clinical guidance. In Malawi, the ART guidelines adopted from the outset a more operational and programmatic approach with recommendations on health systems and services that were needed to deliver HIV treatment to affected populations. Seven years after the start of national scale-up, Malawi launched a new strategy offering all HIV-infected pregnant women lifelong ART regardless of the CD4-cell count, named Option B+. This strategy was subsequently incorporated into a WHO programmatic guide in 2012 and WHO ART guidelines in 2013, and has since then been adopted by the majority of countries worldwide. In conclusion, the Malawi experience of ART scale-up has become a blueprint for a public health response to HIV and has informed international efforts to end the AIDS epidemic by 2030.

Keywords: HIV/AIDS, Antiretroviral therapy, Malawi, Policy, World Health Organization

Abbreviations: 3TC, Lamivudine; AIDS, Acquired immune deficiency syndrome; ART, Antiretroviral treatment; AZT, Zidovudine; D4T, Stavudine; EFV, Efavirenz; GFATM, Global Fund to Fight AIDS, Tuberculosis and Malaria; HIV, Human immunodeficiency virus; NVP, Nevirapine; PEPFAR, President's Emergency Fund for AIDS Relief; PMTCT, Prevention-of-mother-to-child-transmission of HIV; TB, Tuberculosis; TB-DOTS, Tuberculosis directly observed treatment, short course; TDF, Tenofovir; UNAIDS, Joint United Nations Program on HIV/ AIDS; UNICEF, United Nations Children's Emergency Fund; WHO, World Health Organization

Main text

Background

In 2004, Malawi, which is one of the poorest countries in the world [1], started scaling up antiretroviral therapy (ART) on a national scale. Since 1985, the country had been struggling to cope with a massive HIV/AIDS epidemic, and when ART scale-up began in 2004, approximately 930,000 people (approximately 10 % of the population) were thought to be HIV-infected, there were an estimated 100,000 new HIV infections occurring annually and 170,000 people were thought to be in immediate need of ART without which they were likely to be dead within 2 years [2].

In January 2004, before the national scale-up of ART started, there were just nine facilities in the public sector delivering ART to about 3000 patients. Treatment was unstructured, few health care workers had received formal training in ART, patients in general had to pay for medication, and there were no national systems of monitoring and evaluation. Patients had restricted access to

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ART largely due to the requirement for CD4-cell count testing for which patients had to pay out of their own pocket. National ART guidelines, which were developed by a working technical committee formed by the National AIDS Commission and which were published in late 2003, laid out for the first time a simplified and standardised approach taking into account the severe health system constraints and the huge epidemic burden of disease [3]. These guidelines informed the national scale up plan that was launched in February 2004. Within 4 months, ART was being delivered at health facilities within the public sector, with treatment rapidly brought to scale in both public and private sectors in the subsequent years. By 30th June 2015, (11 years after the start of national scale-up) there were 711 ART clinics in the public and private sector that had newly registered 820,367 patients on ART [4]. Both the public and private health sectors implement the same standardised systems of delivering and monitoring treatment, and by the end of June 2015 a total of 565,105 patients were recorded as alive and on ART (see Table 1). Despite the large number of patients who died soon after accessing ART or who were lost to follow-up (which included unreported deaths), ART was estimated to have averted 275,000 deaths in Malawi [5].

Of the 15 million people globally living with HIV/AIDS and accessing ART as of mid-2015, over two thirds are in Africa [6]. Despite being a small country, Malawi has made a significant contribution to achieving this total both in terms of contributing substantial numbers of people on treatment and, importantly, contributing policy and service delivery innovations that have supported scale up in other countries. The aim of this paper is to discuss Malawi's preparations and implementation of ART scale up at the national level over the last 15 years and to assess how these have influenced the thinking and development of international guidelines.

Table 1 Characteristics and outcomes of patients ever started on antiretroviral treatment (ART) in Malawi up to June 30th, 2015

	Number	(%)
Total ART clinic registrations (these include first-time ART initiations, re-initiations after treatment interruption and patients transferring from one site to another)	1,025,754	(100)
Registration type:		
First time ART initiations	820,367	(80)
ART re-initiations after treatment interruption	11,520	(1)
ART transfers from one clinic to another	193,867	(19)
Gender at ART initiation:		
Male	369,284	(36)
Female	656,470	(64)
Non-pregnant	536,145	(82)
Pregnant	120,325	(18)
Age at ART initiation:		
Adults aged 15 years and above	936,603	(91)
Children 0–14 years	89,151	(9)
Reason for starting ART:		
Presumed severe HIV disease	3520	(<1)
Confirmed HIV infection—WHO Stage 1 or 2	447,066	(43)
Confirmed HIV infection—WHO Stage 3	467,590	(47)
Confirmed HIV infection—WHO Stage 4	100,379	(10)
Unknown	7199	(<1)
Primary outcomes by 30 June 2015:[a]		
Alive on ART	565,105	(69)
Lost to follow up	174,554	(21)
Stopped ART	3366	(<1)
Died	77,342	(10)
Total died:		
Died month 1	19,087	(25)
Died month 2	11,998	(16)
Died month 3	7075	(9)
Died month 4 and later	39,182	(50)

ART antiretroviral therapy, *WHO* World Health Organization, *HIV* human immunodeficiency virus

[a]these are primary outcomes for those who were first-time ART initiations ($N = 820367$

The data are taken and modified from reference 4

The thinking behind Malawi's First ART Guidelines

The Durban World AIDS Conference in 2000 was a turning point for sub-Saharan Africa in the fight against HIV/AIDS, and within the next 2–3 years a number of key events took place. The UN Secretary General Kofi Annan conceived the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM). President GW Bush of the United States launched the President's Emergency Fund for AIDS Relief (PEPFAR) with ambitious targets for HIV prevention, care and treatment. JW Lee, director general of the World Health Organization (WHO), along with the joint United Nations Program on HIV/ AIDS (UNAIDS), launched the "3 by 5" initiative—with the aim of getting 3 million people in developing countries on ART by 2005 [7]. The funds and international support to deliver and scale up ART to HIV-infected eligible persons in sub-Saharan Africa were now at hand.

The will to confront the HIV/AIDS epidemic in Malawi also found new energy and direction. In 2001, the directors and staff from the National TB Control Programme and the National AIDS Control Programme in Malawi published a viewpoint paper in the Lancet outlining their thoughts on an ART Framework for the resource-constrained arena of sub-Saharan Africa [8]. The authors proposed and discussed the goal, strategy, policy package and key operations that would be needed to deliver and monitor services and which were based on those that had been successfully used for implementing the global TB strategy. This paper was used by the leadership of the National AIDS Commission and the Ministry of Health, Malawi, as the blueprint and the core of the country's submission to the GFATM in 2002.

The country was successful about 1 year later in obtaining a large grant from the GFATM for ART scale up. The HIV Department of the Ministry of Health, working with various other country-based stakeholders, also used this Lancet paper to develop the nation's first ART Guidelines in 2003 [3], and the first national scale up plan in 2004.

The key was simplicity and standardisation, which took into account the weaknesses of the health sector, the serious shortfall in trained health care workers, especially doctors, throughout the country and the principle of equity of access—namely that the same standards of care would apply from north to south and from central hospital to peripheral health centre. Details of how the national scale up was to be done, and particularly how the response to ART was to be monitored and evaluated, were refined in subsequent publications from Malawi in 2004 [9, 10].

At the time of national scale up, WHO had already published two guidelines, one in 2002 and a revised version in 2003, emphasising a public health approach [11, 12]. The 2003 guidelines were those mainly used by sub-Saharan African countries to guide their initial ART scale up plans. These were valuable for clinical guidance about i) when to start ART, ii) what antiretroviral regimens to start with, iii) when and what drugs to change to if toxicity or failure occurred, iv) how to do clinical and laboratory monitoring and v) what to do for specific categories of patients such as pregnant women, children and patients with HIV-associated tuberculosis. However, there was no specific guidance at that time from the WHO on operational or programmatic issues such as the process by which patients should be enrolled and started on ART, how to monitor medication adherence, the registration of patients, recording or reporting systems to keep track of enrolled patients and their outcomes and drug procurement and distribution. A HIV/AIDS technical working group in Malawi developed the country's first standardised guidelines using the clinical guidance articulated in the WHO 2003 document, and complemented this with operational and programmatic guidance based on contextual principles of a public health approach, borrowing heavily from the experience with tuberculosis (Table 2) [3, 13].

Scaling up ART in Malawi

Factors important for success

A number of factors were important to the success of national ART scale up [14]. Malawi was not a U.S. President's Emergency Plan for AIDS Relief (PEPFAR) focus country, and financial support for ART scale-up was from one source only—the GFATM. This allowed the country to build and sustain a cohesive national programme with a uniform direction for scale-up and no competing interests.

The Malawi Ministry of Health, through the director and staff officers of the HIV Department, took clear leadership and assumed responsibility for national scale up. As a consequence all implementing partners and stakeholders agreed to work together with the Ministry to develop and use one national standardised system to deliver and monitor ART. Standardised systems were instituted in line with the national ART Guidelines, so that at whatever type of health facility ART was being delivered (tertiary care hospital, district or mission hospital or health centre), the same methods of assessing patients for eligibility for treatment, initiating first line treatment, and registering and reporting cases and outcomes were followed. The Ministry worked fast with stakeholders, implementers and donors to develop and then implement a 2-year (2004–2005) followed by a 5-year (2006–2010) scale up plan based on the national guidelines with clear objectives, activities and time-lines as well as specific details about where ART delivery sites should be situated.

An ART site accreditation process was established. This began with an intensive training schedule with novel training and assessment methods that took place in early 2004 and focused particularly on paramedical officers and nurses learning the ART guidelines and passing a formal examination based on these guidelines. Following classroom training, the paramedical officers and nurses had to undertake practical attachments at experienced ART sites in order to be certified as ART providers. Trained staff returned to their health facilities to brief the officers in charge, the district assembly, the neighbouring health centres and the community about ART. The HIV Department of the Ministry of Health then carried out a formal accreditation of the ART facility. Once accredited, the public was informed through announcements in the media that antiretroviral drugs (ordered some months before in good faith that the site would pass its assessment) were available and ART delivery could commence.

Every quarter, the HIV Department and its partners conducted supportive supervisory and monitoring visits to all ART sites in the country. During these visits, they ensured that health care workers were adhering to guidelines, checked and collected data for national reporting, provided encouragement and support to staff and recorded drug stock levels for drug forecasting and procurement planning [15]. Each quarter, facilities were awarded a certificate of excellence if the register and treatment cards were completed according to national guidelines and the cohort analyses had been accurately performed. Underperforming facilities were given warnings.

In the first few years of ART scale up, the HIV Department developed a centrally coordinated "push system"

Table 2 Main similarities and differences between the WHO 2003 ART Guidelines and the Malawi 2003 ART Guidelines

	WHO 2003 ART Guidelines	Malawi 2003 ART Guidelines
When to start ART	Stage 4, Stage 3, Stage 2 with CD4 count or Total Lymphocyte count below threshold, Stage 1 with CD4 count below threshold	Followed WHO Guidance
What to start	Choice of 4 first-line ART regimens based on d4T/AZT, 3TC or EFV/NVP	One first-line ART regimen only (d4T + 3TC + NVP) with alternatives if toxicity occurred
How to start ART	No specific advice	Advice about staging patients, group counselling and individual counselling and how to manage the first 2 weeks on half-dose nevirapine
Clinical and laboratory monitoring	Recommended tiered laboratory capabilities based on level of health care facility	Emphasised clinical monitoring only due to poor country-wide laboratory infrastructure
Adherence to medication	General advice about adherence and monitoring	Specific advice around pill counting
Children	Advice about dosing—recommendations for not splitting fixed-dose tablets	Advice about splitting first-line fixed-dose ART according to weight
HIV-Tuberculosis	Advice based on CD4 count or consideration of ART based on clinical judgement	Advice about starting all HIV-infected TB patients on ART in continuation phase with isoniazid and ethambutol
Standardised treatment outcomes on life-long ART	No advice given	Standardised treatment outcomes defined
Programmatic monitoring, recording and reporting	No advice given	Advice about patient identity cards, patient treatment master cards, patient ART registers and patient cohort analysis
Supervision	No advice given	Advice about quarterly supervision of all ART clinics including drug security checks
ARV drug procurement and distribution	No advice given	Advice about "start packs" and "continuation packs" and how to forecast drug needs

ART antiretroviral therapy, *WHO* World Health Organization, *HIV* human immunodeficiency virus, *TB* tuberculosis, *d4T* stavudine, *AZT* zidovudine, *NVP* nevirapine, *EFV* efavirenz

for ARV supply management. Six-monthly rounds of procurement and distribution (through UNICEF) were based on categorizing facilities according to their estimated burden of disease and by the number of new and retained patients on ART at the end of each quarter. Pre-packed kits with starter packs (for the first 2 weeks of treatment) and continuation packs were allocated and distributed based on this site-level quantification. Between 2004 and 2006, no stock-outs were encountered nationally or at individual sites [16].

Within 6 months of establishing ART in the public sector, the private sector was brought on board with their agreement to follow national systems, undertake a modified weekend ART training course with an examination of competence, and be accredited in the same way as the public sector. Private facilities received antiretroviral drugs free of charge, but charged patients for the drugs at approximately USD$3.5 per course of treatment per month. These monies were partly used to cover dispensing costs and partly to cover other costs of the programme, such as training and supervision.

Challenges

Challenges in the early years of ART scale up abounded. On the technical side, few children were accessing ART due to the absence of paediatric drug formulations and a dearth of paediatric specialists in the country who felt confident enough to provide care and treatment for this sub-group of patients. There were difficulties in managing patients with HIV-associated tuberculosis due to the well- known interactions between rifampicin and nevirapine. High early death rates after starting ART were a concern for health care workers, patients and the wider community-at large.

On the logistic side, huge efforts were required to keep up with the demands for stationary (patient registers and treatment cards), to undertake quarterly and countrywide supervision especially during the rainy season and to ensure a high quality delivery of services. In more recent times, the huge expansion of ART clinics, substantial annual increases in people initiating ART and a diversification of antiretroviral therapy regimens has put a strain on the procurement and distribution system for antiretroviral therapy drugs. Nevertheless, maintaining uninterrupted drugs supplies is a top priority for the ART programme. The April to June 2015 HIV report indicated that less than 2 % of ART sites experienced stock-outs for that quarter, with these stock-out events typically affecting small peripheral sites and usually being of short duration as a result of the bi-monthly scheduled distribution cycle and the ad-hoc stock relocation facility coordinated through a toll-free supply hotline [4].

During those early years, all countries in sub-Saharan Africa were tasked with the challenge to rapidly scale up ART in a context of limited resources. In order to share experiences with its neighbours, the HIV Department and its implementing partners presented on progress with national scale-up along with successes and challenges at international conferences, at meetings and committees convened by the WHO and in peer-reviewed publications [17, 18]. Data collected from the routine monitoring systems were used to show how ART scale up was benefiting the health sector in terms of reducing morbidity and mortality in health care workers and to support the quarterly supervision to all ART sites to ensure good quality data [19, 20]. A demographic surveillance survey in northern Malawi showed a significant reduction in mortality amongst adults within a year of offering ART services [21], and similar findings were observed through a more operational research study in the southern part of the country [22].

Using operational research to learn while doing

As there was no programmatic guidance from the WHO during these first few years of ART scale-up, Malawi undertook a number of operational research studies to generate local evidence to support activities and interventions around some key areas [23].

Cotrimoxazole preventive therapy

The high early mortality being documented for patients starting ART was of national and international concern [24]. While the efficacy of cotrimoxazole preventive therapy in reducing early mortality had been demonstrated in randomized trials [25], the routine use of this adjunctive treatment in the field was limited. An operational study implemented at ART clinics around the country showed that cotrimoxazole preventive therapy, given before or with ART, significantly reduced this early mortality [26]. The presentation of these data, along with additional evidence from other studies in Africa, led to a national policy decision that cotrimoxazole preventive therapy should always be given and continued indefinitely in any person starting ART: this policy was included in the second edition of the Malawi ART Guidelines [27], and formed part of the evidence base for the WHO 2006 guidelines on cotrimoxazole prophylaxis [28].

Task shifting and decentralisation

As ART scale up progressed, the need for increased expansion of services to rural areas became a priority among stakeholders. After much discussion, the medical and nursing councils of Malawi (who have regulatory responsibility and lay down the terms of reference for what doctors, paramedical officers and nurses can and cannot do) authorized nurses to initiate ART and the decision was made to extend HIV treatment services to peripheral health centres. This policy of task shifting and decentralisation was reflected in the third edition of the Malawi ART Guidelines in 2008 [29]. Subsequent operational research at health centres where nurses initiated ART showed that this policy was feasible and effective with treatment outcomes as good as those achieved from district hospitals [30, 31]. This evidence, which came several years ahead of formal evidence from randomized trials [32], helped to inform early WHO guidance on task shifting [33]. Subsequent experience in Malawi piloting less frequent clinic visits for stable patients on ART to reduce the clinic workload also informed the 2016 revision of the WHO ART guidelines [34].

Electronic medical record systems

While the national monitoring and reporting system initially performed well at facility and national level, it was essentially paper-based, and in busy clinics the rapidly growing cumulative burden of patients registered for ART threatened to overwhelm the capacity to collect, collate and analyse data on a quarterly basis. For busy sites with over several thousand patients cumulatively registered for ART, the tasks to manually count characteristics and outcomes for each individual patient took several days to perform each quarter and began to detract from patient care. The need for an electronic medical record system for use in busy clinics became an urgent imperative.

In 2005 a task force created by the HIV Department investigated the feasibility of introducing computers to capture patient data and produce cohort reports at ART clinics. Two electronic medical record system models were considered. The first model employed a dedicated clerk to enter patient information retrospectively from patient treatment cards to a single desktop computer. The second comprised computers in every clinic room, connected to a central server that stored the data. With the second model, designed by a local non-governmental organization called Baobab Health Trust, healthcare workers used simple, robust, touchscreen computers to enter patient information during clinical encounters at the point of care. Based on experiences of using these touchscreen systems in various domains in healthcare in Malawi since 2001, the task force chose the second model and established core functionality requirements for the touchscreen point of care system [35].

The system was first piloted at a busy ART clinic in a central hospital in 2005 and then rolled out to further hospital ART clinics in 2006 and 2007. Key challenges that needed to be overcome included: i) low computer literacy among target users, ii) the need for unique patient identifiers, iii) maintaining clean and reliable electrical power and iv) managing the transition from

paper to electronic-based records and accurately back-entering large numbers of paper-based treatment cards and registers. Baobab Health Trust approached and solved each of these challenges using hardware and software innovations [35].

On-going challenges include validating the accuracy of data in the electronic medical record system, the quarterly production of complete and accurate cohort reports, the logistics of nationwide supervision and the immediate attention needed when the computer-based systems become dysfunctional at a clinic. Despite these challenges, the system has been gradually scaled up and by 30th June 2015, a total of 495,974 patients had ever been registered for ART through electronic medical records at 60 government clinics throughout the country.

Malawi and Option B+

In 2010, guidance was issued from the WHO on prevention-of-mother-to-child-transmission of HIV (PMTCT) [36]. It was recommended that HIV-infected pregnant women have their CD4 cell count assessed. Women with a CD4 cell count < 350 cells/mm^3 or who were clinically immune suppressed based on WHO clinical staging were to start life-long ART for their own health while asymptomatic women with a CD4 count ≥350 cells/mm^3 were to be offered Option A (maternal zidovudine + infant antiretroviral therapy prophylaxis) or Option B (maternal triple antiretroviral therapy prophylaxis). This PMTCT strategy depended on countries having capacity to carry out CD4 testing for all HIV-infected pregnant women.

Malawi was requested to conduct a feasibility appraisal of this new guidance. The weak laboratory infrastructure in the country meant that CD4 count capacity was severely limited: for example, in quarter 4, 2010, only 60 out of 417 ART clinics in the country had a CD4 machine of which only 53 produced any results in that 3-month period [37]. Furthermore, antenatal care as the main point of diagnosis and management for HIV-infected pregnant women was highly decentralized and over 50 % of women needing PMTCT were seen at peripheral health centres. Option B (with triple ART taken from 14 weeks gestation to 1 week after all exposure to breast milk had ended) was the logical choice to keep procurement and distribution streamlined and drug administration manageable for peripheral health care staff. However, total fertility rate in Malawi was high at 5.6 births per women with a median duration of breastfeeding for each woman of 23 months [38]. Soon after the breastfeeding period had finished ART would be stopped, but many women would soon become pregnant again needing to restart ART. This stop-start approach to ART did not make sense programmatically. Nor did it make sense clinically as there was also evidence that CD4+ count guided interruption of ART was associated with increased morbidity and an increased risk of death [39].

The country therefore proposed a new strategy to offer all HIV-infected pregnant women lifelong ART regardless of WHO clinical stage or CD4 cell count, named Option B+ [38]. The rationale, the implementation and benefits of such a strategy have been evaluated in several studies and are shown in Table 3 [40–42]. This proposal was translated to national policy and implemented in Malawi in July 2011 [43]. The optimal delivery models for Option B+ in different settings are the subject of ongoing operational research to ensure high uptake and retention in care [44, 45].

Despite limited evidence of efficacy, the WHO incorporated Option B+ into its 2012 programmatic update on treating pregnant women and preventing HIV infection in infants [46], and then into its 2013 consolidated ART guidelines [47]. For programmatic and operational reasons, especially in generalized epidemics, a conditional recommendation with low quality evidence was made that all pregnant and breastfeeding women with

Table 3 Advantages of Option B+ in Malawi

Advantage	Explanation
Simple to implement	One tablet a day of TDF + 3TC + EFV for the woman with NVP infant prophylaxis for 6 weeks. Reinforces the nationwide message that ART is taken for life; procurement and distribution needs for the country made easier compared with having Option A or Option B.
Reduced vertical transmission from mother to child	For current pregnancy ART offers protection from time of administration and is continued in breast feeding period. For future pregnancies, ART offers protection from time of conception.
Avoids stop-start ART	Interrupted ART has risks for increased morbidity and mortality.
Improved maternal health and survival	Post-partum women in Zimbabwe with CD4 count > 350 cells/mm^3 have an elevated risk of death six times higher than non-infected women [40].
Reduced sexual transmission of HIV to discordant couples	HIV-infected persons on ART have significantly reduced risk of HIV transmission through sexual intercourse to non-infected partners even at high CD4 cell counts [41].
Reduced risk of tuberculosis	ART reduces the risk of tuberculosis in people living with HIV, even at high CD4 cell counts [42].
Treats hepatitis B infection	Tenofovir and lamivudine are active against hepatitis B virus, and about 15 % of people living with HIV in Malawi are also infected with hepatitis B.

ART antiretroviral therapy, *HIV* human immunodeficiency virus, *TB* tuberculosis, *TDF* tenofovir, *3TC* lamivudine, *EFV* efavirenz, *NVP* nevirapine

Table 4 Evolution of national and international guidance, and supporting evidence

Policy	Year of implementation in Malawi	Year recommended by WHO	Supporting evidence from randomized trials or systematic reviews
Lifelong cotrimoxazole preventive therapy	2006	2006 WHO Cotrimoxazole Guidelines [28]	Reference [51]
Task shifting for the delivery of ART	2003	2008 WHO Guidelines for task shifting [33]	References [32, 52]
Decentralization of ART delivery	2003	2013 WHO Consolidated Guidelines [47]	References [53, 54]
PMTCT Option B+	2011	2012 WHO Programmatic Update [46]	None
		2013 WHO Consolidated Guidelines [47]	

ART antiretroviral therapy, *PMTCT* prevention of mother to child transmission of HIV

HIV should initiate ART as lifelong treatment. The policy, probably because of its simplicity and potential for rapid scale up, was taken up quickly by countries, with the majority of countries adopting PMTCT Option B+ within 2 years [48]. Subsequent WHO guidelines released in late 2015 [49] and the new guidance in 2016 [34] recommend Option B+ as the preferred way to prevent mother-to-child transmission, to supersede all previous options. A recent evaluation of the first 3 years of Option B+ in Malawi has found that the risk of loss to follow-up during the third year is low and similar for patients retained for 2 years, with retention remaining stable as the Option B+ programme has matured [50].

Conclusion

The role of national policy initiatives as the driver for international policy development can rarely be established with certainty. Malawi's practical and pragmatic approach to developing national ART guidelines that acknowledged health system weaknesses and services needed to deliver and monitor treatment was well received by the international community. The national quarterly reports on all patients in the country being registered for ART along with censured standardised quarterly outcomes were unique in the early phases of scale up [18]. Malawi's public health stance to ART scale-up was adapted to its resource-poor setting, and despite pressure from both within and outside Malawi to use advanced laboratory technology to support the initiation and continuation of ART, this was resisted in favour of a more clinical and programmatic outcome orientated approach. This allowed a rapid and successful countrywide scale up, opened up the possibilities of decentralization and task shifting and paved the way for Option B+ 7 years after the first steps in ART delivery were taken.

Table 4 illustrates this evolution of national and international guidance along with the supporting evidence, further demonstrating that Malawi implemented interventions based on local evidence and context often long before there was supporting data from randomized trials and before WHO had released its international guidance [28, 32, 33, 46, 47, 51–54].

The launch of the new WHO Guidelines in 2015 recommending that ART be initiated in everyone living with HIV at any CD4 count and that daily oral pre-exposure prophylaxis be offered to anyone at substantial risk of HIV infection as part of combination prevention approaches will significantly impact global public health [49]. These recommendations form part of the revised consolidated guidelines on the use of ARV drugs to treat and prevent HIV infection published by WHO in 2016 [34], and these will facilitate the achievement of UNAIDS Fast-Track targets for 2020 [55].

Malawi had already formulated a "test and treat" approach in its' new national strategic plan, with implementation planned for 2016. It will be a major undertaking and one for which core principles such as uninterrupted drug supplies, patient adherence to therapy and compliance with follow-up will be needed for success, not only in Malawi but globally as well.

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Authors' contributions

ADH wrote the first draft of the manuscript to which all other authors (NF, AJ, EJS, EL, FC and DM) contributed. All authors (ADH, NF, AJ, EJS, EL, FC and DM) contributed to subsequent drafts and revisions of the paper in response to editorial and reviewer comment. All authors read and approved the final paper for submission. All authors are responsible for the views expressed in this paper and they do not necessarily represent the decisions or policies of their institutions.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Patient consent for publication was not obtained as individual patient data were not used in the study.

Ethics approval and consent to participate

Ethics approval was sought from the Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease, Paris, France, that responded to say that the need for ethics approval was waived as the data presented were aggregate and anonymised and already in the public domain (EAG No: 55/16). At the same time Ethics approval was sought from the Malawi National Health

Science Research Committee that responded to say that there was no need for ethical approval as the data were from HIV/AIDS Programme reports that were already in the public domain (letter written on 13th April 2016). Consent to participate was not needed as individual patient data were not used.

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An Epidemiological Study of Drug Resistant Tuberculosis Cases: Survey in the Northern Part of Bangladesh

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Abstract **Background:** Drug resistant tuberculosis (DR TB) is a global concern due to high fatality, and high cost and hazardous treatment. It is important to know the epidemiological factors of DR TB for effectively controlling this infectious disease. The aim of the present study was to indentify the epidemiological factors of DR TB patients in the Northern part of Bangladesh. **Methods:** A cross-sectional study was conducted of registered DR TB patients at two chest diseases hospitals (CDH) in Northern part of Bangladesh. Data was collected from 164 registered DR TB cases (male 113 and female 51) using pre and post tested standard questionnaire. Some information was also collected from available records at those hospitals. **Results:** The present study demonstrated that male (68.9%) was more affected by DR TB than female (31.8%). A decreasing trends was observed in DR TB patients with increasing age (excluded, age group (6-15)). When we adjusted age and sex, higher percentage of DR TB cases was especially pronounced among who were living in Rajshahi division (72.6%) and rural areas (86%), came from 'Failure of Category–1' (24%), 'Relapse after Category–1' (33%) and 'Non Converters of Category–1' (21%) and low income family (44%, BDT ≤10000). Among the cases, 32% were illiterate and 28% had primary level education, and the percentage of male DR TB patients habituated smoking were 56.63%. **Conclusions:** This study suggested that sex, age, type of treatment, residence, education and smoking status were important factors for getting MDR TB. It is expected that this study can help government to take activities for controlling and prevent MDR TB disease.

Keywords Drug Resistant Tuberculosis, Northern Part of Bangladesh, Cross Sectional study

1. Introduction

Tuberculosis (TB) is a major Public health problem in Bangladesh. Considering the estimated number among total population, Bangladesh is a High TB Burden and High DR TB Burden country and it ranks 7th among 22 High TB Burden Countries [1]. The history of Tuberculosis in Bangladesh has different stages. 1965, tuberculosis services were mainly curative and based in TB clinics and TB hospitals. TB services were expanded to 124 Upazila Health Complexes (UHCs) during the 2nd Health and Population Plan (1980-86), and were operationally integrated to Leprosy during the 3rd Health Population Plan (1986-91) under the Mycobacterium Disease Control (MBDC) unit of the Directorate General of Health Services (DGHS). The National TB Control Program (NTP) adopted the revised DOTS strategy during the 4th Population and Health Plan (1992- 98) under the project "Further Development of TB and Leprosy Control Services". The NTP started its field implementation in November 1993 in four Thanas (Upazilas) and progressively expanded to cover all Upazilas by mid 1998, The NTP was integrated into the Communicable Disease Control component of the Essential Service Packages under the Health and Population Sector Program (HPSP). In 2003, HPSP was renamed as Health Nutrition and Population Sector Program (HNPSP) (2003-2011). Now Ministry of Health and Family Welfare (MOHFW) has been implementing the Health Population and Nutrition Sector Development Program (HPNSDP) for a period of five years from July 2011 to June 2016. In all the sector programs tuberculosis control program has been recognized as one of the priority program [2]. The program is maintaining the high treatment success rates from the beginning and met the target of 85% treatment success since 2003. The program has been maintaining the treatment success rate of New Smear Positive (NSP) cases over 90% since 2006. Regarding case notification of NSP cases, the program made slow and steady

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progress from 2003 to latest year. In 2003 the notification rate of NSP cases was 40/100,000 population. It became 61, 73, 74, 70.5 & 68 during 2005, 2006, 2009, 2010 & 2013 respectively [2].

At present, DR TB cases in Bangladesh are relatively low and a few XDR TB Cases exist. Along with the present DR TB Case load, Bangladesh falls into the category of High MDR TB Burden Country and ranks 13th among 30 such High MDR TB Burden Countries [1]. The NTP has carried out its first nation-wide Drug Resistance Survey (DRS) in Tuberculosis Patients in collaboration with WHO and Supra National Reference Laboratory (SNRL), ANTWERP, Belgium in 2010-2011. The result shows the overall number of MDR TB cases is low, 1.4% among new cases and 28.5% among retreatment cases. Although the rates of MDR TB in Bangladesh do not appear to be high, but the absolute number of MDR TB Cases is higher considering the overall high TB burden. MDT TB prevalence of 1.4% in new cases and 28.5% in Retreatment cases translate approximately an estimate of 4496 MDR TB cases among notified TB cases in 2013 [3]. In August 2008 NIDCH started enrollment of MDR TB patients with GLC approved 24 months regimen and supported by the Global Fund. By the end of December 2013 a total of 1301 confirmed MDR TB patients including 330 in 2013 have been enrolled. As a part of Programmatic Management of Drug Resistance TB (PMDT) plan NTP established one Regional TB Reference Laboratory (NTRL) at Chest Disease Hospital (CDH) of Chittagong in 2011 and also managing MDR TB patients from that year. In 2013 NTP has also started managing MDR TB in CDH Pabna and Khulna. The MDR TB patients are also managed in the CDH of Rajshahi division and in three other hospitals of Damien Foundation at Jalchatra under Tangail Hospital, Anantapur under Netrakona District and Shambhuganj under Mymensingh district with shorter regimen of 9 months and supported by Damien Foundation, Bangladesh under operational Research. Since May 2005 those centers have been managing MDR TB patients, and by end of December 2013 a total of 1161 patients including 189 in 2013 have been enrolled [2]. It is evident that the gap between estimation and diagnosis of DR TB cases is very high in Bangladesh. Those missing DR TB cases are a very big threat for the society as well as for the country.

From the above discussion, we can have a clear picture of the problem of DR TB case diagnosis and management situation in Bangladesh. In comparison with the yearly estimation, the diagnosis is very low. In 2011, 2012 & 2013 NTP had diagnosed only 10%, 12% and 15% of the estimated cases. To increase the DR TB case detection, we have to know the epidemiological factors of presently detected DR TB cases. From the study we will be able to know the most vulnerable and risk groups for the development of DR TB. Thus we shall be able to design strategy to find DR TB cases in most effective way. It will also help to manage DR TB case in most efficient way. There are large numbers of studies on DR TB issues that had been carried out in different countries of the world. However, the study with DR TB patients has been poorly documented in Bangladeshi population.

The purpose of the present study was to identify the epidemiological factors of DR TB among registered patients at two chest disease hospitals in the Northern part of Bangladesh.

2. Methods

The northern part of Bangladesh consists of 2 divisions; Rajshahi and Rangpur. There are 16 districts under these two divisions. The two divisions cover together an area of 34,338 square kilometers which is 23.26% of the total area and have a population of 36,541,453 which is 23.63% of the total population of the country [2]. There are 4 Chest Disease Hospitals (CDH) at Rajshahi and Rangpur division for the treatment of TB and other chest diseases. Only Rajshahi and Pabna CDH among 4 CDH have the facility to treat DR TB patients. DR TB patients, who are diagnosed from different Upazilas of Rajshahi and Rangpur division, have to get admission and registered under those two hospitals. After necessary investigations and formalities, treatment is initiated for each DR TB patients. After certain period of initial treatment at those hospitals, patients are shifted to community to continue the rest of the treatment. The DR TB management program is implemented countrywide following a National Guideline.

Present study was a cross-sectional descriptive study. The study area covered all 16 districts under Rajshahi and Rangpur divisions. The period of the study was May 2014 to December 2014. The target population included all registered DR TB patients at Rajshahi & Pabna CDH during the year 2013 and 2014. Non-random purposive sampling technique was used for selecting the sample. During the year 2013 & 2014, total 156 and 62 DR TB cases were registered at Rajshahi and Pabna CDH respectively. There were total 218 DR TB patients at both hospitals during study period. Minimum sample size was determined as 140 after statistical calculations. Finally 164 respondents were brought under the study to cover the minimum sample size. DR TB patients registered at Rajshahi & Pabna CDH but residing at out of the study area were excluded from the study to make it confined within Rajshahi & Rangpur divisions.

Data were collected following pre-coded, open ended, pre and post tested questionnaire. One to one direct interview method with respondents was used in present study. Some data were also collected from registers, treatment cards and other documents of individual patients available at Rajshahi & Pabna CDH. The completed questionnaire was collected and checked for the completeness and clarity of the information to exclude missing or inconsistent data and then compiled together. Data was edited properly before analysis.

3. Statistical Analysis

Frequency distribution was done in this study. Data analysis was done by using appropriate statistical software. Final analysis of the data was carried out using percentage, absolute numbers for categorical variables in IBM SPSS 20. For some purpose, Excel program was also used for analyzing the data.

4. Ethical Approach

The study was conducted following the ethical consideration and all ethical issues were handled with appropriate care. A written document describing the purpose of the study and the individuals' rights as study participants was prepared and it was informed clearly for every individual. All rules and regulations of the ethics committee, Institute of Biological Science (IBSC), Rajshahi University, Bangladesh have been followed in this study. Written consent forms were collected from each participant after a detailed oral explanation about the study.

5. Results

Socio demographic profile

Among 164 participants, 113 were male (68.9%) and 51 were female (31.1%). M:F was 2.2:1. Minimum age was 8 and maximum age was 85. The most vulnerable age for MDR TB was marked as 16 to 45. In this group total number of respondents was 129 which were 78.7% of total respondents. Highest number of respondents was from 16 – 25 (33%) age group, second highest was from 26 – 35 (29%) age group and third one was from 36 – 45 (16%) age group. We have also the division and district wise distribution of 164 respondents. It was found that 72.6% respondents are from Rajshahi division and only 27.4% respondents were from Rangpur division. In the study, we had checked the occupation of the respondents. Male had more variety in occupation than female. The data showed that most of the female are housewife. They were 17.7% among total and 56.86% among all female. For male, most were farmer and they were 21% among total & 30.97% among total male. There was a good number of students among male and female. Student occupied 14% among total respondents. 8.5% of the total respondents were Garments worker. All sorts of day labor accounts for 9.1%, different service occupied 4.3% and business occupied 6.1% among the respondents (Table 1).

The analysis displayed that a high number of respondents were illiterate. Total 32.3% participants had no education. Among Male, 34.5% and among Female, 52.94% were illiterate. 28% of respondents had primary level of education. It was found by the study that most of the respondents were within family income group of BDT ≤10,000. It consisted 64% among the total. In 2nd group there were 49 respondents which consisted of 30% among total having a family income of BDT 10001 - 20000. Another 6% came from the group of ≥20,001. In general it can be said that most of the MDR TB patients were from very low income group. It is observed by the study that most respondents were from rural area (86%) and only 14% were from urban area. Among 164 respondents, 95.1% were Muslim, 4.9% were Hindu and Christian (Table 1).

Table 1. Socio-demographic profile of the study subjects

Variables	No. of patients			Percentage of total
	Male	Female	Total	
Sex (n=164)				
Male	113	0	113	68.9
Female	0	51	51	31.1
Age (n=164)				
6 – 15	2	3	5	3.0
16 – 25	31	23	54	32.9
26 – 35	32	16	48	29.3
36 – 45	21	6	27	16.5
46 – 55	10	3	13	7.9
56 – 65	11	0	11	6.7
66 – 75	4	0	4	2.4
75+	2	0	2	1.2
Marital status (n=164)				
Married	91	36	127	77.4
Un married	20	13	33	20.1
Widower /Widow/Divorced	2	2	4	2.4
Education (n=164)				
Illiterate	39	14	53	32.3
Primary	30	15	45	27.4
Below SSC	24	11	35	21.3
SSC & Higher	20	11	31	18.9
Occupation (n=164)				
Farmer	35	0	35	21.3
Housewife	0	29	29	17.7
Student	12	11	23	14.0
Garments worker	6	8	14	8.5
Day labour	14	1	15	9.1
Business	10	0	10	6.1
Service	7	0	7	4.3
Transport worker	6	0	6	3.7
Other	23	2	25	15.2
Geographic distribution (n=164)				
Rajshahi division	83	36	119	72.6
Rangpur division	29	16	45	27.3
Monthly income (n=164)				
≤ BDT 10000	69	36	105	64.0
BDT 10001 – 20000	36	13	49	29.9
BDT >20000	8	2	10	6.1
Residence (n=164)				
Rural	98	43	141	86.0
Urban	15	8	23	14.0
Religion (n=164)				
Muslim	107	49	156	95.1
Other than Muslim	6	2	8	4.9

Disease specific results

Anatomical site of DR TB:

From the study it was observed that most of the MDR cases had pulmonary TB (97%). Only 3% had extra pulmonary DR TB.

Registration group of DR TB patients

In this study, the registration group of each DR TB patients was analyzed. Those groups are determined based on previous anti-TB treatment history of DR TB patients. The study showed that most of the DR TB cases were from 'Relapse after receiving Category 1' group. It consisted 33% among total. Next high group was 'Failure after Receiving Category 1' and it is 24% among total. 'Non-Converter after category 1 treatment' also had high number which was 21%. Another 8% patients were in 'New' group who never took any anti-TB treatment before being diagnosed as DR TB patient. If we make a total, we can see that 88% of the respondents were from new or first time treatment group and 12% from re treatment group (Fig.1).

Registrartion Group	Nos	%
New (No anti TB Rx)	13	8%
Non Converter - Cat 1	34	21%
Non Converter - Cat 2	1	1%
Failure after - Cat 1	40	24%
Failure after - Cat 2	4	2%
Relapse after - Cat 1	54	33%
Relapse after - Cat 2	14	9%
Other	4	2%
Total	**164**	**100%**

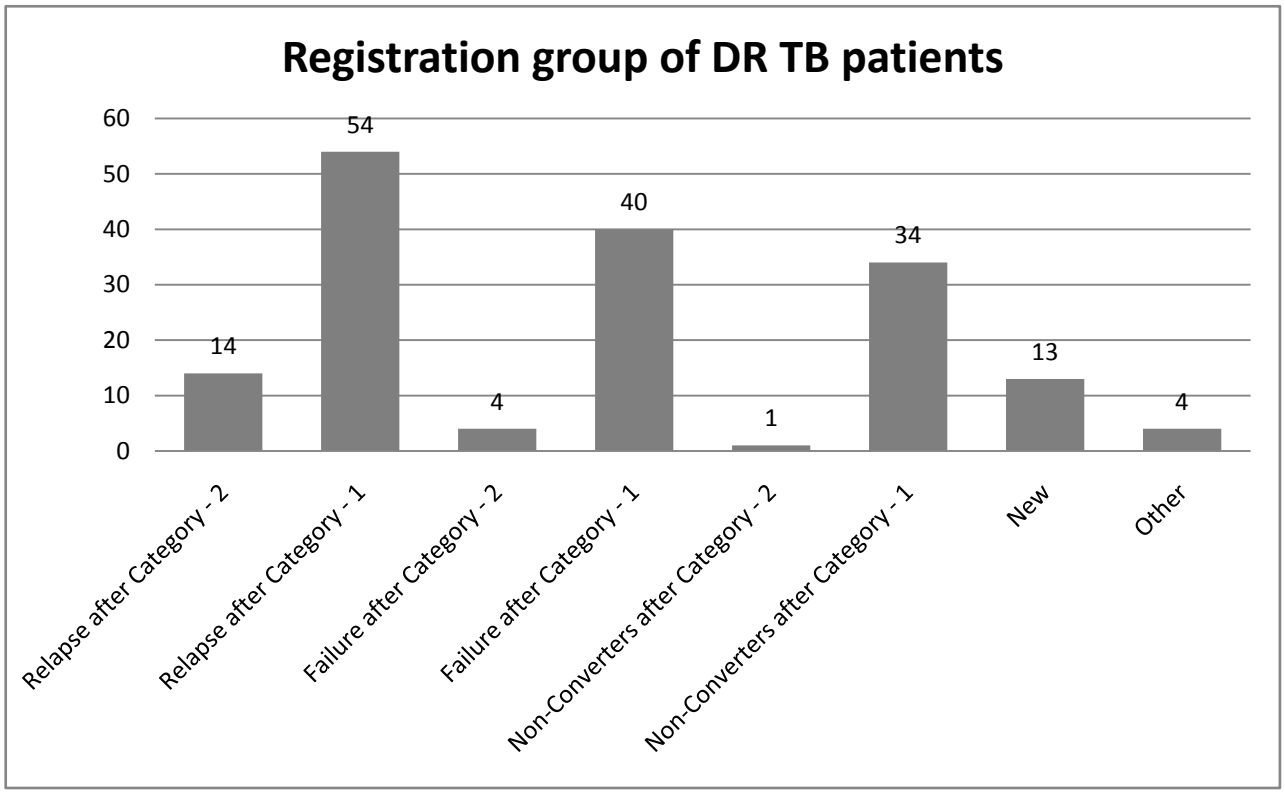

Figure 1. Registration group of the respondents

History of previous Anti TB Treatment

After compiling and analyzing the response, the study showed that 150 respondents had received one episode of anti-TB treatment of any duration among 164. Among those 150, 139 took the treatment regularly (93%) and 126 took the treatment under DOT (84%). From the table we can find that 20 respondents among 164 received 2 episodes of treatment. Among those 20, 15 (75%) took the treatment regularly and 15 (75%) took the treatment under DOT. Only one respondent found among 164, who received 3rd episode which is actually treatment of MDR TB. That was 9 month regimen and he failed that treatment

Contact history with known TB / DR TB patients

History of contact with known TB cases, DR or Non-DR TB, was checked during interview of respondent. From the table, we can see that only 44 MDR TB case had a history of contact with known TB cases (27%). Among 44 cases, 20 (45%) had a history of contact with known DR TB patients and 24 had history of contact with non-DR TB patients. The contact cases were also divided in to two groups – family members and non-family members. It is found from the table that 27 (61%) MDR cases among 44, have contact TB patients within their family members and 17 (39%) have contact with known TB cases who are not their family member.

Co-morbidity with other chronic disease

From the table below we can see that only 34 (21%) respondents were suffering with other chronic diseases beside MDR TB. Those chronic diseases were mainly Asthma and Diabetics. Among 34 MDR patients had other chronic diseases, 14 (43%) have Asthma and 13 (34%) had Diabetics. Rest of 7 had other diseases like HTN, eye problem, hypothyroidism etc. During interview, most of the respondents told that they had general weakness. But it is not considered as disease as it is an unstable physical condition due to many reasons.

Addiction status

From the present study we observed that among 113 male respondents, 70 male had any addiction which is 92% among respondents having any addiction. Only 6 female (8%) had any addiction. At the same time, 45 female & 42 male did not have any addiction. In total, 76 respondents had any addiction among 164 respondents which was 47%. 53% had no addiction (Table 2).

Table 2. Respondents having any addiction and its nature

Addiction Status	Respondents – No. & %					
	Male	%	Female	%	Total	%
Having No addiction	43	49	45	51	88	54
Having any Addiction	70	92	6	8	76	46
Total	113	69	51	31	164	100

Source: Data collected from Rajshahi & Rangpur division, Bangladesh.

Type of addiction

We had collected the information regarding the types of addiction of DR Patients. Among 6 female, all were addicted with tobacco (Jarda). Among 70 male, most were addicted with smoking of biri or cigarette. It was found from the table that 7 respondents smoked Ganja along with cigarette or biri, 6 used to drink alcohol with smoking. One respondent confesses that he used to take all sorts of addiction materials like Heroin, Fensidril, Ganja, Alcohol etc. (Table 3).

Table 3. Type of addiction among respondents

Type of Addiction		No.	%
Among Female	Tobacco (Jarda)	6	8
Among Male	Smoking	51	67
	Smoking + Ganja	7	9
	Smoking + Alcohol	6	8
	Tobacco (Jarda/Powder)	3	4
	Other	3	4
	Total	76	100

Source: Data collected from Rajshahi & Rangpur division, Bangladesh.

Resistant patterns of DR TB patients

All the registered DR TB patients were first time diagnosed by using GeneXpert Machine which is the latest diagnostic tools in the field of TB. Treatment was initiated on the basis of that result. GeneXpert machine only can determine Rifampicine Resistance. Rajshahi CDH performed Slide Culture for 105 DR TB cases who were registered there. From the slide culture result, we came to know that only 16 patients out of 105 had additional drug resistance beside Rifampicin. The resistance pattern is displayed in the table below. Most important finding from the study was identification of one XDR TB case. The XDR case was a female of 40 years of age and Failure of Category 1.

Table 4. Respondents having other Drug resistance beside Rifampicin

Resistance drugs	No. of respondents
R + Z	11
R + Z + O	3
R + Z + K	1
R + Z + O + K + C + S	1
Total	**16**

(R= Rifampicin, Z= Pyrazinamide, O=Ofloxacine, K = Kenamycine, C = Clofazimin, S = Streptomycin)

6. Discussion

The terminology “DR TB” and “MDR TB” both are used in this study synonymously. By definition they are different but the DR TB management program treats DR TB cases diagnosed by GeneXpert machine as MDR TB and they are treated under standard regimen of MDR TB [3]. For MDR

TB, TB patients must have resistance to two most potent Anti TB Drugs – Rifampicin and Isoniazid. Similarly, DR TB is specified for patients who have resistance to any Anti TB Drugs. So it can be said that, all MDR TB are DR TB but not all DR TB are MDR TB. In our study, the DR TB patients are detected through GeneXpert MTB/RIF, a rapid diagnostic tool, which detects only Rifampicin resistance. But it has been proven by most of the studies that 95-99% Rifampicin resistance has co-resistance with Isoniazid. So, evidentially they are termed as DR TB but conceptually they are considered as MDR TB as we do not have any rapid testing tool to diagnosis Isoniazid resistance. To have evidence of Isoniazid resistance, it needs to perform Culture and Drug Susceptibility Test (DST) which takes comparatively longtime and not supportive in public health approach.

It needs to make clear that the drugs that are used for normal TB treatment are called 1st line drugs. They are – a) Injection Streptomycin, b) Capsule Rifampicin, c) Tablet Isoniazid, d) Tablet Pyrazinamide and e) Tablet Ethambutol. In case of unexpected results in 1st line treatment, susceptibility tests are done for those drugs. The drugs that are used for DR TB treatment are called 2nd line Drugs. They are many in number and a combination is used by physicians. Any national program usually use combination (regimen) approved by WHO. The regimen that is used in Bangladesh National TB Control Program is a 24 months regimen and has the following drugs: a) Injection Kenamycin, b) Tablet Levofloxacin, c) Tablet Cyclocerine, d) Tablet Protheonomide and e) Tablet Pyrazinamide. Physician may use alternative from same group for adverse effect due to any specific drug.

This study was conducted with a view to analyze the socio-demographic and epidemiological factors among registered DR TB cases at two chest disease hospitals of northern part of Bangladesh. Among the study subjects, male were more prevalent and the age group from 16-45 were mostly vulnerable. The mean age was 33.85 years. In late age, women were less likely to develop MDR TB but there were evidences of male having TB in the age of 80 or more. A study was conducted by Bhatt et al. (2012) at Ahemedabad of India on age and sex distribution of MDR TB [4]. That study had almost same finding in this regard. The study reports 2/3rd male and highest age group was 16-45 [4]. It should be a concern of policy maker's to prevent DR TB in most productive age.

More MDR TB was diagnosed at Rajshahi division and less in Rangpur division. It was a very important finding from the point of geographical distribution of MDR TB in Bangladesh. Number of TB case detection was higher in Rangpur division than Rajshahi division [2]. If we calculate 1.4% MDR among new and 29% among re-treatment TB, the number of DR TB cases should be higher at Rangpur division. But there were only 27.44% among 164 study subjects. It needs further research to explore the facts and under lying causes of low DR TB detection at a particular region. Most of the MDR patients had no education or low education. So, awareness level, motivation, understanding of risks may be low due to education. As an impact of no or low education can lead to creation of MDR TB. We did not find much study on educational impact of MDR TB. But it was also found in the study performed by Bhatt et al. (2012) where the educational level of the MDR cases was found primary level. Further study may help to conclude the findings [4]. Among the 164 respondents, 150 had at least one episode of Anti TB drug history which was 91.5%. At the same time, 12.2% had history of taking 2 episode of ATT. Most MDR cases were diagnosed from Category 1 or having no treatment. They were about 80%. From re-treatment category MDR cases were 20% of total. Primary MDR may be more emerging as around 8% DR TB had not received any ATT and around 21% had received only 2 months of ATT mostly under DOT. It needs to conduct an analytical study only on this topic. The finding of this study also provokes us to conduct Drug Resistance Survey (DRS) to know the latest DR TB pattern.

It is commonly said that TB is a disease of poverty. It is also true for DR TB. The study showed that MDR TB was more prevalent among low socio-economic group of people. Due to low income, their life style may be affected positively to develop MDR TB. This was also established by several other studies [5]. In general, rural people were mostly affected by MDR TB and there was no ethnic sensitivity. DR TB developed from different religion group. This study was not suitable to make any comment on whether any religion is more vulnerable for TB or not. A number of occupations had been identified among the respondents. This study showed that DR TB a generalized disease. But at the same time some occupations were found more prone for developing DR TB. In this category garments workers are remarkable. Previous history was important for developing DR TB. Most of the MDR cases had previous anti TB drug history [5, 6]. Regularity of treatment and regular supervision of Drug intake (DOT) was important for development of DR TB.

In this study, we had inquired about presence of contact history either with TB or DR TB. It was considered an important risk factor. Contact with MDR TB is most likely to produce MDR TB. MDR TB cases may have contact with Non-MDR TB but there may not have association to be transmitted from each other. Both may have different source of infection. It was identified from the study that 44 DR TB patients among 164 (26.8%) had history of contact with TB or DR TB patients. Among 44 DR TB cases 20 had history of contact with DR TB patients. This finding was very alarming and needs to take initiative to detect DR TB cases early and put them on treatment. Some other study also recommended the same [5]. In this study we had also inquired about co-infection of DR TB cases with other chronic disease. We had found that 9.1% DR TB patients were suffering from Asthma and 7.3% DR TB patients were suffering from Diabetes. DM patients are most vulnerable to develop TB & MDR TB. Also Asthma was a remarkable chronic disease among MDR TB. Some other study also had the similar findings [4]. Around 46% DR TB patients were addicted

with smoking of Cigarette, Ganja, Tobacco and Alcohol. Some patients had addiction with single item and some had with multiple items. Studies in Russia showed alcohol abuse/dependence and smoking were associated with Drug Resistance. Several other studies also mentioned related findings [6-8]. Smoking was common for male and chewing Tobacco was common for female. Addictions with multiple items were also risk factor for developing MDR TB. MDR TB became more complicated if turns into XDR. XDR TB is an emerging threat to the world. In this study, we had learned about one XDR TB cases by performing culture & DST for 2nd line AT drugs. We should have established mechanism to detect XDR cases early and strong program to prevent development of XDR from MDR.

This study presented us a clear view of socio-demographic status and epidemiological factors of registered MDR TB cases at Rajshahi and Rangpur divisions over the year 2013 & 2014. From the results, risk factors associated with MDR TB and elements for strategic planning can be identified.

7. Conclusions

The study concluded that among the respondents, majority were within productive age group (16-45 years). Surveillance program need to conduct at Rangpur division to explain low MDR case detection in spite of high TB notification rate. Some important indicative risk factors for developing DR TB were identified such as education, low income, previous history, addiction, contact history, existence of XDR TB etc. It also urges to establish strong mechanism for early diagnosis and effective management of DR TB. The study put emphasis on effective contact tracings of the already detected DR TB patients, increase awareness of the patients and their family members regarding regularity of treatment and treatment under DOT. As the present study was confined only to MDR TB cases and there was no comparison group, definite conclusion regarding the factors responsible for developing MDR TB cannot be drawn. However, this study opens several scopes of further study and research on multiple issues. Based on the preliminary findings of this study, various social, behavioral and environmental aspects and their relationship with drug resistance TB can be better examined and analyzed. The study recommends that for early diagnosis of DR TB, National TB Control Program may develop policy for all new Smear Positive TB cases to be tested by GeneXpert during diagnosis as most of the cases are from Category – 1 treatment group. It can reduce treatment hazards and cost of treatment if DR TB treatment is provided from the beginning rather than a period of treatment under Category – 1 or Category – 2.

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PLOS ONE

RESEARCH ARTICLE

Decentralization of Acid Fast Bacilli(AFB) External Quality Assurance Using Blind Rechecking for Sputum Smear Microscopy in Ethiopia

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Abstract

Introduction

Ethiopia achieved a rapid expansion of TB microscopic centers for acid fast bacilli (AFB). However, external quality assurance (EQA) services were, until recently, limited to few regional and sub-regional laboratories. In this paper, we describe the decentralization experience and the result of EQA using random blinded rechecking.

Materials and Methods

The routine EQA quarterly report was compiled and analyzed. A positive result by the microscopic center while the EQA center reported negative result is categorized as false positive (FP). A negative result by the microscopic center while the EQA center reported positive is considered false negative (FN). The reading of EQA centers was considered a gold standard to compute the sensitivity, specificity, positive predictive (PPV) and negative predictive values (NPV) of the readings of microscopic centers.

Results

We decentralized sputum smear AFB EQA from 4 Regional Laboratories (RRLs) to 82 EQA centers and enrolled 956 health facilities in EQA schemes. Enrollment of HFs in EQA was gradual because it required training and mentoring laboratory professionals, institutionalizing internal QA measures, equipping all HFs to perform diagnosis, and establishing more EQA centers. From 2012 to 2014 (Phase I), the FP rate declined from 0.6% to 0.2% and FN fell from as high as 7.6% to 1.6% in supported health facilities (HFs). In HFs that joined in Phase II, FN rates ranged from 5.6 to 7.3%. The proportion of HFs without errors has

increased from 77.9% to 90.5% in Phase I HFs and from 82.9% to 86.9% in Phase II HFs. Overall sensitivity and specificity were 95.0% and 99.7%, respectively. PPV and NPV were 93.3% and 99.7%, respectively.

Conclusion

Decentralizing blinded rechecking of sputum smear microscopy is feasible in low-income settings. While a comprehensive laboratory improvement strategy enhanced the quality of microscopy, laboratory professionals' capacity in slide reading and smear quality requires continued support.

Introduction

Direct sputum microscopy for acid-fast bacilli (AFB) using light microscopy is the most widely used tuberculosis (TB) diagnostic and monitoring tool worldwide [1–4]. Quality-assured TB microscopy is one of the key elements of DOTS in the STOP TB strategy of the World Health Organization (WHO) [4]. It is simple and cost effective and does not require sophisticated training or setup [4–6]. But it does require a very good system of quality assurance [6–7].

Quality assurance consists of quality control (QC), external quality assurance (EQA), and quality improvement (QI). To yield reliable, reproducible results, all three components should be implemented across the laboratory network [8]. Reliable AFB microscopic results such as smear positivity rates also help planners to understand the progress of TB control measures [9–11]. Implementation of EQA for microscopy helps to improve the quality of diagnosis of TB and measure the cure rates of TB patients on treatment. EQA is needed to ensure that smears are performed and interpreted correctly and that all microscopy centers perform at an acceptable level [5,11,12].

Despite rapid expansion of TB microscopic centers in Ethiopia for Ziehl-Neelsen (ZN), EQA services were, until recently, limited to a few regional and sub-regional laboratories. To fill this gap, the Ethiopian Public Health Institute (EPHI) introduced a decentralized EQA system using randomized blinded rechecking (RBRC) [7]. RBRC involves the collection of smears from the microscopy center laboratory for blinded re-reading at a regional reference laboratory (RRL) or other designated EQA center, with feedback to the microscopy center [7]. WHO has recommended this approach to evaluate the performance of AFB microscopy centers [13].

RBRC has been used successfully in many pilot and research projects [9,13–16]. In India, for example, RBRC has been used to measure the performance of laboratories and assess errors [13,16]. In other settings, it has been used for QI of diagnosis and monitoring of treatment response [17,18] and for QA where culture or fluorescent microscopies cannot be routinely used [19]. In Ethiopia, we supported the implementation of a decentralized EQA system for ZN microscopy over 1,600 health facilities (HFs) in two large regions. This paper presents the process of decentralization, its outcomes, and the factors that contributed to successful establishment of RBRC services.

Materials and Methods

Setting

In Ethiopia, which is one of the 22 high-TB-burden countries,[5] the Federal Ministry of Health (FMOH) provides guidance for implementation of the national TB program, while the EPHI is

responsible for all laboratory-related standardization and quality issues. In 2008, EPHI designed an EQA system for sputum smear Z-NAFB microscopy [7]. The system was organized so that EPHI conducts panel testing for RRLs and the RRLs conduct RBRC of sputum smear slides for hospitals. Selected hospitals with good EQA performance ($\geq$ 95% concordance for 2–3 quarters) conduct EQA for health centers in their catchment areas (Fig 1).

Operationalization of decentralized EQA

The Amhara and Oromia Regional Health Bureaus (RHBs) receive support from the US Agency for International Development (USAID) through the Help Ethiopia Address the Low Performance of TB (HEAL TB) project managed by Management Sciences for Health. The RHBs operationalized the decentralized EQA model through a process that involved several stakeholders.

When the project began in 2011, QA measures for AFB were weak and in most cases HFs had no QA mechanism. Following a baseline assessment, HEAL TB supported the RHBs to design a decentralized EQA system. The support included training laboratory personnel, providing standard registers, supplying microscopes and reagents, and providing quarterly supportive supervision and on-site technical support to every HF. During supervision visits, laboratory experts checked for complete registration and proper storage of the sputum smear slides and sequential labeling. The senior laboratory expert assisted in establishing internal QA measures during the site visits, including weekly checking of reagent quality with five known negative and positive slides. When errors were identified, the laboratory experts explored the cause of the error and took corrective measures with the HF laboratory personnel. After two or three quarters of follow-up and on-site support, the HFs were ready to join the country's RBRC scheme. To assure their quality, reagents were prepared at national or regional level and distributed to all health facilities.

Training of district TB focal persons as supervisors and slide randomization

Once the HFs were prepared for EQA participation, trained *woreda* (district) TB focal persons took the lead in supervising them. The woreda TB focal persons were trained in supervisory skills for laboratories, including checking for proper registration, labeling, and storage of slides. Every quarter the woreda TB focal persons supervised each HF in their catchment area and randomized slides for blinded rechecking following the Lot Quality Assurance Sampling guidelines for AFB slides. The nationally agreed-on sample size is based on 80% sensitivity, 100% specificity, and accepting number $d = 0$ (Table 1) [20]. The TB focal persons then delivered the collected slides to the RRLs or EQA hospitals to conduct the EQA. The EQA readers were laboratory experts from the RRLs or hospitals, who were different from those who randomized the slides.

Blind re-checking procedures

The experts involved in EQA reading have demonstrated a 95% concordance rate for at least two quarters. EPHI assesses the RRLs' EQA through panel testing, since EPHI does not routinely collect slides for patient care. RRLs check hospitals' EQA quarterly, and designated hospitals check the EQA of health centers (Fig 1). The quality officer of the EQA center assigns slides to a reader (controller). After the first reader completes the reading, the result is submitted to the quality officer to reconcile with the initial reading of the microscopic center. The quality officer assigns all discrepant slides from the first reader to a second reader (senior expert). If the result of the second reader agrees with that of the first, it becomes the final result.

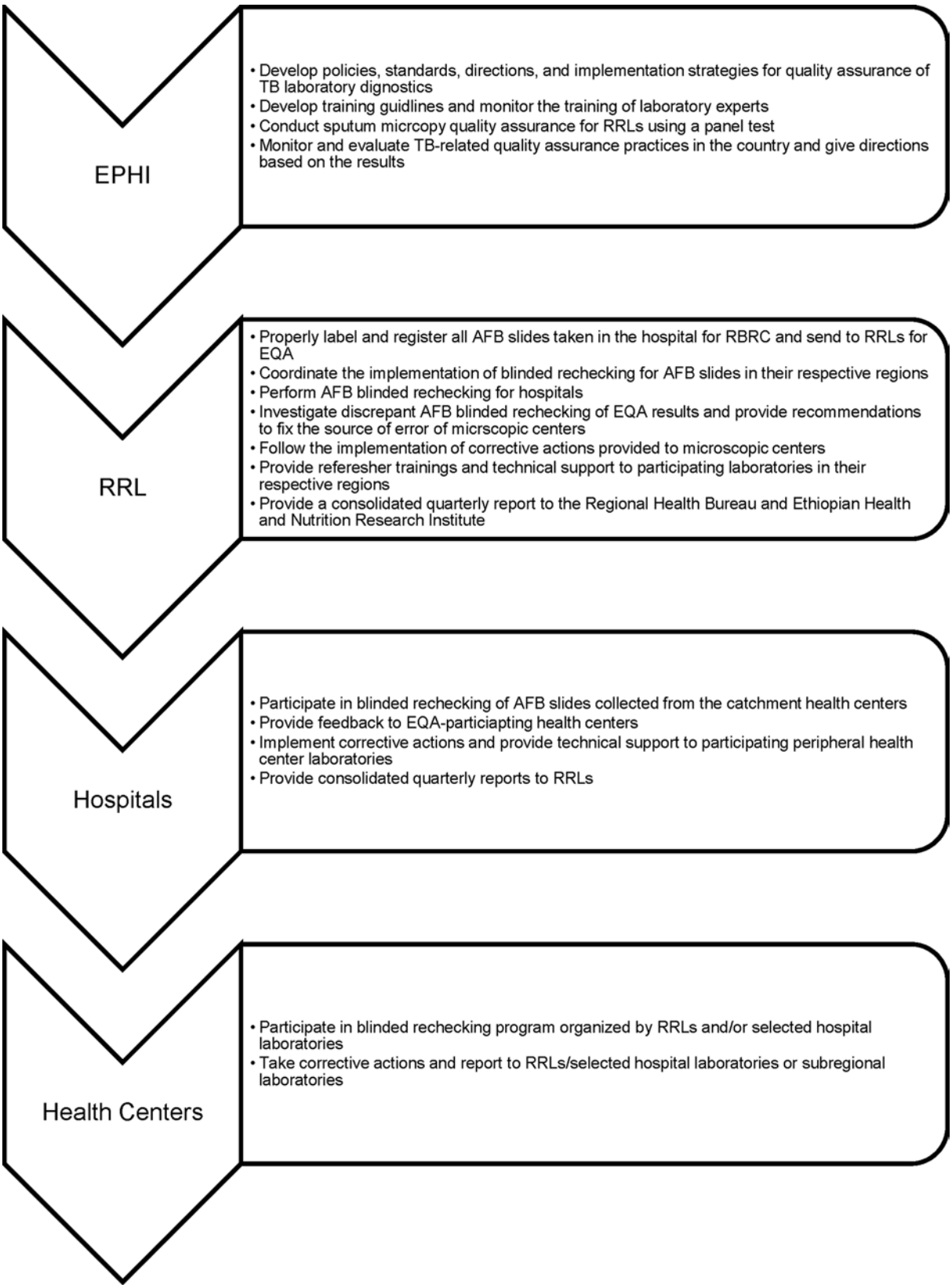

Fig 1. Model for decentalized AFB random blinded rechecking in Ethiopia.

doi:10.1371/journal.pone.0151366.g001

Table 1. Sample size based on annual slide volume and slide positivity rate.

Number of negative slides in the microscopic center in a year	Annual sample size of both positive and negative slides for EQA(quarterly sample sizes appear in parenthesis)				
	2.5–4.9	5.0–7.49	7.5–9.9	10–14.9	15 and above
301–500	243(62)	154(40)	114(30)	89(23)	62(16)
501–1,000	318(81)	180(45)	128(33)	96(25)	66(17)
>1,000	456(114)	216(54)	144(37)	104(27)	69(18)

doi:10.1371/journal.pone.0151366.t001

If the readings are still discordant, a third expert reads the slide, and any two concordant expert readings become the EQA result. The RRLs or hospital controllers travel to health facilities with discordant slides to identify the cause of the discordance (e.g., poorly functioning microscope, reader capacity, quality of reagent, or fading). The final result is recorded after agreement with the HF laboratory professionals is reached. (Fig 2). If the final result is different from the original report of the microscopic center, it is communicated to the treating clinicians for decision making Each EQA center covers 11–15 HFs (Table 2), and controllers conduct EQA mostly in their spare time and are paid overtime. EQA reading takes one month, and on-site evaluations of HFs with discordant slides, takes another two months.

Data management and analysis

The reading results of peripheral laboratories were entered in Excel, the EQA results tabulated, and the analysis done based on internationally accepted definitions. The false-positive and false-negative errors were calculated using standard definitions [21]. A positive result by the microscopic center while the EQA center reported negative result is categorized false positive (FP). Similarly, if the microscopic center indicates a negative result while the EQA center reported positive, it is considered false negative (FN). Sensitivity, specificity, and positive and negative predictive values of the readings were then calculated using the EQA center controller's final result as a gold standard, per the international guideline [20].

Ethical Considerations

The Ethiopian Public Health Institute (EPHI) has released an AFM microscopy EQA guideline to be implemented in all microscopy centers and using a Lots Quality Assurance, sputum smear slides collected through to the routine clinical practice are randomized for RBRC. The data for this paper is acquired through this routine lab quality monitoring system, but not collected from patients directly for research purpose. As per the guiding, the sputum smear slides randomized have no patient identification information and the result is reported to evaluate the lab performance, but not directly related to patient management. EPHI has given the permission to publish the experience from the nationally reported data as the practice of decentralized EQA system has much application for low-income countries.

Results

Baseline data

During the first phase of project implementation (July 2011-June 2013), 691 DOTS-providing HFs were supported through HEAL TB in Amhara and Oromia regions. At baseline in October 2011, 465 HFs were providing TB diagnostic services, and 104 were participating in sporadic AFB on-site quality checks but not RBRC using proper sampling. By the end of 2013, the remaining 226 non-diagnostic HFs were equipped to become diagnostic and all 629 were

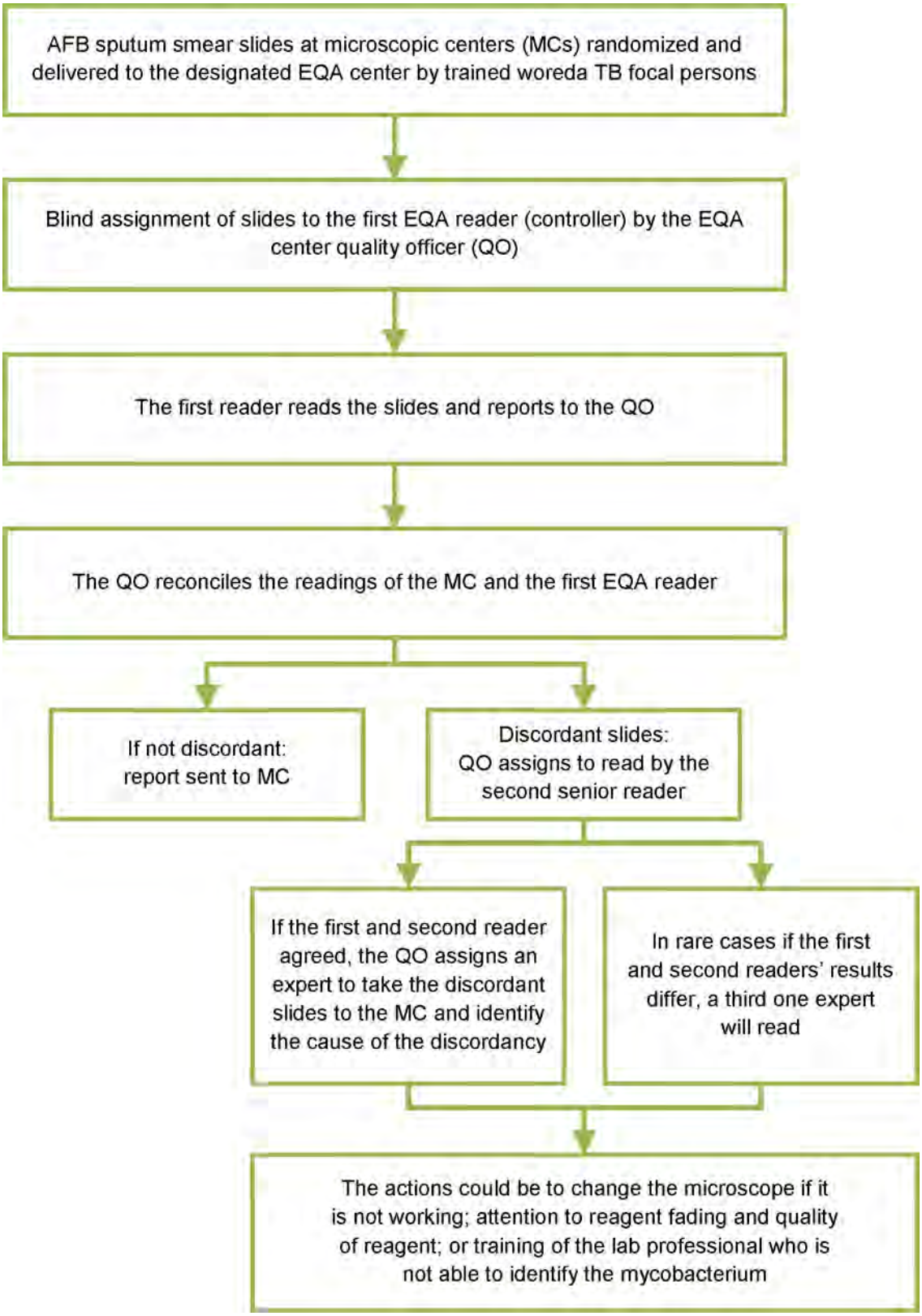

Fig 2. Flow chart of procedures for blinded random rechecking.

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Table 2. AFB microscopy EQA coverage for all HEAL TB-supported zones, April 2012-June 2014.

Indicator	April-June 2012	July-Sept 2012	Oct-Dec 2012	Jan-Mar 2013	April-June 2013	July-Sept 2013	Oct-Dec 2013	Jan-Mar 2014	April-June 2014
Total number of HFs participating in EQA RBRC	353	413	533	607	583	773	872	956	895
Total number of slides collected for EQA	13,809	16,275	22,421	27,477	22,805	30,681	37,086	41,323	36,955
Total number of EQA centers	22	38	39	40	40	56	74	80	82
Ratio HF to EQA center	16	11	14	15	15	14	12	12	11

doi:10.1371/journal.pone.0151366.t002

enrolled in RBRC. During the second phase of the project (July 2013-present), 909 more HFs were included and at the time of this analyses 335 of them were enrolled in RBRC. The rest were under mentorship to be part of the RBRC scheme.

Trends in EQA participation

The number of diagnostic HFs participating in RBRC increased from none at baseline to 956 by the end of March 2014. Ninety-one percent of the 691 DOTS centers in Phase I HFs were able to participate in the quarterly RBRC scheme, while the remaining 9% were checked on site because of low slide volume. Of the Phase II HFs, 37% have started to participate in EQA. In June 2014, the number of EQA-participating facilities decreased because the HFs with heavy patient loads shifted from Ziehl-Neelsen microscopy to iLED (light-emitting diode) fluorescence microscopy. Enrollment of HFs in EQA was gradual because it required training and mentoring laboratory professionals, institutionalizing internal QA measures, equipping all HFs to perform diagnosis, and establishing more EQA centers (Table 2).

The EQA centers grew from 4 at baseline to 82 by the end of June 2014 (Table 2). Between April 2012 and June 2014, the EQA centers had read 248,832 slides. In Phase I HFs the false-positive rate declined from 0.6% (95% CI, 0.4–0.7) to 0.2% (95% CI, 0.2–0.3) and false negatives had a steady decline from 7.6% (95% CI, 6.1–9.6) to 1.6% (95% CI, 1.0–2.6) over two years, with a slight increase in the last quarter in Phase I HFs (Table 3, Fig 3). The denominator used to calculate the false negative is positive readings and for that false positives is negative readings. The proportion of HFs with no errors at this increase in Phase I reached 90.5% as opposed to 77.9% at the beginning of the project (Fig 4). In Phase II HFs the false-negative rate ranged from 5.6% to 7.3% while false positives ranged from 0.5% to 0.3% (Table 3, Fig 3).

By the end of the study, overall sensitivity and specificity for the Phase I HFs were 95% and 99.7%, respectively, and the positive predictive value (PPV) and negative predictive value (NPV) were 93.7% and 99.7% respectively. In Phase II HFs, sensitivity and specificity were 94.1% and 99.6% respectively. The PPV and NPV were 93.3% and 99.7% respectively.

In Phase I HFs, the average quality of staining at baseline was 71.1% and by June 30, 2014, it reached 81.4%. In Phase II HFs, it increased from 61.7% at baseline to 72.7% by June 2014. Smear thickness also improved, from 62.1% to 69.8% in Phase I HFs, but in Phase II HFs it improved from 59.3% to 71% and then decreased to 57.0%. In Phase I HFs cleanliness of the slides improved from 72.6% to 86.3%, but in Phase II HFs cleanliness improved from 80.7% to 88.4% and then declined to 81.6% in June 2014 (Table 4).

Discussions

This study demonstrates that decentralizing AFB EQA services to hospitals is a feasible, low-cost approach for countries like Ethiopia that have few higher-level laboratories [8,13,22,23]. With

Table 3. False-negative and false-positive rates per quarter, April 2012-June 2014.

Quarter-Year	Phase I: Implementation Zones			
	Number of slides collected from microscopic centers		Error rates reported by the EQA centers	
	Negative results by the laboratory	Positive rate by the laboratory	%[95%CI] false-negative slides	%[95%CI] false-positive slides
II- 2012	12,894	915	7.6 [6.09, 9.56]	0.6 [0.44, 0.70]
III- 2012	15,373	902	7.5 [5.78, 9.21]	0.6 [0.51, 0.76]
IV- 2012	21,248	1,173	6.0 [4.74, 7.48]	0.4 [0.33, 0.51]
I- 2013	26,171	1,306	4.8 [(3.71, 6.05]	0.3 [0.26, 0.40]
II- 2013	21,563	1,242	3.1 [2.29, 4.27]	0.3 [0.22, 0.36]
III- 2013	23,444	1,268	4.0 [3.06, 5.26]	0.4 [0.30, 0.46]
IV- 2013	24,420	1,203	2.2 [1.53, 3.26]	0.1 [0.09, 0.19]
I- 2014	25,158	1,114	1.6 [(1.01, 2.56]	0.2 [0.14, 0.24]
II- 2014	21,046	894	5.2 [4.16, 7.18]	0.2 [0.18, 0.31]
Phase II: Implementation Zones				
Quarter-Year	Negative results by the laboratory	Positive rate by the laboratory	%[95%CI] false-negative slides	%[95%CI] false-positive slides
III- 2013	5,636	333	5.6 [3.39, 8.43]	0.5 [0.37, 0.76]
IV- 2013	10,848	615	5.4 [3.82, 7.46]	0.4 [0.34, 0.59]
I- 2014	14,335	716	4.9 [3.52, 6.74]	0.3 [0.19, 0.36]
II- 2014	14,356	659	7.3 [5.65, 9.71]	0.3 [0.19, 0.36]

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the decentralized approach, nearly 1,000 HFs participated in RBRC. It takes approximately 6–9 months to prepare the HFs for RBRC, but in Phase II, 335 HFs enrolled in EQA, which was faster than expected because of the experience gained during Phase I implementation.

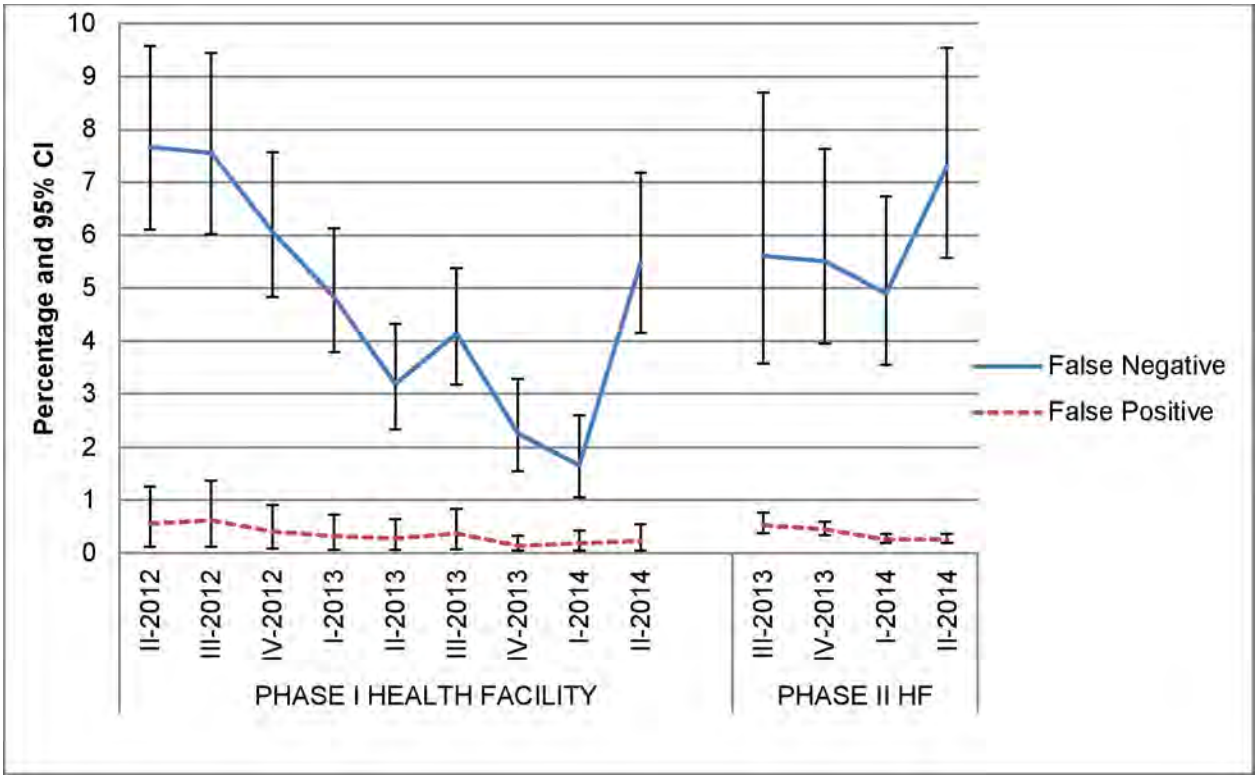

Fig 3. Health facilities' reported false-negative and false-positive error rates per quarter, April 2012-June 2014.

doi:10.1371/journal.pone.0151366.g003

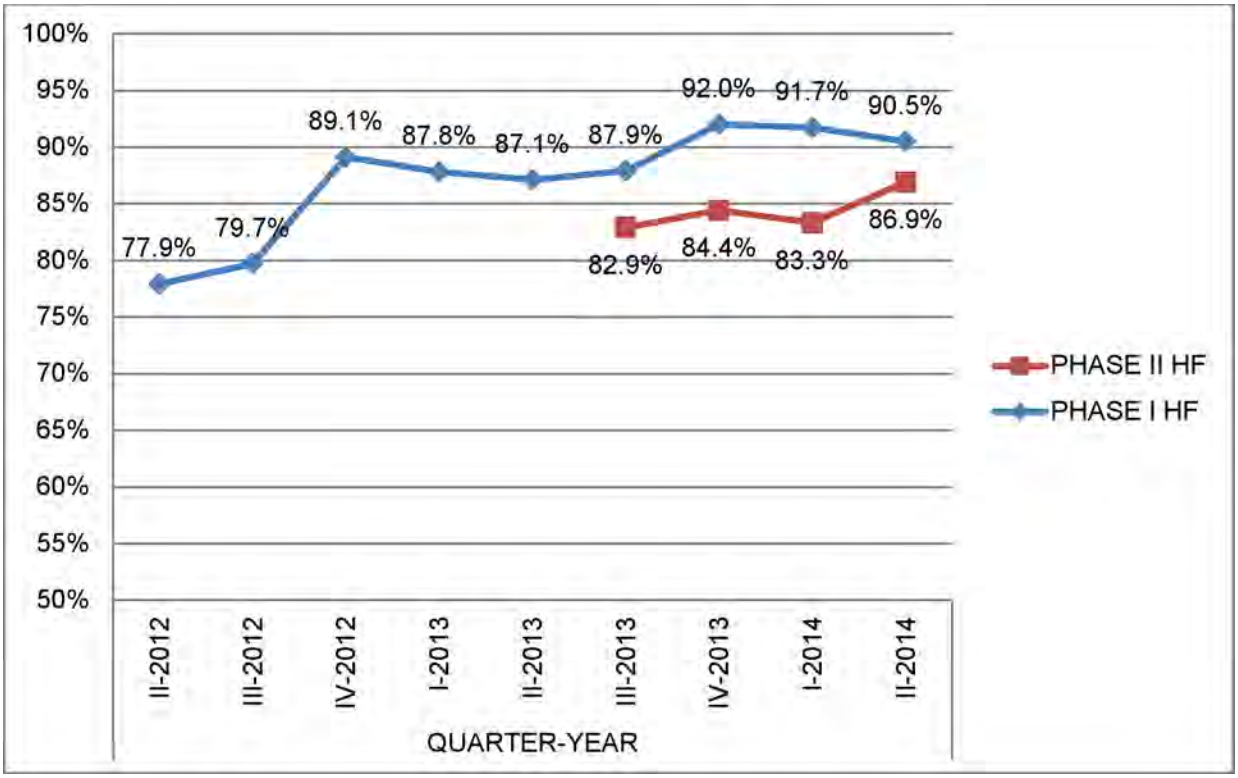

Fig 4. Percentage of health facilities without any error per quarter, April 2012-June 2014.

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The rapid capacity building of HFs in sputum smear microscopy, coupled with on-site supervision, helped decrease the numbers of false-positive and false-negative slides. Other countries have reported improvements using similar mechanisms [8,18] Our experience is that the proportion of HFs with no errors improved from quarter to quarter but the error rate fluctuated because of HFs enrolled in EQA for the first time or new, less-trained laboratory professionals assigned to the HFs. The HFs began EQA in different phases, but in three quarters the false-negative rate declined significantly (Table 3). In 507 Phase I HFs with EQA results, for example, in April-June 2014, only 48 contributed to the reported errors. False-positive errors were low from the beginning, and there was statistically significant improvement in both phases.

Another possible reason for errors was smear quality, although there were improvements from quarter to quarter because of comprehensive capacity building (Table 4). We addressed challenges by providing refresher training at sites with poor performance and at laboratories with new personnel. In addition, the EQA centers served as mentors and trainers for new laboratory professionals and underperforming laboratories. Every week the HF also checks reagent quality with known negative and positive slides. RRL staff also visit and identify the causes of errors with the HFs' laboratory experts. If fading is suspected, they re-stain the slides and read them on-site with the same microscope used for diagnosis by the HF.

The overall sensitivity of 95.0% and specificity of 99.7% in our health facilities are high, per international standards [20], and the national recommendation about the sample size for RBRC for Ethiopia might need revision. The revised international recommendation for EQA of AFB smear microscopy is to use a 75–80% sensitivity rate to calculate sample sizes for blinded rechecking [7,20]. Ethiopia has already adopted this recommendation, so the sample

Table 4. Sputum smear quality assessment by the EQA centers, April 2012-June 2014.

Phase I Implementation Zones						
Quarter	**Number of HFs enrolled in EQA**	**Total number of sampled slides**	**Good-quality staining (%)**	**Smear thickness (%)**	**Cleanliness of slides (%)**	**Evenness of smearing (%)**
II- 2012	353	13,809	71.1	62.1	72.6	53.0
III- 2012	413	16,275	69.8	62.5	82.4	59.1
IV- 2012	533	22,421	72.9	67.1	83.7	63.7
I- 2013	607	27,477	74.9	71.1	84.8	66.1
II- 2013	583	22,805	75.4	70.3	87.1	67.5
III- 2013	626	24,712	75.1	67.7	85.2	67.2
IV- 2013	603	25,623	77.2	71.8	88.3	69.7
I- 2014	614	26,272	78.2	70.9	85.4	68.8
II- 2014	560	21,940	81.4	69.8	86.3	66.6
Total		*201,334*				
Phase II Implementation Zones						
Quarter	**Number of HFs enrolled in EQA**	**Total number of sampled slides**	**Good-quality staining (%)**	**Smear thickness (%)**	**Cleanliness of slides (%)**	**Evenness of smearing (%)**
III- 2013	147	5,969	61.7	59.3	80.7	54.7
IV- 2013	269	11,463	63.9	59.7	79.7	51.7
I- 2014	342	15,151	77.0	71.0	88.4	65
II- 2014	335	15,015	72.7	57.0	81.6	55.0
Total		*47,498*				

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size for blinded rechecking was calculated based on a sensitivity of 80% [7]. Future samples will be large, if Ethiopia plans to revise the sampling based on the improved EQA results. EQA centers may be overloaded with large numbers of slides.

The decentralized approach is cost effective because the EQA readers and district TB focal persons who randomize slides for EQA are all government workers paid according to government rates. EQA readers are paid US$5 per 20 slides in Oromia Region and US$2 in Amhara. The per diem and transport for the district focal person is US$7.50 per HF. These costs are manageable for the government, which will help to sustain the system. The experience in scaling-up of EQA, the progressive improvement in quality and the cost-effectiveness of the approach heralds that such system can easily be easily replicated in similar settings.

There are some limitations of the study. The false-positive and false-negative rates at EQA center level were not reported using the scanty, 1+, 2+, and 3+ categories, but for four quarters in the initial period the regions were reporting summary data, so we could not compute error rates by category. Therefore the analysis is limited to false positives and false negatives rather than detailed classifications. The data did not capture whether the AFB slides included in the EQA were collected for diagnostic purpose or TB treatment follow-up. As a result, we were not able to compare the EQA in the two groups independently. However, the regularity of data collection and the huge number of HFs covered represent strengths of this study.

Conclusion

A decentralized EQA scheme was feasible in a large number of HFs in Ethiopia. Involving hospitals has contributed to rapid scale-up of the EQA scheme to thousands of HFs every quarter. AFB quality has improved gradually and error rates have declined in many HFs. The model is

scalable and sustainable because it was designed and built within the Ethiopian health care system. Close on-site mentoring of DOTS centers and of HFs with errors are critical for the success of this approach. Pre-placement trainings for newly assigned laboratory personnel should be implemented routinely to prevent the high error rates reported from sites with new staff. Smear quality improvement is a priority to further reduce errors. The overall impact of the decentralized EQA scheme on improving the quality of TB care should be evaluated. A clear sputum sample transport to the expanding GeneXpert and culture centers should be established to improve the diagnosis of TB those cannot be by microscopy.

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Author Contributions

Conceived and designed the experiments: MM JS YK BG DH DJ NH. Analyzed the data: MM DJ DH G. Ayana G. Alem JS FB SN YK YKH NH PGS. Contributed reagents/materials/analysis tools: MM DJ DH G. Ayana G. Alem JS FB SN YK YKH BG PGS. Wrote the paper: MM DJ DH G. Ayana JS FB SN YK YKH PGS.

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RESEARCH ARTICLE Open Access

Diagnostic performance of smear microscopy and incremental yield of Xpert in detection of pulmonary tuberculosis in Rwanda

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Abstract

Background: Tuberculosis control program of Rwanda is currently phasing in light emitting diode-fluorescent microscopy (LED-FM) as an alternative to Ziehl-Neelsen (ZN) smear microscopy. This, alongside the newly introduced Xpert (Cepheid, Sunnyvale, CA, USA) is expected to improve diagnosis of tuberculosis and detection of rifampicin resistance in patients at health facilities. We assessed the accuracy of smear microscopy and the incremental sensitivity of Xpert at tuberculosis laboratories in Rwanda.

Methods: This was a cross-sectional study involving four laboratories performing ZN and four laboratories performing LED-FM microscopy. The laboratories include four intermediate (ILs) and four peripheral (PLs) laboratories. After smear microscopy, the left-over of samples, of a single early-morning sputum from 648 participants, were tested using Xpert and mycobacterial culture as a reference standard. Sensitivity of each test was compared and the incremental sensitivity of Xpert after a negative smear was assessed.

Results: A total of 96 presumptive pulmonary tuberculosis participants were culture positive for *M. tuberculosis*. The overall sensitivity in PL of ZN was 55.1 % (40.2–69.3 %), LED-FM was 37 % (19.4–57.6 %) and Xpert was 77.6 % (66.6–86.4 %) whereas in ILs the same value for ZN was 58.3 % (27.7–84.8 %), LED-FM was 62.5 % (24.5–91.5 %) and Xpert was 90 (68.3–98.8 %). The sensitivity for all tests was significantly higher among HIV-negative individuals (all test p <0.05). The overall incremental sensitivity of Xpert over smear microscopy was 32.3 %; $p < 0.0001$. The incremental sensitivity of Xpert was statistically significant for both smear methods at PL (32.9 %; $p = 0.001$) but not at the ILs (30 %; $p = 0.125$) for both smear methods.

Conclusions: Our study findings of the early implementation of the LED-FM did not reveal significant increment in sensitivity compared to the method being phased out (ZN). This study showed a significant incremental sensitivity for Xpert from both smear methods at peripheral centers where majority of TB patients are diagnosed. Overall our findings support the recommendation for Xpert as an initial diagnostic test in adults and children presumed to have TB.

Keyword: Tuberculosis microscopy in routine conditions, LED-FM versus ZN, Incremental yield of Xpert, Tuberculosis diagnosis in Rwanda

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Background

Despite the recommendations of the World Health Organization to use Xpert [1] as a first line diagnostic test, smear microscopy remains the most available and affordable test in low-income countries. Microscopy is inexpensive and highly specific in areas where there is a high prevalence of tuberculosis. However, it has several limitations including the fact that it is examiner-, technique-, and prevalence-dependent and in addition, it lacks sensitivity [2].

Studies evaluating the performance of LED-FM have shown that in addition to higher sensitivity (an average of 10 % higher than conventional ZN), it had qualitative, operational and cost advantages over both the conventional FM and ZN. On the basis of these findings, the World Health Organization (WHO) recommended in 2011 to replace conventional FM with LED-FM and phase in LED-FM as an alternative to ZN microscopy [3]. On the other hand, in 2010 WHO recommended that Xpert be used at district and sub-district levels as the initial diagnostic test in individuals suspected of having MDR-TB or HIV-associated tuberculosis. The WHO further updated recommendations on the use of Xpert including a follow-on test for smear-negative patients in other settings [1]. In a Cochrane meta-analysis, sensitivity and specificity of Xpert compared with culture were 88 % (95 % CI 83 to 92 %) and 98 % (97 to 99 %), among smear-positive cases, and 98 % (97 to 99 %) and 68 % (60 to 75 %) among smear-negative cases [4].

In Rwanda, the national tuberculosis control program has started the phase-in of LED-FM as an alternative to ZN microscopy in peripheral (PLs) and intermediate health facility laboratories (ILs). To date, 40 % of laboratories have implemented LED-FM and 16 health facilities started using Xpert for TB detection in 2012. A sample transportation system was organized to facilitate transfer of samples from health facilities without an Xpert machine. The ILs or district hospital laboratories have an average of six qualified laboratory technologists and they are supervised, trained and mentored by the National Reference Laboratory (NRL) whereas peripheral laboratories or health center laboratories have an average of two laboratory technicians and they are subsequently supervised, trained and mentored by ILs. In regards to the workload, PLs test more than 75 % of pulmonary tuberculosis presumptive yet most of these facilities have very few technologists who also perform other requested laboratory tests. Based on the countrywide data of external quality assurance of smear microscopy (annual blind rechecking and proficiency panel test), the results of PLs tend to be better than those of ILs. However, no study of accuracy has been done to assess the significance of this difference. Therefore, this study aimed to determine the sensitivity of smear microscopy and the incremental gain of Xpert for the detection of pulmonary tuberculosis at PLs and ILs to support the scale up of this new molecular technology. The present study assessed the performance of the two sputum smear microscopy techniques and the incremental yield of Xpert over microscopy among individuals with presumptive pulmonary tuberculosis, taking mycobacterial culture as the reference standard.

Methods

Setting, study design and population

This was a cross-sectional study involving eight health facilities which were purposively selected due to the high numbers of presumptive pulmonary tuberculosis recorded in the year 2013. Four PLs (two performing ZN and two performing LED-FM) and four intermediate laboratories (two performing ZN and two preforming LED-FM). Based on quality control of smear microscopy (QC) data of 2012 and 2013 these eight laboratories performed equally well, though the QC for intermediate is performed by the NRL whereas QC for peripheral are subsequently done by ILs.

After smear microscopy, the left-over of the samples, of a single early-morning sputum from 648 new presumptive pulmonary tuberculosis patients, were tested using Xpert and mycobacterial culture as a reference standard.

Laboratory procedures

For each eligible participant, three to five mL of morning sputum specimen were collected in a clean plastic container with wide-mouthed, screw-capped and leak proof. A direct sputum smear was prepared, stained and examined by laboratory technicians at health facility laboratory. The left-over of sputum specimens and the examined corresponding sputum smear were immediately shipped to the tuberculosis laboratory of NRL. Sputum specimens not shipped immediately were refrigerated (4 to 8 °C). All sputum specimens collected were transported in a cool box (4–8 °C) and were processed on the same day at NRL TB laboratory.

At the NRL, sputum specimens were recorded and decontaminated using N-Acetyl-L-Cysteine Sodium hydroxide (NALC-NaOH) procedure followed by neutralization with phosphate buffer, centrifuged and the deposits (0.5 ml) inoculated in Mycobacterial growth indicator tube (BBL MGIT, Becton and Dickson, Franklin Lakes, NJ USA) and two Home-made Lowenstein Jensen (LJ) tubes respectively. The remaining pellet was used to prepare a smear and to run Xpert. For Xpert 0.5 mL of decontaminated and concentrated sputum was added to 1.5 mL of the sample reagent (i.e., a ratio of 1:3). After 15 min, two mL of the mixture was added to the Xpert cartridge and then run in the machine in accordance

with manufacturer's guide (Cepheid, Sunnyvale, CA, USA). The smears prepared from pellet were stained using auramine for LED-FM examination and NRL results were considered final for those who tested negative at the health facility. Inoculated MGIT were incubated in an automated BD BACTEC 960 machine for up to 42 days according to manufacturer's guide (MGIT, Becton and Dickson, Franklin Lakes, NJ USA) while the two LJ tubes were incubated in manual incubator at 37 °C and inspected weekly for up to eight weeks. Positive cultures were confirmed for presence of acid fast bacilli by ZN microscopy and strain identification was done using an immunochromatographic test (SD MPT64TB Ag kit; SD Bioline, South Korea). Reexamination of smear from health facility at NRL, results of concentrated smear and Xpert provided preliminary results for treatment of pulmonary tuberculosis cases missed by health facility laboratories. The final results were provided by Mycobacterial culture.

Data management and analysis

As the presence of MTB cannnot be excluded among contaminated cultures and cultures positive for non tuberculous mycobacterial (NTM), these results were excluded from the analysis as they may have led to an under-estimation of the sensitivity of Xpert or smear microscopy. The sensitivity and specificity was calculated for each method and type of health facility stratified by HIV-status using MGIT and/or LJ culture as gold standard. The incremental sensitivity of Xpert test to smear microscopy method was defined as the percentage of smear microscopy negative but Xpert positive by health facility among culture positive for *M. tuberculosis.* The McNemar statistical test was used to assess the significance of the differences in results obtained from smear microscopy using ZN versus LED-FM and the incremental sensitivity of Xpert. Based on these results, we compared the effectiveness of diagnostic strategies to propose the most accurate algorithm for the diagnosis of pulmonary tuberculosis at PLs and ILs. A p-value <0.05 was considered statistically significant. All data analysis was performed using SPSS version 21.0 software (Armonk, NY: IBM Corp.).

Results

Participants' characteristics and microbiological profile

Among the 648 patients enrolled, 48 were excluded for analysis due to incomplete results (23; 3.5 % contaminated cultures, 22; 3.4 % cultures positive for NTMs and 3; 0.5 % invalid Xpert results). Of the 600 included, 372 (62 %) were male and median age was 37 years (interquartile range 28–50). A total of 390 (65.0 %) and 210 (35.0 %) participants were from PLs and ILs respectively of whom, 318 (53 %) were from laboratories performing ZN and 282 (47 %) from laboratories performing LED-FM microscopy, Fig. 1.

The prevalence of HIV in this study population was 162 (27.0 %). The smear positivity rates were 12.0 % and 5.0 % among ZN and LED-FM laboratories respectively, whereas the positivity rate for Xpert was 13.7 % of whom seven (1.2 %) had rifampicin resistant *M. tuberculosis*. A total of 96 (16.0 %) participants had culture confirmed TB of whom 28 (29.2 %) were HIV-infected, Table 1.

Senstivity of smear methods and Xpert assay

Among 96 culture positive for *M. tuberculosis* by MGIT and/or LJ method, 47 (49.0 %) were smear negative of which 20 (42.6 %) were tested with LED-FM and 27 (57.4 %) with ZN. Among 82 patients found MTB positive with the Xpert assay, 36 (43.9 %) were smear microscopy negative of whom 13 (36.1 %) were HIV-infected. In regard to rifampicin resistance, seven rifampicin resistant MTB cases were detected by Xpert, among which only two were smear positive. The overall sensitivity of Xpert was 80.2 %, 95%CI (70.8–87.6). Xpert at PLs had a sensitivity of 77.6 %, 95%CI (66.6–86.4) as compared to 90 %, 95%CI (68.3–98.8) among ILs the overall sensitivity of smear microscopy was 51.0 %, 95 % CI (40.6–61.4 %). Overall sensitivity for smear microscopy among PLs was 48.7 %, 95 % CI (37.0–60.4) whereas for ILs was 60.0 %, 95%CI (36.1–80.9). The overall sensitivity of smear microscopy was 39.3 %, 95%CI (21.5–59.4) and 55.9 %, 95%CI (43.3–67.9) among HIV-positive and HIV-negative TB patients respectively. By smear microscopy method, smear by ZN at PLs had sensitivity of 55.1 %, 95 % CI (40.2–69.3) as compared to LED-FM 37.7 %, 95%CI (19.4–57.6). For ILs, the sensitivity for ZN smear microscopy was 58.3 %, 95%CI (27.7–84.8) as compared to LED-FM 62.5 %, 95%CI (24.5–59.4), Table 2. The overall specificity of smear microscopy 99.8 % 95 % C.I (99.4–100 %). The overall sensitivity of smear microscopy was 55.7 %, 95 % C.I (42.4–68.5–63.2 %) and 42.9 % (26.3–60.6 %) among ZN and LED-FM using laboratories respectively, Table 2.

Incremental senstivity of Xpert assay over the smear microscopy results

The overall incremental sensitivity (IS) of Xpert over smear microscopy at all HF was 32.3 %, 95 % CI (23.1–42.6 %). The overall IS of Xpert for either smear microscopy was 35.7 %, 95%CI (18.6–55.9) and 30.9 %, 95%CI (20.2–43.3) among HIV-positive and HIV-negative individuals respectively. The IS of Xpert among PLs using ZN was 32.7 %, 95 % CI (19.9–47.5); whereas for PLs using LED-FM was 33.3, 95%CI (16.5–54.0). Among ILs using ZN, the IS of Xpert was 25.0 %, 95%CI (5.5–57.2)

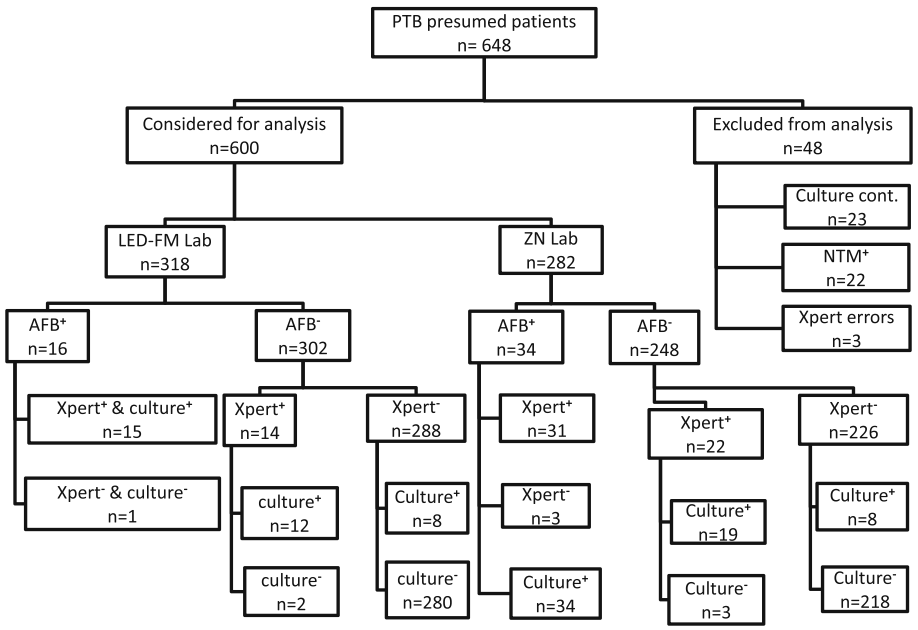

Fig. 1 Flow chart showing series of participants' recruitment and the outcome of different tuberculosis testing methods used. +: Positive, -: Negative, AFB: Acid Fast Bacilli, PTB: Pulmonary tuberculosis, ZN Lab: Ziehl Nelsen health facility laboratories-, LED-FM Lab: Light emitting diode-fluorescence microscopy using health facility laboratories, NTM: Non-tuberculous Mycobacteria, cont.: contaminated

as compared to ILs using LED-FM 37.5 %, 95%CI (8.5–75.5), Table 2.

Discussion

In this cross-sectional study aimed at assessing the accuracy of smear microscopy and the incremental sensitivity of Xpert in presumptive pulmonary tuberculosis patients at tuberculosis laboratories in Rwanda, we document low sensitivity of sputum smear microscopy in tuberculosis diagnostic laboratories, particularly in peripheral laboratories. The added value of Xpert was particularly important among HIV-infected patients and for detection of drug-resistant cases. We further confirm a significant gain from Xpert when used as an initial diagnostic test at health facility laboratories. For both health facility levels, the sensitivity of Xpert was significantly higher than either smear microscopy methods. As expected, the sensitivities of both smear methods including Xpert was higher among HIV-negative participants. Replacing ZN smear microscopy with LED-FM did not increase the detection of TB at both health facility levels. The incremental detection of Xpert from both smear methods was significantly higher among PLs but not at ILs.

The sensitivity found in this study was however in the range of findings from several studies where the sensitivities of conventional ZN microscopy ranged from 32 to 94 % and the sensitivities of fluorescence microscopy ranged from 52 to 97 %, with the fluorescent method being on average 10 % more sensitive than light microscopy [5]. In contrast to earlier findings, however, the current study did not find the sensitivity of LED-FM to be statistically different from ZN ($p = 0.371$). These results differ from several previous studies where LED-FM

Table 1 Participant characteristics ($n = 600$)

Characteristic	Frequency	Percentage
Sex		
Male	372	62.0
Female	228	38.0
Age category		
1 (15–35)	287	47.8
2 (36–55)	202	33.7
3 (≥56)	111	18.5
HIV status		
Positive	162	27.0
Negative	438	73.0
Mycobacterial testing results		
ZN smear positive	34	12.1
LED-FM smear positive	16	5.0
Xpert positive	82	13.7
Culture (MGIT and/or LJ) positive	96	16.0

MGIT mycobacterial growth indicator tube; *LJ* Lowenstein Jensen; *LED-FM* light emitting diode fluorescence microscopy; *ZN* Ziehl Nelsen Xpert: Xpert MTB/RIF test; *HIV* human immunodeficiency virus

Table 2 Yield of smear microscopy versus Xpert among culture confirmed tuberculosis patients (*n* =96)

		Xpert		Sensitivity of SM % (95 %, CI)	Incremental sensitivity of Xpert % (95 %,CI)
		Positive	Negative		
Overall SM at all HF *n* = 96	positive	46	3	51.0 (40.6–61.4)	32.3 (23.1–42.6)
	negative	31	16		
SM in all HIV positive *n* = 28	positive	10	1	39.3 (21.5–59.4)	35.7 (18.6–55.9)
	negative	10	7		
SM in all HIV negative *n* = 68	positive	36	2	55.9 (43.3–67.9)	30.9 (20.2–43.3)
	negative	21	9		
SM at all PL *n* = 76	positive	34	3	48.7 (37.0–60.4)	32.9 (22.5–44.6)
	negative	25	14		
SM at all IL *n* = 20	positive	12	0	60.0 (36.1–80.9)	30.0 (11.9–54.3)
	negative	6	2		
SM at ZN PL *n* = 49	positive	24	3	55.1 (40.2–69.3)	32.7 (19.9–47.5)
	negative	16	6		
SM at LED-FM PL *n* = 27	positive	10	0	37.0 (19.4–57.6)	33.3 (16.5–54.0)
	negative	9	8		
SM at ZN IL *n* = 12	positive	7	0	58.3 (27.7–84.8)	25.0 (5.5–57.2)
	negative	3	2		
SM at LED-FM IL *n* = 8	positive	5	0	62.5 (24.5–91.5)	37.5 (8.5–75.5)
	negative	3	0		

LED-FM light emitting diode fluorescence microscopy; *ZN* Ziehl Nelsen Xpert: Xpert MTB/RIF test; *HIV* human immunodeficiency virus; *CI* confidence interval; *SM* smear microscopy; *IL* intermediate laboratories; *PL* peripheral laboratories; *SM* smear microscopy

increases an average of 10 % of sensitivity over the conventional ZN technique [6–10]. Other studies have shown equal sensitivity or low specificity of LED-FM compared to conventional ZN technique [9, 11–13]. In these studies, readers had no previous experience with fluorescence microscopy, which is the most likely explanation for sensitivity differences compared with other studies and indicating the importance of adapting training intensity according to the level of operator proficiency. Our findings showed that smear microscopy performed better at intermediate laboratories compared to peripheral; the sensitivity for LED-FM 62.5 % vs. 37.0 %, $p = 0.023$ but not for ZN 58.3 % vs.55.1 %; $p = 0.265$. This may either be explained by the fact that LED-FM was implemented at IL prior to peripheral and therefore technologists acquired experience earlier compared to those at IL or due to small sample size at the ILs.

The sensitivity of sputum smear microscopy in HIV-infected participants was found to be low and are in agreement with findings of previous studies, where it ranges from 30 to 48 % [14–16]. The poor performance of sputum smear microscopy in HIV patients can be explained in part by the fact that pulmonary tuberculosis in these patients presents with paucibacillary TB and lack cavitation [16].

The overall prevalence of smear negative pulmonary tuberculosis using either smear method in HIV-infected PTB presumptive participants was found to be high and are in line with those of previous studies [17, 18]. The level of immunosuppression among HIV-infected patients affects significantly the results of the sputum smear; less severely immunocompromised HIV-positive patients tend to have classic cavitary tuberculosis with smear-positive results; as the level of immunocompromised increases with advancing HIV disease, atypical pulmonary features predominate and smear examinations prove less sensitive [17].

Although, the overall sensitivity of Xpert for the detection of *M. tuberculosis* was slightly lower, its specificity was consistent with those of previous studies in a Cochrane review even when stratified by HIV status [4]. The insignificant incremental sensitivity of Xpert test over smear microscopy at ILs is likely to be more explained by the small sample size we had at these facilities.

The significant incremental sensitivity of Xpert from either smear method at PLs supports the WHO recommendation for using Xpert as an initial test for TB diagnosis [19]. Although the cost per test and compulsory required maintenance of Xpert machine (annual calibration, replacement of modules, good and constant power

supply) may be not affordable by many poor resource settings given the limited heath budgets [20], the savings from increased case detection and timely initiation of treatment due to early diagnosis, may be more cost effective in terms of supplies savings as well as patient savings from repeat facility visits. In addition, early diagnosis may reduce the risk of TB transmission. It is worth noting that the effectiveness of Xpert testing is likely to depend on utilization as the test tends to be less effective in low workload settings [21] as the low numbers of patients tested at IL could have affected the strength of obtained significance measure.

Our study had some limitations; the level of immunosuppression for HIV positive PTB presumptive participants was not measured (CD4); this could lead to poor classification and consequently low differences in terms of smear sensitivity among HIV-infected participants. Secondary, the low samples size obtained from ILs which probably masks the obvious significant incremental detection of Xpert; among the 600 participants of this study, only 210 (35 %) participants and 20 (20.8 %) pulmonary tuberculosis confirmed cases were from ILs. The few numbers of HIV-infected patients in this study could not allow for meaningful comparison of incremental sensitivity by HIV-status, however, significant Xpert IS among HIV-infected patients was previously documented [22]. Lastly, excluding samples which became contaminated or positive for an NTM from the analysis may have led to an under-estimation of the sensitivity of Xpert and smear microscopy, as tuberculosis cannot be definitively excluded for these patients. TB-NTM coinfection has been reported, but is supposed to be a relatively rare clinical entity in Rwanda. However, excluding these participants may have over-estimated the specificity of microscopy, as smear-positive NTM infections were not taken into account in the analysis, while the specificity of Xpert would probably have been much less affected by the presence of NTM.

Conclusions

The findings from this study revealed a low detection rate of both LED-FM and ZN smear microscopy at health facility tuberculosis diagnostic laboratories in Rwanda. This study revealed a low sensitivity of LED-FM smear microscopy compared to ZN-microscopy among PLs whereas for ILs, the senstivity of LED-FM was higher than that of ZN microscopy, indicating differences in skills requirements among microscopy methods. This study revealed a signicant incremental detection gained from Xpert. Hence, the data from this study strongly support the conditional recommendation of WHO for Xpert; where the Xpert may be used as initial diagnostic test in adults and children presumed to have TB. Nevertheless, other studies of cost-effectiveness and feasibility of the proposed strategy at large scale are necessary.

Abbreviations

AFB: acid fast bacilli; BD: Becton Dickinson Company; FM: fluorescence microscopy; HIV: human immunodeficiency virus; ILs: intermediate laboratories; LED-FM: light emitting diode fluorescence microscopy; LJ: Löwenstein-Jensen; MDR-TB: multi-drug resistant tuberculosis; MGIT: mycobacterium growth indicator tube; MTB: *mycobacterium tuberculosis* complex; NRL: National Reference Laboratory; NTM: Non Tuberculosis Mycobacterium; PLs: peripheral laboratories; PTB: pulmonary tuberculosis; RIF: rifampicin; TB: tuberculosis; WHO: World Health Organization; ZN: Ziehl Neelsen staining

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Availability of data and materials

All data supporting the findings are contained within the manuscript.

Authors' contributions

JCSN, FM, DM and CM were the primary researcher, conceived the study, designed the study, participated in data collection, conducted data analysis and drafted the initial manuscript. WS, SU and MG participated in data collection, data analysis and reviewed the initial and final manuscript. WS, AUN, AD, EA and GT revised critically the initial and the final manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests

Consent for publication

Not applicable

Ethics approval and consent to participate

Ethical approval was obtained from Rwanda National Ethical Committee and Kenyatta National Hospital/University of Nairobi Ethics and Research committee. Written informed consent was obtained from participants and the results were communicated via respective health facilities. All tuberculosis cases received appropriate treatment as per national guidelines.

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Perspective

Impacts of neglected tropical disease on incidence and progression of HIV/AIDS, tuberculosis, and malaria: scientific links

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SUMMARY

The neglected tropical diseases (NTDs) are the most common infections of humans in Sub-Saharan Africa. Virtually all of the population living below the World Bank poverty figure is affected by one or more NTDs. New evidence indicates a high degree of geographic overlap between the highest-prevalence NTDs (soil-transmitted helminths, schistosomiasis, onchocerciasis, lymphatic filariasis, and trachoma) and malaria and HIV, exhibiting a high degree of co-infection. Recent research suggests that NTDs can affect HIV and AIDS, tuberculosis (TB), and malaria disease progression. A combination of immunological, epidemiological, and clinical factors can contribute to these interactions and add to a worsening prognosis for people affected by HIV/AIDS, TB, and malaria. Together these results point to the impacts of the highest-prevalence NTDs on the health outcomes of malaria, HIV/AIDS, and TB and present new opportunities to design innovative public health interventions and strategies for these 'big three' diseases. This analysis describes the current findings of research and what research is still needed to strengthen the knowledge base of the impacts NTDs have on the big three.
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1. Introduction

The Millennium Development Goals were established in the year 2000 to combat various dimensions of extreme poverty, including the sixth goal: "to combat HIV/AIDS, malaria, and other diseases." Since that time, new financing and delivery mechanisms for disease control have been introduced through the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), as well as the US President's Malaria Initiative (PMI) and the President's Emergency Plan for AIDS Relief (PEPFAR). To date, approximately USD $32 billion has been committed to the Global Fund,[1] USD $3 billion to PMI,[2] and USD $45 billion to PEPFAR.[3] Many billions of additional funding has made a huge difference in the lives of the world's poorest people. However, millions of people are still affected by these diseases, especially in the most remote and marginalized populations. Evidence suggests that co-infections between HIV, malaria, and TB exacerbate the individual diseases. Indeed, this is the reason that funding for the 'big three' is linked.[4,5] New research also suggests the highest-prevalence NTDs (soil transmitted helminths, schistosomiasis, onchocerciasis, lymphatic filariasis, and trachoma) result in increased susceptibility to and worsen the disease course for people infected with one or more of HIV, TB, and malaria. This paper summarizes the new evidence on how NTDs impact the progression and severity of HID/AIDS, TB, and malaria infections, and outlines priorities for future research.

2. Geographic overlap

Over the past several years, detailed mapping of NTDs has confirmed previous modeling based on statistical and spatial analyses,[6] and has demonstrated large degrees of geographical overlap between multiple NTDs and HIV and malaria.[7] For example, Sub-Saharan Africa has not only the world's highest incidence of HIV but also has more than 100 million people infected with soil-transmitted helminth infections and approximately 200 million people with schistosomiasis.[8] The geographical overlap is particularly prominent between urogenital schistosomiasis caused by *Schistosoma haematobium* and HIV and AIDS in the large southern and east African countries of Kenya, Mozambique, South Africa, Tanzania, Zambia, and Zimbabwe, and to some extent, Cameroon in West Africa.[9] Additionally, one-quarter of all schoolchildren in Sub-Saharan Africa are simultaneously at risk for both hookworm and malaria.[6] This pattern has also been noted between malaria and schistosomiasis.[10]

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3. Evidence on clinical links between NTDs and HIV

New research is beginning to suggest increased susceptibility and enhanced progression of HIV disease as a result of several helminthic, bacterial, and protozoan NTD co-infections. Soil-transmitted helminth infections have had a contributing, albeit largely hidden, impact on the AIDS epidemic.[6,10–12] In a study in Ethiopia, helminth co-infection was associated with increased T-cell activation; subsequent anti-helminthic treatment appeared to reduce the degree of T-cell activation, leading to a significant increase in absolute CD4 cell counts (192 vs. 279 cells/mm^3).[13] A systematic review of treatment of HIV-1 and helminthic co-infections found reductions in viral load following deworming, ranging from 0.17 $\log_{10}$ to 2.10 $\log_{10}$ copies/ml drop in plasma.[11] In addition, studies on the treatment of schistosomiasis and lymphatic filariasis in HIV-infected individuals have demonstrated a 0.39 $\log_{10}$ and 0.77 $\log_{10}$ reduction in viral load, respectively, noting that a 1.0 $\log_{10}$ viral load reduction corresponds to a halving of transmission risk and a 2-year delay in the development of AIDS.[12,14] The decreases they noted after treatment for helminth co-infection are comparable to decreases in viral load associated with the treatment of malaria and sexually transmitted diseases such as gonorrhea and syphilis.[11]

Although data conflict on the absolute impacts of treatment,[6,15,16] a Cochrane analysis of randomized clinical trials has demonstrated the benefits of deworming on HIV incidence and prevalence.[15] Evidence also suggests that maternal helminth infections increase the likelihood of mother-to-child transmission of HIV, possibly as a result of increased maternal HIV viral load.[6] A plausible mechanism suggests that helminth infections have an immunomodulatory effect, possibly diminishing host innate immunity to HIV, promoting viral replication and T-cell reduction.[11,12] Although the exact immunological mechanisms are yet to be elucidated, it is known that helminths skew the immune response toward Th2 (T helper cell) characterized by cytokines including interleukins IL-4, IL-5, and IL-13.[16]

Growing evidence from two studies in Zimbabwe demonstrates that female genital schistosomiasis occurs in up to 75% of women with *S. haematobium* infection and shows a threefold increase in the risk of women acquiring HIV infection.[17,18] Several reasons have been given to explain this increased correlation. Kjetland et al. suggest increased physical scarring on the vaginal walls of girls with female genital schistosomiasis that may increase transmission of the virus during intercourse.[19] Secor showed that patients with active schistosomiasis exhibit increased expression of the chemokine receptors and major HIV-1 co-receptors (CCR5 and CXCR4) on peripheral CD4 T-cells and monocytes.[20]

These associations are not unprecedented. Years of studies have demonstrated a large amount of evidence in the links between several protozoan diseases and HIV infection. The links between malaria and HIV have been well documented.[6,21,22] Patients with HIV infection frequently have a higher malaria parasite burden, more complications, and higher fatality rates than HIV-negative individuals.[23]

4. Evidence on clinical links between NTDs and malaria

Malaria is a leading cause of anemia in pregnant woman and young children. NTD co-infections have been shown to worsen anemia, potentially leading to large numbers of maternal deaths during pregnancy and to premature births.[7,24] Chronic anemia in young children is associated with reductions in physical growth and impaired cognition and school performance,[6,25] and many of the NTDs, but especially hookworm and schistosomiasis, cause anemia in low- and middle-income countries.[7,26] An estimated 7.5 million pregnant women (approximately one-third) living in Sub-Saharan Africa are infected with hookworm.[27] In Kenya, hemoglobin concentrations were found to be 4.2 g/l lower among children harboring hookworm and malaria co-infections than in children with only malaria infection.

Beyond the health improvements that would result from less anemia, some evidence indicates that selected NTDs may immunomodulate their host and promote increased susceptibility to malaria. To date, the data available on the effects of NTDs on malaria have been conflicting, especially in the older age groups. However, a study by Kirwan et al. demonstrated that repeated four-monthly anti-helminthic treatments for 14 months resulted in a significantly lower increase in prevalence of *Plasmodium falciparum* malaria infection in preschool children, coinciding with a reduction in the prevalence and intensity of ascariasis.[28] Research has also demonstrated that the use of an anti-helminthic reduces the clinically observable cases of malaria,[29] and ivermectin mass drug administration for onchocerciasis and lymphatic filariasis in humans has been shown to disrupt malaria parasite transmission in Senegalese villages.[30]

Additionally, research into social aspects of community health has demonstrated co-benefits between malaria and NTD prevention. Community-directed NTD treatments have increased the use of not only antimalarial bed-nets but also micronutrients and childhood immunizations.[31] The control of mosquito-borne diseases such as lymphatic filariasis can work in synergy with bed-net distributions and other disease control measures, such as intermittent preventive treatment and mosquito control, to reduce malaria incidence.[7,25] A study conducted in Nigeria demonstrated a nine-fold increase in households (with children under 5 years old, pregnant woman, or both) with more than one long-lasting insecticide-treated bed-net, when bed-net distribution was coupled with ivermectin and with albendazole treatment for lymphatic filariasis, onchocerciasis, and soil-transmitted helminths.[32] Other opportunities for integration with other diseases are currently being explored, such as combining malaria and trachoma treatments in Ethiopia.[33]

5. Evidence on clinical links between NTDs and TB

Soil-transmitted helminth infections have been evaluated as epidemiological risk factors for developing active TB. In one study, among 230 smear-positive TB patients and 510 healthy household contacts, an analysis showed a strong association between TB and intestinal helminth infection (odds ratio 4.2), and the odds of being a TB patient increased with the number of helminth species per person.[34]

TB patients with helminth infections present with more severe pulmonary disease, diminished anti-*Mycobacterium tuberculosis* immunity, and diminished responses to anti-TB chemotherapy.[31] Helminth infections also reduce the immunogenicity of bacille Calmette–Guérin (BCG) vaccine in humans,[35] and have been shown to interfere with diagnostic tests for TB.[36]

6. Need for further research

Even as NTD treatment programs scale up and the evidence base of the beneficial health effects of treatment is growing, the scientific knowledge of the health benefits of NTD treatment for HIV, TB, and malaria patients still needs more research. A recent study by Walson et al. noted that there were no significant increases in CD4 cell counts and no reductions in HIV RNA concentrations when people were treated presumptively for helminths.[37] However, they acknowledge that their study may not have been powered to detect the small differences in outcomes in individuals with helminth infection. Earlier work by Walson and

John-Stewart demonstrated that the treatment of known helminth-infected adults produced delayed HIV progression.[38] Such discrepancies between the studies may be explained by differences in the age groups studied, prevalence and intensity of helminth species, type and frequency of medication, and length of time post-treatment before the determination of viral load. Similar issues have been noted in research of NTDs with malaria, and several studies have demonstrated conflicting results. A recent review of these studies demonstrated a trend towards a protective effect of *Ascaris lumbricoides* and *S. haematobium* against severe malaria and a worsening effect of hookworm and *Schistosoma mansoni* on the pathogenesis and incidence of malaria, respectively.[39] The conflicting results listed above demonstrate the need for further studies on how individual NTDs affect the course of HIV and malaria infections and the immunological factors involved. Among the three diseases, scientific knowledge about the links with NTDs and TB remains the weakest.

The World Health Organization recently identified the need for further research into potential pharmacological interactions between antiretroviral and NTD drugs. This could be enhanced by conducting pharmaco-epidemiological studies to evaluate the safety of co-administration of such drugs and their therapeutic efficacy. Last but not least, further research will be required to address the social factors and logistical factors in implementation and operational challenges that arise from linking these programs.

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RESEARCH ARTICLE

Uptake of Isoniazid Preventive Therapy among Under-Five Children: TB Contact Investigation as an Entry Point

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Abstract

A child's risk of developing tuberculosis (TB) can be reduced by nearly 60% with administration of 6 months course of isoniazid preventive therapy (IPT). However, uptake of IPT by national TB programs is low, and IPT delivery is a challenge in many resource-limited high TB-burden settings. Routinely collected program data was analyzed to determine the coverage and outcome of implementation of IPT for eligible under-five year old children in 28 health facilities in two regions of Ethiopia. A total of 504 index smear-positive pulmonary TB (SS+) cases were reported between October 2013 and June 2014 in the 28 health facilities. There were 282 under-five children registered as household contacts of these SS+ TB index cases, accounting for 17.9% of all household contacts. Of these, 237 (84%) were screened for TB symptoms, and presumptive TB was identified in 16 (6.8%) children. TB was confirmed in 5 children, producing an overall yield of 2.11% (95% confidence interval, 0.76–4.08%). Of 221 children eligible for IPT, 64.3% (142) received IPT, 80.3% (114) of whom successfully completed six months of therapy. No child developed active TB while on IPT. Contact screening is a good entry point for delivery of IPT to at risk children and should be routine practice as recommended by the WHO despite the implementation challenges.

Introduction

Tuberculosis (TB) remains one of the world's deadliest communicable diseases. In 2014 globally 9.6 million people are estimated to have fallen ill with TB, amongst which children constituted 1.0 million of the total. The actual burden is likely to be higher, because diagnosing TB in children is challenging and is a low priority in low-resource settings [1].

Ethiopia is also one of the 22 high-burden countries for TB, and childhood TB accounts for 13% of the overall TB burden with case notification among children below 15 years of age

estimated to be 15,917 [1]. Even this could be an underestimate due to difficulty in confirmation of diagnosis of TB in children. The World Health Organization (WHO) states in its post-2015 global recommendation the need for preventive treatment of persons at high risk as one strategy for prevention, care, and control of TB [2]. There is a road map for childhood TB and global pediatric TB guidelines and preventive therapy is one of the key interventions. Ethiopia has also developed a national roadmap for prevention and control of childhood TB which emphasizes on the implementation of contact screening & provision of isoniazid preventive therapy (IPT) for under-5 years as one intervention to prevent childhood TB. However, the gap is in the implementation of the recommended strategies/activities.

Isoniazid (INH) preventive therapy (IPT) is currently recommended for the treatment of latent TB infection among people living with HIV and children under five years of age who are contacts of patients with TB [3]. Isoniazid prophylaxis can reduce the risk of developing tuberculosis by 59% among children aged 15 years or Younger [4]. The WHO also recommends offering IPT for at least six months to all children below five years of age who have household contact with an infectious TB case, after ruling out active TB disease [5]. Ethiopia has accepted and is implementing the WHO's recommendation of a six-month course of IPT for under-five children who have a history of contact with a sputum-smear-positive (SS+) pulmonary TB index patient, after ruling out the presence of active TB disease [6].

Even though IPT is a global recommendation, its initiation and completion rate is sub-optimal. The level of awareness among health care providers, interruption of INH supply, co-infection with HIV, lack of recording tools for IPT and distance from health facilities affect uptake of the service in different settings. The IPT initiation and completion rates reported in research settings ranged between 18–33% and 23–50% respectively [7–10]. Whereas the IPT initiation and completion rates reported in program implementation settings were between 21–58% and 13% respectively [11–12].

Most studies conducted on IPT focus on the setting of TB/HIV co-infected populations and research settings. However, research settings on IPT uptake may be more controlled as compared to routine implementation setting which reflect real life experiences and bottlenecks. We present the IPT implementation experience under routine program intervention; regional and health facility type comparisons were also made to understand the experience of IPT implementation in diverse settings. Hence the objective of this implementation study was to assess the effectiveness of contact screening as an entry point for IPT implementation and treatment among eligible under-five children initiated under normal program conditions

Methods

Ethics

Ethical approval was obtained from the Amhara and Oromia Regional Health Bureau institutional review boards (IRBs). Patients' identifier information was anonymized and de-identified prior to analysis. The finding of the analysis will be shared with federal ministry of health and regional health bureaus for evidence based decision making.

Setting

We implemented household contact screening and identified eligible children for IPT implementation in a regular program setting in the Amhara and Oromia Regional States of the Federal Democratic Republic of Ethiopia, with case notification rate (CNR) of 117 and 146 per 100,000 respectively [13]. In the two regions, there are 64 hospitals and 2,122 health centers providing TB services. The Help Ethiopia Address the Low TB Performance (HEAL-TB) Project, funded by the US Agency for International Development and operated in collaboration

with the Amhara and Oromia Regional Health Bureaus, standardized the activity of contact screening of SS+ pulmonary TB index cases. Contact screening of SS+ pulmonary TB cases was used as entry point to identify and enroll eligible under-five contacts in IPT. Health workers were oriented on the importance of IPT through individualized mentorship and continuing medical education sessions specifically designed for mid- and low-level health workers. Additionally, job aids and recording and reporting formats were supplied for routine use. We previously reported our experience in contact investigation and its yield [14].

Study Population and Data Source

Contact screening of family members of index SS+ pulmonary TB patients is routinely conducted by TB focal persons at TB clinics, while index TB patients receive DOTS at TB clinics. We used the national clinical TB screening algorithm (Fig 1). Eligible under-five children for IPT are initiated and followed in the TB clinic where monthly refill, symptom screening and care taker counselling, was performed as per the national TB/Leprosy guideline [6]. We used the data routinely recorded in the contact investigation register at health facilities providing TB program services. Data was retrieved from health facilities every quarter. Based on our routine program data, we analyzed IPT-related information from 28 health facilities (7 hospitals and 21 health centers) out of the total 64 hospitals & 2,122 health centers in the period between October 2013 and June 2014. The 28 health facilities were selected based on their high TB case load and also in that we were able to re-count the routinely submitted IPT report by zonal TB focal persons in these health facilities. Additionally we made sure that the selection covered different geographic areas with different settings. We were able to do IPT data quality checking in all 28 health facilities.

Data was gathered on the following variables: number of SS+ cases; number of household contacts; proportion of under-five-year-old household contacts for whom symptom-based screening was done as per the national recommendation (Fig 1); and the number of eligible under-five children who were started on and completed IPT.

Data Analysis

Data was entered in Excel and exported to Stata for statistical analysis. We computed frequency, percentage, and 95% confidence interval to present the findings. We used the chi-square test to assess differences between categories. P-values less than 0.05 were considered statistically significant.

Results

A total of 504 index SS+ cases were reported between October 2013 and June 2014. There were 282 under-five children registered as household contacts of the SS+ index cases, accounting for 17.9% of all household contacts (Fig 2). Of these, 237 (84%) were screened for TB using the national symptom-based TB screening algorithm [6] and 16(6.8%) were identified as having presumptive TB (Fig 1). TB was confirmed in 5 children, producing a yield of 2.11% (95% confidence interval, 0.76–4.08%). Of 221 children without presumptive TB and eligible for IPT, 142 (64.3%) received IPT, of whom 114 (80.3%) completed the six-month course while 28 (19.7%) interrupted treatment (Fig 3). Among the children who interrupted IPT treatment (n = 28), 14 children did so in the first month, 1 child in the second month, 10 children in the third month, and 3 in the fourth.

Of the total of 852 household contacts in Oromia Region, 180 (21%) were under-five child contacts, while in Amhara under-five children constituted 102 (36%) of the total 727 household contacts. There was no regional variation in terms of the proportion of the presumptive

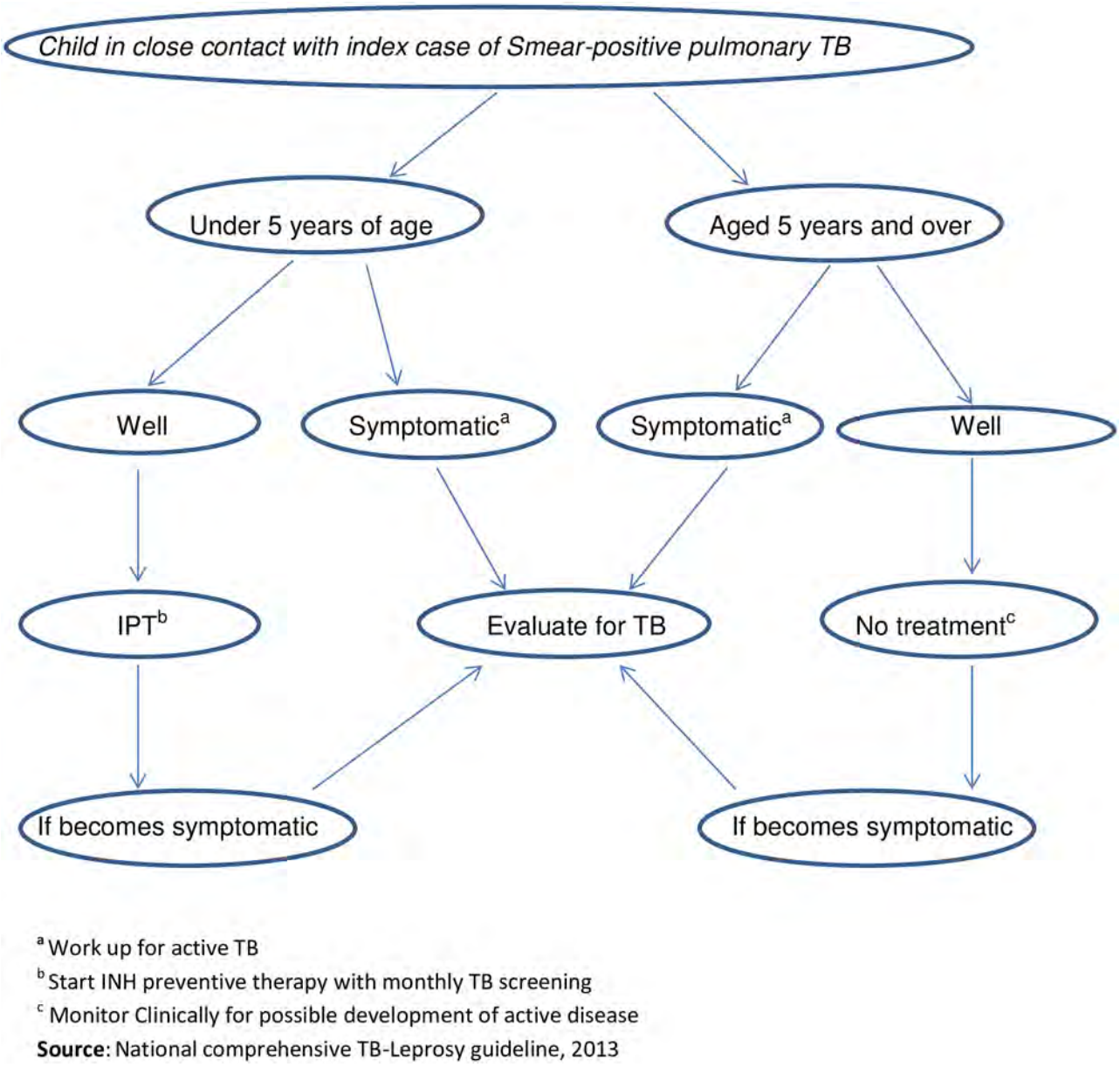

Fig 1. Algorithm for childhood TB management according to the national guidelines in Ethiopia.

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TB identified, active TB detected, IPT coverage, and completion rate of IPT treatment among the children ($p > 0.05$).

The proportion of registered under-five child household contacts who were clinically screened for TB at the health centers and hospitals was 85% and 82%, respectively ($p = 0.26$). Health centers contributed more than 70% (157/221) of the IPT-eligible under-five children and 62% (10/16) of the presumptive TB cases identified. Hospitals contributed nearly 30% (64/221) of IPT-eligible children and 38% (6/16) children with presumptive TB. The proportion of the eligible children put on IPT at health centers was 65% (102/157), while it was 62.5% (40/64) at hospitals. The IPT completion rate was 85% (80/102) at health centers as compared

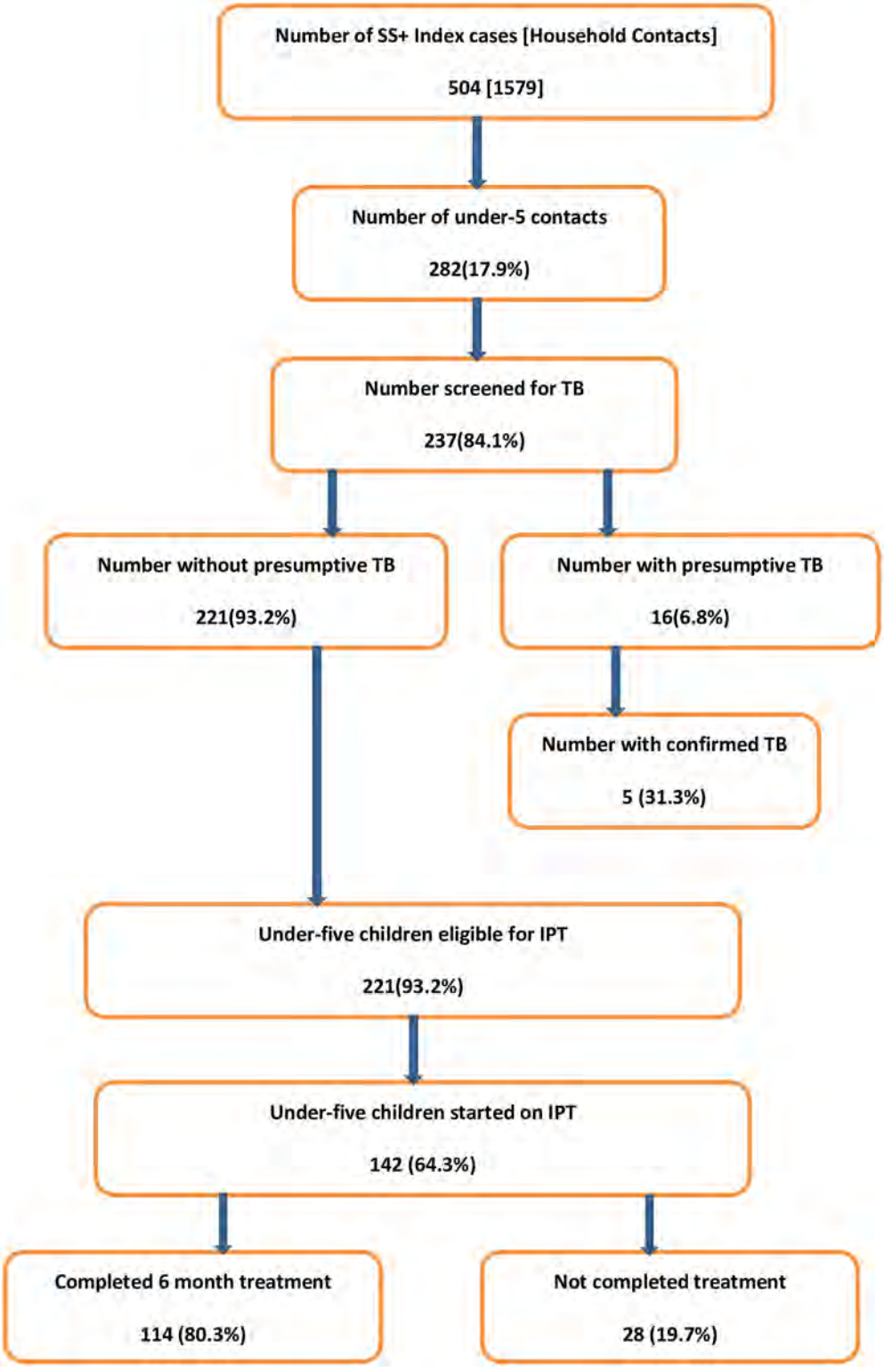

Fig 2. Contact screening and IPT among under-five children, Oct. 2013-June 2014, Ethiopia.

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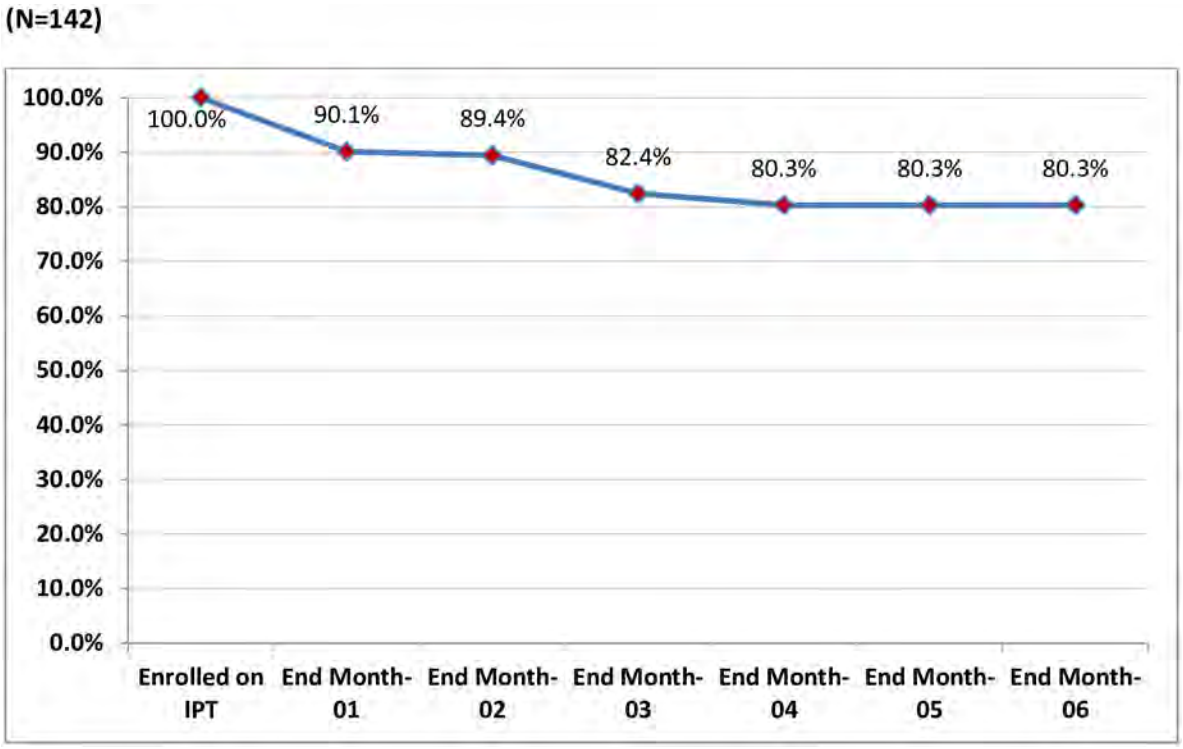

Fig 3. Percentage of under-five children retained on IPT during six-month follow-up.

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to 78.4% (34/40) at hospitals, but the difference was not statistically significant ($p > 0.05$) (Table 1).

Discussion

This study demonstrated the feasibility of providing a six-month course of IPT under routine program conditions to eligible under-five children who were in close contact with SS+ index

Table 1. Contact Screening and IPT among Under-five Children, by Health Facility Type.

Variables	Facility Type		
	Health center	Hospital	P- value [a]
Number of SS+ index cases	334	170	
Number of total household contacts	1036	543	
Ratio of index cases to household contacts	1:3	1:3	
Number (%) of under-five contacts	197 (19%)	85 (15.7%)	0.19
Number (%) of under-fives screened for TB	167 (85%)	70 (82%)	0.26
Number (%) of under-fives with presumptive TB	10 (6%)	6 (8.6%)	0.23
Number of under-fives diagnosed with TB and treated	2	3	
Number of children eligible for IPT	157	64	
Number (%) of children put on IPT	102 (64.9%)	40 (62.5%)	0.70
Number (%) of children who completed the six-month IPT	80 (78.4%)	34 (85%)	0.08

SS+, sputum-smear positive; IPT, isoniazid preventive therapy.

[a] Two-sample test for proportions using Stata.

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cases. We confirmed that contact investigation was an important entry point to identify under-five children with TB and those who needed preventive therapy against TB. The IPT completion rate was within a reasonable range, but the factors contributing to IPT interruption such as lack of leadership by national TB control programs (NTPs) of preventive interventions such as IPT, low awareness & experience of health care workers of the benefits of IPT, providers' perceived fear of toxicity of INH & generating drug resistance, lack of parent/caretaker knowledge as to benefits of IPT [15, 16] need to be addressed.

The WHO recommends clinical evaluation of household contacts of SS+ index cases for active TB. The two main purposes of contact screening and management are: first, to identify contacts of all ages with undiagnosed TB disease among the contacts of an index case, and second, to provide preventive therapy for contacts without TB disease who are susceptible to developing disease following recent infection [5].

The IPT initiation rate of 64.3% in our study is slightly lower than the 68% reported from South Africa [17]. However, it is higher than the 33% rate in southern India [12] and the 18% reported in Timor-Leste [9]. In addition, a study in Malawi showed that only 23 (6%) of 365 under-five child household contacts received IPT [18].

Even though the setting for IPT implementation among HIV infected populations is different from childhood IPT, the IPT initiation rate in the current study is much better than the 39% reported among a cohort of HIV-infected people in Southern Ethiopia [19], and 3.8% reported from Addis Ababa [20]. Uptake and adherence to IPT among HIV-infected people was difficult due to the use of multiple drugs at a time which is not the case for IPT among children [14, 15, 19].

In our study, over two-thirds of eligible children received IPT, with most of them successfully completing the recommended dose. The IPT completion rate of 80% in this study was much higher than the 23% reported from southern India, 24% reported among HIV-infected patients [18] and 12% reported from another study in southern Ethiopia [21. In Pakistan, of 184 under-five children enrolled in IPT, 60 (32.6%) completed six months of IPT [22]. But in the South African report [18], only 15% achieved four months of therapy. Hence, the higher IPT completion rate in our study is encouraging, but more effort is needed to ensure 100% adherence.

Achievement of a higher IPT completion rate in this study also demonstrates that IPT is feasible in a resource-limited setting and that contact investigation of index TB cases can be used as a core entry point for TB case detection and prevention in the childhood population in similar settings. With further strengthening of health workers' capacity, even higher rates of initiation and completion are within reach [23]

Of the total of 28 IPT interrupters, 25 (89%) children discontinued within the first three months after initiation of IPT. There was no interruption after completion of the fourth month of preventive treatment. The major reason for the high interruption rate in a study done in southern Ethiopia was families' refusal to have an otherwise healthy child treated for six months in a TB clinic (where TB treatment is provided) [21], similarly the long duration of treatment was a factor in 28% of cases in India [12]. Although 28 children interrupted preventive therapy in this study, evidence has shown that IPT is safe and well tolerated by children; major potential serious adverse events, including hepatotoxicity and pyridoxine deficiency, are rare in children [24–26]. As this was a routine reported data, there was no specific side effect related information. In a Kenyan study, among HIV-infected children below 14 years of age who were started on IPT, the main reasons for discontinuation of preventive therapy were developing active TB, frequent treatment interruptions, and being lost to follow-up [27].

It is encouraging to attain an overall IPT completion rate of 80%, but we still need to understand the factors contributing to IPT interruption early in the course of therapy and to address

the remaining 20% who interrupted IPT. Further studies are needed to provide evidence to improve completion rate and monitor adherence of IPT. Since IPT completion rather than initiation is the key protective indicator, studies on factors that contribute to completion of unsupervised IPT, such as parent/caretaker education, uninterrupted drug supply, and tracing of those lost to follow-up, should be emphasized. The effectiveness of delivering IPT in kits and directly observing parent-child pairs should be evaluated as there exists evidence showing that introduction of individualized TB treatment kit has beneficial effect in ensuring uninterrupted drug supply with fewer stock outs, minimizing lost to follow ups and building patient confidence with improved adherence to TB treatment [28].

Screening of contacts of TB cases helps to identify at-risk contacts, such as HIV-infected under-fives who require preventive therapy, and of any age who have active TB [29]. Contact screening also contributes significantly to identify children with active TB disease early to prevent childhood morbidity and mortality. In one study it was found that there is an eight-fold increased risk of TB mortality in children living in households with someone who has active TB [30]. Moreover, about 81% of missed opportunities for IPT in at-risk children who later presented with confirmed TB were under three years of age, 25% had disseminated TB, and 5% died [31]. Yet our study demonstrated that 45 (16%) children of index TB cases were not screened for TB. Another study in Malawi in 2006 reported that only 8% of parents with SS+ TB brought their children to a clinic for screening despite provision of clear information [32]. In Addis Ababa, only 23.6% of index cases reported that a health care worker instructed them to bring their child for TB screening [19]. These gaps could indicate that health care providers should also be equipped with the knowledge, skills, and tools to counsel parents or caregivers about the importance of screening children who are in contact with TB patients and about preventive treatment even for otherwise healthy children.

In terms of the capacity to initiate IPT for eligible children, 65% of eligible children at health centers were initiated on IPT, while 62.5% of eligible children at hospitals were initiated on IPT, which is not a statistically significant difference ($P > 0.05$). This indicates that mid-level health workers at peripheral health facilities can implement IPT and that IPT can be decentralized in order to make it more accessible to rural communities. The success can be attributed to capacity building of health care workers, especially at the primary health care level through training, mentorship, program monitoring, and supportive supervision. As reported elsewhere [33], provision of job aids (screening algorithms) and monitoring tools provided by the project were instrumental in improving the awareness of program managers and health care providers in implementing IPT as a childhood TB prevention strategy.

A review of clinical trials indicated that IPT reduces the risk of TB by about 60% among the infected contacts of all ages [34] and that the efficacy of IPT is even higher in children, at 80–90% [35]. The review also showed that 1 case of active TB (over the next five years) can be prevented for every 35 TB contacts who are prescribed INH for six months [35]. In the year of data collection, there were 38,403 registered cases of SS+ TB in the two regions support by the HEAL-TB Project (unpublished report). Extrapolating similar ratios of under-five contacts per index case and IPT completion rate in this analysis to the project regions, there would be 21,487 under-five contacts, of whom 8,686 had completed IPT. Accordingly, contact investigation and IPT intervention for the under-fives in the two largest regions of Ethiopia likely prevented about 248 cases of TB-related morbidity in under-five children (1 in 35 treated with IPT), provided that the findings in this analysis represent the overall project. If IPT had reached all under-five contacts without presumptive TB in the year, the corresponding number of children prevented from acquiring active TB in the two regions would have been 572.

The study has some limitations. Because we carried out the analysis in purposively selected health facilities, its findings might not be generalizable to the remaining health facilities. Also

unavailability of detailed data with respect to gender, age and smear positivity grading of the index case can be considered as limitations. However, the findings provided program-level evidence about the actual implementation of contact screening and IPT. Because contact screening and provision of IPT form part of regular program implementation, the development of TB among those who completed IPT was not assessed.

Conclusions

The findings demonstrated that tracing infants and young children who are contacts of infectious TB cases and offering them preventive therapy was feasible in the regular DOTS program setting. Services for IPT at health centers and at hospitals showed comparable IPT initiation and completion rates. Contact screening is a feasible entry point for IPT and the IPT completion rate was good, but the remaining gaps should be addressed. Comprehensive support provided by the project was instrumental in improving the awareness of program managers and health care providers in implementing IPT as a childhood TB prevention strategy.

Further studies are needed to better understand factors contributing to IPT interruption early in the course of therapy, the feasibility of delivering IPT in kit form, and the long-term benefits of IPT in terms of reducing TB-related morbidity and mortality among under-five child contacts of SS+ TB cases.

Supporting Information

S1 Table. List of Health Facilities.
(DOCX)

S1 Text. Ethical Approval from Amhara Regional Health Bureau.
(JPG)

S2 Text. Ethical Approval from Oromia Regional Health Bureau.
(PDF)

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Author Contributions

Conceived and designed the experiments: YT ZG DH NH SN KM DJ YKH YK MM. Analyzed the data: NG SD ZG PS. Wrote the paper: YT ZG DJ DH NH SN KM MM NG SD YKH YK PS.

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HIV and related infections in prisoners 5

HIV and tuberculosis in prisons in sub-Saharan Africa

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Given the dual epidemics of HIV and tuberculosis in sub-Saharan Africa and evidence suggesting a disproportionate burden of these diseases among detainees in the region, we aimed to investigate the epidemiology of HIV and tuberculosis in prison populations, describe services available and challenges to service delivery, and identify priority areas for programmatically relevant research in sub-Saharan African prisons. To this end, we reviewed literature on HIV and tuberculosis in sub-Saharan African prisons published between 2011 and 2015, and identified data from only 24 of the 49 countries in the region. Where data were available, they were frequently of poor quality and rarely nationally representative. Prevalence of HIV infection ranged from 2·3% to 34·9%, and of tuberculosis from 0·4 to 16·3%; detainees nearly always had a higher prevalence of both diseases than did the non-incarcerated population in the same country. We identified barriers to prevention, treatment, and care services in published work and through five case studies of prison health policies and services in Zambia, South Africa, Malawi, Nigeria, and Benin. These barriers included severe financial and human-resource limitations and fragmented referral systems that prevent continuity of care when detainees cycle into and out of prison, or move between prisons. These challenges are set against the backdrop of weak health and criminal-justice systems, high rates of pre-trial detention, and overcrowding. A few examples of promising practices exist, including routine voluntary testing for HIV and screening for tuberculosis upon entry to South African and the largest Zambian prisons, reforms to pre-trial detention in South Africa, integration of mental health services into a health package in selected Malawian prisons, and task sharing to include detainees in care provision through peer-educator programmes in Rwanda, Zimbabwe, Zambia, and South Africa. However, substantial additional investments are required throughout sub-Saharan Africa to develop country-level policy guidance, build human-resource capacity, and strengthen prison health systems to ensure universal access to HIV and tuberculsosis prevention, treatment, and care of a standard that meets international goals and human rights obligations.

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This is the fifth in a Series of six papers about HIV and related infections in prisoners

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Background

Countries in sub-Saharan Africa have borne the brunt of the generalised HIV and tuberculosis epidemics, which have strained health systems and devastated populations in the region.[1,2] As reported by Dolan and colleagues[3] in another paper in this Series, the prevalence of HIV infection among detainees was 15·6% (95% CI 11·8–19·8%) in east and southern Africa and 8·2% (6·2–10·5) in west and central Africa, suggesting a higher prevalence in prison populations than in non-incarcerated populations. Prevalence of tuberculosis was also extremely high: it was estimated at 5·3% (2·1–10·0) in east and southern Africa, and 2·9% (2·4–3·6) in west and central Africa.[3]

To control the HIV and tuberculosis epidemics and achieve ambitious international targets, countries are called upon to scale up prevention, testing, and treatment for vulnerable groups, including detainees.[4,5] Although incarceration necessarily restricts liberty, detainees have a right to a minimum standard of health care at least equivalent to that in the community,[6,7] including effective services along the entire continuum of HIV and tuberculosis prevention, treatment, and care.

In this Series paper, we provide a descriptive overview of prison populations in sub-Saharan Africa and the epidemiology of HIV and tuberculosis therein; discuss policies and interventions for the prevention, diagnosis, and treatment of HIV and tuberculosis within these

Key messages

- Despite global commitments to end HIV and tuberculosis, in the fourth decade of the HIV pandemic, most countries in sub-Saharan Africa do not collect or report comprehensive information about the incidence, prevalence, or clinical outcomes of HIV infection and tuberculosis in detainees, even though it is the region most affected by these diseases.
- Where data are available, the prevalences of HIV infection and tuberculosis in detainees in sub-Saharan Africa are almost always greater than those in non-incarcerated populations; detainees should be thought of as a priority population for HIV and tuberculosis interventions.
- Few countries have comprehensive prison HIV or tuberculosis policies or programmes, and, where programmes exist, they frequently cover only some detainees and provide inadequate services.
- Governments, donors, non-governmental organisations, and advocates urgently need to promote policy reform and guideline development to ensure the inclusion of incarcerated populations in national HIV/AIDS and tuberculosis programmes, with care provision and structured supervision consistent with community programmes. Specific requirements set by donors, regional governing bodies, and other multilateral organisations could contribute to advancement of both policy and service delivery to detainees.
- To ensure a data-driven and appropriate public health response, surveillance and quarterly monitoring systems, programme assessment, and operational research should be undertaken to ensure that the health needs of detainees are prioritised, ethically studied, and reported upon.
- Criminal-justice reform and conditions within prisons—including nutrition, substance use, mental health, infrastructure, and ventilation—should be prioritised by governments, donors, and human-rights advocates, and recognised as important areas of research, policy, and programme development.

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Panel 1: **Limitations of the data presented**

The aim of this Series paper is to provide an overview of the epidemiology of HIV and tuberculosis in prison populations in sub-Saharan Africa, the services available and challenges to service delivery, and priority areas for programmatically relevant prisons research. We did not do a systematic review of all available information; rather, we summarise publicly available grey and peer-reviewed literature published in the past 5 years (but also include older work when data were limited or not available). To supplement this information, we sought additional data from experts, which yielded very limited information, did case studies in specifically selected countries, and investigated funding for HIV and tuberculosis programmes within prisons. Detailed epidemiological descriptions of HIV and tuberculosis in prisons in each country of sub-Saharan Africa, and detailed, contemporary information about prison populations, HIV and tuberculosis policies, funding, and services are beyond the scope of this Series paper.

The quality of the epidemiological data included is variable, and should be interpreted with caution. All data identified are presented (appendix) without exclusion. As a systematic review was not done, some data published between 2011 and 2015 might have been missed. For each study included, details about the study period, number of prisons included, sampling methods, screening or diagnostic procedures, and case definitions are in the appendix. When interpreting the data, the generalisability of findings, sample sizes, potential biases, confounding factors that might be unaccounted for, and the comparability of findings with non-incarcerated populations, other studies, and over time should all be considered.

Between 2011 and 2015, there were 48 publications from 24 (of 49) sub-Saharan African countries—19 in peer-reviewed journals, 26 in conference proceedings, and three in institutional reports. Eight studies included no information about when they were done and 12 were done before 2011 (one in 2007, two in 2008, four in 2009, and five in 2010). In the 40 studies in which time to publication of data could be determined, 32 were published within 2 years, seven within 3–5 years, and one within 7 years.

Nine studies aimed to provide nationally representative prison data; the remainder were subnational, with 13 focusing on individual prisons. Therefore most data cannot be generalised to the country's total prison population. Different methods and case definitions were used in each study, which prevents easy comparison. In several, inadequate information was provided about the sampling methods, which means that selection bias cannot be fully explored. Some studies were done in a convenience sample or had poor uptake, which could result in selection bias. Routine notification or programme data were used in some, which could have led to underestimation of prevalence, whereas others were done in purposively screened populations.

In most tuberculosis studies, a positive symptom screen was needed before participants underwent microbiological testing, which could have led to underestimated prevalence; diagnostic tests with sensitivities less than 100% were used in many, and thus the number of cases could have been under-ascertained. Concurrent sampling of prison and non-incarcerated populations to allow a direct and valid comparison of the prevalence of HIV infection and tuberculosis between these populations was not done in any study. Trends in prevalence cannot be ascertained from the data. These limitations should be considered when using and interpreting the epidemiological data presented in this Series paper.

populations, and the barriers to their implementation; and recommend a policy and service-delivery agenda for detainee health in sub-Saharan Africa, together with the associated research agenda.

Overview of methods

See Online for appendix

Full methods and a full list of search terms are detailed in the appendix. In brief, we reviewed grey and peer-reviewed literature published between Jan 1, 2011, and Dec 31, 2015, to identify available abstracts, publications, and other reports (published in English, French, or Portuguese) on HIV and tuberculosis epidemiology in prison populations in sub-Saharan Africa, and approaches to prevention, screening, diagnosis, and treatment of these diseases. When no data were available after 2011, the most recent literature before 2011 was included instead. We did case studies in five countries (Zambia, South Africa, Malawi, Nigeria, and Benin), which were purposively selected on the basis of regional spread and data availability to examine prison-specific HIV and tuberculosis policies and services in different regions of sub-Saharan Africa. Information about international donor funding between 2005 and 2015 was sought from four major international donors: the Global Fund Against AIDS, Tuberculosis and Malaria, the US President's Emergency Plan for AIDS Relief, the UK Department for International Development, and the European Union Funding Programme (panel 1).

In this paper, we use the term "detainee" to represent both people awaiting trial (on-remand detainees) and those who have been sentenced (convicted detainees). The term "prison" is used to represent facilities housing on-remand detainees (including jails, police holding cells, and other detention centres) and convicted detainees. We specify when data pertains to only one group or type of facility. This review does not include information about prison staff.

Prison populations in sub-Saharan Africa

Between 2011 and 2015, the estimated average daily census of detainees in sub-Saharan Africa was around

	Prison population (n)	Prisons (n)	Year	Source	Incarcerated per 100 000 population (n)	Pre-trial detainees (%)	Occupancy (%)	Estimated funding from Global Fund for prison HIV and tuberculosis programmes			
								Total budget (US$)	Proportion of total HIV and tuberculosis funding to the country (%)	Period	Annual funding per detainee (US$)
Angola	22 826	34	2014	Ministry of the Interior	106	47·1%	167%	$534 340	6%	November, 2011–August, 2016	$4·68
Benin	7247	9	2012	Government of Benin	77	74·9%	364%	$890 652	2%	October, 2010–September, 2015	$24·58
Botswana	3960	23	2015	Ministry of the President	192	24·5%	92%	..	..	..	..
Burkina Faso	6251	25	2014	US State Department	34	48·0%	171%	$47 547	1%	June, 2010–June, 2015	$1·52
Burundi	8646	11	2014	National prison administration	93	47·5%	214%	..	..	..	..
Cameroon	25 914	78	2013	Ministry of Justice	115	59·9%	138%	$4 835 690	20%	August, 2006–December, 2015	$20·73
Cape Verde	1434	5	2013	US State Department	286	29·6%	122%	..	..	..	..
Central African Republic	764	5	2015	UN mission	16	70·2%	..	$125 046	1%	December, 2011–May, 2014	$65·50
Chad	4831	45	2011	National prison administration	39	63·4%	232%	..	..	..	..
Comoros	233	3	2014	US State Department	31	55·8%	388%	..	..	..	..
Congo (Brazzaville)	1240	12	2014	US State Department	27	60·0%	483%	$702	<1%	January, 2011–December, 2015	$0·14
Democratic Republic of the Congo	21 711	120	2013	UN mission	32	82·0%	271%	..	..	..	..
Côte d'Ivoire	10 850	34	2014	US State Department	52	42·0%	218%	$4 163 261	3%	January, 2010–December, 2015	$63·95
Djibouti	600	2	2014	US State Department	68	50·0%	171%	$303 132	9%	October, 2013–September, 2015	$252·61
Equatorial Guinea	1000	15	2014	Estimate by Government officials	129	..	..	..	..	..	..
Eritrea	..	..	..	..	..	..	..	..	..	..	..
Ethiopia	111 050	126	2012	US State Department	128	14·0%	..	..	..	..	..
Gabon	3500	9	2013	US State Department	210	33·0%	..	..	..	..	..
The Gambia	1121	3	2014	UN Human Rights Rapporteurs	58	22·2%	173%	$90 008	3%	July, 2010–December, 2015	$16·06
Ghana	14 534	43	2016	National prison administration	53	18·7%	147%	$740 568	4%	May, 2006–April, 2011	$10·19
Guinea	3110	31	2014	Ministry of Justice	26	65·0%	175%	$4 493	<1%	February, 2007–January, 2012	$0·29
Guinea-Bissau	92	3	2013	US State Department	..	Vast majority*	102%	..	..	..	..
Kenya	54 154	108	2015	National prison administration	118	40·4%	202%	$434 360	4%	January, 2011–December, 2015	$1·60
Lesotho	2073	12	2014	National prison administration	92	19·5%	71%	$250 839	3%	October, 2010–March,2016	$24·16
Liberia	1719	15	2014	National prison administration	39	83·0%	138%	..	..	..	..
Madagascar	18 719	82	2013	US State Department	83	53·0%	181%	$203 431	1%	October, 2009–March,2016	$1·67
Malawi	12 156	30	2014	National prison administration	73	16·1%	174%	..	..	..	..
Mali	5209	58	2014	US State Department	33	52·8%	222%	..	..	..	..
Mauritania	1768	18	2014	Ministry of Justice	44	41·0%	102%	$1 290 980	15%	September, 2006–August, 2015	$81·08
Mauritius	2137	10	2016	National prison administration	159	41·1%	117%	$928 838	16%	January, 2010–June, 2015	$79·02
Mozambique	15 976	184	2015	Presidential quote	57	32·9%	195%	$1306	<1%	July, 2008–June, 2017	$0·01
Namibia	3560	13	2015	Ministry of Justice	144	6·6%	96%	$682 075	4%	October, 2011–September, 2016	$23·95
Niger	7424	38	2014	US State Department	39	53·4%	60%	..	..	..	..

(Table continues on next page)

	Prison population (n)	Prisons (n)	Year	Source	Incarcerated per 100 000 population (n)	Pre-trial detainees (%)	Occupancy (%)	Estimated funding from Global Fund for prison HIV and tuberculosis programmes			
								Total budget (US$)	Proportion of total HIV and tuberculosis funding to the country (%)	Period	Annual funding per detainee (US$)
(Continued from previous page)											
Nigeria	56 620	240	2014	US State Department	31	69·3%	114%	$4 090 276	7%	July, 2010–December, 2015	$13·38
Rwanda	54 279	14	2015	National prison administration	434	7·1%	96%	$21 232	<1%	January, 2005–June, 2010	$0·07
São Tomé and Príncipe	201	1	2014	US State Department	101	10·9%	77%	$165 582	16%	December, 2009–June, 2015	$147·11
Senegal	8630	37	2014	Groupe de Presse Walfadjri	62	41·4%	117%	$473 248	8%	January, 2012–December, 2016	$10·97
Seychelles	735	3	2014	US State Department	799	15·5%	143%†	..	..	..	..
Sierra Leone	3488	19	2015	National prison administration	55	54·3%	195%	$97 100	1%	November, 2008–October, 2015	$3·97
Somalia	3450‡	..	2012	US State Department	..	..	..	..	..	..	..
South Africa	159 563	236	2015	National prison administration	293	27·1%	133%	$4 963 001	31%	January, 2012–March, 2016	$7·76
South Sudan	6504	80	2015	National prison administration	52	28·9%	329%†	..	..	..	..
Sudan	19 101	125	2013	US State Department	50	20·4%	255%	..	..	..	..
Swaziland	3616	12	2014	National prison administration	289	18·1%	127%	..	..	..	..
Tanzania	34 196	126	2014	US State Department	69	50·1%	120%	..	..	..	..
Togo	4493	12	2014	US State Department	64	65·2%	165%	..	..	..	..
Uganda	45 092	247	2015	National prison administration	115	55·0%	273%	..	..	..	..
Zambia	18 560	88	2015	National prison administration	125	23·2%	229%	..	..	..	..
Zimbabwe	18 857	46	2015	National prison administration	145	17·1%	111%	..	..	..	..

Data are from the Institute for Criminal Policy Research[8,9] or the Global Fund, unless otherwise specified. The year column refers to the year in which the prison population estimate is from. Global Fund=Global Fund to Fight AIDS, Tuberculosis and Malaria. *Term used in the US State Department human rights report. †Based on occupancy at one prison.[8] ‡Estimate—no official figures available.

Table: **Overview of prison population in sub-Saharan Africa and estimated funding from the Global Fund to Fight AIDS, Tuberculosis and Malaria for prison HIV and tuberculosis programmes, by country**

600 000 (table, appendix).[9] On-remand detainees constitute 50% or more of the prison population in 40% of countries. 23 countries reported occupancy of more than 150%. Accounts of prison conditions are scarce and are likely to vary across countries. However, food rationing and poor-quality food (Mwapasa V, College of Medicine, Blantyre, Malawi, personal communication);[10,11] poor hygiene, water supply, and sanitation (Mwapasa V, College of Medicine, Blantyre, Malawi, personal communication);[10,11] frequent stockouts of basic drugs, including antibiotics (Mwapasa V, College of Medicine, Blantyre, Malawi, personal communication; unpublished UN Office on Drugs and Crime Data); and physical and psychological abuse[11] have all been reported. Such poor prison conditions—including overcrowding—are inconsistent with the basic principles set forth in the Mandela Rules, could constitute human rights violations, and pose serious risks to individual and public health (panel 2).[7]

Even among the prison population as a whole, access to health care, treatment of prisoners, and prison conditions differ substantially between specific groups. Ethnic minorities, migrants, poor people, foreigners, and socially marginalised populations such as sex workers, people who use drugs, lesbian, gay, bisexual, and transgender (LGBT) individuals, and on-remand detainees could be at increased risk of abuse, poor conditions, or lack of access to care.[6,16] Women and juvenile detainees, who have increased and distinct health needs, constitute 5% or less of the prison population in most countries, but often have poorer access to high-quality health care than do male detainees (panel 3).[18,19]

Epidemiology of HIV and tuberculosis among detainees in sub-Saharan Africa

Data for HIV or tuberculosis in prisons, published between 2011 and 2015, were identified from 24 of 49 sub-Saharan African countries (appendix). Data published before 2011 were available for three other countries. Studies were limited in number, varied in quality, and had differing methods (panel 1). Therefore caution is advised when comparing or generalising findings and making inferences from the data.

Most studies consistently showed a higher prevalence of HIV infection and tuberculosis among detainees than among unmatched non-incarcerated populations. Reported prevalence of HIV infection ranged from 2·3% to 34·9% (2·3%–10·8% in west Africa; 4·2%–23·0% in east Africa; and 7·2%–34·9% in southern Africa); tuberculosis prevalence ranged from 0·4% to 16·3% (1·2%–16·3% in west Africa; 0·5%–12·1% in east Africa; and 3·6%–7·6% in southern Africa).

Female sex was associated with prevalent HIV infection in prison; prevalence was also higher in women in prison than in those in the surrounding or non-incarcerated population. Although the reasons for this increased prevalence are unclear, the high background prevalence of HIV infection among younger women or behaviours associated with both incarceration and HIV, such as sex work, could have roles. One cross-sectional study[20] in Zambia showed a higher prevalence among already-incarcerated detainees than among those entering prison. Whether HIV transmission during incarceration or other epidemiological factors contributed to this difference is unclear.

When data were available, a large proportion of tuberculosis cases were in people with HIV (range 5–70%).[10,21–28] Overcrowding, incarceration in windowless cells, and sharing cells with patients with tuberculosis or a chronic cough were associated with increased tuberculosis prevalence among detainees in some studies. Furthermore, in a modelling study in a South African prison, annual tuberculosis transmission risk was estimated to be as high as 90%,[29] suggesting that prisons could be places of high transmission intensity.

The revolving-door effect (appendix)—as a result of detainees, prison personnel, and visitors cycling into and out of prisons—can result in the concentration of HIV and tuberculosis in prisons, and could amplify these diseases in the wider communities into which detainees are released and in which prison personnel live.[20,30] For example, in a study in Zambia,[20] the total prison population over 6 months was double the average static population (n=1300) for that period, and 24% of detainees entering prison had been previously incarcerated. Several other studies have also shown the high turnover of detainees.[10,21,31,32] Therefore, HIV and tuberculosis control in prisons benefits not only the individual and other detainees, but could also affect control in the community. Additionally, community and prison HIV and tuberculosis programmes face substantial challenges in ensuring appropriate services and continuity of care for detainees upon incarceration and release.

Understanding risk factors for HIV and tuberculosis in sub-Saharan African prisons is essential to the implementation of appropriate prevention interventions and services. The available empirical data do not allow determination of the relative contribution of transmission before and after incarceration to prevalence within prisons. The very limited data available suggest, however, that transmission during both periods might play a part.

Panel 2: Experience of detainees in sub-Saharan African prisons

Pre-trial detention

"I have stayed here for five years, and have not seen a plaintiff, and have not seen a judge. The court has not called the case."
Male detainee, South Sudan[12]

Sexual violence

"We called to the police and screamed for help, saying, 'These guys are forcing us to have sex with them.' But the police said, 'That is good, that's what you want.' So the police were encouraging the guys in there. There were about 50 other detainees, and five of them were raping us. Three of them raped me personally."
Male detainee, Tanzania[13]

Food

"Often there was no wood to cook, so [the deputised prisoner guards] would say, 'OK, spend the night without eating.' Once we went three days without eating. Even the children do not eat when there is no wood."
Male detainee, Rwanda[14]

Poor access to care

"There are delays in getting to the clinic. It depends on the officials, if they want to take you there or not. Sometimes you can go as long as a month waiting to go to the clinic.... They don't open the door in the cell at night for anything. There are no windows, no air. Someone who was 28 years old died at night in my cell and they didn't open the door until the morning."
Male detainee, Zambia[15]

Inadequate mental health care

"When I was brought here, I didn't believe I would come out of that place [Juba Central Prison]. At night, people fight themselves. Some use razor blades. Others they insult, others they cry. Others are innocent. Others are angry. Others laugh but are not happy. Others are quiet. Others do not wear clothes—they move naked."
Male detainee, South Sudan[12]

HIV care

"I normally get my medicine once a month and I take it each day. I started ARVs in 2006, but when I was in *Kwa Kabuga* I did not get them."
Female detainee, Rwanda[14]

"When I told the prison officer I was HIV positive, he said, 'Fight on, complete the sentence, go home, and get treatment.' It meant he can't do anything for me. There were wardens I informed. They said prison has nothing to offer me.'"
Female detainee, Uganda[11]

ARVs=antiretrovirals.

Panel 3: Experiences of children in adult prisons in Zambia

Zambia has no dedicated juvenile justice system, and children in conflict with the law face trial in the adult court system. Even after an initial appearance before a judge or magistrate, juvenile detainees can wait for lengthy periods while their cases are being concluded.

One 17-year-old detainee told researchers, "I am here on remand; I came in July, 2007. I am done with my trial, just waiting for judgment…The trial didn't take too long, it is only the judgment that has taken long. It's been a year and four months since my trial ended. I've been back to court four times just for the judgment but it never comes."

International law mandates that people who are charged with a criminal offence be informed of their right to have access to a lawyer. However, many juvenile detainees in Zambia report no legal representation. Even children appearing before the High Court were rarely represented by counsel. As one teenage detainee reported, "I had no representation, I stood on my own behalf. It was my first time in a police station or in court. I was just speaking, and I was scared. So I didn't know what I was saying… As young people, it is very threatening to see the inside of the court. Even if you are not guilty, you end up pleading guilty."

Children held with adults often face sexual violence. "By the time we are discharged, we will go out of here with disease", said another adolescent detainee. "Juveniles are either taken advantage of or enticed because of our vulnerability. We are young, we don't have people to bring us food and clothes. They make sure we consume what they give, then are unable to refuse."

Access to health care, which is often difficult for adults, can be especially difficult for children. "Sometimes it is difficult getting to the clinic, sometimes you may not get to go. We ask the cell leader—[and even if they agree] the guards might say no", said a third detainee. Another 16-year-old concluded, "If you are sick, then you can't go to the clinic."

Source: Todrys & Amon, 2011.[17]

Robust studies of the bio-behavioural, social, and structural factors underpinning the risk of HIV and tuberculosis among prison populations in sub-Saharan Africa are needed to answer these questions.

Tools, approaches, and structural interventions to prevention, screening, diagnosis, and treatment

International guidelines recommend a package of HIV and tuberculosis interventions for prisons in low-income and middle-income countries.[7,33] The recommended interventions can be organised into three categories: structural approaches to reduce overcrowding, improve tuberculosis infection control, and provide adequate nutrition; prevention and harm-reduction activities, including interventions to reduce transmission of HIV and tuberculosis; and HIV and tuberculosis diagnosis, treatment, and care, which should adhere to national guidelines and be linked operationally to national programmes.

Despite endorsement from regional and international governing bodies,[34,35] these interventions are rarely fully available in sub-Saharan African prisons because of a host of financial, policy, and systems-related barriers, including financial constraints,[36] inadequate infrastructure,[37] laws criminalising sex between men,[38] overcrowding,[39] absent health-information management systems,[39] inadequate infection-control procedures,[40] lack of transport to off-site clinics,[39] fragmented care due to facility transfers and release back to the community,[39] and scarce human resources for health.[39]

Prison overcrowding is a recognised problem globally,[36] and mathematical modelling suggests that implementation of internationally recommended cell-occupancy standards could reduce the annual risk of tuberculosis transmission by 50% in the specific case of South Africa.[29] However, there are limited data from sub-Saharan African countries describing the use of structural or criminal-justice interventions to mitigate overcrowding.[39] South Africa provides a counter-example: reforms to the pre-trial detention system have helped to reduce overcrowding by creating alternatives to detention for on-remand detainees unable to post bail, including release on warning and the use of electronic monitors.[41–43] Partly as a result of these reforms, the South African prison population declined between 2004 and 2014, from 187 036 to 157 170 detainees.[44] Another policy change identified in one prison was increasing food rations, which correlated with a reduction in reported tuberculosis incidence and all-cause mortality.[45]

In some cases, better service delivery for HIV and tuberculosis prevention and treatment could be politically and logistically more feasible than structural changes as a first step towards improvement of detainees' health. With respect to HIV prevention, behaviour-change communication and educational interventions have been implemented in some prisons, although their reach and effectiveness are unknown.[37,46–48] Crucial concerns, such as mitigation of sexual violence and coerced sex,[49] appear to be minimally addressed, with no reports of clearly effective strategies.[50,51] Provision of condoms, post-exposure prophylaxis, and pre-exposure prophylaxis could reduce HIV transmission in facilities. Condoms are available in prisons in Burundi, Lesotho, and South Africa;[38] non-occupational post-exposure prophylaxis is reported to be available only in South Africa. Data for uptake (how often, when, and by which detainees) or effectiveness of these preventive measures are unavailable. Condom provision is illegal in prisons in many countries, including Ethiopia,

Malawi, Namibia, Rwanda, Senegal, Swaziland, Tanzania, Uganda, Zambia, and Zimbabwe. We identified no reports suggesting that pre-exposure prophylaxis is being prepared for implementation in sub-Saharan African prisons at present.

International guidelines state that mandatory HIV testing is a violation of human rights and endorse the availability of voluntary, confidential, on-site HIV counselling and testing for all people within closed settings.[52] Despite potential concerns about stigma, voluntary HIV counselling and testing seems to be accepted by detainees, as shown by several reports of uptake and a study of detainee satisfaction.[10,20,32,53–55] It is available in prisons in some countries, including Cameroon,[56] Côte d'Ivoire,[10] Democratic Republic of the Congo,[53] Kenya,[46,57] Malawi,[58] South Africa,[31] Uganda,[37] and Zambia.[59]

Although the availability of antiretroviral therapy (ART) in prisons in sub-Saharan Africa is limited,[30,31,60] when combined with comprehensive, voluntary HIV counselling and testing, initiation of ART can, in some cases, occur earlier in prisons than in the community. For example, the median CD4 cell count among male detainees initiating ART in South Africa appears higher than that among men in neighbouring community programmes.[31,61,62] Once in care, people who remain in prison can achieve excellent clinical outcomes: viral-load suppression was 93% at 12 months at an on-site treatment clinic[31] and 92% at 96 weeks at an off-site HIV clinic.[60] A description of the HIV treatment continuum in Kenyan prisons suggests that service uptake along the cascade might be similar to that in the community, and is in need of strengthening: 48 535 detainees received HIV counselling and testing and 2782 (5·7%) received a diagnosis of HIV, of whom 1493 (53·7%) enrolled into HIV care and 505 initiated ART (18·2%).[46,63]

Frequently set apart from HIV services, tuberculosis prevention activities in prisons have historically involved passive approaches to case detection.[29,64] By contrast, active case-finding—the aims of which are to systematically screen, diagnose, and treat detainees with tuberculosis early, with the goal of interrupting transmission—has been reported in prisons in Cameroon,[32] Malawi,[65] Nigeria,[66] South Africa,[67] Tanzania,[68] and Zambia.[59] Evidence shows that, with support and funding from implementing partners, mass and at-entry screening for tuberculosis—frequently integrated with HIV counselling and testing—is feasible, acceptable, and results in high uptake.[20,59,69] In Zambia in 2010, through a collaboration between the Zambia Correctional Service, Ministry of Health, and a Zambian non-governmental organisation (NGO), 4879 detainees and neighbouring community members were screened for HIV, and 7638 for tuberculosis;[59] 564 individuals were newly diagnosed with HIV and linked to care, and 409 were diagnosed with tuberculosis, with 372 (91%) initiating treatment. These results demonstrate what can be achieved when prison leadership, donor funding, and NGOs align to support implementation of tuberculosis programmes in prisons. Nonetheless, solutions embedded within and linking prisons and mainstream health systems will be required to achieve sustained screening, service-delivery, and health improvements.

To maximise efficiency and control costs, evidence-based screening tools are needed,[70] but few reports from sub-Saharan Africa have been published to guide how to screen detainees for tuberculosis. The sensitivity and specificity of symptom screening varies depending on the number of symptoms included.[27,70] In Zambian detainees, low body-mass index and HIV infection had moderate sensitivity (60%) for tuberculosis.[70] Among South African detainees, the use of chest radiography in addition to symptoms improved screening sensitivity from 24–38% to 70–80%.[27] These results are in keeping with findings from other continents,[71,72] which suggests that use of chest radiography is beneficial among prison populations. However, chest radiography necessitates resources, including health-care workers or computer-aided diagnostic algorithms to interpret or score radiographs, respectively.

Tuberculosis diagnosis in sub-Saharan African prisons often relies on sputum smear microscopy, (usually performed off site),[28] which misses about half of all cases.[73] Improving access to tuberculosis culture, chest radiography, and newer nucleic acid amplification tests could increase diagnostic yield in prisons and allow for earlier detection of multidrug-resistant tuberculosis. In South Africa, testing symptomatic on-remand and convicted detainees (both new entrants and those incarcerated) identified by the WHO symptom screen[74] with on-site nucleic acid amplification was feasible and affordable: 87% of all new entrants and 23% of incarcerated detainees were reached, and costs were similar to those of other screening modalities (US$1513 per case of tuberculosis identified).[67]

Some evidence suggests that detainees in sub-Saharan Africa might experience suboptimal retention along the tuberculosis care continuum. Among 466 detainees beginning tuberculosis treatment at ten regional Ugandan prison health centres, only 222 (48%) completed treatment (202 [43%] were lost to follow-up and 22 [5%] died).[22] A chart review[75] of 202 detainees initiating tuberculosis treatment at one South African prison showed similar challenges: 92 (46%) patients were cured, but 103 (51%) had no ascertainable outcome because they were transferred before treatment completion. Findings that less than 50% of patients completed treatment or had documented cure are concerning, and have implications for the health of detainees and the potential development of drug-resistant tuberculosis. Early reports suggested a high prevalence (9·5%) of multidrug-resistant tuberculosis in one Zambian prison.[76] However, subsequent studies in Zambia[20] and South Africa[67] have shown a much lower prevalence (1·1% and 1·0%, respectively) similar to general population estimates in sub-Saharan Africa (1·5% prevalence among treatment-naive patients with tuberculosis),[77] suggesting that

Panel 4: South Africa and Malawi—strong policies, but work still to do

South Africa's prison system serves a prison population larger than any other African country and is administrated by a dedicated government ministry (table). Unusually in the African context, South Africa has both policy and stand-alone guidelines outlining a comprehensive package of HIV and tuberculosis prevention, diagnosis, care, and treatment actions (appendix). Malawi also has strong policies addressing prison tuberculosis services. The publication of the Malawi Policy on Tuberculosis Control in Prisons,[100] which incorporates some actions on HIV, demonstrated unusual alignment of political and technical commitment, by recommending provision of entry screening, active case-finding, HIV testing, DOTS, antiretroviral therapy, and treatment follow-up for all post-release detainees with tuberculosis. The National Strategic Plan for Prevention and Control of TB 2015–2020 additionally articulated plans to align tuberculosis registration in Malawi's five largest prisons with Ministry of Health and National Tuberculosis Control Programme protocols, and to provide tuberculosis and HIV training for prison officers.[101]

Policies and guidelines provide an important framework for planning, financing, and implementation of HIV, tuberculosis, and other essential prison services, yet by themselves are insufficient. In South Africa, despite a well defined package of HIV and tuberculosis service entitlements and comparatively high levels of funding, key informants noted that prison health care remains suboptimal. All South African prisons have internal clinics but these clinics are understaffed. Lack of medical doctors (eight of 48 prison doctors' posts were filled in June, 2014) and a nursing act that prevents nurses prescribing without authorisation contribute to timelags and bottlenecks in chronic-disease management and increase dependence on non-governmental organisations to deliver tuberculosis and HIV testing and treatment. Prevention services are weak because nurses frequently are not adequately trained in primary care or preventive health. Infrastructural issues also limit tuberculosis infection control because prisons were not built to allow adequate airflow, and there is a high demand for isolation cells for purposes other than infection control (eg, for so-called trouble makers). High levels of stigma for HIV and a reluctance to report sexual abuse limit access to HIV preventive and treatment services. Continued treatment once detainees are released from prison has also proved problematic, and is exacerbated by inconsistent referral practices, reluctance of detainees to access services once released, and reported maltreatment of former prisoners in public health services.

Key informants noted that Malawi, too, is facing systemic barriers to realising its far-reaching tuberculosis and HIV prison policies. Although the four largest prisons have static antiretroviral therapy clinics (registering around 600 detainees annually), the prison system struggles with human-resource capacity: only 20 health-care professionals are employed (one medical doctor, five clinical officers, five medical assistants, five nurses, and four microscopy technicians), with support from 30 patient-attendants. Challenges with supervision, supply chain, and disease notification are ongoing. In several smaller prisons, health services—including HIV and tuberculosis testing and treatment—are provided by visiting Ministry of Health staff, with occasional support from local or international non-governmental organisations. In many smaller sites, however, detainees must continue to be accompanied to external health centres.

detainees might not be disproportionately affected by multidrug-resistant disease. Screening, diagnosis, and effective treatment should be linked to preventive therapy (ie, isoniazid preventive therapy and ART) to control tuberculosis in high-risk populations such as detainees.[78] No published reports from sub-Saharan African prisons include descriptions of initiation or completion of isoniazid preventive therapy, or associated adverse events.[79] There was a notable dearth of sex-disaggregated and age-disaggregated data describing HIV or tuberculosis treatment outcomes for women and children within sub-Saharan African prisons.[19]

The breakdown of continuity of care for HIV and tuberculosis as a result of inter-facility transfer and release have been frequently noted.[31,60] The transition into detention often starts in police detention facilities or holding cells within police stations—facilities that generally lack health services.[80,81] For individuals already on ART or tuberculosis treatment, or both, who transition into prison, breaks in treatment of as little as several days can have serious adverse consequences, including the development of drug resistance.[82] Within prison and after release from prison, continuation of ART and tuberculosis treatment is essential for sustainment of individual health, prevention of development of drug resistance, and reduction of the risk of transmission to other detainees and the communities into which detainees are released. On the basis of data largely from Europe and North America,[83–85] retention in HIV or tuberculosis care, or both, after release from prison is thought to be challenging for various psychosocial, health-systems, and structural reasons. In the only sub-Saharan African study[60] in which retention in HIV care after release is discussed, 23 (68%) of 34 detainees visited the same South African HIV clinic at which they received care during incarceration at least once after release.

Prison populations are likely to have a higher prevalence of substance-use and mental health problems than the general population. These issues can compromise HIV and tuberculosis prevention, treatment, and care efforts within prisons through poor adherence to treatment, transactional sex for drugs, and high-risk sexual behaviours.[55,86,87] However, data for

prevalence and strategies to address these issues are scarce. Substance use in the past month (mostly cannabis or alcohol) has been reported by about 5% of detainees in Nigeria[88] and Kenya.[89] In a South African study[90] in which urine testing was done, either cannabis or methaqualone was detected among 45% of detainees at the time of police arrest. Although anecdotal reports describe the use of injection drugs in sub-Saharan African prisons, the frequency is unknown, but appears low.[89] Depressive and anxiety disorders have been reported in a large proportion of detainees in several studies.[91,92] Despite the probable burden of these comorbidities, we identified only one description of mental health activities (in Malawi)[93] and one drug harm-reduction programme (in Mauritius) in prisons.[94]

The lack of sufficient numbers of health workers and training[95] to provide HIV and tuberculosis treatment and other services[95] is a severe constraint on delivering care in sub-Saharan African prisons. Task-sharing and involving detainees themselves in health-service delivery could help to overcome some gaps in the system.[59,96] Reports from Rwanda, South Africa, Zambia, and Zimbabwe highlight the role of inmate peer educators in the provision of a host of services, including health education, psychosocial support, symptom screening and sputum collection for tuberculosis, referral for HIV testing, and social mobilisation for uptake of health services.[48,97–99] Sustainment of these programmes necessitates dedicated financing, ongoing training and peer-to-peer mentoring to maintain the cadre, and training of prison personnel to supervise and support peer educators.[59,97]

HIV and tuberculosis prevention, care, and treatment policies, and availability of services

Few sub-Saharan African countries have comprehensive policies in place guiding the implementation of HIV and tuberculosis prevention, care, and treatment activities in prisons. The appendix shows differing progress in this field, with summaries of the state of HIV and tuberculosis policies for detainees in five countries. Whereas South Africa has fully developed prison guidelines for tuberculosis, HIV, and sexually transmitted infections that outline a comprehensive package of interventions specific to detainees, prisons in Benin, Zambia, and Nigeria remain dependent on guidelines developed for the general community, with little or no reference to the epidemiological or structural particularities of prison populations. Malawi has a specific policy for tuberculosis management in prisons, but not for HIV or other sexually transmitted infections.

Policies provide clarity, direction, and normative standards to guide planning and service implementation and help to hold government institutions accountable. But, as shown by experiences in South Africa and Malawi (panel 4), comprehensive policies are not a guarantee of service implementation or operational efficacy (appendix). As demonstrated by Zambia and Benin (panel 5), innovations to improve HIV and tuberculosis care in prisons are possible despite weak or absent policies, but will probably remain limited in their sustainability and strategic impact (appendix). In many countries, NGOs often make a large and unmeasured contribution to essential services.[102]

Panel 5: Zambia and Benin—working outside the box

Benin and Zambia have small absolute numbers of detainees by international standards but their prisons are severely overcrowded (table). Such conditions pose particular risks in relation to the spread of tuberculosis and HIV, and, in the absence of prison-specific policies, the evolution of HIV and tuberculosis care in prisons in these countries has been iterative (appendix).

Key informants report that health care in Benin's nine prisons is delivered by a small team of under-resourced nurses employed by the prison authority, *La Direction de l'Administration Pénitentiaire et de l'Assistant Social* (DPAS). In recognition of the potential health threat posed by overcrowding in 2010, the country's national tuberculosis programme, *Programme National contre la Tuberculose, Bénin* (PNT, Bénin), recruited five new nurses, one at each of the five largest prisons. The nurses were tasked with providing HIV and tuberculosis counselling, conducting tuberculosis case-finding, collecting sputum samples, recording results, and overseeing referrals to PNT-run basic management units. Detainees with confirmed tuberculosis were also tested and treated for HIV. The nurses additionally provided general support to DPAS health staff.

In December, 2014, all five PNT-recruited nurses were absorbed (ie, employed and deployed by the Ministry of Health) in a national recruiting round, and, because of cost and supervisory complications, not replaced. In 2015, the PNT, Bénin announced a new policy to train DPAS nurses to do the same tasks. According to key informants, however, the capacity of existing staff to absorb the full suite of HIV and tuberculosis activities in prisons remains limited. So far, no specific policies for prison health, or prison HIV and tuberculosis services are being developed.

17 of Zambia's 87 prisons have internal health clinics. With only 34 health professionals employed (as of January, 2015), these clinics remain poorly staffed and resourced. At the central level, inadequate prison-health financing hampers implementation of health-workforce planning and limits health surveillance and monitoring.

Despite these and other policy barriers, Zambia has made some gains in prison-based HIV and tuberculosis care and treatment. Funded by the TB Reach initiative of the Stop TB Partnership, the Zambia Correctional Service and the national tuberculosis programme in 2011 worked with non-governmental organisations to optimise HIV and tuberculosis detection among detainees, prison staff, and the communities in and around six of the prisons with the heaviest tuberculosis burdens. The same project also reinvigorated efforts to institute routine tuberculosis screening at entry and train a cadre of prison peer educators in several facilities. Under one partner-supported project, testing for tuberculosis with Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) has been introduced in five Zambian prison clinics, along with protocols and training for staff. Concurrently, a second partner project supported the Zambia Correctional Service to form the first 11 prison health committees, comprising both officers and detainees, with a mandate to do facility-based needs assessments, basic service planning, and data collection.

International donor funding for HIV and tuberculosis services within prisons

Estimation of total national funding for prevention and treatment services for HIV and tuberculosis in prisons is complicated by multiple funding sources and frequent lack of transparency in the reporting of funding. Funding can

come from domestic government, NGOs, and international donor sources, and could be channelled through health, justice, or interior ministries, or through NGO interventions. Available data for domestic funding, although sought, were not comprehensive and therefore are not presented. We also sought information about international donor funding from four major funders, which is presented.

Among the Global Fund to Fight AIDS, Tuberculosis and Malaria's grant agreements to 49 sub-Saharan African countries between 2005 and 2015, only 24 included indicators of prison-related HIV or tuberculosis initiatives. Total funding for these activities was less than $100 000 in seven countries; another five countries reported more than $1 000 000 in prison-related funding (table). In 15 countries, less than 5% of the total budget for HIV and tuberculosis programmes was allocated to interventions in prisons.

Planning and budgeting documents for 2007–14 for the 21 sub-Saharan African countries that are part of the US President's Emergency Plan for AIDS Relief included references to HIV or tuberculosis programmes, or both, addressing prisoners in all countries, except South Sudan. The most frequently proposed intervention was HIV testing (16 [80%] of 20 countries). Other frequently proposed programmes mentioning prisons included HIV treatment, technical assistance, and research (11 countries [55%]); tuberculosis case-finding, abstinence, and general education about HIV prevention (eight countries [40%]); programmes for prison staff (six countries [30%]); and tuberculosis treatment (five countries [25%]). With the exception of Ethiopia and Kenya, prison-related funding for HIV and tuberculosis was rarely continuous (data not shown). Many of the interventions in which detainees were mentioned were part of larger programmes targeting most-at-risk populations, making it difficult to determine if—and the extent to which—programme activities actually included prison-specific activities.

Only one prison-related programme supported by the UK Department for International Development was identified: the Evidence for HIV Prevention in Southern Africa project. This initiative provides funding for research into HIV prevention in key populations, including detainees, in sub-Saharan Africa, with two research projects funded in 2015. Although the European Union did not provide information about prison programmes funded in sub-Saharan Africa, experts in the field report two projects funded by them—a 3 year project targeting health-systems strengthening in Zambian prisons, which began in February, 2013, and a multi-year project to build prison-service capacity to protect detainees' human rights in Uganda.[103,104]

A policy, service-delivery, and research agenda for detainee health in sub-Saharan African prisons

Provision of HIV and tuberculosis prevention and care services for detained populations is not only a human right, but also crucial for overall disease prevention and improved population health. To understand and address the gaps in HIV and tuberculosis services in prisons, political will, leadership, operationally relevant research, and long-term funding are needed to enable implementation of crucial programmes. Greater transparency and accountability are also needed to ensure that interventions and reforms are properly implemented and detainee rights are respected.

Reflecting the low political priority of detainees as a group, prison-specific policy guidance and adequate sustained funding for health-service delivery in prisons are absent in many sub-Saharan African countries—an issue that needs to be urgently addressed. Additionally, donors and governments have an obligation to report funding transparently, and should support efforts to track detainee health funding from domestic and international sources to ensure comprehensive coverage of prevention and treatment programmes.

Although specific interventions for HIV and tuberculosis are important, an overall health-systems-strengthening approach is required in prisons to address the pervasive barriers of poor infrastructure, shortages of human resources for health, scarce medical supplies, and inadequate information systems. Specific reforms include the adoption of a harmonised, intersectoral approach to recruitment, supervision, and remuneration of prison health professionals and the inclusion of prisons in quarterly facility-based reviews by community HIV and tuberculosis programmes. Such actions could form the basis for implementation of comprehensive, integrated screening, diagnosis, and treatment services for HIV and tuberculosis—as well as nutrition, substance-use, and mental health services—within a primary care framework, tailored to the prison context, and linked to community services. Services provided by NGOs should also be integrated into, and aligned with, prison and mainstream health systems to promote local ownership and ensure a continuum of care.

Criminal-justice reforms that address policies or practices that limit bail and reduce long delays in access to courts would probably reduce exposure to, and incidence of, disease. Limitation of arbitrary and extended pre-trial detention is a cost-effective criminal justice measure, as are large-scale interventions such as release of people detained for minor, non-violent offences. Interventions such as reformation of bail guidelines, restriction of overly broad police authority to detain so-called co-conspirators with no evidence, expansion of community service and parole programmes, increasing the numbers of judges, and improvement of access to legal representation, could all contribute to the reduction of prison populations in a sustained manner.[39] These interventions would probably reduce the risk of acquiring HIV and tuberculosis and recidivism, facilitate access to care, and ensure respect for international laws requiring prompt access to justice and freedom from pre-trial detention except in exceptional circumstances.

Strengthening of prison health and criminal-justice systems will require engagement by advocacy groups and

civil society to raise attention and apply political pressure for reform. Where improvements in prevention and treatment services have occurred, advocacy or legal action, or both, have frequently been instrumental (eg, Botswana withheld ART from non-citizen detainees until a constitutional court overturned this policy,[105] South Africa expanded HIV and tuberculosis services in prisons in response to legal action).

Optimal prevention and treatment strategies are best implemented when informed by regularly updated epidemiological and programmatic data. These data should inform priority health-service needs, service-implementation strategies, and guidelines within countries. The transparency of these data will enable best practices in the region to be shared. Priority programme and research questions that could guide the evidence-based implementation of services within prisons include sensitive entry and mass-screening algorithms for tuberculosis with universal access to diagnostic testing; the feasibility, uptake, and completion of isoniazid preventive therapy with or without ART and effects on tuberculosis epidemiology; and the burden and causes of mental health and substance-use problems and their association with HIV and tuberculosis epidemiology and clinical outcomes. Additional robust evidence of longitudinal clinical outcomes and linkage to and retention in high-quality treatment services for HIV and tuberculosis for prison populations was notably lacking. Implementation and assessment of new strategies are urgently needed to reinforce a continuum of care for detainees at incarceration, during inter-facility transfer, and after release. Additionally, it is important to understand the differing needs of ethnic minorities, children, migrants, LGBT people, people with disabilities, and people who use drugs in prisons, and to ensure effective and tailored services.

Conclusion

Good-quality data for HIV and tuberculosis in prisons in sub-Saharan Africa are rare; recent (ie, in the past 5 years) research is lacking in more than half the countries, and capacity to determine national estimates or monitor trends is limited. Available data suggest inadequate health services incommensurate with high disease burden. Funding is minimal, and policies guiding service implementation are often missing. Although some promising practices exist, increased political commitment and dedicated resources are needed to ensure universal access to high-quality prevention, treatment, and care of HIV and tuberculosis for detainees in sub-Saharan Africa.

Contributors

All authors contributed to the design of the study. LT, SC, SMT, MEH, CJH, and JJA undertook the searches and case studies, interpreted the findings, and wrote the Series paper. EJS, RZ, and ADH provided data or information for the study. All authors reviewed and edited the final paper.

Declaration of interests

We declare no competing interests.

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Public Health Action

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Health solutions for the poor

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NOTES FROM THE FIELD

The role of technical assistance in expanding access to Xpert® MTB/RIF: experience in sub-Saharan Africa

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To improve tuberculosis (TB) diagnosis, many national TB programmes have committed to deploying Xpert® MTB/RIF. Implementation of this relatively new technology has suffered from a lack of comprehensive technical assistance, however, including the formulation of policies and plans to address operational issues. While providing technical assistance, we observed numerous operational challenges in the implementation and scale-up of Xpert in five sub-Saharan African countries: low coverage, poor laboratory infrastructure, limited access, poor linkages to treatment, inadequate data on outcomes, problems with specimen transport, diagnostic algorithms that are not aligned with updated World Health Organization recommendations on target patient groups and financing challenges. We recommend better country preparedness and training, laboratory information and quality systems, supply management and referral mechanisms.

An estimated 9.6 million people worldwide develop tuberculosis (TB) each year, yet only 6.3 million cases are reported and treated.[1,2] Limited availability of sensitive, rapid TB diagnostics impedes case detection for both drug-susceptible and drug-resistant (DR) TB.

In 2010, the World Health Organization (WHO) endorsed the use of Xpert® MTB/RIF (Cepheid, Inc, Sunnyvale, CA, USA), a rapid diagnostic assay that can identify *Mycobacterium tuberculosis* and resistance to rifampicin (RMP).[3] Its availability at lower-level health facilities is an added benefit to improving access to testing. The WHO recommends using Xpert as a primary diagnostic test for adults with suspected DR-TB, for children and adults with human immunodeficiency virus (HIV) with suspected TB in settings with high HIV prevalence, for children with suspected TB and for the detection of extra-pulmonary TB. Resources permitting, Xpert may also be used as an initial diagnostic test for all patients with suspected TB or as a follow-on test to microscopy for adults with smear-negative results. Such an algorithm may require additional screening, using either chest X-ray or further clinical assessment as a pre-test screening tool, to reduce the numbers of individuals to be tested.[4,5]

Globally, the scale-up of Xpert remains the most important change in the TB diagnostics landscape, with over 4.8 million Xpert cartridges procured in the public sector in 116 of the 145 countries eligible for concessional pricing in 2014.[6] Studies have documented the effectiveness of Xpert for detecting *M. tuberculosis* in clinical specimens[7–12] and for detecting RMP resistance.[8] Commentaries, studies and models have presented potential uses and impacts of the test,[4] but few results have been published on the programmatic implementation of large Xpert networks.

Implementers, policy makers and donors need information about real-world implementation. This paper presents the challenges, lessons and recommendations from our experiences in providing technical assistance in five countries.

INTERVENTION

National policy reform and strengthened laboratory capacity are vital for country uptake of new TB diagnostic technologies. The WHO has established a process to rapidly review the evidence base for new TB diagnostics and ensure that new tools meet performance standards. In parallel, the environment in which new diagnostic devices are being implemented is important. All the essential elements of laboratory services must be addressed, including laboratory infrastructure, biosafety measures and maintenance, equipment validation and maintenance, specimen transport and referral mechanisms, management of laboratory commodities and supplies, information and data management systems, quality management systems, strategies and funding for development of laboratory human resources and integration of diagnostic algorithms into laboratory strengthening plans.

To fulfil these requirements, countries must coordinate the support of donors and partners and propose a budget and plan that covers technical assistance needs, the development of a TB laboratory strategic plan—including the roll-out of Xpert—and the coordination of support from donors and partners.

Specific intervention

Management Sciences for Health (Arlington, VA, USA) has provided south-to-south technical assistance for the implementation of Xpert in five sub-Saharan African countries—the Republic of Congo, Eritrea, Ethiopia, Ghana and Kenya—in collaboration with the US Agency for International Development, the African Society of Laboratory Medicine, the WHO and the Global Fund to Fight AIDS, Tuberculosis and Malaria. This assistance has included support to develop scale-up plans, increase awareness of global policy guidance, train hundreds of technicians and clinicians

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KEY WORDS
TB diagnostic technology; Xpert; TB laboratory services; technical assistance; implementation of innovations

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and install 55 Xpert GX4 machines in collaboration with Cepheid between July 2013 and March 2015.

The technical assistance provided to countries included, to varying extents, the following interventions:

- Inform countries about the availability of the WHO checklist to assess the readiness and appropriateness of sites. Recommendations relate to optimising the placement and use of machines, aligning clinicians' case-finding practices to the recommended use of Xpert and supporting supply and specimen referral systems.
- Improve coordination between donors and partners to ensure that the purchase of equipment and reagents is in alignment with a national implementation plan and budget that follows WHO policies.
- Improve the linkage between Xpert test results and the comprehensive management of patients, including confirmatory testing and linkages to care and patient outcomes.

Results from two countries illustrate the direct impact of these interventions: in Kenya, 8221 Xpert tests were conducted during the first quarter of 2015, of which 1830 (22.3%) were positive for *M. tuberculosis* and 81 (4.4%) were RMP-resistant. In Ethiopia, an evaluation after the first year of implementation (July 2013–December 2014) showed a 22% increase in the number of DR-TB cases detected, while total TB cases detected rose from 58 802 to 63 168 (7.5%). The contribution of Xpert to TB case detection was 2% (source: Ethiopia National TB Programme, 2015).

RESULTS

Integration of Xpert as a point-of-care test into national policies

In most countries, Xpert is not used as a point-of-care test, and the status of integration of this novel diagnostic tool into national algorithms varies among countries.

Impact of Xpert on case notification

In all countries, we observed an increased number of bacteriologically confirmed cases. This observation was counterbalanced by an irregular impact on the total number of cases notified. Generally, Xpert allowed more rapid diagnosis for HIV-TB co-infected patients and notification of RMP-resistant cases.

Impact of Xpert on patient care

There were no significant or systematic improvements in the linkage of diagnosed patients to treatment or in terms of mortality. Empirical treatment generally remains the rule, despite the availability of additional information about drug resistance, for example, with Xpert testing. The utilisation of the Xpert machines is at 15% of full capacity overall, representing a missed opportunity to diagnose potential TB and DR-TB cases due to poor referral and transport systems.

Linkages between Xpert assay results and other technologies and treatment are weak. Follow-up cultures and drug susceptibility testing (DST) may not be undertaken, mainly due to a lack of capacity for DST.

LESSONS LEARNT

Although Xpert is a diagnostic device with demonstrated performance in research environments, the literature is equivocal about its impact in programmatic conditions. Impacts on case notification or measurable patient outcomes should be considered the main indicators of success.

To increase the chances of achieving these results, the introduction of Xpert or any novel tool requires not only funding but also technical support for the revision of diagnostic and treatment guidelines. Furthermore, monitoring the progress and constantly evaluating the impact of new policies on indicators such as case detection, programmatic management of DR-TB and integration of TB-HIV activities are essential.

CONCLUSION

Realising the potential of WHO-recommended technologies such as Xpert to reduce the burden of TB depends on the behaviour of patients and providers, access to new tools, and the quality of TB treatment following diagnosis. Any Xpert roll-out strategy must balance the need to accelerate implementation with overall health systems strengthening. To achieve the maximum impact from novel diagnostics, countries should improve the quality of health care, commit the resources needed to develop and implement a strategic plan for laboratory services and involve laboratory experts to guide implementation.

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De nombreux programmes nationaux tuberculose (TB) se sont engagés à déployer le Xpert® MTB/RIF afin d'améliorer le diagnostic de la TB. La mise en oeuvre de cette technique relativement nouvelle a cependant souffert d'un manque d'assistance technique d'ensemble, notamment la formulation de politiques et de plans destinés à prendre en compte les problèmes opérationnels. Lorsque nous avons fourni cette assistance technique, nous avons observé de nombreux défis opérationnels dans la mise en oeuvre et l'expansion du Xpert dans cinq pays d'Afrique sub-saharienne : une faible couverture, une infrastructure de laboratoire limitée, un accès limité, des liens médiocres avec la prise en charge thérapeutique, des données insuffisantes sur les résultats, des problèmes de transport des échantillons, des algorithmes de diagnostic qui ne sont pas en accord avec les dernières recommandations de l'Organisation Mondiale de la Santé relatives aux groupes cibles de patients et des défis financiers. Nous recommandons une meilleure préparation et formation des pays, une information des laboratoires et des systèmes de contrôle de qualité, une gestion des stocks et des mécanismes de référence.

Con el propósito de mejorar el diagnóstico de la tuberculosis, muchos programas nacionales han decidido generalizar la práctica de la prueba Xpert® MTB/RIF. Sin embargo, la introducción de esta técnica relativamente nueva se ha dificultado debido a una falta de asistencia técnica integral, que comprenda la formulación de normas y de planes que aborden los aspectos operativos. Durante la experiencia de prestación de asistencia técnica, se observaron múltiples dificultades operativas en la ejecución y en la ampliación de escala de la técnica Xpert en cinco países de África subsahariana, a saber: la baja cobertura, la insuficiencia de las infraestructuras de laboratorio, el acceso limitado, la escasa vinculación con el tratamiento, la deficiencia de los datos sobre los desenlaces, los problemas relacionados con el transporte de las muestras, los algoritmos diagnósticos que no corresponden a las recomendaciones actualizadas de la Organización Mundial de la Salud en materia de grupos destinatarios de pacientes y las dificultades de financiamiento. Se recomienda procurar una mejor preparación y una mayor capacitación en el país, perfeccionar los sistemas de información y control de calidad de los laboratorios y poner en práctica procedimientos de gestión de los suministros y mecanismos de remisión.

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The socioeconomic impact of multidrug resistant tuberculosis on patients: results from Ethiopia, Indonesia and Kazakhstan

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Abstract

Background: One of the main goals of the post-2015 global tuberculosis (TB) strategy is that no families affected by TB face catastrophic costs. We revised an existing TB patient cost measurement tool to specifically also measure multi-drug resistant (MDR) TB patients' costs and applied it in Ethiopia, Indonesia and Kazakhstan.

Methods: Through structured interviews with TB and MDR-TB patients in different stages of treatment, we collected data on the direct (out of pocket) and indirect (loss of income) costs of patients and their families related to the diagnosis and treatment of TB and MDR-TB. Direct costs included costs for hospitalization, follow-up tests, transport costs for health care visits, and food supplements. Calculation of indirect costs was based on time needed for diagnosis and treatment. Costs were extrapolated over the patient's total treatment phase.

Results: In total 406 MDR-TB patients and 197 other TB patients were included in the survey: 169 MDR-TB patients and 25 other TB patients in Ethiopia; 143 MDR-TB patients and 118 TB patients in Indonesia; and 94 MDR-TB patients and 54 other TB patients in Kazakhstan. Total costs for diagnosis and current treatment episode for TB patients were estimated to be USD 260 in Ethiopia, USD 169 in Indonesia, and USD 929 in Kazakhstan, compared to USD 1838, USD 2342, and USD 3125 for MDR-TB patients, respectively. These costs represented 0.82–4.6 months of pre-treatment household income for TB patients and 9.3–24.9 months for MDR-TB patients. Importantly, 38–92 % reported income loss and 26–76 % of TB patients lost their jobs due to (MDR) TB illness, further aggravating the financial burden.

Conclusions: The financial burden of MDR-TB is alarming, although all TB patients experienced substantial socioeconomic impact of the disease. If the patient is the breadwinner of the family, the combination of lost income and extra costs is generally catastrophic. Therefore, it should be a priority of the government to relieve the financial burden based on the cost mitigation options identified.

Keywords: Tuberculosis, Multi-drug resistance, Patient costs, Cross-sectional survey, Ethiopia, Indonesia, Kazakhstan

Abbreviations: AHRI, Armauer Hansen Research Institute; CSO, Civil society organization; DOT, Directly observed therapy (for (MDR)TB); HIDN, Office of Health Infectious Disease and Nutrition; IQR, Interquartile range; MDR, Multi-drug resistance (i.e. resistance to rifampicin and isoniazid); NGO, Non-governmental organizations; NTP, National Tuberculosis Program; TB, Tuberculosis; TORG, Tuberculosis Operational Research Group; USAID, United States Agency for International Development; USD, United States dollar; WHO, World Health Organization

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Background

One of the main goals of the post-2015 global tuberculosis (TB) strategy is that no families affected by TB face catastrophic costs [1]. There is no universal definition of catastrophic costs and a threshold for TB-related catastrophic costs still needs to be defined [2]. Although drugs for TB treatment are free in most high TB-burden countries, TB patients face costs due to charges for related health services, costs for transport, accommodation, nutrition and suffer lost income. A recent systematic review showed that the financial burden of both diagnosis and treatment was high and varied widely across settings, the total costs amounting to 58 % (range 5–306 %) of annual patient income [2]. These costs are expected to be higher for patients with multidrug resistant (MDR) TB than for other TB patients given the three to four times' longer treatment period. Although there is a paucity of data, the data at hand indicate that, during treatment, patients with MDR-TB face 5–20 times higher costs than patients with drug-susceptible TB, due to relocation costs and longer pre-diagnosis and treatment periods involving more visits and procedures and inability to work [3, 4]. Patients who cannot afford to start or continue treatment will suffer from more extensive morbidity [5]. This may result in higher health system costs, and is likely to result in continued transmission [6].

Policy makers need to understand patient costs to assess how many families face catastrophic costs, to identify the main cost components in TB diagnosis and treatment that lead to catastrophic costs, to develop mitigation policies and to identify and tackle bottlenecks in access to and continuation of TB and MDR-TB treatment. Thus, measurement of financial burden and the main cost drivers for TB and MDR-TB diagnosis and treatment is needed. We conducted such a survey in three different settings; in Ethiopia, Indonesia, and Kazakhstan. We adapted a previously developed tool to estimate TB patients' costs that has been implemented in several countries. That work had a positive impact resulting in improvements in access, nutrition support, adoption of a shorter treatment regimes, and the inclusion of TB services under insurance [7–9]. However, this tool was not meant to include both TB and MDR-TB patients and compare costs between both patient groups. The tool was, therefore, adapted for inclusion of MDR-TB patients' costs to determine the main cost drivers for TB and MDR-TB diagnosis and treatment. The results observed in the three study countries were presented and discussed in in-country workshops for policy makers, focusing on ways to relieve the financial burden of diagnosis and treatment for TB and MDR-TB patients. The results from the surveys in Ethiopia, Indonesia, and Kazakhstan are described here together with identified mitigation strategies.

Methods

Study design

We conducted a cross-sectional survey in six public hospitals (and their satellite clinics) providing TB and MDR-TB (from now on referred to as (MDR)TB) services in Ethiopia, Indonesia, and Kazakhstan. These three countries were selected purposefully as to have representation from three different settings: one in Africa, one in South-Asia and one in Central Asia. Details on methods and results per country are available in the individual country reports and a summary report [10–13].

The (MDR)TB patients were interviewed once, at the health facility. In Ethiopia patients were interviewed at all three MDR-TB hospitals (St. Peters and ALERT in Addis Ababa and University of Gondar Hospital in Gondar). In Indonesia patients were interviewed at two MDR-TB referral hospitals on Java Island (Persahabatan hospital in Jakarta and Dr Moewardi hospital in Solo) and five satellite sites. In Kazakhstan patients were interviewed at one MDR-TB hospital caring for MDR-TB patients from Akmola oblast and its satellite sites providing directly observed therapy (DOT) for (MDR)TB patients in Kokshetau city.

The previous version of the questionnaire [7] was used as the basis for a new generic questionnaire. It was shortened to exclude questions not informative with respect to TB costs (on delays in health seeking behavior, on additional costs for other illnesses, and on impact of disease on social life). Included were some questions expected to be applicable mostly for MDR-TB patients; on adverse effects of treatment and related costs, relocation costs, and on receiving incentives and enablers (e.g. transport or food vouchers).

We did not aim to collect longitudinal data of patients covering the full pathway of diagnosis and treatment, since this would make data collection a lengthy and complicated undertaking when done prospectively. Retrospective data collection over a prolonged period of time would yield unreliable results [9], especially for MDR-TB patients, probably leading to underestimation of costs. To get insight in costs of the different phases of diagnosis and treatment of (MDR) TB, we included patients in different phases of treatment.

Study population

We categorized and selected patients from five groups of TB and MDR-TB patients, representing different phases of diagnosis and treatment:

1. TB patients who completed at least 1 month of treatment and were within last month of the intensive phase of drug-susceptible TB treatment;

2. TB patients who started at least 3 months previously with the continuation phase of drug-susceptible TB treatment;
3. Patients diagnosed with MDR-TB within the month before the interview;
4. MDR-TB patients who started at least 3 months previously with the intensive phase of MDR-TB treatment;
5. MDR-TB patients who started at least 3 months previously with the continuation phase of MDR-TB treatment.

We excluded patients not consenting to the study, those not able to answer the questions in the interview, and those younger than 21 years of age since most of those below the age of 21 are not economically independent and still mainly live on their parent's earnings. Also, we excluded patients who died or transferred out while on treatment because of logistic difficulties of reaching them or family members for reliable information. In Indonesia, bedridden patients were also excluded as these could not be interviewed in a private environment. In Kazakhstan, two additional exclusion criteria were applied: 1. patients diagnosed by Xpert MTB/RIF were excluded as this diagnostic tool only very recently had been introduced and only small numbers of patients had been diagnosed with it, and 2. patients who receive home-based care, as they are a small group with very distinct costs compared to other patients.

Sampling

We aimed to include 50 patients per group in each of the three countries. We applied consecutive sampling, inviting all patients coming to the included health facilities to participate in the study until the target sample size was reached or until the end of the study period, whichever came first.

Data collection

Structured interviews were conducted by trained interviewers with (MDR)TB patients in different stages of treatment. Eligible patients were invited to participate in the interview by the doctor or nurse they were seeing during their scheduled visit to the health care facility. After this visit, those patients wishing to participate in the study were sent to a separate room where they were interviewed by the study staff, i.e. not involved in the patients' care. Before the start of the interview, written informed consent was obtained. Through a structured questionnaire we collected data on costs related to the diagnosis and treatment of (MDR)TB patients, as well as background information of the patients (age, sex, treatment type and phase, socio-economic status, ethnicity and distance to health facilities). To minimize recall bias [9], we restricted collection of most cost data to the last 3 months; but major coping costs were not restricted to this period.

In each country, the structured questionnaire was translated from English to the local language, adapted to the local context for some questions (e.g. insurance types, type of health care facility, reimbursement schemes), and translated back into English by another individual to check for translation and interpretation errors. The questionnaire was pretested to check for clarity on 3–5 patients per country before it was finalized. Face-to-face interviews were conducted in March 2013 (Ethiopia), February-March 2013 (Indonesia), and September-October 2012 (Kazakhstan) at the selected health care facilities. The questionnaire included cross-checks and the interviewers were trained to double-check unusually high costs when reported by the patients. Data on costs were collected in the local currency.

Data analysis

For each country, data were entered in a separate pre-designed data entry file (Microsoft Excel for Ethiopia; EpiData (www.epidata.dk) for Indonesia and Kazakhstan) and analyzed (Microsoft Excel for Ethiopia; STATA/SE 11.1 for Windows (Stata Corp., College Station, Texas, USA) for Indonesia, SPSS v20 IBM, New York, USA) for Kazakhstan).

We calculated costs of getting a (MDR)TB diagnosis, costs of treatment (in the intensive and continuation phase of (MDR)TB treatment) and financial values involved in coping as explained below and summarized in Table 1.

Costs for (MDR) TB diagnosis

Costs were obtained per diagnostic visit. Direct costs included all out-of-pocket payments that the patient had to make, such as paying administration fees, paying for laboratory tests, X-ray, and drugs, for food and accommodation, and for transportation to and from the hospital. Direct costs were summed up per cost item over all visits, after which the sums of the cost items were summed up in a total of direct costs per patient. Indirect costs (loss of income) were calculated by multiplying the total number of minutes spent on diagnostic visits with the patient's income per minute before diagnosis of TB.

Costs for (MDR) TB treatment

Cost items for (MDR) TB treatment included costs made because of taking or picking up drugs at the clinic, costs for follow-up tests, supplements, hospitalization, and treatment of adverse events. Costs for taking or picking up drugs were reported for a typical visit to take or pick up drugs. To get the total costs per month, individual cost items per visit were summed up and the total costs per month were calculated by multiplying these costs with the number of times per week that drugs were taken/picked up and the number

Table 1 Methods used to estimate different types of costs for TB diagnosis and treatment

Type of cost	Elements included in cost type	Methods used to calculate costs
Diagnostic (for those in intensive phase)	Food, travel, accommodation, medical costs, and loss of income during visits	Summed direct and indirect costs of visits
		Indirect costs (income loss) as calculated from total time spent x income/time
Treatment (excluding for those just diagnosed with MDR-TB)	DOT and drug collection visits, follow-up tests, food, travel, treatment of adverse events[a], supplements[b], hospitalization[c], and loss of income	Summed direct and indirect costs, multiplied by number visits/week, weeks/ month, and internationally defined duration of treatment phase
		Indirect costs (income loss) for DOT as calculated from total time spent x income/time
Other Costs	Direct and indirect costs of accompanying persons/attendants	Summed costs related to diagnosis or treatment visits
Coping strategies	Amount borrowed, assets sold	Summed costs

[a]Assuming that all costs for these elements had been made before the time of the interview (hence, costs were not extrapolated to the treatment phase)
[b]Summed direct costs over last month *x* internationally defined duration of treatment phase
[c]In Ethiopia and Indonesia: costs reported up until time of interview. For Kazakhstan, summed direct costs over last month *x* internationally defined duration of treatment phase; summed indirect costs (income loss) for hospitalization as calculated based on internationally defined duration of intensive phase *x* income/time

of weeks per month (4.3). Indirect costs were calculated by multiplying the turn-around-time in minutes for a typical visit with the number of times per week that drugs were taken/picked up, the patients' income per minute, and 4.3 weeks per month. These monthly costs were subsequently extrapolated over the complete treatment phase using the internationally defined durations of the different treatment phases: 2 months of intensive phase and 4 months of continuation phase for new TB patients, 3 and 5 months for retreatment patients and 8 and 12 months for MDR-TB patients [14, 15]. If patient had been longer in their treatment phase at the time of the interview, we assumed they were in the last month of the respective phase during the interview. The main outcomes therefore were total costs incurred by the patient during the phase (intensive or continuation) of treatment they were in.

Costs for follow-up tests were reported from the start of TB treatment till the interview. Since it was assumed that in a typical TB treatment phase, only one or two follow-up tests would be needed, no extrapolation was applied to obtain the costs per treatment phase for patients being treated with TB regimens. To calculate the costs per treatment phase for MDR TB patients, the total costs were multiplied by the internationally defined duration of the treatment phase of the patient, divided by the number of months that the patient had been in that treatment phase.

Costs for supplements were reported over the past month. To obtain the total cost per month, individual cost items were summed up and extrapolated to the total treatment phase. We considered adverse events needing treatment unlikely to occur and did not apply extrapolation of the costs reported to the complete treatment phase.

In Ethiopia and Indonesia most TB and MDR-TB patients are not hospitalized, unless cases are severe or experience serious side effects from treatment. In these two countries we therefore assumed that hospitalization did not occur after the interview and we did not extrapolate the costs of hospitalization to the complete treatment phase. In Kazakhstan however, most patients are hospitalized during the full intensive phase of treatment. As patients are not able to work when hospitalized, loss of income in Kazakhstan was calculated assuming hospitalization for the duration of the intensive phase.

Coping costs

Coping with the financial impact of TB treatment involves multiple strategies, such as borrowing money, asking for donations from family and friends, using savings, selling assets costs and cutting down other expenses. We asked patients for the financial impact of their disease on their family and the coping strategies used. Costs were defined as loss of household income after TB diagnosis (indirect costs), amounts borrowed, and market value of assets sold (both defined as direct costs). We did not extrapolate any of these costs since reduction in household income was reported as monthly reduction in income and it remained unknown when the income had changed. Besides, we assumed that borrowing money and selling assets were one-off actions.

Since the distributions of almost all costs were highly skewed towards higher values, we chose to present median values with 25th and 75th percentiles (also called the interquartile range (IQR)). The total financial value for coping strategies reported by the patient was calculated.

We converted all costs into US Dollar using the average daily midpoint exchange rate over the data collection period [16]. Over this period, the average exchange rates for 1 USD were 18.60 Ethiopian Birr, 9689.86 Indonesian Rupiah, and 148.35 Kazakh Tenge.

Results

In total 197 TB patients and 406 MDR-TB patients participated in the three countries: 25 TB patients and 169 MDR-

TB patients in Ethiopia; 118 TB patients and 143 MDR-TB patients in Indonesia; plus 54 TB patients and 94 MDR-TB patients in Kazakhstan (Table 2). In Ethiopia, the time period allocated for data collection turned out to be too short and it was decided to focus on reaching the targets for the number of MDR-TB patients. In Kazakhstan, the number of eligible TB patients treated at the selected healthcare facilities was below 50 during the period of data collection. In all three countries, the majority of patients were pulmonary sputum smear positive patients.

The median (IQR) number of visits needed for a TB diagnosis was three (2–5) in Ethiopia, three (2–4) in Indonesia, and two (2–3) in Kazakhstan. For Ethiopia, the number of respondents on TB diagnosis was small, and four out of five were from Gondar with a large and remote catchment area. The median time spent per visit for those patients was 43 h for a total median time spent for diagnostic visits of 144 h. The median (IQR) total time in minutes needed for diagnostic visits was 355 (130–600) in Indonesia and 120 (78–273) in Kazakhstan.

TB illness related costs

The median costs (with IQR) for patients in the three countries are shown in Table 3. Costs are separated for diagnostic and treatment expenditure. Also, we show direct (out of pocket) and indirect (foregone income) costs separately. The median estimated total costs for diagnosis and treatment during the current TB treatment episode was USD 260 in Ethiopia, USD 169 in Indonesia, and USD 929 in Kazakhstan, respectively. The median estimated costs for MDR-TB patients were 7.1, 13.9 and 3.4 times higher: USD 1838 in Ethiopia, USD 2342 in Indonesia, and USD 3125 in Kazakhstan, respectively.

Treatment costs were much higher than diagnostic costs in all countries, both for TB and for MDR-TB patients, with median diagnostic costs ranging between USD 9 and USD 75 (Table 3). In Ethiopia and Indonesia but not in Kazakhstan, direct costs for treatment where higher than indirect costs related to treatment. In Kazakhstan, estimated indirect costs were high because of hospitalization in the intensive phase.

Table 2 Patient characteristics

	Ethiopia		Indonesia		Kazakhstan	
	n	(%)	*n*	(%)	*n*	(%)
Patient group						
Intensive phase of standard (re)treatment regimen	12	(6.2)	62	(23.8)	41	(27.3)
Continuation phase of standard (re)treatment regimen	13	(6.7)	56	(21.5)	13	(8.7)
Just diagnosed with MDR-TB	21	(10.8)	29	(11.1)	2	(1.3)
Intensive phase of MDR-TB treatment	85	(43.8)	55	(21.1)	62	(41.3)
Continuation phase of MDR-TB treatment	63	(32.5)	59	(22.6)	32	(21.3)
Type of TB						
Pulmonary smear positive	176	(91.2)	166	(63.6)	121	(80.7)
Pulmonary smear negative	4	(2.1)	72	(27.6)	27	(18.0)
Extrapulmonary	13	(6.7)	16	(6.1)	2	(1.3)
No information	1	(0.5)	7	(2.7)	0	(0.0)
Gender						
Male	107	(55.2)	138	(52.9)	100	(66.7)
Female	87	(44.8)	120	(46.0)	50	(33.3)
No information			3	(1.2)		
Age (years)						
21–29	110	(56.7)	62	(23.8)	47	(31.3)
30–39	49	(25.3)	71	(27.2)	43	(28.7)
40–49	20	(10.3)	66	(25.3)	42	(28.0)
50+	15	(7.7)	61	(23.4)	18	(12.0)
No information			1	(0.4)		
HIV						
Positive	41	(21.1)	8	(3.1)	0	(0.0)
Negative	146	(75.3)	128	(49.0)	150	(100)
not tested/unknown	7	(3.6)	125	(47.9)	0	(0.0)

Table 3 Summary table on median costs (interquartile ranges) in US dollars for TB and MDR-TB patients in the three study countries, related to costs for diagnosis, and treatment in the intensive phase and continuation phase

	TB			MDR-TB		
	Ethiopia	Indonesia	Kazakhstan	Ethiopia	Indonesia	Kazakhstan
Direct pre(diagnosis) costs (costs in last 3 months)	14 (4–109)	33 (9–64)	5 (1–13)	68 (35–191)	39 (12–63)	N.A.[b]
Indirect pre(diagnosis) costs (costs in last 3 months)	0 (0–30)	4 (0–9)	3 (1–5)	0 (0–8)	3 (1–6)	N.A.[b]
Total pre(diagnosis) costs (costs in last 3 months)	14 (6–129)	35 (16–69)	9 (4–19)	75 (40–191)	46 (16–82)	N.A.[b]
Direct treatment costs						
Subtotal for intensive phase	104 (10–231)	41 (8–108)	0 (0–74)	639 (259–968)	596 (342–1035)	165 (0–541)
Subtotal for continuation phase	80 (34–156)	59 (17–224)	179 (90–328)	634 (458–1048)	976 (558–1584)	754 (344–2022)
Indirect treatment costs						
Intensive phase	0 (0–34)	10 (0–40)	404 (303–674)	220 (89–374)	315 (153–848)	1537 (0–2696)
Continuation phase	0 (0–4)	9 (0–57)	104 (70–159)	73 (1–375)	254 (0–504)	227 (0–300)
Total treatment costs						
Intensive phase	119 (19–260)	52 (17–134)	607 (317–809)	831 (462–1525)	1079 (600–2299)	1914 (175–3370)
Continuation phase	128 (34–177)	82 (26–286)	319 (236–702)	931 (494–1296	1227 (730–1846)	1202 (657–2245)
Total (pre)diagnosis and treatment costs[a]	260	169	929	1838	2342	3125

[a]Sums are based on adding up medians from different groups of patients, and therefore must be interpreted with caution
[b]Not available as only two patients were interviewed with a diagnosis of MDR-TB in the last month

The main cost components related to (MDR) TB diagnosis and treatment varied between countries.

In Ethiopia the highest cost element in the diagnostic phase was for food expenditure and for food supplements during treatment, both for TB and MDR-TB patients. In Indonesia the largest cost share during diagnosis was for travel and food for TB patients, and for laboratory tests and administration fees for MDR-TB patients. For both TB and MDR-TB patients, travel expenditure was the highest cost element during treatment. In Kazakhstan, transport expenditure was responsible for most costs during diagnosis, and indirect costs of hospitalization and direct costs related to food supplements and travel for DOT visits during treatment.

Socio-economic impact of TB illness related costs

Table 4 shows the main indicators of the socioeconomic impact of MDR-TB disease in the three countries. Most patients reported income loss due to TB illness, ranging from 33 % of TB patients in Ethiopia to 100 % for MDR-TB patients in Kazakhstan (where no outpatient treatment during the intensive phase was available at the time of the data collection). The median value of this reduction in income was 100 % except for TB patients in Indonesia 25 %). A highly varying proportion of patients received assistance, ranging from 17 % of TB patients in Kazakhstan to 73 % of MDR-TB patients in Ethiopia. However, in all countries the amount of financial assistance received in general was low, including through health insurance. The proportion of patients who sold property or took out loans to cope with TB related costs, was especially high in Ethiopia: 56 % of TB patients and 41 % of MDR-TB patients took out loans.

Figure 1 shows patient and household income before TB illness and at the time of interview. Mean incomes were much higher than median incomes, especially in Indonesia and to a lesser extent in Ethiopia, representing the highly skewed distributions with a few patients have relatively much higher incomes than the rest.

In Ethiopia the median TB and MDR-TB patient income fell from USD 43 and USD 54 to before TB illness, respectively, to zero at the time of the interview. The fast majority (88 % of TB patients and 76 % of MDR-TB patients) did not have any income after (MDR) TB diagnosis, compared to 8 and 14 % before (MDR)TB diagnosis. The median monthly household income of TB patients dropped by 50 % (from USD 75 to USD 38), and by 33 % (from USD 81 to USD 54, respectively). Although many patients were primary income earners before TB diagnosis, household members started to work more to compensate for lost income. The total costs of TB and MDR-TB diagnosis and treatment equaled 4.6 and 24.9 months of pre-diagnosis household income.

In Indonesia, the median TB and MDR-TB patient income dropped from 134 and 103, respectively, to zero. The proportion of TB patients with no formal income increased from 29 % before diagnosis to 52 % at the time of the interview, and from 22 to 74 % for MDR-TB patients. The median household income dropped by 10 % (from USD 206 to 186) and 40 % (from USD 206 to

Table 4 The main indicators of financial impact of TB illness experienced by the (MDR) TB patients in the three countries

	Ethiopia		Indonesia		Kazakhstan	
	TB	MDR-TB	TB	MDR-TB	TB	MDR-TB
Patients who were primary income earner before TB illness	N.A.[b]	N.A.[b]	44 %	24 %	61 %	53 %
Patients who lost their job	76 %	72 %	26 %	53 %	31 %	41 %
% of patients reporting income loss due to TB	92 %	79 %	38 %	70 %	67 %	56 %
% reduction in median income *(for those reporting an income change)*	100 %	100 %	25 %	100 %	100 %	100 %
Patients hospitalized for TB	36 %	82 %	33 %	62 %	98 %	100 %
median duration of hospitalization (days)[a]	40	80	7.5	10	90	195
Patients who received assistance from government or other organizations	24 %	73 %	22 %	34 %	17 %	27 %
median value of assistance in last 3 months (USD)[c]	76	33	0	41	88	31
Coping costs						
patients who sold property	24 %	38 %	3 %	21 %	0 %	1 %
patients who took out loans	56 %	41 %	9 %	27 %	0 %	4 %
patients who received donations from family/friends	N.A.	N.A.	32 %	43 %	57 %	66 %
Patients with health insurance	0 %	1 %	22 %	25 %	0 %	1 %
Of those, patients who received reimbursements	0 %	0 %	N.A.[d]	N.A.[d]	0 %	0 %

[a]For those patients in hospitalized at time of interview, assuming hospitalization for patients during standard duration of intensive phase
[b]Not available as this question was taken out of the locally used questionnaire
[c]For Ethiopia and Kazakhstan, this includes the value of vouchers; for Indonesia it only includes cash assistance
[d]In principle, insured patients receive specified services for free. However, not all services provided are necessarily included

124), respectively. The total costs of TB and MDR-TB diagnosis and treatment equaled 0.82 and 11.4 months of pre-diagnosis household income.

In Kazakhstan, the median TB and MDR-TB patient income dropped from USD 236 and 202 USD to zero, respectively. Fifty-nine percent and 67 % of TB and MDR-TB patients, respectively, did not have any income at the time of interview, compared to 13 and 36 % before diagnosis. The median household income of TB and MDR-TB patients dropped by 20 % (from 708 to 566 USD), and 31 % (from 489 to 337 USD), respectively. As in Ethiopia, many patients were primary income earners before TB diagnosis, and household members started to work more to compensate for lost income. In Kazakhstan, the median household income dropped by 31 % both among TB and MDR-TB patients, and the total costs of TB and MDR-TB treatment equaled 2.8 and 9.3 months of median pre-diagnosis household income.

Mitigation policy options

Policy options for mitigating patient costs due to (MDR) TB were listed during national workshops with participants representing different Ministries, Universities, hospitals, non-governmental organizations (NGOs), civil society organizations (CSOs), and patients. Options related to TB service improvements prioritized in all three countries were 1) to ensure that the policy of free care for all (MDR) TB services is fully implemented and 2) that services are brought closer to patients, followed by social service improvements related to 3) inclusion of direct (transport, food support) costs in social support schemes provided through TB services, 4) inclusion of indirect (sick leave allowance) costs in social protection schemes, and 5) improvements of employment protection. Note that these recommendations are not mutually exclusive – to improve the situation of especially MDR-TB patients, it may be necessary to apply more than one strategy at the same time.

Discussion

The findings from all three countries showed that, although MDR-TB diagnosis and treatment services are supposed to be free for patients, patients have other direct and indirect costs and the financial impact was significant for most patients. For most respondents, direct and indirect costs increased while income decreased. The estimated costs of MDR-TB patient diagnosis and treatment were 3.4–13.9 times greater than those for other TB patients, mainly due to the longer time period for treatment. Aggravating this situation, MDR-TB patients more often lost their jobs.

We probably underestimated direct and indirect costs in our study. Firstly, costs for the pre-diagnosis period may have been underestimated as patients may spend a long time getting an accurate diagnosis, making full recall difficult. Secondly, for some patients treatment duration may be prolonged, e.g. due to missed doses during TB treatment or lack of culture conversion during the intensive phase of

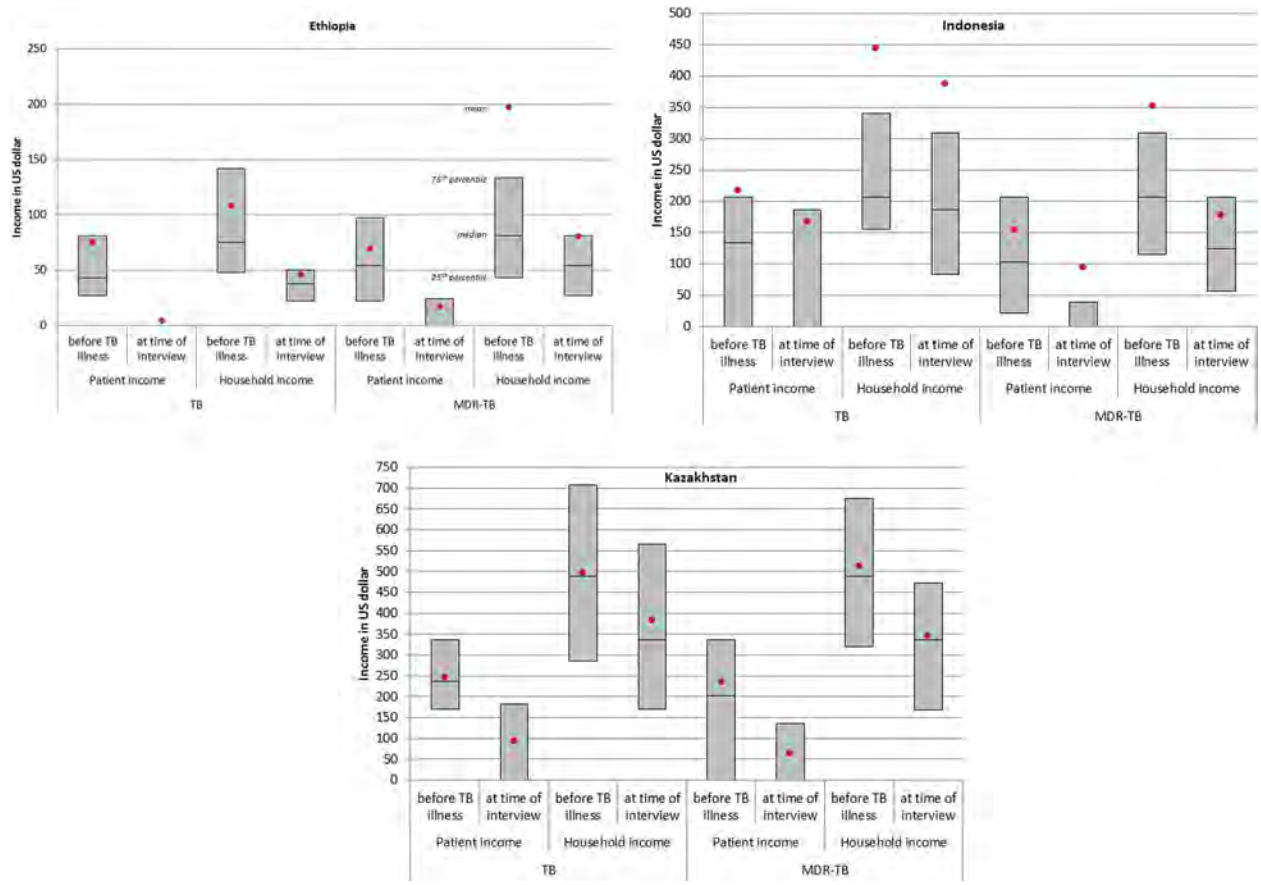

Fig. 1 Box plots showing mean, median and interquartile range of patient and household income before TB illness and at the time of the interview, stratified for TB and MDR-TB patients. Plots are provided separately for patients interviewed in Ethiopia, Indonesia and Kazakhstan. Note the different y-axis scales used. Whiskers are not included as distributions are highly skewed to high incomes, with some patients and household having an income far above the 75th percentile

MDR-TB treatment. Thirdly, we only included costs of the current treatment episode while especially MDR-TB patients may have been treated previously. Fourthly, indirect costs presented here do not include costs after the end of treatment, especially further loss of income for those who have lost their jobs or who have developed disabilities not allowing them to do the work they did before. Fifthly, loss of income was estimated only as a result of time spent obtaining diagnosis and for getting treatment. In reality, some patients may not work at all because they are not feeling well, because they lost their job, or because they are not allowed to work (i.e. in Kazakhstan). This may be the reason why we found a smaller proportion of costs incurred before TB diagnosis than the 50 % estimated in a recent systematic review [2]. That is why the updated version of the questionnaire –currently applied in several countries under leadership of WHO- also collects information on time off work. Of note, we did not discount financial assistance that patients had received. Although a substantial proportion of patients did report to receive financial assistance from the government or other organizations, the majority of patients received only incident and little to no actual reimbursements. So this would far from compensate patients' actual costs including reduced income.

This study has several other limitations. Most importantly, due to limitations in time and budget, only patients being under care at health facilities were interviewed. It was not feasible to conduct interviews to collect data from people who did not attend a facility during the period of the study. Such people may have been too poor to seek diagnosis and treatment. Among those who initiated treatment, some stopped treatment – an unknown proportion because of associated costs - or died during treatment – the impact on family income would be greatest for those households. Therefore, the study population may have been biased against the less socio-economically vulnerable groups [17]. Globally, 16 % of MDR TB patients are lost to follow-up and another 16 % die during treatment [18]. Their families lose the income of the deceased household member. A substantial but unknown proportion of patients die before accessing appropriate diagnosis and treatment.

A consequence of our study design is that we did not collect total costs of (MDR) TB treatment per patient – which would have required longitudinal follow-up - but instead extrapolated costs per stage and to the total (MDR) TB episode. Also, the study was limited to a few public health facilities in Indonesia and Kazakhstan – all three MDR-TB treatment centers in Ethiopia were included - and thus, rather than providing an estimate of the costs incurred by the average (MDR) TB patient in those countries, it does give insight into the major cost components and it provides an idea of the financial burden that a free public health program poses on its patients.

Although many patients were primary income earners before TB diagnosis in Indonesia and Kazakhstan (results not available for Ethiopia), household members started to work more to compensate for lost income. Less MDR-TB than TB patients were primary income earners and on average they earned less than TB patients; this may be explained by the fact that most already were being treated for TB at the time of MDR diagnosis.

Transport costs to reach the DOT facility may be small, but may add up to a substantial amount if made every day during ambulatory treatment. For some patients, these costs can be brought down by bringing DOT facilities closer to the patients' homes. It is important that the facility staff or community health workers do have sufficient expertise to manage MDR-TB patients, including those needed to recognize treatment failure and adverse drug reactions at an early stage to ensure patients can access clinical services when necessary and will not stop treatment [16]. Several reviews concluded that ambulatory and community-based MDR-TB models of care are equally or more effective than hospital-based models in treatment outcomes and may be more cost-effective 19–23]. However, even community-based treatment models may face high proportions of patients lost to follow-up [24] and economic support may still be required [25].

Only a few studies collected patient cost data specifically both for TB and MDR-TB patients and numbers of patients usually were small [2]. In Ecuador, average patient costs were estimated at USD 960 among 104 TB patients compared to USD 6880 for 14 MDR-TB patients [4]. In Cambodia, total household costs for eight MDR-TB patients was USD 1525 compared to USD 477 for 261 HIV-negative TB patients and USD 555 for eight HIV-positive TB patients [26]. Only in Brazil, patient costs were not very different for MDR-TB patients, although health service costs were 37 times higher: total household costs were estimated to be USD 266 for new TB patients compared to USD 333 for MDR-TB patients [27]. In the Dominican Republic, 20 out of 198 TB patients had MDR-TB. Total costs were estimated at UDS 3557 for MDR-TB patients compared to USD 908 for new patients [8]. Our study confirmed previous findings that in general MDR-TB patients face much higher costs than other TB patients as a result of longer duration of treatment, more adverse drug reactions due to the more toxic drugs used in MDR-TB treatment, and related need for (additional) hospitalization.

Policy implications

The recommendations we made were similar to the ones based on studies with the previous version of the questionnaire, not specifically including MDR-TB patients [7]: bringing services closer to patients, reducing expenditures on transport and invested time, increasing efforts to find cases early to reduce indirect costs related to inability to work, informing health care workers and the public about TB diagnosis and treatment to reduce costs unrelated to TB, and including TB-related out-patient costs in social protection schemes (Table 5 and Table 6 in Appendix). Indonesia is rapidly expanding the number of satellite sites. All three countries are moving towards outpatient care, with expansion of DOT services in primary health care services. This study shows the importance of using freed up resources from hospital-based care to support patients during treatment.

Based on results from the previous version of the tool, several countries took action to implement one or more of the identified solutions for TB patients [7]. For example, policy makers in Ghana agreed to include TB care interventions as part of its pro-poor strategies in the delivery of health care and nutrition guidelines were developed to address the specific needs of TB patients. Given the identified high burden for female TB patients in Ghana, the national tuberculosis program (NTP) focused on addressing gender-sensitive challenges of poor TB patients. Also the insurance coverage for all TB patients was increased to also cover health-related costs other than anti-tuberculosis treatment. In Vietnam, the NTP decided to increase the involvement of the private sector in public-private-mix projects focusing on reducing travel, accommodation and hospitalization costs for TB patients and guardians. Also, the NTP worked on the expansion of its NTP network to provide TB services at more public and private hospitals. In the Dominican Republic the Ministry of Health decided to move forward with allocating public funds for food supplements for TB patients and including in- and outpatient TB services in the national health insurance schemes. In Kenya, TB treatment services were decentralized, local partners were approached for sputum sample transport reduce patients' transport costs and time spent on the road, and other health programs were approached for nutritional support of TB patients. A TB and poverty subcommittee was convened to develop a comprehensive pro-poor approach within the routine TB program [9].

Table 5 Summary of policy options to mitigate (MDR) TB patients' costs considered per country

	Ethiopia	Indonesia	Kazakhstan
TB service improvements			
Ensure that policy of free care for all (MDR) TB services is fully implemented	X	X	X
Bring services closer to patients	X	X	X
Detect and treat MDR-TB cases earlier	X	X	X
Raise the awareness of health workers	X	X	X
Involve local NGO's and civil society organizations		X	X
Reduce hospitalization			X
No unnecessary or substandard tests		X	
Obligatory treatment for MDR-TB patients		X	
Social protection improvements			
Include direct (transport, food support) costs in social support schemes provided through TB services	X	X	X
Include indirect (sick leave allowance) costs in social protection schemes	X	X	X
Improve employment protection	X	X	X
Reduce stigma and acceptance of outpatient treatment	X	X	X
Increase re-socialization and employment possibilities	X	X	X
Use social health insurance	X	X	
Consistency across social assistance programs and over time	X		
Assure continuation of education			X
Involve local NGO's and civil society organizations		X	
Provide convenient lodging		X	
Empower patient groups that can support MDR-TB patients		X	

This shows that action may be taken only after studies can show policy makers what the issues are.

Both in Ethiopia and Indonesia, a considerable proportion of MDR-TB patients may not start treatment after diagnosis and another considerable proportion is lost to follow-up before completion of treatment. We do not know in how far economic consequences are a key reason for this but they may be a relevant contributor. In Ethiopia as many as 29 % of patients diagnosed with MDR-TB may not have started second-line drug treatment and 3 % are lost to follow-up during treatment (unpublished data: Ministry of Health progress report to the Green Light Committee, April 2013). In Indonesia around one-third of diagnosed MDR-TB patients is not started on MDR-TB treatment, whereas up to one-third of those starting treatment is lost to follow-up during treatment (unpublished NTP data, Indonesia).

Treatment cost data were collected during a single interview and extrapolated over the treatment phase the patient was in during the interview, i.e. intensive or continuation phase. As costs were estimated per treatment phase and not per patient, it means that this study did not yield total costs of (MDR) TB treatment incurred per patient. To give an idea of the costs of a total episode of (MDR) TB, we did add median costs per stage, thus assuming that patients interviewed per stage were representative of all patients. These summed medians must therefore be interpreted as crude estimates, meant to indicate what were the main cost drivers. With this cross-sectional method we were able to capture the major cost components in a relatively short timeframe. Capturing the total costs per patient requires follow-up of a sample of patients during their treatment, which may take more than 2 years for MDR-TB patients and takes at least 6 months for TB patients. To get an exact estimate of total costs incurred, other methods than (repeated) interviews would have been required, such as patient diaries. However, it is known that it is difficult to motivate patients to keep diaries for a longer time period and this may lead to selective dropout of the less well educated and socially engaged patients.

Conclusions

In conclusion, while the financial burden of MDR-TB patients was (much) higher than that of TB patients in all three countries, all patients experienced substantial socioeconomic impact of TB disease, most importantly due to inability to work and job loss. If the patient is the breadwinner of the family, the combination of lost income and extra costs generally is catastrophic. A too high financial burden may cause patients to not get diagnosed, to not start treatment, or to stop treatment, leading to prolonged transmission of the disease to others. Patients stopping treatment as soon as they feel better may need retreatment, which is more expensive, takes longer and is more toxic than initial treatment. Therefore, it should be a priority of governments to relieve the financial burden especially for MDR-TB patients. The cost mitigation options in all three countries should be used to prepare an action plan for mitigating patient costs under the guidance of NTP, indicating main stakeholders, and with whom, how and when the option can be worked out into a strategy, and when and how this strategy can be implemented. However, the effectiveness of such strategies will depend on the countries' willingness and ability to address these problems.

Appendix

Table 6 Policy options to mitigate (MDR)TB patients' costs considered per country (expansion of Table 5 in manuscript)

	Ethiopia	Indonesia	Kazakhstan
TB service improvements			
Ensure that policy of free care for all (MDR) TB services is fully implemented. Agreements need to be in place so that presumed TB patients can make use of the necessary diagnostic tools for free.	X	X	X
Bring services closer to patients. Further decentralization should reduce patient expenditures on transport and patient time and should reduce detection and treatment delays, especially for MDR-TB patients. For areas where there is no public transport, transport for patients or home visits should be arranged. This includes improving downward referral from national or provincial MDR-TB treatment centers to local community health centers.	X	X	X
Detect and treat MDR-TB cases earlier. Especially detection of drug-resistant TB should reduce the time to appropriate treatment, and thus reduce direct and indirect treatment costs for patients, especially the amount of income lost due to inability to work during initial first-line drug treatment. Full implementation of new diagnostics such as Xpert MTB/RIF should reduce time to diagnosis and thus patient costs.	X	X	X
Raise the awareness of health workers. Provide education and training of primary level health workers to recognize suspects and ensure speedy diagnosis, and to follow up on cases and contact tracing.	X	X	X
Involve local NGO's and civil society organizations to support patients and hereby improve (MDR) TB treatment adherence.		X	X
Reduce hospitalization. Kazakhstan has moved in recent years from full in-patient treatment to partial outpatient treatment, usually in the continuation phase. The country plans to move towards full outpatient care. This has the potential to greatly reduce indirect patient costs.			X
No unnecessary or substandard tests. Sometimes, tests are being prescribed by physicians that are not needed (e.g., X-ray for diagnosis of smear-positive TB patients). Private laboratories sometimes use substandard tests (e.g., IS*6110* based PCR for detection of *Mycobacterium tuberculosis*) and serological tests. Such tests are not only unnecessary, but also may importantly increase the costs of (MDR) TB diagnosis.		X	
Obligatory treatment for MDR-TB patients may be needed in parts of the country where a large proportion of MDR-TB patients refuses MDR-TB treatment, due to lack of knowledge or support, to protect the community against the spread of MDR-TB. MDR-TB patients may fear the costs and side effects related to MDR-TB treatment. Patient education, installation of patient organizations (as is starting up now in different hospitals), and provision of living allowances may help to remove some of these obstacles.		X	
Social protection improvements			
Include direct (transport, food support) costs in social support schemes provided through TB services. Such incentives and enablers should reduce direct costs associated with TB treatment and improve treatment adherence.	X	X	X
Include indirect (sick leave allowance) costs in social protection schemes. Review, standardize and expand current social protection mechanisms and schemes by the government. Social protection schemes, including temporary disability allowances, should be made available to those (MDR) TB patients who need it, from the moment they are diagnosed. Include social protection for (MDR) TB under disability policy strategies while ensuring that the protection is provided from the time of confirmed diagnosis to those who are at risk of becoming poor or not seeking or completing treatment. Professional guidance by health care workers or social workers for submitting applications for social support is needed for many patients. Possibilities for agreements on delaying or waiving payments (e.g. mortgage loans, school fees) are to be investigated.	X	X	X
Improve employment protection. Advocate for regulations and policies that mandate that both public and private employers pay employees (a portion of) their salary while they are unable to work. Also advocate for patients to be able to return to previous positions once they are fully cured and clinically fit to perform their assignments.	X	X	X
Reduce stigma and acceptance of outpatient treatment. Improve education to the public on TB and MDR-TB, e.g. through primary level services, in order to reduce stigma of (MDR) TB and reduce fear of transmission during outpatient treatment.	X	X	X
Increase re-socialization and employment possibilities. Develop mechanisms to involve socially vulnerable patients in different re-socialization activities provided e.g. through temporary, assisted living facilities. Develop mechanisms to involve patients in income generating activities and advocate government to support this, for example through microfinance.	X	X	X

Table 6 Policy options to mitigate (MDR)TB patients' costs considered per country (expansion of Table 5 in manuscript) *(Continued)*

Use social health insurance. Advocate with government to incorporate TB services in the future social health insurance system to provide sustainable financing. Also advocate for social protection to be included in the benefits package on the grounds that this will reduce severity of illness and transmission and thus save on treatment costs.	X	X	
Consistency across social assistance programs and over time. The data collected on vouchers indicates that the amounts provided are very low compared with the patient costs and taking into account reductions in income. In addition there may be inconsistency in the amounts provided across facilities and over time. It is recommended that the government develops a standard.	X		
Assure continuation of education. When rendered non-infectious, children and students need to be able to continue their education.			X
Involve local NGO's and civil society organizations and empower community health workers in provision of (MDR) TB drugs to improve (MDR) TB treatment adherence, since this will increase the population that can be targeted.		X	
Provide convenient lodging to those MDR-TB patients who cannot travel back and forth for receiving DOT. Since MDR-TB treatment roll out is still ongoing distances that MDR-TB patients have to travel for receiving DOT can be long in Indonesia and this may mean that patients need to move to a shelter close to the PMDT site. It is expected that the number of patients needing such housing will decrease with the roll out of the PMDT program.		X	
Empower patient groups that can support MDR-TB patients in a practical way during MDR-TB treatment. Being a new development in Indonesia, MDR-TB peer educator groups are being set up by ex MDR-TB patients. MDR-TB patient support groups provide information to MDR-TB patients regarding side effects, reimbursements systems, etc., and thus serve as a valuable and easily accessible information point to MDR-TB patients.		X	

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Availability of data and materials
The datasets supporting the conclusions of this article are available on request from the authors.

Authors' contributions
SvdH, DC and ET designed and coordinated the study, supervised data collection, performed the statistical analysis, and drafted the manuscript. FH, DB, and AT supported the design, coordinated the data collection in their respective countries and helped to revise the draft manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
Ethics approval was sought and received from Armauer Hansen Research Institute (AHRI)/ALERT ethics review committee in Ethiopia, the institutional review board of Gadjah Mada University in Yogyakarta and the ethical review boards of Persahabatan and Dr Moewardi hospital in Indonesia, and the National Center for Problems of Tuberculosis and the Akmola oblast tuberculosis dispensary in Kazakhstan. Written informed consent was obtained before patients were interviewed. The interviewers wore N95 respirators when interviewing smear-positive TB patients and culture-positive MDR-TB patients. Interviews were done in separate rooms to ensure confidentiality, or outside if such a room was (temporarily) not available. In Indonesia, patients received a free hygiene kit after the interviews. Data were stored and analyzed without personal identifiers.

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RESEARCH ARTICLE

The Effects of Psycho-Emotional and Socio-Economic Support for Tuberculosis Patients on Treatment Adherence and Treatment Outcomes – A Systematic Review and Meta-Analysis

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Abstract

Background

There is uncertainty about the contribution that social support interventions (SSI) can have in mitigating the personal, social and economic costs of tuberculosis (TB) treatment on patients, and improving treatment outcomes.

Objective

To identify psycho-emotional (PE) and socio-economic (SE) interventions provided to TB patients and to assess the effects of these interventions on treatment adherence and treatment outcomes.

Search strategy

We searched PubMed and Embase from 1 January 1990–15 March 2015 and abstracts of the Union World Conference on Lung Health from 2010–2014 for studies reporting TB treatment adherence and treatment outcomes following SSI.

Selection criteria

Studies measuring the effects of PE or SE interventions on TB treatment adherence, treatment outcomes, and/or financial burden.

Data collection and analysis

Two reviewers independently assessed titles and abstracts for inclusion of articles. One reviewer reviewed full text articles and the reference list of selected studies. A second reviewer double checked all extracted information against the articles.

reflect the views of USAID or the United States Government. The funder was not involved in conception of the study, study design, data collection and analysis and preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

Main results

Twenty-five studies were included in the qualitative analysis; of which eighteen were included in the meta-analysis. Effects were pooled from 11 Randomized Controlled Trials (RCTs), including 9,655 participants with active TB. Meta-analysis showed that PE support (RR 1.37; CI 1.08–1.73), SE support (RR 1.08; CI 1.03–1.13) and combined PE and SE support (RR 1.17; CI 1.12–1.22) were associated with a significant improvement of successful treatment outcomes. Also PE support, SE support and a combination of these types of support were associated with reductions in unsuccessful treatment outcomes (PE: RR 0.46; CI 0.22–0.96, SE: RR 0.78; CI 0.69–0.88 and Combined PE and SE: RR 0.42; CI 0.23–0.75). Evidence on the effect of PE and SE interventions on treatment adherence were not meta-analysed because the interventions were too heterogeneous to pool. No evidence was found to show whether SE reduced the financial burden for TB patients.

Discussion and Conclusions

Our review and meta-analysis concluded that PE and SE interventions are associated with beneficial effects on TB treatment outcomes. However, the quality of evidence is very low and future well-designed evaluation studies are needed.

Background

In 2013, 9 million people developed TB and 1.5 million died from this disease [1,2]. TB is the most common cause of death in people with HIV [1]. The treatment duration for TB is long, at least 6 months for drug-susceptible TB and 18–24 months for multidrug-resistant tuberculosis (MDR-TB) that does not respond to the two most effective anti-TB drugs isoniazid and rifampicin. The long treatment, adverse drug reactions during treatment, stigma and financial burden of TB contribute to non-adherence to treatment and unsuccessful treatment outcomes [3–8]. In addition, ensuring patient adherence to treatment through facility-based directly observed therapy (DOT) competes with work related priorities of patients, adding to the financial burden coming from out-of-pocket and indirect costs related to treatment [7,9], even though anti-TB drugs are provided free of charge in most countries [1,10]. The quick improvement of TB symptoms early in treatment also contributes to patients' stopping treatment prematurely (i.e. loss to follow-up) as competing interests take priority [9,11]. Poor treatment adherence and loss to follow-up increase morbidity, mortality, and the risk of drug resistance development, and can lead to prolonged transmission of TB [12–17].

Adherence to tuberculosis treatment improves the chance of cure and reduces acquisition of drug resistance and ongoing transmission of TB. The use of DOT through a patient-centered approach, which often requires enablers, is recommended to encourage adherence to TB treatment [18,19]. In some settings and circumstances, incentives alone or in addition to enablers are used to motivate patients to adhere to and complete their full course of treatment [9,16,20–22]. Social support through various educational, emotional, and/or material (in-kind or services) interventions are being provided by numerous TB programmes to remove or alleviate barriers to treatment adherence [9,20,23–25], including the financial burden associated with TB illness and its treatment. Despite the fact that different types of social support interventions (SSI) are implemented, countries still struggle to develop systems that are able to provide SSI in an efficient, effective and sustainable way [26]. WHO guidelines for the programmatic

management of drug resistant TB and the new End TB Strategy recommend the use of SSI in TB patients, though WHO has not yet systematically assessed the evidence to support such a recommendation [2,19,27]. Hence, a systematic review of relevant literature on the effects of SSI on TB treatment adherence, treatment outcomes, and financial burden will be informative for national and global policy making.

The primary aim of this systematic review was to identify SSI provided to TB and MDR-TB patients and assess the evidence of their effects on treatment adherence, treatment outcomes and financial burden related to TB illness. The secondary aim was to describe the funding sources for and ownership of local organizations in the identified interventions.

Methods

This review followed standard methods as defined by the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [28,29]. The PRISMA checklist is enclosed in the supporting information (S1 PRISMA Checklist).

Literature search

In this review we searched for two main categories of SSI, namely PE support and SE support. PE support includes both emotional support through psychological interventions (e.g. counseling by health care workers) and companionship support through provision of help for patients to participate in a social network (e.g. peer counseling for patients and their support network) [19]. We did not consider interventions aimed only at providing improved information or education to TB patients, given the recent systematic review showing a lack of evidence related to TB treatment [17]. In addition, reminder systems were not considered social support interventions [30]. SE support entails delivering services, material goods and/or financial assistance [19,31,32]. Financial assistance was categorized according to Richter et al. [7] as"direct transfers of money, such as cash paid as part of a social security system or a program incentive, transport reimbursements, treatment allowances, and the like that are paid directly to affected individuals". Indirect assistance was defined as: "indirect transfers through, for example, food packages or vouchers, travel vouchers, and payment of health insurance for individuals, households or families". Some forms of indirect assistance may also be converted into cash. We included tax exemption under indirect assistance. Enterprise assistance was defined as"training programs or microcredit that aim to assist individuals or families to generate income" [7]. We searched for studies assessing the effects of socio-economic and/or psycho-emotional interventions on treatment adherence and/or treatment outcomes and/or financial burden. The study population consisted of patients initiated on anti-TB treatment, including treatment for MDR-TB.

Outcome measures

Treatment adherence, treatment outcomes and financial burden were considered as the primary outcome measures. Adherence was calculated as the percentage of prescribed doses actually taken. Treatment outcomes were defined according to WHO definitions, where cure and completed treatment are defined as successful treatment outcomes [1]. Unsuccessful treatment outcomes for active TB treatment included death, treatment failure and loss to follow-up (previously named default). Patients with transfer-out or missing treatment outcomes were excluded from the analysis. As timing of loss to follow-up per individual was not available for studies reporting on treatment outcomes but not treatment adherence, for these studies loss to follow-up was not included in calculation of treatment adherence. Financial burden was

reported according to the definitions used in the individual studies. We also extracted information about how the SSI were financed and organized.

Search strategy

We systematically searched PubMed and Embase for primary articles and reviews reporting on SSI and tuberculosis treatment for human subjects, published from 01 January 1990–15 March 2015, on the grounds that relevant old information would emerge from previous reviews and references lists. We reviewed the reference lists of identified articles, editorials and reviews. Additionally, we hand searched the 2010–2014 abstract books of the Union World Conference on Lung Health to identify recent studies that were not published in the literature yet. Databases were searched using the full text search strategy as described in S1 Web annex. We contacted authors when we were not able to extract required information from the identified publication on the SSI provided and its effects.

Eligibility criteria

Eligibility of studies was based on predetermined inclusion criteria. Original studies including a description of SSI had to be in place, as well as an evaluation of the association of SSI on treatment adherence, treatment outcome and/or financial burden. This was evaluated either by means of a comparison between outcomes of an intervention group and a group receiving standard support (which could be none or a more limited package), or by means of a comparison of the occurrence of interventions in those with positive and negative outcomes (case-control studies). The search strategy was restricted to certain languages including publications in Dutch, English, French, German, Portuguese, Russian and Spanish. No age restriction was applied. We chose not to exclude studies that did not provide DOT to their patients as there is no hard evidence that DOT in a strict sense (i.e. direct observation of medication ingestion) without the DOT provider supporting the patient through education and counseling improves treatment outcome under programmatic conditions [22,33].

Data collection and analysis

Selection of studies and data extraction. One reviewer conducted the literature search (RH) based on the search strategy developed by all authors. Subsequently, two reviewers (SH, RH) independently examined titles and abstracts retrieved by the search. One reviewer (RH) reviewed full texts and the reference lists of selected articles, and extracted study data, which were then verified by a second reviewer (SH). For data extraction and management, a pre-piloted form was developed to list study characteristics including: study design and study aim, type(s) of patients, type(s) of TB treatment, descriptions of intervention and control group, descriptions of intervention and routine support, coverage of patients that received the intervention, results of the intervention and control group and differences between these groups. Duplicate publications of included studies were taken into account if they provided additional information. When disagreements occurred, a third independent reviewer was consulted and discrepancies were resolved by consensus among the three.

Risk of bias and quality of evidence. Risk of bias was assessed separately for Randomized Controlled Trial (RCTs) and Non Randomized Studies (NRS). We used the Newcastle Ottawa Scale for NRS [34] and The Cochrane Collaboration's Tool for RCTs [35]. Furthermore, an additional assessment was made for Cluster Randomized Trials on recruitment bias, baseline imbalance and loss of clusters [36]. For NRS, we considered $<10\%$ of subjects lost as indicative of low risk of bias. The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool [37–40].

Data analysis. All SSI were described, irrespective of inclusion in the meta-analysis. We analyzed the dichotomous outcomes using Risk Ratios (RR) for RCTs and cohort studies, and Odds Ratios (OR) for case-control studies, together with corresponding 95% confidence intervals. Ratios were (re)calculated from the data provided in the publications. Subsequently, the (calculated) intervention effects were combined in the meta-analysis. Studies were assessed on clinical diversity (e.g. differences in patient spectrum, type and dose of treatment) and methodological diversity (e.g. differences in methods: blinding of patients, concealment and randomization). Additionally, (statistical) heterogeneity was examined with the I^2 test along with the visual assessment of the forest plots [28,41]. An I^2 of 0–40% was considered as low heterogeneity, 30–60% was defined as moderate heterogeneity, 50–90% substantial heterogeneity and 75–100% as high heterogeneity [42]. Furthermore, the I^2 was interpreted along with the directions and magnitudes of the different studies observed in the forest plots. A p-value for the Chi^2 test of ≤ 0.10 was considered as a cut-off point for statistically significant heterogeneity. In case of statistically significant heterogeneity, sensitivity analysis were performed based on patient type (e.g. MDR-TB or not) and risk of bias (e.g. low vs. high risk of bias)[42]. Funnel plots were created to assess for publication bias. To execute the meta-analysis, a random effects model was used, considering the diversity in participants (e.g., susceptible TB-patients and MDR-patients) and interventions (e.g. self-help groups and counseling). The DerSimonian Laird method is based on the inverse-variance approach [42]. Due to the potential heterogeneity of the interventions (PE support, SE support and combined PE and SE support) also stratified analyses were performed [43]. Stata (STATA/SE 13.1) was used to perform the meta-analysis. To visualize the risk of bias assessment, Review Manager (Review Manager (RevMan) 5.3, The Nordic Cochrane Centre, Copenhagen) was used.

Results

In total, we identified 2443 articles. After removal of 694 duplicates, two reviewers screened titles and abstracts of the 1752 citations. Twenty-five articles were eligible for inclusion in the description of included studies (Fig 1).

Description of included studies

Fourteen NRS and eleven RCTs were included in the description of interventions from 15 different countries. Study populations ranged from 46 to 4,091 participants. Eight studies included both children and adults [44–51]. Three studies explicitly included adults [52–54]. For the other studies the age range was not reported, however mean age was provided frequently [20,55–64]. Most studies were conducted in middle income countries, 9 in upper middle income countries and 7 in lower middle income countries [65]. Six studies were performed in high income countries and the remaining three studies in low income countries. Eleven studies provided SE support only, seven studies provided only PE support, while the remaining seven studies provided a combination of PE and SE support [44,52,56,57,61,66,67] (Table 1). Table 2 includes a comprehensive summary of studies including the frequency of the intervention provided and sustainability of the below described interventions.

Psycho-emotional support. Seven studies provided counseling, exclusively [46,53] or in combination with other PE and or SE interventions [44,51,52,61,67]. The scope of the additional interventions varied from food supplementation [44] combined with home visits [67], direct economic support constituted after an exploratory quality study [52], cash coupons at every monthly visit and at the end of treatment [61], arrangement of a self-chosen treatment supporter [51]. See Table 2 for details.

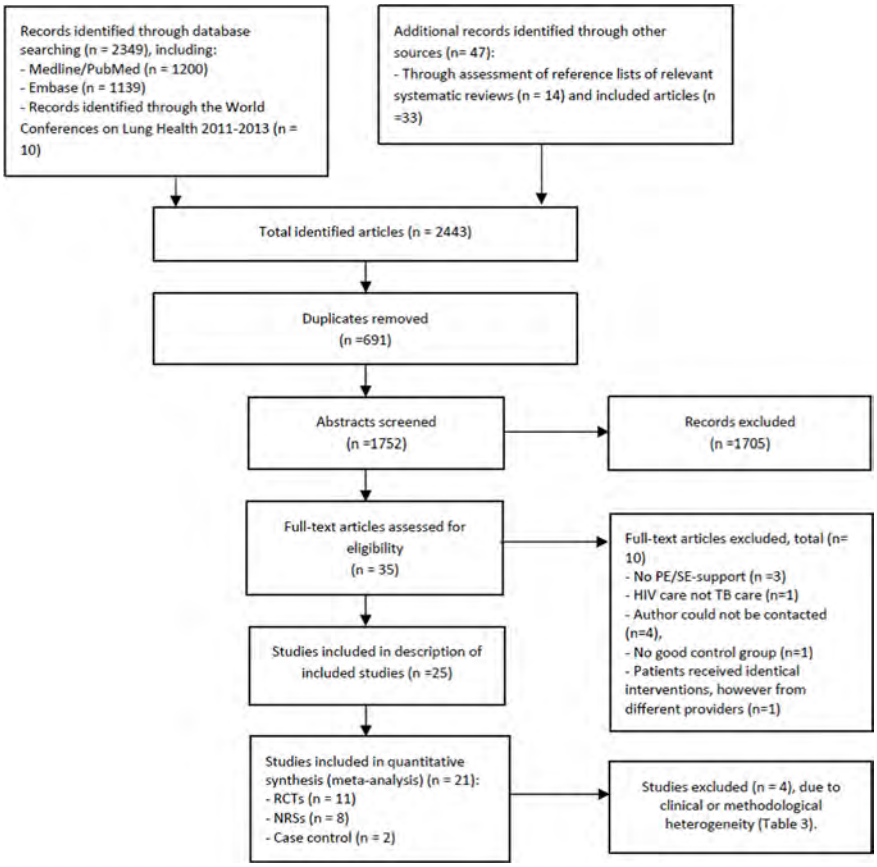

Fig 1. Flow diagram for review and meta-analysis.

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Furthermore, 2 studies organized self-help groups [50,59], one of these studies along with stigma reduction and home visits [59]. TB clubs were raised in the form of self-help groups in combination with support to reduce stigma and home visits to get insight in the social network of the patients and to plan activities to support the patient [59]. In the second study, the patients could choose the number of meetings and the topics discussed [50]. Another 6 studies arranged home visits together with other interventions [51,57,59,66–68].

Socio-economic support. Eight studies provided food supplementation consisting of fresh food supplies [58,60], hot meals [44] and/or food packages [44,45,49,54,60,67,68]. Four of them exclusively provided food supplementation [45,49,58,60]. Other studies also provided food supplementation, in combination with direct economic support and/or other material support through provision of e.g. clothing and legal support [44], assistance in providing documentation for health care access and social security [54], or establishing a supportive social network of organizations that could provide support to the local community, such as public day care centers and employment agencies [68]. One study additionally provided PE support [67].

Four studies provided indirect economic support including food and transport vouchers [20,47,56,61]. Coupons varying from 5 to 15 US$ were given when attending each appointment or at drug collection each month. Some studies provided additional coupons varying from 40 to 60 US$ after completion of 3 months of treatment or at the end of treatment [56,61]. Seven studies granted direct economic support, mainly financial support varying from 19 to 240 US$

Table 1. Overview on types of support and inclusion in the quantitative analysis.

	Counseling	Self-help groups	Stigma reduction	Psychotherapy	Involvement of a treatment supporter	Home visits	Other psycho-emotional support	Food supplementation	Other material support	Direct economic support	Indirect economic support	Included in quantitative analysis?
	PSYCHO-EMOTIONAL SUPPORT							SOCIO-ECONOMIC SUPPORT				
Non-Randomized Studies												
Bock et al. 2001 [20]											X	
Cantalice Filho 2009 [45]								X				**X**
Davidson et al. 2000 [56]											X	
Farmer et al. 1991 [57]						X				X		**X**
Finlay et al. 2012 [53]	X											**X**
Garden et al. 2013 [54]								X	X			**X**
Gelmanova et al. 2011 [66]						X	X		X			
Jakubowiak et al. 2007 [44]	X							X	X	X		**X**
Lu et al. 2013 [48]										X		**X**
Macq et al. 2008 [59]		X	X		X	X						**X**
Soares et al. 2013 [68]						X		X	X			
Sripad et al. 2014 [62]										X		**X**
Wei et al. 2012 [63]										X		
Zou et al. 2013 [64]										X		**X**
Randomized Controlled Trials												
Alvarez et al. 2003 [50]		X										**X**
Baral et al .2014 [52]	X									X		**X**
Drabo et al. 2009 [67]	X					X		X				**X**
Jahnavi & Sudha 2010 [58]								X				**X**
Janmeja et al. 2005 [55]				X								**X**
Liefooghe et al. 1999 [46]	X											**X**
Lutge et al. 2013 [47]											X	**X**
Martins et al. 2009 [60]								X				**X**
Morisky et al. 1990 [61]	X										X	**X**
Sudarsanam et al. 2011 [49]								X				**X**
Thiam et al. 2007 [51]	X				X	X						**X**

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Table 2. Summary table for all studies included in the qualitative analysis.

Study	Country income*	Study type	Enrolment period	N*	Population	Comparison	Intervention(s)	Funding source and organization	Outcome(s)	Other
Alvarez Gordillo et al. 2003 [50]	Chiapas, Mexico,UMIC.	Parallel cluster-randomized study (23 intervention and 25 control health centers).	Febr 2001-Jan 2002.	87 (I: 44, C: 43).	Smear positive pulmonary TB patients 15–89 years, 51% male. Patients with documented resistance were excluded.	Self-help groups vs no support.	Self-help groups. Monthly meetings under coordination of doctors from the specific health unit where the patients received treatment.	Funded by the System Research Benito Juárez, System SEP / CONACYT of Oaxaca, Mexico.	Adherence, defined as Minimal 75% of prescribed dosages taken; treatment completion was defined as 100% of the dosages taken; cure according to the WHO definitions.	Patients could choose the number of meetings and the topics discussed. The health personnel (staff doctors, nurses and social health workers) were trained; they had 6 multidisciplinary workshop days in total. Topics discussed: health, social-economic and cultural aspects of tuberculosis. Theory and practice of diagnosis and treatment of TB and formation of self-help groups.
Baral et al. 2014 [52]	Kathmandu Valley, Nepal, LIC.	Parallel cluster-randomized study.	Jan-Dec 2008.	156 (I1: 33, I2; 42, C: 81).	MDR-TB patients. 83% 21–60 years; 65% male.	1) Counseling only 2) counseling and financial support vs 3) usual care. 7 DOTS plus centers (3:2:2).	1) Counselling on individual level and in small groups, every 2–3 weeks. Or 2) counselling on individual level and in small groups, every 2–3 weeks and US$ 28 per month meant to cover local transport, food and rental costs, but free to use as they chose.	Funded by UK Aid from DFID. Patients receiving financial support were given Nepali Rupees (NRs) 2000 (US$ 28) per month.	Cure, as internationally defined (treatment success).	The intervention was designed after exploratory qualitative study. No adequate sample size calculation (not taking into account clustering), and sample size was smaller than anticipated (partially compensated by including larger number of control patients).
Bock et al. 2001 [20]	Fulton County, Georgia, USA, HIC.	Historically controlled study.	I: Nov 1996—Oct 1997; C: April 1995 -March 1996.	107 (I: 55, C: 52).	TB patients who demonstrated non-adherence by missing at least 25% of DOT doses over a 4-week period. Mean age: 36–38 years; 58% male; HIV infected 34%; alcohol or injection or non-injection drug abusers 56%. Patients, who died, transferred out, lost or uncooperative, were excluded.	Incentive program vs historical controls in the same county. =, who would have been eligible for the incentive under the incentive program.	A coupon redeemable for five dollars in merchandise at a regional chain of grocery stores was given to the patient (or parent/guardian) at each DOT and physician appointment after enrolment. Frequency is unknown.	Partial funding was provided by the Georgia Chapter of the American Lung Association. The cost of incentives for 55 patients was approximately US$ 10.000, less than the cost of treating 1 TB case.	Treatment completion, not defined.	.
Cantalice Filho 2009 [45]	Duque de Caxias, Brazil, UMIC.	Historically controlled study	I:2004 –Jul 2006; C: Sept 2001 – Dec 2003	142 (I: 74, C: 68)	TB patients > 15 years old with confirmed TB. Mean age: 37 years; 59% male; 20% patients with a history of TB; 2% HIV positive.	Treatment and provision of food baskets vs treatment only. Historical controls.	Provision of food baskets on a monthly basis (non-perishable food, the content of the food baskets was not further described).	Funding source is not reported.	Cure, loss-to-follow up, failure and death are not defined.	.
Davidson et al. 2000 [56]	New York City, United States of America, HIC.	Case-control study.	Oct 1992—March 1996.	365 (Cases: 147, controls: 218).	TB patients. Mean age: 40 years; 75% male. 84% were currently unemployed, 74% had no income at the time of the study. 58% was in prison in the past year.	Adherent (attending 80% of the prescribed visits) vs non-adherent patients. Comparison within the same time range. From 6 DOT programs from different city-districts.	10 subway tokens (cash value 15 US$) for attendance at all scheduled appointments each week throughout the course of treatment. Later it changed to 20 tokens a month (cash value 30 US $) at the end of each of the first 2 months and a bonus of 40 tokens at the end of the 3rd month. The 3-month cycles were repeated until treatment ended.	Funded by grants from the Aaron Diamond Foundation and the New York State Department of Health.	Adherence, defined according to a 1990 USPHS report that has been widely cited as a standard for TB treatment. Patients were considered adherent if they attended 80% of their prescribed visits every month of their treatment during the study period.	Not clear what the coverage of support was in the adherent and non-adherent group.

(*Continued*)

Table 2. (*Continued*)

Study	Country income*	Study type	Enrolment period	N*	Population	Comparison	Intervention(s)	Funding source and organization	Outcome(s)	Other
Drabo et al. 2009 [67]	Burkina Faso, LIC.	Parallel cluster-randomized study	Oct 2005-Dec 2007.	333 (I: 178, C: 155).	Smear positive TB patients, further characteristics unknown.	3 intervention vs 3 control districts.	Community groups were raised. Material (food), home visits and psychosocial support was provided to patients. Support was partially provided when needed and educational information was given to the community.	The organizational costs for support committees were included in the annual budgets of respective health districts.	Loss to follow-up, cure and death are not defined.	The community group included 14 people. 2–3 traditional healers, 2 former TB patients, 1–2 community health care workers, 3–4 religious leaders, 2–3 people from community associations and 2 nurses.
Farmer et al. 1991 [57]	Haiti's central plateau, Haiti, LIC.	Non-randomized controlled study.	Febr 1989—June 1990.	60 (I: 30, C: 30).	(Extra) pulmonary TB (mostly rural) patients. Mean age: 45 years; 33% male; 5% HIV infected patients.	Intervention vs free usual medical care, comparison within the same time frame. Two districts geographically distinct, but are contiguous to each other.	Daily home visits during first month and-, a monthly reminder for clinic visits by the community health worker, and no-show home visits by clinic staff, for food supplements 30 US$ per month for the first 3 months and 5 US$ for travel expenses per month.	Funding source is not reported., however, support was organized by 'Proje Veye Sant'.	Cure: negative sputum smear at the end of treatment (treatment success).	Other support: nutritional supplementation.
Finlay et al. 2012 [53]	8 out of 9 provinces, South Africa, UMIC.	Case-control study.	Jan 1—Dec 31 2002.	1164 (I: 232, C: 932).	TB patients > 18 years old from facility-based national TB registers. HIV rate is unknown. Median age new cases, I: 30 years C: 34 years; median age re-treatment patients, I: 33 C: 39; 58% male.	Patients that were lost to follow-up vs patients that cured, completed or failed treatment. Comparison within a similar time range and geographical location.	Given adequate counselling or information.	Funding source is not reported.	Loss to follow-up is defined as interrupting treatment for two or more consecutive months during treatment.	Also information on TB treatment was measured. Sample selection was conducted by multistage sampling of urban and rural sub-samples.
Garden et al. 2012 [54]	Saint Petersburg, Russia, HIC.	Non-randomized controlled study.	I: 2001–2004, C: 1998–1999.	518 (I:142, C:376).	Homeless TB patients. Age range 23–70. 94% male; 77% has been treated previously for TB; 45% was registered as alcoholics and for 38% no information on this topic was available.	Intervention vs historical controls (no DOT was provided to the controls).	Food incentives, and assistance in providing documentation for health care access and social security	Two Swedish governmental organizations (Swedish East Europe Committee (SEEC) and the Swedish International Development Cooperation Agency (SIDA): Stockholm Sweden).	Loss to follow-up is defined as: when not turning up at the dispensary during three consecutive days. Completion: not interrupting treatment.	.
Gelmanova et al. 2011 [66]	Tomsk City, metropolitan region, Russian Federation, HIC.	Case series (uncontrolled longitudinal study).	17 Dec 2006–30 Nov 2008.	46.	TB patients that participated in at least one intervention to improve adherence before referral to the Sputnik program.68% aged < 38 years; 76% male, 79% was unemployed, 83% had chronic alcoholism, and 72% had MDR-TB.	Before and after the referral to Sputnik's program. Participants came from all over the Tomsk City region.	More attention and care by health staff, psychological and social assistance (e.g. clothing and assistance with procuring documentation required to access state social service).	Funding source is unknown. The 'Sputnik' program was implemented as a joint program by the Tomsk Oblast Tuberculosis Services (TOTBS) and Partners in Health (PIH).	Adherence: the proportion of doses taken over the total prescribed. Loss to follow-up if they missed all doses for 2 consecutive months. Cure, death and failure according to international consensus definitions	Sputnik' has a high nurse to patient ratio (2:15), more staff time per patient, provision of cellular telephones to nursing staff (which increases flexibility and easier access to specialists and expanded social and psychological support). Program nurses had training on how to care for patients facing myriad bio-social challenges).

(*Continued*)

Table 2. (*Continued*)

Study	Country income*	Study type	Enrolment period	N*	Population	Comparison	Intervention(s)	Funding source and organization	Outcome(s)	Other
Jahnavi& Sudha 2010 [58]	16, villages in India, LMIC	Randomized controlled study.	Aug–Dec 2005	100 (I: 50, C: 50)	TB cases, culture or sputum positive; BMI < 20. 89% aged 18–65 years old; mean age 37; 74% male; Patient with HIV, DM or other severe underlying diseases were excluded.	Food supplementation and dietary plan vs only general advice and instructions to increase food intake.	Advice on dietary intake with locally available foods was provided to the patient, to meet the target intake of 35 kcal /day/kg body weight. Every day, the patients also received sweet balls made from wheat flour, caramel, groundnuts and vegetable ghee (6 grams protein and 600 kcal of energy), and 100 grams of sprouted grams and nuts for vitamins and minerals), to be consumed in presence of community worker.	Funded by the Padova University, Italy.	Cure: when initially smear-positive who completed treatment had negative smear results on at least two occasions. Completed: When an initially smear-negative patient received the full course of treatment. Death: patients who died during the course of the treatment regardless of the cause.	The community worker ensured that these supplements were collected and distributed to the patients, and consumed.
Jakubowiak et al. 2007 [44]	Six different regions, Russian Federation, HIC.	Case-control study.	March-Sept 2003.	1527 (I: 1444, C: 84)	New pulmonary smear positive and smear-negative TB patients 16–86 years old. Mean age: 43 years; 73% male; 37% was unemployed; 13% imprisonment history; 24% alcohol abuse.	Success vs default, measured in the same time range, from six different regions.	Varying daily to monthly social and economic support (cost 5–30 US$ per package provided): protein food parcels, food supplementation, hot meal, hygiene kits, clothing and/or footwear, newspapers, board games, reimbursement of travel, legal support, household goods on treatment completion. Psychological support (counselling).	Funded by the WHO, IFRC and local authorities. Now already 20 regions are implementing joint social support programs to motivate patients to adhere to treatment.	Treatment success and loss to follow up are according to the WHO definitions.	Social support was organized and implemented by regional TB services, social welfare services, and the local International Federation of the Red Cross and Crescent Societies (IFRC). The support differed intensely per region. 43.3% of the success group did not received social support. 12.1% of the lost to follow-up group received social support
Janmeja et al. 2005 [55]	Chandigarh, India, LMIC.	Non-randomized controlled study.	2001	200 (I: 100, C: 100)	Confirmed new adult cases of pulmonary and extra pulmonary TB patients. Mean age approximately 31 years; 75% male; 38% illiterate.	NTP program + intervention vs usual NTP program care (routine motivation and education). Measured in the same time range and at the same location.	Psychotherapy (8 sessions combined with drug-collection visits), biweekly during the first two months, then monthly.	Funding source is not reported.	Successful treatment: cure and completed. Cured: 6 months of treatment and negative sputum smear at the end of treatment. Completed: negative sputum smear at 2–6 months, without sputum results at completion. Treatment failure: positive sputum smear or culture at 5 months. Loss to follow-up: stopped taking treatment for 2 months or more.	The themes for psychotherapy sessions were structured according to the conceptual understanding of an individual patient obtained from pretreatment psychological assessment. Costs: 12 US $ per patient.

(*Continued*)

Table 2. (*Continued*)

Study	Country income*	Study type	Enrolment period	N*	Population	Comparison	Intervention(s)	Funding source and organization	Outcome(s)	Other
Liefooghe et al. 1999 [46]	Sialkot, Pakistan, LMIC	Randomized controlled trial.	1 Jan—30 Nov 1995	1019 (I: 504, C: 515)	Adult TB patients, age: 15–45+ years; 42% male; 81% new cases; 40% had a low income job.	Intervention vs. usual explanations and treatment by medical staff. Measurements at one hospital.	Counseling. Patients received individual counseling each time they attended for follow-up assessment, and admitted patients received weekly counselling in the tuberculosis ward. Counseling was combined with health education.	Funded by the Vlaamse Interuniversitaire Raad, the Belgian co-operation and the Damien Foundation. The intervention was conceived within the framework of Bandura's social-cognitive learning theory.	Adherence: drug collection at the drug s at the scheduled appointments. Loss to follow-up: no drug collection for 2 months or more.	The social counsellors had several tasks: verify correct understanding of drug intake, to increase the patients' motivation, anticipate problems and/or critical moments, to activate a social network and involve family members and to act ombudsperson between the hospital/paramedical team and the patient. Two male and two female para-medics received a 2-week training course in counselling. They belonged to the same socio-economic background as the majority of the patients, and were fluent in the different local vernaculars.
Lu et al. 2013 [48]	Shanghai, China, UMIC.	Controlled before-and-after study.	Baseline 2006 and Intervention 2010	1935 (I: 2006: 961, 2010: 734, C: 2006: 281, 2010: 229)	Migrant active TB cases; 59% male, 64% aged 15–34; 86% new cases.	Intervention group vs control group without support in 2006 and 2010. Both groups consisted of 3 districts that have the same geographical characteristics.	Transportation subsidies of US$ 14.63 a month and living allowances of US$ 4.39 a month.	The initial project was made possible through a governmental special financing program (WHO Regional Office for the Western Pacific)	Treatment success: cure (with bacteriologic evidence of success), or completion (without bacteriologic evidence of success).	.
Lutge et al. 2013 [47]	KwaZulu-Natal, South Africa, UMIC.	Randomized controlled trial.	July 2009—March 2010	4091 (I: 2107, C: 1984)	Adults and children diagnosed with pulmonary, drug-sensitive TB, mean age: 31 years; 52% male; 49% HIV positive patients; 56% unemployed.	Incentive treatment vs usual care. 20 public sector clinics were enrolled in rural and urban districts (10:10)	15 US$ voucher was offered to patients every month on collection of their treatment, to a maximum of eight months. Vouchers were redeemed at local shops	Governmental funding.	Successful treatment, the sum of those patients cured and completing treatment. Loss to follow-up and failure was a secondary outcome, however not defined.	In many cases nurses withheld vouchers from eligible patients whom they felt were relatively better off financially.
Macq et al. 2008 [59]	9 rural municipalities, Nicaragua, LMIC.	Non-randomized controlled study.	Diagnosed between March 2004 and July 2005	286 (I: 122, C: 146)	New AFB positive TB patients. Average age: 35 years; 73% male; 49% without declared income.	5 intervention municipalities vs 4 control municipalities (these are the municipalities were the intervention was not effectively implemented).	Strengthening the TB patients through TB clubs taking the form of self-help groups. Additionally arranged home visits, reduce stigma and choice of DOT supporter. At least home visits and TB clubs were implemented in de intervention municipalities	TB clubs were chaired by TB patients and appointed an executive board. A local NGO supported this. The project influenced the National policies about the care of TB in government health services. The National TB program of the Nicaraguan Ministry of Health, the administer of the Global Fund (the NGO NICASALUD), the Damian Foundation (Belgian NGO) and a public health school were involved	Treatment success and loss to follow-up (and stigma reduction), no definition(s) available.	The aim was to increase the relationship between health personnel and TB patients and their realities through performing patient centered home visits to support the patient. And also plan social network activities the patient during the treatment. The interventions received full participation of MOH authorities. And TB clubs had been included in the 2005 Global Fund grant for Nicaragua.

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Table 2. (*Continued*)

Study	Country income*	Study type	Enrolment period	N*	Population	Comparison	Intervention(s)	Funding source and organization	Outcome(s)	Other
Martins et al. 2009 [60]	Dili, Timor-Leste, LMIC.	Randomized controlled trial.	March 2005—Nov 2005	270 (I: 137, C: 133)	Outpatient participants with newly diagnosed pulmonary tuberculosis. Mean age: 33 years; 65% male; 43% unemployed.	Routine care and nutritional support vs routine care and nutritional advice. The moment of measurement differed between the two groups. From 3 community districts, geographically distinct zones.	Food provision. The participants received food every time they attended the clinic. In the intensive phase, each day they were provided with one bowl food. During the continuation phase, patients were given a food parcel containing unprepared food to take home; quantities were for one meal per day.	Funded by Unicef/UNDP/World Bank/WHO Special program for research and training in tropical diseases	Adherence: not defined. Completion: the clearance of acid fast bacilli from the sputum after treatment or the completion of eight months of treatment, or both, including cure.	.
Morisky et al. 1990 [61]	California, United States of America, HIC.	Randomized controlled trial.	Nov 1985—March 1987	88 (I: 43, C: 45)	Subjects receiving preventive therapy and subjects receiving treatment for active TB (divided into two subgroups). Mean age: 35 years; 55% male.	Intervention vs standard clinic treatment including the use of community workers. Interventions and control came from the same 2 districts.	Health education counselling for 5–10 minutes and 10 US$ (in coupons) at every monthly visit and 40 US$ at the end of treatment (in coupons). (An incentive scheme to reward positive health behaviors plus targeted educational counseling session).	Funded by centers for Disease control. Assistance of the project 'Clerk', the project health educators and clinical staff	Treatment adherence: 95% of prescribed medicines taken. And the extent to which a person's behavior (in terms of keeping appointments, taking medications, and executing life-style changes) coincides with medical advice. Loss to follow-up was not defined.	When an active case missed a clinic appointment (interventions and controls), clinical personnel contacted that individual by phone or by home visit to reschedule a new appointment. Intervention subjects were questioned about their specific regimen, and any misunderstandings concerning their medical treatment program were clarified.
Soares et al. 2013 [68]	Rio de Janeiro, Brazil, UMIC	Historically controlled study.	Controls: 2001–2003 and intervention: 2003—Jun 2008	2623 (I: 1771, C: 852)	TB cases from an urban slum	Intervention group vs historical control group without support. Similar geographical location. No DOT provided in control group	DOT, establishment of community health care workers (CHWs) who, led by nurses, established a supportive social network, through this activity the team managed useful services such as transport to TB clinics and donation of food baskets. Also, they and carried out educational activities to enhance TB awareness and promoted breakfasts for patients and their families. The CHWs also collected sputum at home, monitored medical appointment attendance, sent contacts for evaluation and made home visits to supervise treatment	Funded by United States Agency for International Development through the Johns Hopkins University and the US National Institutes of Health Fogarty International Center, Bethesda USA	Treatment outcome (and TB notification rates).	Additionally educational activities were supported. The program was an ongoing training program based on regular feedback of the results of the local team and an on-site supervision scheme implemented by the City TB Program staff. The CHW's have contact with the municipal government, which minimizes employee turnover, making the team stable and avoiding the need for constant training. Regimen was intermittent (twice weekly) in continuation phase during intervention.

(*Continued*)

Table 2. (*Continued*)

Study	Country income*	Study type	Enrolment period	N*	Population	Comparison	Intervention(s)	Funding source and organization	Outcome(s)	Other
Sripad et al. 2014 [62]	Four regions, Ecuador, UMIC.	Historically controlled study.	Jan 2010-Aug 2010, and from Aug 2011-Jan 2012	191 (I: 105, C: 86)	DR-TB patients [resistance to at least one FLD] that received in-patient care for three months and then outpatient care. Mean age: 38 years; 73% male; 63% MDR TB.	Intervention group vs historical control group without support. 3 different regions vs whole Ecuador.	All DR-patients received a US$240 bonus after each month of adherence, defined as taking medications on 26 days per month for up to 24months. They can spend their bonuses according to their needs. They planned to spend their money on food, vitamins, rent, transportation, children's needs and medicine mainly.	The program was covered by governmental funds. Payments were arranged by the Central Bank of Ecuador, the Ministry of Economic and Social Inclusion and the NTP.	Loss to follow-up rate, not defined.	The program is part of the Ecuador's National Tuberculosis Program (NTP) NTP is a branch of the Ministry of Public Health, is a DOTS-based program with its headquarters in Quito
Sudarsanam et al. 2011 [49]	Southern Indian state of Tamil Nadu, India, LMIC	Randomized controlled trial.	Jan 2005 – Nov 2005	97 (I: 48, C: 49)	Newly diagnosed TB patients. Age: >12 years; 61.2% male; 20.6% HIV positive	Supplementation vs non-supplementation group	The supplementation group received a mixture of cereal and lentil. Three servings a day were provided (930 kcal and 31.5 g protein) and an one-a-day multivitamin tablet.	Funded by the Fogarty AIDS International Research and Training Program and the Global Infectious Disease Research Training grant	Cure: pulmonary smear-positive, completed treatment and had negative smear results on two occasions, one of which is at the end of treatment. Completion: Either pulmonary smear positive, completed treatment with negative smears at the end of the intensive phase but none at the end of treatment or pulmonary smear-negative or extra pulmonary and completed treatment. Unsuccessful: failure, death and loss to follow-up	.
Thiam et al. 2007 [51]	Senegal, LMIC.	Randomized controlled trial.	June 2003—May 2004	1522 (I: 778, C: 744)	Newly diagnosed smear positive pulmonary TB. 88% between 15–49 years; 67% male.	Intervention vs usual NTCP care. Geographical locations of the groups differed. Participants from 16 government districts in Senegal (8:8).	Reinforced counseling and communication between health personnel and patients, involving community health workers, choice of DOT supporter and reinforcement activities.	Funded through a special program from the French Ministry of research, called PAL, which was granted in September 2000.	Cure: negative sputum smear at 8 months and on at least 1 previous occasion. Completion: missing smear results but who had finished their treatment regimen. Loss to follow-up: definitely stopped treatment before completion.	The total support was divided into four components: improving counseling and communication between health personnel and patients through appropriate training, decentralizing treatment to remote health posts and involving community health workers, strengthening the DOT strategy by giving patients the opportunity to choose their treatment.

(*Continued*)

Table 2. (*Continued*)

Study	Country income*	Study type	Enrolment period	N*	Population	Comparison	Intervention(s)	Funding source and organization	Outcome(s)	Other
Wei et al. 2012 [63]	Shanghai, China, UMIC.	Controlled before-and-after study.	Baseline: July 2006—Sept 2007, intervention period: Oct 2007 –Dec 2008	183 (I: 90, C: 93)	Migrant pulmonary TB cases. Average age approx. 33 years; 9% male; 13% illiterate or semi-illiterate. 83% employed.	Intervention group vs control group without support. The two district names were anonymous to protect the patient's identities.	2 US$ per month for transportation for all migrants, and for all poor migrants (after assessment of poverty) a living allowance of 157 US $ was provided (in four installments 47 US$ at the time of diagnosis, 47 US$ at the end of the second month of treatment, 31 US $ at the end of the fourth month of treatment and 31 US$ at the end of the treatment). 78% and 60% of I and C were assessed to live in poverty; 60% of those in I received a living allowance and the transport subsidy.	Funded by the government. The intervention was designed to fit into the routine practices and job descriptions of the health providers from the CDC, TB clinic in the designated hospitals, and CHCs.	Loss to follow-up: the proportion of migrant TB patients who defaulted from treatment. Completion: the proportion of TB patients who have successfully completed treatment among all the migrant TB patients (treatment success). Financial burden: Percentage of total costs.	Incremental cost-effectiveness analysis. In total, this project involved an investment of RMB 52,400, which consisted of RMB 46,000 of financial subsidy and RMB 6,400 of transport incentives. This additional cost prompted an increase of 8% in treatment completion rate in the intervention district as compared to the control district. This suggests that for each percent increase in treatment completion, an additional cost of RMB 6,550 (US$ 1301) was invested in the intervention district. Similarly, this additional cost delivered a reduction of 10% in the default rate in the intervention district compared with the control district, showing that an additional cost of RMB 5,240 (US$825) was needed to reduce each percent in default rates.
Zou et al. 2013 [64]	Shanghai, China, UMIC.	Controlled before-and-after study.	For baseline: July 2006—Sept 2007. For intervention: Oct 2007—Dec 2008	787 (I1: 90, baseline: 143. I2: 173, baseline: 155. C:93, baseline 133)	Rural to urban migrant active TB cases. Average age, I1: 30, I2: 33, C: 35 years; more patients from I1 and I2 came to Shanghai alone (65% and 47% compared to 30%) other characteristics for the whole population are unclear.	Intervention 1 or intervention 2 vs control group without support. Participants came from 3 districts in downtown Shanghai (1:1:1)	1: A living subsidy of US$ 146 was provided to each poor migrant TB patients (after financial assessment) in four instalments. Every migrant also received US$ 1.50 per month as a transportation incentive. 2: All TB patients, regardless of economic status received a living subsidy of US$ 114 (US$ 19 per month over 6 months) and a transportation incentive of 4.4 US$.	Intervention 1 funded by the Communicable Disease Research Consortium (COMDIS) for the UK Aid Program. Intervention 2 was funded by the Global Fund. The COMDIS approach did not require extra investment from the health provider as the Global Fund approach did. The COMDIS approach might achieve better cost savings as it focused on providing financial incentives only to poor migrant TB patients	Treatment success (completion and cure), loss to follow-up and death. Nod definitions available. Financial burden was described as: cost-effectiveness.	For each percent increase in treatment completion, an additional cost of US$ 1301 was invested in the intervention district. For each percent decrease in loss to follow-up additional costs of US$ 825 was needed.

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per month [44,48,52,57,62–64]. Four studies provided direct economic support exclusively [48,62–64]. Other studies only provided economic support for the first three months and 5 US $ per month for travel expenses [57] or arranged reimbursement of travel for an unknown amount of money, combined with food supplementation, other material support and psycho-emotional support [44]. The remaining three studies also combined socio-economic support with psycho-emotional support. No studies on 'enterprise assistance' were found. Details on economic support provided per study are retrievable in Table 2.

Funding sources and organization. Information on funding sources and involvement of local bodies in the organization of the interventions can be found in Table 2. Seven SSIs were financed through governmental funding or local authorities. Another nine interventions were funded by foreign donor assistance (e.g. WHO, Unicef). Three interventions received combined funding (local and foreign donor assistance). For the remaining five interventions the funding source was unknown.

In total nine studies provided information on the organization of interventions, including six RCTs [46,50–52,55,67] and three NRS [44,59,66]. A study from Russia organized and implemented support by regional TB services and a local international organization[23] and a study from Nicaragua raised TB clubs organized by TB patients, with the help of local non-governmental organizations [59]. Community involvement was integrated into regular patient management in Burkina Faso [44,59,67]. The remaining studies reported very limited information on organizational sustainability.

Incentives and enablers. All the RCTs defined their support as incentives. Incentives are rewards for adherence while enablers assist patients to overcome barriers to treatment adherence. Most studies provided support to all TB patients. In studies where only poor patients were supported [64]; it may be that the support in fact was in the form of enablers.

Risk of bias and quality of evidence

Risk of bias was assessed for all included RCTs, including six Cluster Randomized Trials [47,50–52,60,67]. Only five out of eleven RCTs described an adequate randomization approach [50–52,58,60]. For the majority of the studies it was not described whether investigators were blinded to the outcome, and assessment of reporting bias was not possible due to a lack of information. None of the Cluster Randomized Trials assessed baseline imbalances between clusters or took random effects into account in the analysis. Ten NRS were assessed on risk of bias, including eight cohort studies and two case-control studies. Four studies [20,56,63,66] were not included in the meta-analysis and risk of bias assessment; reasons for exclusion are described in Table 3. Only three NRS adjusted for one or more confounders in the analysis [44,48,53]. Five additional studies were not included because of inadequacy of follow-up and/or assessment of outcome measures [44,48,53,62,68]. More information on the risk of bias assesment of the RCTs and NRS can be found in the supportive information S1–S3 Tables. Quality of evidence was assessed for the included RCTs per outcome measure. The quality of evidence for the RCTs was downgraded with one level for risk of bias, two levels on indirectness of studies and one level for limitations in consistency of the results. Hence, the overall quality of evidence of this systematic review is considered to be very low [40,69–74]. The quality of evidence per outcome measure is similar to the overall quality of evidence and retrievable in the summary of findings table (Table 4). No rating up for the overall quality of evidence was possible. Based on the funnel plot for the results of the ten RCTs included in the meta-analysis, it was not possible to determine whether publication bias was present (Fig 2)[28]

Table 3. Studies excluded from quantitative analysis.

Study	Type of study	Population	Dot	intervention	Outcome	Effect	Reason(s) for exclusion
Bock 2001 [20]	Historically controlled study	Non-adherent TB patients	Yes	Indirect economic support	Adherence	≤32 weeks OR 5.73 [CI 2.25–14.84] ≤52 weeks 7.29 [2.45-22-73]	Methodological diversity: outcome different than in other studies.
Davidson 2000 [56]	Case-control study	TB patients	Yes	Indirect economic support	Adherence	The odds that a patients with 100% adherence under incentives program will adhere 2.7 (1.01^{100}) times as great as person receiving the basic incentive package.	Methodological diversity: not possible to calculate absolute numbers from the effects.
Gelmanova 2011 [66]	Case series	TB patients that participated in at least one intervention to improve adherence before referral to the Sputnik program.	Yes	Home visits, other psychological and other social support	Adherence	Increased from 52.2% [CI 47.5–56.9] to 81.4% [CI 76.8–86.0]	Methodological and clinical diversity: high risk of bias on the 'selection' and 'outcome' domain (S2 Table). Study population only includes non-adherent patients, which were their own controls.
Wei 2012 [63]	Controlled before–and–after study	(Poor) Migrant TB patients	Unclear	Direct economic support	Treatment success, loss to follow-up and death.	Significant reduction of default rates (11% vs 1%, P = 0.03) in intervention district compared to the control district	This study was part of a bigger study (Zou et al. 2013 [64]), therefore this study was excluded.

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Meta-analysis

Eleven RCTs, eight cohort studies, and two case-control studies were included in the meta-analysis, including 17 743 patients (9655 patients participating in RCTs and 8088 patients in NRS). Most data originated from Brazil, China, Russia, Senegal and South Africa. No evidence was found concerning the effect of SSI on financial burden. Only one NRS measured the cost-effectiveness ratio of the provided economic support [64]. Studies assessing the effect of SSI on treatment adherence were too heterogeneous to pool. Meta-analysis of different outcome measures are presented separately (Figs 3 and 4).

Treatment outcomes. In total, nine RCTs had treatment success as an outcome measure (Fig 3). The overall effect of these studies showed a significant positive effect (RR 1.17; CI 1.09–1.25), however significant heterogeneity was observed (I^2 of 72.8%, P = <0.001). Stratified analyses were performed for the different types of interventions. Three studies provided PE support [50,52,55] including counseling, psychotherapy and the organization of self-help groups. A significant pooled effect was found for this intervention (RR 1.37; CI 1.08–1.73). The association between SE support and treatment success was examined by four studies [47,49,58,60] providing food supplementation and economic support. A significant pooled effect was found for this intervention (RR 1.08; CI 1.03–1.13). Combined support was provided by three studies [51,52,67]. Also, a significant pooled effect was found for these interventions on successful treatment outcomes (RR 1.17; CI 1.12–1.22). No significant heterogeneity was observed in two of three stratified analyses (SE: I^2 of 14%, P = 0.32; combined: I^2 of 0%, P = 0.42). Studies that provided PE support were substantially heterogenic and the p-value for the Chi^2 test was significant (I^2 of 78%, P = 0.01) (Fig 3). A sensitivity analysis was performed on the effect of PE support on treatment success, comparing high vs. low risk of bias studies. Omitting one high risk of bias study removed heterogeneity (I^2 of 0%, P = 0.53) (data not shown), and did not change effect size (RR 1.20; CI 1.07–1.35) [55]. Sensitivity analysis on MDR-TB patients vs. non-MDR-TB patients did not change the effect size and statistical significance (data not shown).

Table 4. Summary of findings.

Outcomes	Social support intervention (s)	Relative risk (CI)	Number of participants (studies)	Quality of evidence*	Risk of bias	Inconsistency	Imprecision	Indirectness
Treatment success	Social support interventions (overall)	1.17 (1.09–1.25)	6547, 10 studies	Very low	Serious risk of bias	Serious inconsistency, downgraded with one level due to high heterogeneity (I^2 of 72.8%, P = <0.001).	No serious imprecision, adequate sample size (n = 345).	Very serious indirectness
Treatment success	Psycho-emotional support	1.37 (1.08–1.73)	400, 3 studies	Very low	Serious risk of bias, downgraded with one level for high risk of bias on two domains for one study.	Serious inconsistency, downgraded with one level due to high heterogeneity (I^2 of 78%, P = 0.011) and large variation in point estimates.	No serious imprecision, adequate sample size (n = 44)	Very serious indirectness, downgraded with two levels. The studies provided different PE interventions (counseling, psychotherapy and self-help groups). One study provided the intervention to a different population (MDR-TB patients). In addition, mostly indirect comparisons are made.
Treatment success	Socio-economic support	1.08 (1.03–1.13)	4324, 4 studies	Very low	Serious risk of bias, downgraded with one level on high risk of bias on one domain in three studies.	No downgrading for inconsistency	No serious imprecision, adequate sample size (n = 748).	Very serious indirectness, downgraded with two levels. Three included studies provided food supplementation; one study provided indirect economic support. In addition, mostly indirect comparisons are made.
Treatment success	Combined support	1.17 (1.12–1.22)	1823, 3 studies	Very low	Serious risk of bias, downgraded with one level for high risk of bias on two domains in one study.	No downgrading for inconsistency	No serious imprecision, adequate sample size (n = 133).	Very serious indirectness, downgraded with two levels. All studies provided counseling and one or more PE and/or SE interventions. One study provided the intervention to a different population (MDR-TB patients). In addition, mostly indirect comparisons are made.

(*Continued*)

Table 4. (*Continued*)

Outcomes	Social support intervention (s)	Relative risk (CI)	Number of participants (studies)	Quality of evidence*	Risk of bias	Inconsistency	Imprecision	Indirectness
Unsuccessful treatment outcomes	Social support interventions (overall).	0.53 (0.41–0.70)	7301, 10 studies	Very low	Serious risk of bias	Serious inconsistency, downgraded with one level due to high heterogeneity (I^2 of 80.2%, P = <0.001) and large variation in point estimates.	No serious imprecision, adequate sample size (n = 358)	Very serious indirectness
Unsuccessful treatment outcomes	Psycho-emotional support	0.46 (0.22–0.96)	1419, 4 studies	Very low	Very serious risk of bias, downgraded with two levels for high risk of bias in two studies with high risk of bias on two domains.	Serious inconsistency, downgraded with one level due to high heterogeneity (I^2 of 85.5%, P = <0.001) and large variation in point estimates.	No serious imprecision, adequate sample size (n = 267).	Very serious indirectness, downgraded with two levels. The studies provided different PE interventions (counseling, psychotherapy and self-help groups). One study provided the intervention to a different population (MDR-TB patients). In addition, mostly indirect comparisons are made.
Unsuccessful treatment outcomes	Socio-economic support	0.78 (0.69–0.88)	3967, 2 studies	Very low	Serious risk of bias, downgraded by one level for high risk of bias on one domain in 2 studies.	Serious inconsistency, downgraded with one level due to large variation in point estimates (RR = 0.2 and 0.78).	No serious imprecision, adequate sample size (n = 1059).	Very serious indirectness, downgraded with two levels. The studies provided different SE interventions (food supplementation and indirect economic support). In addition, mostly indirect comparisons are made.
Unsuccessful treatment outcomes	Combined support	0.42 (0.23–0.75)	1915, 4 studies	Very low	Serious risk of bias, downgraded by one level for high risk of bias on two domains in one study and one study with high risk of bias on one domain.	Serious inconsistency, downgraded with one level due to high heterogeneity (I^2 of 64.2%, P = 0.039) and large variation in point estimates.	No serious imprecision, adequate sample size (n = 127).	Very serious indirectness, downgraded with two levels. All studies provided counseling and one or more PE and/or SE interventions. One study provided the intervention to a different population (MDR-TB patients). In addition, mostly indirect comparisons are made.

* GRADE Working Group levels of evidence.

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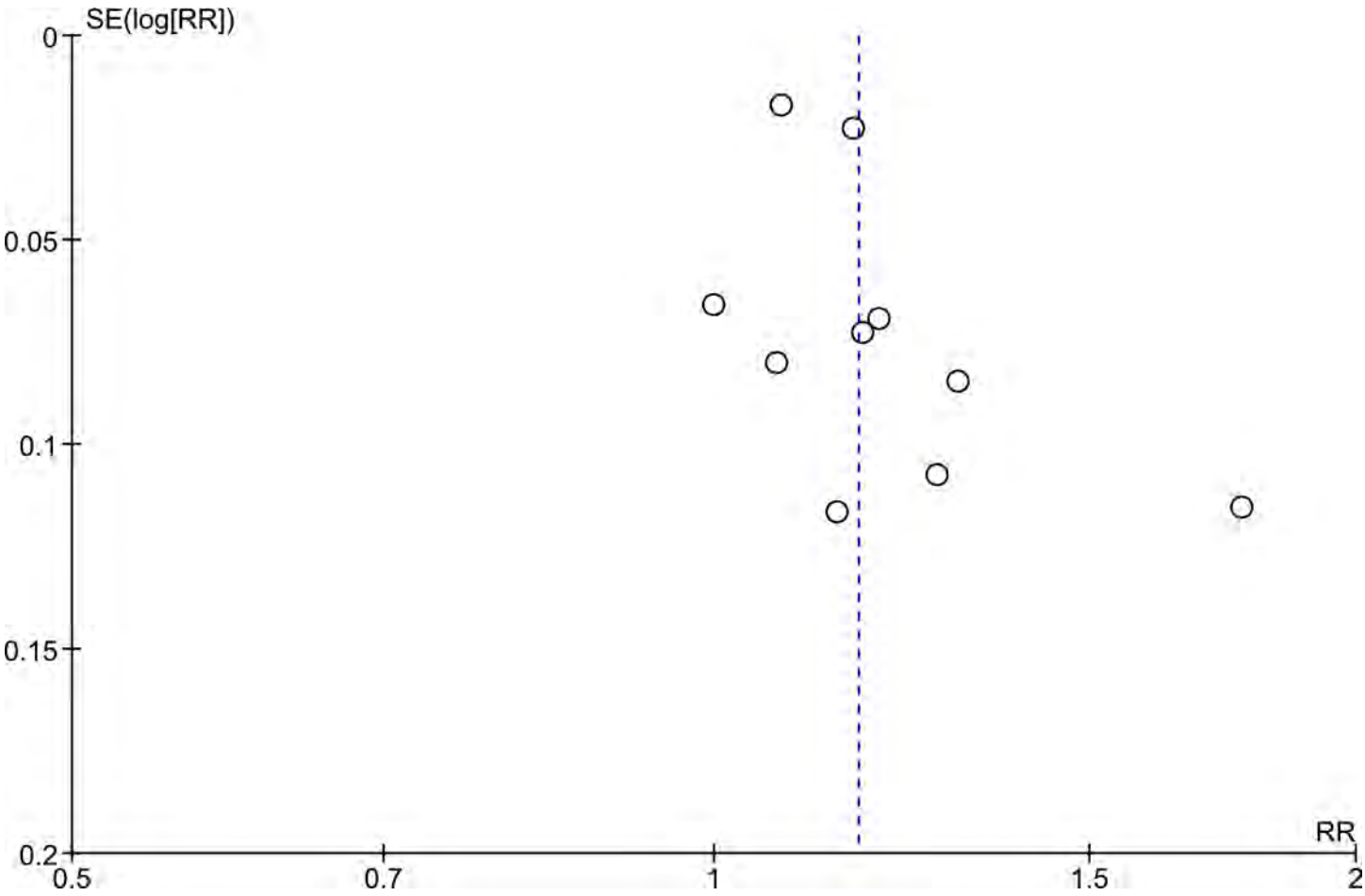

Fig 2. Funnel plot to evaluate publication bias in Randomized Controlled Trials on the effects of social support interventions on treatment outcomes.

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Nine studies had unsuccessful treatment outcomes as an outcome measure including seven also having treatment success as an outcome measure (Fig 4). An overall significant protective effect was found (RR 0.53; CI 0.41–0.70), however, substantial heterogeneity was observed (I^2 of 80.2% and P = <0.001). Stratified analyses were performed on the different interventions provided. Four studies investigated the effect of PE support on unsuccessful treatment outcomes, including counseling, psychotherapy and the organization of self-help groups [46,50,52,55]. Two studies examined the effect of SE support, including food supplementation and economic support [47,58] and four studies assessed the effect of combined support [51,52,61,67]. A significant reduction in unsuccessful treatment outcomes was found for all three stratified analyses: PE support (RR 0.46; CI 0.22–0.96), SE support (RR 0.78; CI 0.69–0.88) and a combination of PE and SE support (RR 0.42; CI 0.23–0.75). Heterogeneity was considered to be very low for the studies that provided SE support interventions (I^2 of 0% and P = 0.37). The studies that provided PE support and combined support were substantially heterogenic (PE: I^2 of 85%, P = <0.001 and combined: I^2 of 64% (P = 0.03) (Fig 4). A sensitivity analysis was performed in the PE stratum on the basis of higher risk of bias compared to the other studies [46,55]. Removal of one high-risk of bias study [46] decreased the I^2 to 0% (P = 0.54) and the effect size changed but remained statistically significant (RR 0.33; CI 0.22–

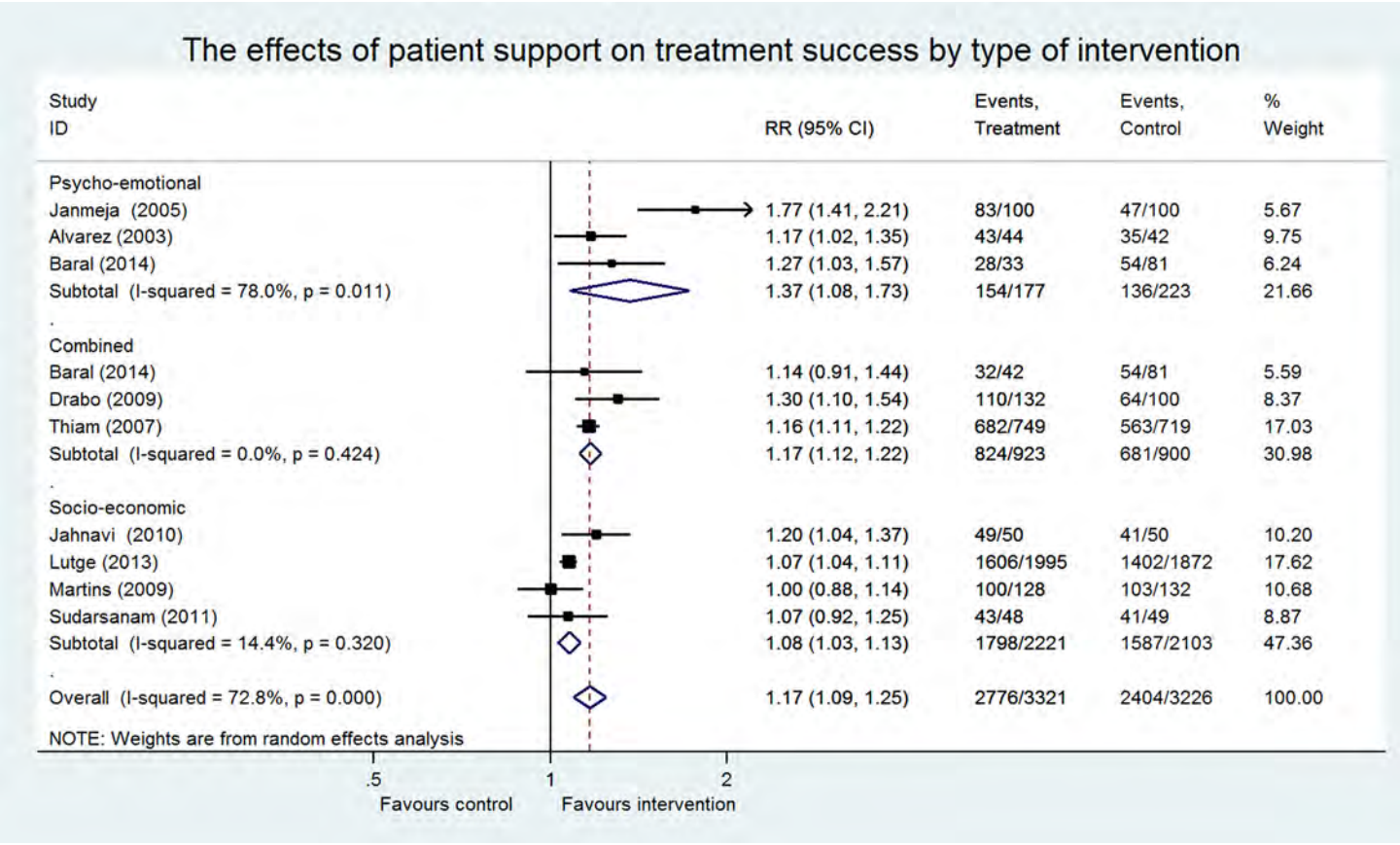

Fig 3. The effects of social support on treatment success by type of intervention in Randomized Controlled Trials.

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0.50). Omitting both biased studies did not change heterogeneity or the effect size. Sensitivity analysis on risk of bias was not possible in the studies providing a combination of PE and SE support, due to the fact that 3 out of 4 studies were classified as biased studies. Sensitivity analyses on MDR-TB patients vs. non-MDR TB patients did not change the effect size or heterogeneity significantly (data not shown).

Treatment adherence. Three RCTs assessed the effect of PE and/or SE on treatment adherence. A PE-intervention study conducted in Mexico showed a significant improvement in treatment adherence (RR 1.20; CI 1.03–1.39). A study from the USA did not show significantly higher levels of adherence in the intervention group compared to the group that received usual care (RR 1.11; CI 0.92–1.33). A third study from Timor-Leste showed no effect for patients that received SE support compared to patients that did not receive this support (RR 1.01; CI .0.85–1.21). Above-described interventions were not pooled as they were too heterogeneous.

Financial burden. None of the RCTs examined the effect of PE or SE support on financial burden for TB patients.

Non-randomized studies. Due to the fact that the studies' characteristics were heterogeneous on several levels and at higher risk of bias than the RCTs, we chose not to pool the effects for these studies (S1 and S3 Figs) [28,75]. Seven NRSs reported an effect of social support on successful treatment outcomes. Effects of interventions on successful treatment outcomes (RR) ranged from 1.03 to 2.51 (CI 0.96–2.99). Five of seven NRSs reported significant effect sizes

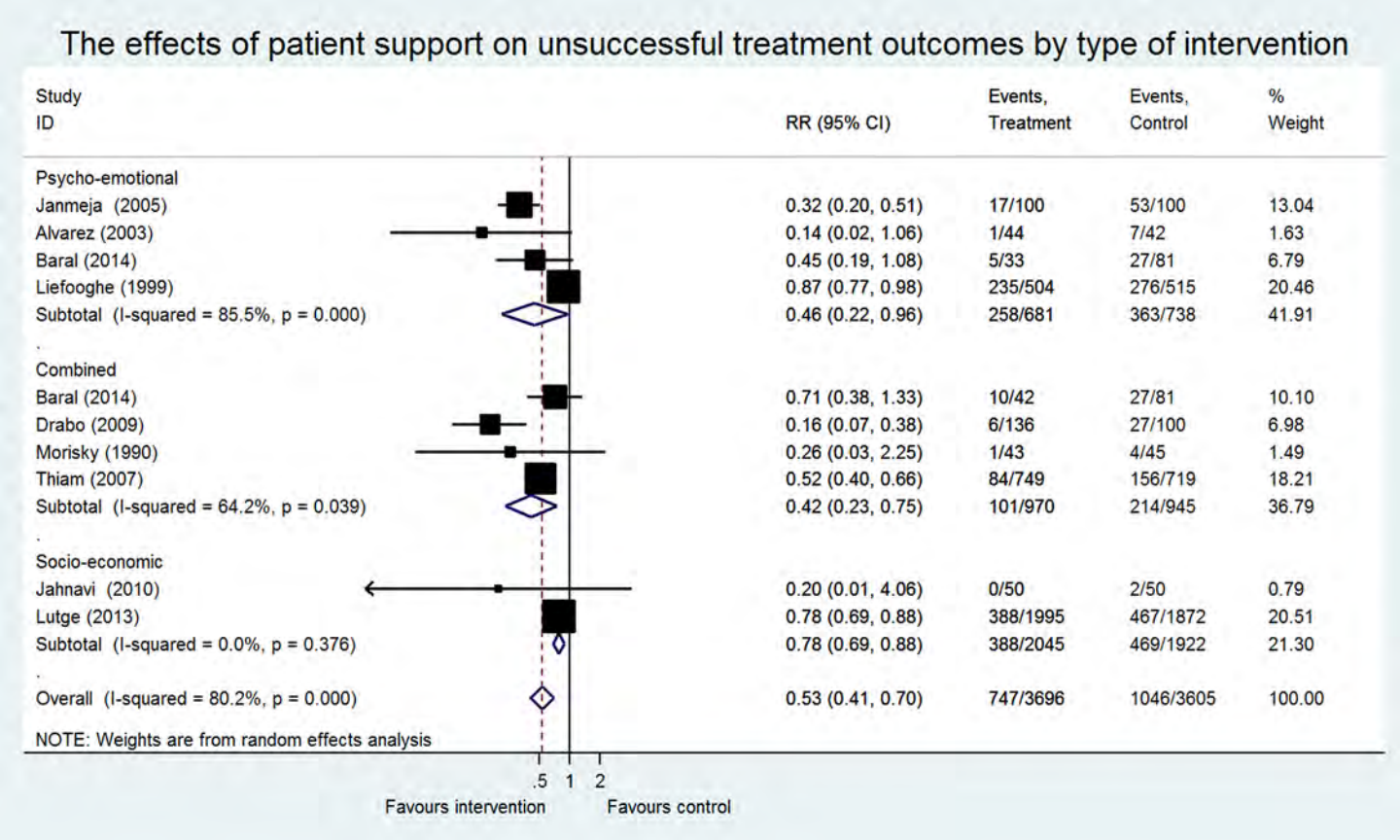

Fig 4. The effects of social support on unsuccessful treatment outcomes by type of intervention in Randomized Controlled Trials.

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[48,54,57,64,68]. Two studies found no significant effects [45,59]. Furthermore, six NRSs examined the effect of social support on unsuccessful treatment outcomes. Effect sizes varied from RR 0.32–0.96 (CI 0.18–3.49). Five out of six NRSs showed significant beneficial effects [45,54,62,64,68]. Only one study reported a non-significant effect [59]. In addition, two case-control studies investigated the effect of social support on unsuccessfull treatment outcomes. Both studies showed significant beneficial effects (RR 0.51 (CI 037–0.70) and RR 0.10 (CI 0.05–0.20)).

Discussion

This review found that PE and SE support did improve treatment outcomes across a variety of settings and patient populations, with a tendency towards better outcomes with PE interventions or a combined approach. However, the quality of evidence was classified as "very low" under the GRADE approach. Food supplementation and counselling were commonly included in the package of support. PE, SE and combined interventions improved treatment outcomes; only for interventions including SE support exclusively there was no significant improvement in treatment success. Overall, support interventions were associated with significantly higher treatment success (overall RR 1.08; CI 1.03–1.13) and reductions in unsuccessful treatment outcomes (overall RR 0.53; CI 0.41–0.70). Hardly any studies assessed the effect of interventions on treatment adherence. However, improved treatment adherence is an intermediate goal with the final aim to improve treatment outcomes, which was shown to improve.

A recent systematic review concluded that the economic burden for patients is considered to be high, loss of income is an important indirect cost factor for TB patients, and transport and nutritional supplementation were important direct cost components [8]. A study in Peru evaluated the expenses for MDR-TB patients that received free treatment and found that having MDR-TB was associated with high costs, which was associated with adverse outcomes (population attributable fraction 18–20%) [76]. In line with our review, these two studies suggest that economic support is of great importance for improving treatment outcomes. Some of the findings of this review however differ from those from other SSI-related reviews. A recent review [77] on RCTs assessing the effect of material incentives on TB treatment adherence and completion of TB treatment identified two trials, both included in our review as well [47,60], and neither demonstrated a clear benefit. However, in one trial the incentive was not well received by the patients and in the other trial fidelity to the intervention was low. A review of Sinclair et al. did not find any evidence that food supplementation had a beneficial impact on treatment outcomes [78]. This may be explained by their focus on micronutrient supplementation alone as reflected in their search strategy. In a systematic review about strategies to reduce loss to follow-up in drug-resistant patients, a comprehensive package of interventions (e.g. financial support and food supplementation) was associated with reduced loss to follow-up [79]. Our review included studies focusing on all TB patients, not only those with MDR-TB [79]. As mentioned in the methods section, we did not consider interventions aimed only at providing improved information or education to TB patients, given the recent systematic review showing a lack of its evidence related to TB treatment [17]. Some of the intervention packages included in our review included an information or education component, but it was not possible to delineate the effects of this specific component in our review. We also did not include interventions focusing only on reminder systems, as these are not considered PE or SE support. However, reminder systems can be integrated into SSI programs to enhance its effects since pre-appointment reminder phone calls and letters or home visits did have a small but potentially relevant effect on treatment completion [30].

There were some limitations to our review. Only a limited number of studies were available on the effect of PE/SE support interventions on TB treatment outcomes and very limited evidence on treatment adherence and financial burden. Within the identified studies, we were not able to stratify results by the type of organization and quality of health service delivery due to insufficient information, although it is known that organization and quality of health service delivery influence treatment adherence [9]. Some NRSs only provided support to subgroups of patients including poor patients [64], patients that already received support before referral to the intervention studied [66] and non-adherent patients [20]. This precludes conclusions on the effects of these interventions when provided to all patients. Such patient selection may have led to overestimations in the observed effect of the PE/SE interventions. On the other hand, selecting patients most in need seems prudent and is in practice applied in resource-limited settings. Although the number of studies included in the meta-analysis was small, the optimal size criterion was sufficient both for the overall meta-analysis and stratified analyses as examined by calculation of the sample size for the overall effect and subgroup analyses [72]. We could not examine for a dose response rate across all included studies, as most studies did not include a comprehensive description of interventions. However, one study did show a positive dose-response within their study regarding provision of indirect economic support: among patients in the intervention group who received the voucher at least once, treatment success rates significantly improved [47]. Furthermore, the more frequent the vouchers were received by patients, the higher their probability of treatment success [47]. Plausible heterogeneity was observed and seven out of

eleven RCTs had a high risk of bias on one or two domains. However, we did not exclude studies on the basis of heterogeneity only, as this may introduce bias [42].

Conclusions

This review provides evidence to endorse implementation of SSI in order to improve treatment outcomes. Firstly, PE and combined PE/SE support have a beneficial impact on treatment success. Secondly, SE support and a combination of PE/SE support are associated with reductions in unsuccessful treatment outcomes. No conclusions can be drawn considering the overall effect of PE and/or SE support on treatment adherence and financial burden due to a lack of evidence. Our findings need to be interpreted with caution, as the quality of the evidence included in the meta-analysis is "very low" based on the GRADE approach. In addition, most support included multifaceted types of interventions, so no conclusions can be drawn on the effect of individual interventions. Simultaneously, this might signify that multifaceted types of interventions are needed to improve treatment outcomes. High quality evidence, from well-designed randomized studies in larger sized populations, would provide more certainty on the effects of different PE and SE interventions. Cluster-randomized studies would provide an opportunity to compare differential packages and delineate the importance of specific components. In addition, more systematic data collection on PE and SE as already used by TB programs to monitor implementation and evaluate its effects and qualitative data collection in both studies and program settings to assess which interventions are most appreciated and most feasible to implement on a wide scale, would be useful. Reports should include information on costs and sustainability to provide information on efficiency and scalability.

Supporting Information

S1 PRISMA Checklist. PRISMA checklist.
(DOC)

S1 Fig. The effects of social support on treatment success in non-randomized cohort studies.
(PNG)

S2 Fig. The effects of social support on unsuccessful treatment outcomes in non-randomized cohort studies.
(PNG)

S3 Fig. The effects of social support on unsuccessful treatment outcomes in Case-control studies.
(PNG)

S1 Table. Risk of bias assessment–Cochrane collaborations tool for randomized controlled trials.
(DOCX)

S2 Table. Risk of bias assessment–New-castle Ottawa scale for non-randomized studies.
(DOCX)

S3 Table. Risk of bias assessment–New-castle Ottawa scale for case-control studies.
(DOCX)

S1 Web Annex. Full text search strategy per database.
(DOCX)

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Author Contributions

Conceived and designed the experiments: SH RH. Performed the experiments: SH RH. Analyzed the data: SH RH. Wrote the paper: SH RH DC EJ AG.

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The economic burden of tuberculosis in Indonesia

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SUMMARY

SETTING: Indonesia has a high prevalence of tuberculosis (TB) and is one of the 22 countries with the highest TB burdens in the world.

OBJECTIVE: To understand the economic burden of TB in Indonesia.

DESIGN: TB data for 2015 were combined with cost data using a simple type of cost-benefit analysis in a decision tree model to show the economic burden under different scenarios.

RESULTS: In Indonesia, there were an estimated 1 017 378 new active TB cases in 2015, including multidrug-resistant TB. It is estimated that 417 976 of these cases would be treated and cured, 160 830 would be unsuccessfully treated and would die, 131 571 would be untreated and would achieve cure spontaneously, and 307 000 would be untreated and would die. The total economic burden related to treated and untreated cases would be approximately US$6.9 billion. Loss of productivity due to premature death would be by far the largest element, comprising US$6.0 billion (discounted), which represents 86.6% of the total cost. Loss of productivity due to illness would be US$700 million (10.1%), provider medical costs US$156 million (2.2%), and direct non-medical costs incurred by patients and their households US$74 million (1.1%).

CONCLUSION: The economic burden of TB in Indonesia is extremely high. Detecting and treating more cases would result not only in major reductions in suffering but also in economic savings to society.

KEY WORDS: TB; health care financing; economic burden; costs; patient costs

TUBERCULOSIS (TB) IS A MAJOR global health problem that causes illness in millions of people each year and is one of the 10 leading causes of death worldwide.[1] Apart from its devastating health consequences, the economic impact of TB is extremely high, making TB a significant contributor to world poverty. TB absorbs an estimated US$12 billion from the incomes of the world's poorest communities and, in some countries, loss of productivity attributable to TB represents approximately 4–7% of gross domestic product (GDP).[2]

TB places a significant social and financial burden on the people who have the disease, as well as on their families and communities.[3] The greatest burden of TB falls on young productive adults,[4] who often become unable to work. The burden of caring for sick individuals usually falls to other family members, which in turn lowers their productivity.[5] Children also suffer by having to drop out of school to help support their families.[5] The cost of treating TB, especially drug-resistant TB, can also be significant, with high health system costs as well as household spending, which can account for as much as 8–20% of annual household incomes.[5] However, the most devastating impact of TB is death; without treatment, two thirds of smear-positive cases die within 5–8 years, with most dying within 18 months of being infected.[5] Due to the high social and economic costs, TB detection and treatment is widely regarded as very cost-effective, especially if provided efficiently.[6–8]

Indonesia (population >250 million) has the largest economy in South-East Asia, with a GDP per capita that has risen from US$857 in 2000 to US$3603 in 2016.[9] However, the poverty rate declined by only 1% annually from 2007 to 2011, and by only 0.3% annually since 2011, with the result that more than 28 million Indonesians still live below the poverty line and 40% remain vulnerable to falling into poverty.[9] Poverty rates are especially high among the 60% of Indonesians who live in rural areas with farming as their main occupation.[10] Indonesia's population is spread across more than 13 000 islands covering over 1.9 million km^2.[11] Its health system is largely decentralized across its 34 provinces and more than 500 districts, with local government mainly responsible for financing and providing public health services.[11]

Government spending on health care has been lower than average for countries in the East Asia and Pacific region,[12,] although it was expected to reach 5% of the total state budget for the first time in

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2016.[13] Despite great efforts to improve basic public services, the quality of the care given in health clinics is uneven, contributing to high rates of maternal mortality and stunting in children aged <5 years.[9] There are significant disparities in health indicators across the provinces and socio-economic groups, with infant mortality rates nearly three time higher in some areas than in others.[12]

The private health sector is a major provider of health services in Indonesia, with many hospitals, clinics and private practitioners. Many of the poor rely heavily on the private sector, which accounts for more than two thirds of ambulatory care and more than half of hospital contacts.[12] TB services are integrated into the general health care system, with diagnosis and treatment widely available in public primary facilities and hospitals and across many private sector providers.[14–18]

With an estimated 1 017 378 new active TB cases in 2015, Indonesia has one of the largest TB burdens in the world. In 2015, TB incidence was estimated at 395 per 100 000 population: 12/100 000 for multi-drug-resistant TB (MDR-TB) and 383/100 000 for drug-susceptible TB (DS-TB).[1]

While substantial external funds are currently available for the Indonesian TB National TB Programme (NTP), such as from The Global Fund, these are likely to diminish over the next few years, due mainly to improvements in the status of the Indonesian economy. The government is developing an exit strategy that aims to eliminate dependency on these grants by increasing domestic financing.[19] A major challenge in increasing government budget allocations, however, is the lack of understanding of the economic burden caused by TB and the savings that can be achieved with a successful and well-resourced NTP. A study of the economic burden was requested by the NTP and the Ministry of Health to strengthen their ability to advocate for the funding needed.[20]

STUDY POPULATION AND METHODS

The NTP requested that the economic burden study be based on a previous analysis,[21] and that a simple tool be developed to facilitate future estimation of the burden at both national and local levels. In response, we developed a dynamic, open-source spreadsheet tool called the TB Economic Burden Analysis Tool. Using a decision-tree approach, it lays out an algorithm of likely results of treatment and non-treatment for a cohort of new DS-TB and MDR-TB cases in 1 year. By applying a set of unit costs to the different treatment and non-treatment assumptions, the model uses a simple cost-benefit analysis to estimate the economic burden of DS-TB and MDR-TB on society over a period of years. For easy use, the tool was designed to use mainly data that are routinely available and that reflect the factors that have the greatest influence on the economic burden.

Data on numbers of infections and treatments were largely drawn from the annual World Health Organization global TB reports—which reflect data provided by country NTPs—and from the Indonesia Tuberculosis Prevalence Survey 2013–2014.[22] To calculate the total number of new cases treated in the year, we added an estimate of the number of cases treated in the private sector that are not notified to the NTP and therefore not included in NTP data. Including private-sector anti-tuberculosis treatment was important because a significant proportion of TB patients are treated in the private sector in Indonesia,[14–18,23] and a large number of these are not reported (TB became notifiable in Indonesia only in 2017).[24]

Total costs are based on medical costs, non-medical costs, and productivity losses incurred by persons treated and untreated for DS-TB and MDR-TB. The tool separates the costs into four groups: 1) the costs to health service providers of prevention, detection, diagnosis, and treatment services, including staffing and facility operating costs; 2) non-medical patient costs, such as travel, food, and accommodation, related to diagnosis and treatment; 3) lost productivity due to inability to work while ill with TB; and 4) lost productivity due to premature death from TB.

Service cost data were taken from a 2013 costing study[25] using data from 2011 converted from Indonesian Rupiah (IDR) at the rate of 9587 IDR to US$1. That study estimated the financial costs to public health providers of preventing, diagnosing and treating TB, including facility operating costs, and concluded that the average cost per DS-TB case treated in 2011 was US$233 and the average cost per MDR-TB patient who started treatment in 2011 was US$10 289. These US$ unit costs were inflated by 1% per year to reflect increases in the proportion of costs relating to health facility operations (staffing, TB medicines and supply costs did not change much over the period). The inflated 2015 costs used in the calculations were US$242 for DS-TB and US$10 707 for MDR-TB.

Figures for non-medical patient costs were taken from a study of patient costs conducted in 2013,[26] the results of which were summarized and published in a three-country study in 2016.[3] We only included patient out-of-pocket costs for transport, food and accommodation, on the grounds that patient costs incurred for health services (such as for tests) are already included in the provider costs, and indirect patient costs are already included in the costs related to productivity losses. The 2013 figures were inflated by 5% per year to arrive at the 2015 costs of US$36.60 per DS-TB case and US$1257.29 per MDR-TB case. We assumed that the cost incurred by a person for an untreated case is the same as that for a treated case, as a person generally incurs costs

while seeking or receiving treatment from informal providers.

To calculate the cost of lost productivity we assumed that all persons between the ages of 15 and 60 years perform valuable work in one way or another (for example in formal employment, subsistence farming or looking after a home and family). The upper cut-off age of 60 years was used to facilitate comparison with the figures produced in the previous Indonesian study.[21] We assumed that treated DS-TB and MDR-TB patients are unable to work for respectively 25 days and 102 days after starting treatment, based on the study of patient costs conducted in 2013.[26] We also assumed that untreated patients who do not achieve cure spontaneously would live for 3 years on average before they die,[27] and would be unable to work for half of that time (390 days, based on 260 working days/year). The cost is based on the average minimum wage for the country of US$6.75/day in 2015 (IDR2.7 million/month).[28]

The cost of lost productivity due to premature death was calculated following a simple value of statistical life (VSL) approach.[5] We used the age breakdown of notified smear-positive cases provided by the NTP for 2011 to estimate the average number of patients of each age. To facilitate comparison with the previous Indonesian study,[21] we assumed that only people aged between 15 and 60 years are productive, but that they are all productive in one way or another (paid employment, subsistence farming or unpaid housework). We used an average number of 260 working days/year (52 weeks x 5 days) and the national average minimum daily wage of US$6.75 as the value of the labour. The annual costs were discounted at a rate of 3%/year, which is common for this type of analysis.[5,29–31]

As the data used in this study were obtained from records made available by the Ministry of Health and did not involve interviews with patients or other human subjects or the use of patient records, ethical review was not required.

RESULTS

For the Indonesian population of 257 564 000 in 2015, the total estimated number of new cases was 1 017 378, based on the incidence rate of 395/100 000 as shown in the WHO global tuberculosis report 2016.[1] Of this total, an estimated 986 470 (383/100 000) would have been DS-TB cases and 30 908 (12/100 000) would have been MDR-TB cases.

The estimated number of new DS-TB cases treated was 577 287 (Table 1), comprising 297 118 cases treated in the public sector, 30 258 treated in the private sector and notified to the NTP, and 249 911 treated in the private sector and not notified to the NTP. The private sector figures were based on data from the Indonesia TB Prevalence Survey,[22] which indicates that 46% of all TB cases were seen in the private sector, and data from the 2016 global TB report,[1] which indicates that 9.2% of private sector cases were notified to the NTP.

Of the 577 287 new and relapse DS-TB cases treated, 345 724 (59.9%) would have been new smear-positive cases, 182 395 (31.6%) new smear-negative cases, 35 146 (6.1%) extra-pulmonary cases, and 14 022 (2.4%) relapse cases. It was assumed that 408 367 (72.5%) new and relapse DS-TB cases and 8834 (63%) relapsed DS-TB cases would have been successfully treated and that the 160 086 remaining patients would have died. The number of untreated new and relapse DS-TB cases would have been 409 183 (41.5%), calculated by deducting the number of treated DS-TB cases (577 287) from the total number of new DS-TB cases (986 470) (Table 1). Of these, a total of 122 755 (30%)[27] would reach cure spontaneously and 286 428 (70%) would die.

We estimated that there would have been 30 908 new MDR-TB cases. According to the 2016 WHO global TB report,[1] 1519 (4.9%) MDR-TB cases were treated; we assumed that no additional MDR-TB patients were treated in the private sector, as only certified public facilities are authorised to treat MDR-TB. We assumed that 775 (51%) of the treated cases would be cured and 744 (49%) would die. Of the untreated MDR-TB cases, an estimated 8817 (30%)[27] would achieve cure spontaneously and the remaining 20 572 (70%) would die.

In summary, of the total estimated 1 017 378 new cases in 2015, we assumed that 578 806 (57%) would have been treated, of which 417 976 would be cured and 160 830 would die (Table 2). Of the untreated 438 571 (43%) cases, 131 571 would be cured spontaneously, and 307 000 would die, giving a total of 549 547 cases cured and 467 830 who would die.

The economic costs are summarised under four groups: provider medical costs, patient out-of-pocket costs, productivity losses due to illness, and productivity losses due to premature death (Table 3). Only the figures for the last group were discounted, as the other costs would all be incurred within 3 years.

Provider medical costs

The total cost of medical services is estimated at US$156 million. This was calculated by multiplying the numbers of DS-TB and MDR-TB cases treated by the estimated cost per case of respectively US$242 and US$10 707.

Patient out-of-pocket costs

The total direct household out-of-pocket costs is estimated at US$74 million, based on a cost of US$36.60 for a DS-TB case and US$1257.29 for an MDR-TB case. The largest element is US$36 million, for untreated MDR-TB cases.

Table 1 Numbers of new and relapse TB infections, cases treated, and treatment outcomes, Indonesia, 2015

DS-TB cases	*n*	Rate/ %	Reference
Incidence of DS-TB	986 470	383/100 000	1*
Total DS-TB new and relapse cases notified and treated	577 287	58.5	1,22†
New smear-positive cases treated	345 724	59.9	32
New smear-negative cases treated	182 395	31.6	32
New extra-pulmonary cases treated	35 146	6.1	32
Relapse cases notified	14 022	2.4	32
Relapse TB cases retreated	14 022	100.0‡	
Relapse TB cases become MDR-TB	2 244	16.0	1
Total new DS-TB cases treated	563 265		
Total relapse cases retreated	14 022		
New TB cases successfully treated	408 367	72.5	§
Relapse TB cases successfully retreated	8 834	63.0	1¶
New DS-TB cases treated: died	154 898	27.5	
Relapse DS-TB cases treated: died	5 188	37.0	
Total DS-TB cases treated: died	160 086		
DS-TB cases unidentified	409 183	41.5	
Smear-positive	245 050	59.9	32#
Died	171 535	70.0	27
Cured spontaneously	73 515	30.0	27
Smear-negative and others	164 133	40.1	32
Died	114 893	70.0	27
Cured spontaneously	49 240	30.0	27
Total died	286 428		
Total cured spontaneously	122 755		
MDR-TB cases			
Incidence of MDR-TB	30 908	12/100 000	1**
MDR-TB cases treated	1 519	4.9	1††
MDR-TB cases unidentified	29 389	95.1	
MDR-TB cases successfully treated	775	51.0	1
MDR-TB cases unsuccessfully treated (died)	744	49.0	
MDR-TB cases untreated: was cured spontaneously	8 817	30.0	27
MDR-TB cases untreated: died	20 572	70.0	27

* Excluding data on MDR-TB.[9]
† Public and private sector estimates less MDR-TB. Assumes that all notified cases are treated.
‡ The NTP assumes that all relapse cases notified are treated.
§ Weighted average of 84% (WHO global tuberculosis report, 2016)[1] and 59% (Prevalence Survey Report Table 8).[22]
¶ Assumes all relapse cases are treated in the public sector or the cure rate is the same in both sectors.
** Assumes same percentage as for notified cases.
# WHO global tuberculosis report 2016. Table A4.1. 12 (7.4–17) per 100 000.[1]
†† WHO global tuberculosis report 2016.[1] Assumed all because only a certified public facility can diagnose and treat MDR-TB.
TB = tuberculosis; DS-TB = drug-susceptible TB; MDR-TB = multidrug-resistant TB; WHO = World Health Organization.

Productivity losses due to illness

The total cost of productivity losses due to illness is estimated at US$700 million, based on 25 days lost for a treated DS-TB case, 102 days lost for a treated MDR-TB case and 390 days lost for an untreated DS-TB or MDR-TB case. The days lost, calculated for persons aged 15–60 years, were valued at the minimum wage of US$6.75. The biggest element would be US$583 million for untreated DS-TB patients.

Productivity losses due to premature death

The largest component of the economic burden relates to loss of productivity due to premature death, which, discounted at 3% per year, is estimated at around US$6.0 billion. The total discounted number of productive life-years lost during the ages of 15–60 is 3.4 million years, and the undiscounted value of each year lost was based on 260 working days/year and a minimum wage of US$6.75/day. The group with the largest loss of productivity is untreated DS-TB cases, with an estimated total loss of US$3.6 billion.

The total discounted economic burden from the four components comes to around US$6.9 billion. The biggest component by far is the productivity losses of US$6.0 billion due to premature death. It is important to emphasize that this is the cost borne over a period of years relating to persons infected with TB disease in 2015. Most of the burden relates to

Table 2 Summary of TB treatment rates and outcomes Indonesia, 2015

Outcomes summary: all cases	*n* (%)
Total treated	578 806 (57)
Total successfully treated	417 976 (41)
Total unsuccessfully treated: died	160 830 (16)
Total untreated	438 571 (43)
Total untreated: achieved cure spontaneously	131 571 (13)
Total untreated: died	307 000 (30)
Total new cases	1 017 378 (100)
Total survived	549 547 (54)
Total died	467 830 (46)

Table 3 Total cost by type of treated and untreated TB case, Indonesia, 2015 (in US$)

Total cost (discounted)	Total	Treated DS-TB	Treated MDR-TB	Untreated DS-TB	Untreated MDR-TB
Provider medical costs	156 233 136	139 969 545	16 263 591	—	—
Patient out-of-pocket costs	74 967 714	21 130 453	1 909 825	14 977 312	36 950 123
Patient productivity losses due to illness	700 847 370	74 313 149	808 285	583 796 019	41 929 917
Patient productivity losses due to premature death	6 023 129 571	2 061 045 580	9 582 694	3 687 644 046	264 857 252
Total economic cost per adult TB case treated	6 955 177 790	2 296 458 727	28 564 394	4 286 417 377	343 737 292

TB = tuberculosis; DS-TB = drug-susceptible TB; MDR-TB = multidrug-resistant TB.

untreated DS-TB, followed by treated DS-TB, because the numbers of cases are much higher than the numbers of MDR-TB cases.

The average cost per case is highest for treated MDR-TB, at US$18 805, followed by untreated MDR-TB (US$11 696), then untreated DS-TB (US$10 476) and finally, treated DS-TB (US$3978) (Table 4). It is important to note, however, that these figures do not include the cost of onward transmission from untreated or unsuccessfully treated cases. Assuming that each infectious person infects one other person per month, and that 10% of these people would progress to active TB over their lifetimes,[33] the cost of detecting and treating those persons is likely to make the economic impact of untreated DS-TB and MDR-TB much higher than the cost of treated MDR-TB.

The total economic burden per capita (total population) comes to US$27.00, with the highest burden being US$16.64 for untreated DS-TB (Table 4). We developed a scenario to show the impact of increasing the treatment rates. If the treatment rate for DS-TB is increased from 58.5% by 10% to 64.3%, the number of deaths would fall by 24 402 (5.2%), from 467 830 to 443 429. The total provider medical cost would increase by US$14 million (8.9%), from US$156 million to US$170 million, although productivity losses from illness and premature death would fall by US$389 million, from US$6.7 billion to US$6.3 billion. The net economic burden would fall by US$375 million, from US$6.95 billion to US$6.58 billion, a fall of 5.4%. In other words, an additional investment of US$14 million in provider costs in 1 year would yield an economic return of USD389 million over time, a return of 28 to 1 (excluding the benefits of reducing onward transmission).

DISCUSSION

As in most studies of the economic impact of TB, the cost of productivity losses due to premature mortality is the highest cost element in this study.[5] Comparisons with figures from comparable country-level TB economic impact studies are important; however, a search did not reveal many such studies. It is also not easy to compare costs across studies, because different methods are used. To keep the Indonesia model simple, for example, we only used the number of discounted life-years and the minimum wage with no weighting for age, quality or disability. However, a common method uses disability adjusted life-years (DALYs),[34] which are based on life-years combined with disability and have an age-weighting function as well as discounting.[35] Direct comparisons with the results of other studies that used DALYs therefore have limited value.

An important comparison is with the 2004 costing estimates provided by Gani in 2005, as the present study was intended to update those figures.[21] Those costs were largely based on economic costs related to illness and premature death. Productivity losses due to illness were estimated at US$35 million, which was based on an annual total of 275 000 cases, 75% of these being people of productive age, 105 days lost/case, and a daily loss of IDR15 000 (US$1.65). The equivalent figures used in the current Indonesia study were 1 017 378 cases, 77.42% being people of productive age, 25 days lost/treated TB patient, 102 days lost/treated MDR-TB patient and 390 days lost/

Table 4 Average cost by type of treated and untreated TB case, Indonesia, 2015 (in US$)

Average cost per case (discounted)	Treated DS-TB US$	Treated MDR-TB US$	Untreated DS-TB US$	Untreated MDR-TB US$
Cases, *n*	577 287	1 519	409 183	29 389
Provider medical costs	242	10 707	—	—
Patient out-of-pocket costs	37	1 257	37	1 257
Patient productivity losses due to illness	129	532	1 427	1 427
Patient productivity losses due to premature death	3 570	6 309	9 012	9 012
Total average cost per case	3 978	18 805	10 476	11 696
Average cost per capita (total population)	8.92	0.11	16.64	1.33

DS-TB = drug-susceptible tuberculosis; MDR-TB = multidrug-resistant TB.

untreated patient, and a daily loss of US$6.75. These differences brought the total cost in the current study to US$700 million, compared with US$35 million in the previous study. Productivity losses due to premature death were estimated by Gani at US$631 million, based on 140 000 deaths/year, 75% of the cases being people of productive age, 10 years lost/case (productive age limit of 60 years minus age at death of 50), 365 productive days/year and a daily loss of IDR15 000 (US$1.65). The equivalent figures in the current Indonesia study were 467 830 deaths (between 15 and 60 years of age), an average of 7.3 discounted years/death (16.0 undiscounted years), 260 productive days/year (52 weeks x 5 days), and a daily loss of US$6.75. These differences brought the total cost in the current study to US$6.0 billion (discounted), compared with US$631 million in the previous study. The previous study also included the cost of medicines for treatment, but did not include service provider costs or other patient costs such as transport. While the costs in the current study are much higher, this does not appear unreasonable based on the much higher incidence and death figures and the differing assumptions.

Another useful comparison is with a similar study conducted in the Philippines,[29] which estimated annual economic losses of approximately US$108 million (more than Philippine Peso [PhP] 6 billion) due to morbidity and US$32 million (PhP 1.8 billion) due to premature mortality. These figures are much lower than those found through the 2015 Indonesia study, at respectively USD700 million and USD6.0 billion (discounted). However, the Philippine figures are based on much older data (1997–2001), and the TB incidence and mortality rates used were much lower (233 036 incident cases vs. just over 1 million in Indonesia, and 26 102 deaths vs. 467 830 in Indonesia). The number of years lived with disability (YLD) was lower: 159 418 vs. 284 464 in the Indonesia study (assuming productivity of 365 days/year); the number of years of life lost (YLL) was also lower: 354 882 vs. 3.4 million in the Indonesia study. The number of YLD per incident case was 0.68 compared with the Indonesia figures of 0.41 (based on 360 productive days/year) or 0.68 (based on 260 productive days/year). The YLL per death in the Philippines study was 13.6, whereas the equivalent figure in the Indonesia study was 7.3. However, these figures are not directly comparable, as the Philippines study included disability weights in the YLD calculation and based the YLL on a life expectancy of 82.5 years for females and 80 years for males. The Philippines study also used a DALY approach to estimate economic impact, taking into account prevalence by age, sex, income quintiles and place of residence (urban vs. rural) to estimate wage differentials and lost income. In addition, the daily wage rates used to estimate the economic loss for YLL and YLD reflected a productivity time path where wages increase until an age threshold level and then decrease. It is also important to note that the Philippines study did not take into account the higher YLD related to MDR-TB.

The results of the different data and methods can be summarized as follows: from 1997/2001 data, the Philippines modelling estimated the average economic productivity loss to morbidity per incident case as US$469 and per death as US$1302, whereas the 2014/2015 data used in the Indonesia modelling resulted in losses of respectively US$1022 and US$16 337. The Philippines study did not estimate patient out-of-pocket costs, but did estimate the provider cost of treatment, which ranged from US$34 to US$117, which is lower than the figure of US$233 for DS-TB used in the Indonesia study. It is worth noting that the authors highlighted the difficulties of getting some key data for the study and stated that they had potentially underestimated the burden of disease and economic consequences.

Another study of TB costs conducted in India using data from 1997 to 2006 also used DALYs, but includes some comparable figures.[36] The study estimated that a saving of 1.3 million lives would result in 26.6 million life-years gained (age limits not stated). This is an average of 20.4 life-years saved per death averted, compared with 7.3 estimated in the Indonesia study. To estimate the economic benefit, the study used a 2006 value of statistical life-year of US$1892 for India, compared with the value per life-year of US$1755 estimated in the Indonesia study.

In summary, the cost of premature death estimated in this Indonesia study is higher than the costs found in the previous Indonesia analysis and the Philippines study, but the data used in those two analyses are over 10 years old, and there appear to be sound reasons for the differences. The India study estimated more life-years saved per death averted than the 2015 Indonesia study, but the value per life-year was similar.

While the present study did not set out to examine the best ways of reducing the economic burden of TB, it is worth noting that improving diagnosis in the private and public sectors has been identified as being likely to result in the greatest reduction of deaths and secondary cases in Indonesia, while interventions to improve treatment in either sector will result in the greatest improvement in cures but with less effect on deaths.[8] This reflects the fact that in the base-case analysis most patients are not diagnosed with TB at all. Enhancing diagnosis will result in the greatest increase in health system costs, reflecting the costs of putting more people on treatment, but will also result in the greatest reduction in economic burden.

Limitations

The limited time and resources available for the study and the decision to develop a simple model that can be used easily at subnational levels and in other countries mean that there are some limitations to the

analysis. The study does not take into account future cases caused by the onward transmission of TB from the 2015 new TB cases, which is likely to have a significant impact on costs. The study also does not take into account costs associated with human immunodeficiency virus/acquired immune-deficiency syndrome, diabetes or other diseases, and issues such as smoking. Nor does it consider productivity losses related to persons, such as family members, who provide care and support to patients aged between 15 and 60 years. It also does not take into account loss to follow-up or the differential economic effects of TB on males and females.

As we did not have an estimate of costs for retreatment cases, we assumed that these are the same as the costs of regular DS-TB treatment. We also assumed that untreated persons would incur the same costs as persons receiving approved treatments, as they would still incur costs when seeking care from unapproved providers.

There is a significant level of uncertainty regarding the incidence rates of 395/100 000 for all TB cases and 12/100 000 for MDR-TB cases, ranging from 255 to 564/100 000 for all TB cases and 7.4 to 17 for MDR-TB cases. Sensitivity analysis was conducted using these lower and higher uncertainty intervals in combination. Using both of the lower levels would reduce the total cost from US$6.9 billion to US$3.1 billion, while using both of the higher levels would increase the total cost to US$11.5 billion.

The assumption that people cease to be productive at the age of 60 was made to allow for comparisons with the previous Indonesian study. It is likely that many people over 60 remain somewhat productive, even among the poor, where TB is most prevalent. However, the effect of discounting reduces the impact of errors in this assumption. Sensitivity analysis showed that increasing the upper productive age limit from 60 to 65 years would increase the number of discounted productive years lost from 3.4 million to 3.7 million, and would increase the total cost from US$6.9 billion to US$7.5 billion (around 8%).

A major assumption in the study is that all persons with TB aged between 15 and 60 years are productive in one way or another and that the value of that labour for all of these is the equivalent of the minimum wage. Recognizing that it is difficult to put a value on non-formal labour, we conducted a sensitivity analysis that showed that reducing the proportion of persons with TB aged between 15 and 60 years who are deemed to be productive from 100% to 50% would lower the total cost from US$6.9 billion to US$3.5 billion. This is also the equivalent of reducing by 50% the average value of a day's labour, which is assumed to the equivalent of the minimum wage.

Although the use of a discount rate of 3% per year is common for such an analysis, this has a major impact on the cost. Our sensitivity analysis showed that reducing the rate from 3% to 0% would raise the total cost from US$6.9 billion to US$14.0 billion, whereas increasing the discount rate to 6% would lower the total cost to US$3.9 billion.

The main challenges in estimating the costs of TB were related to the estimates of productivity losses due to illness and premature death. For this study, we kept the assumptions simple so that the study can be easily replicated. For productivity losses due to premature death, we multiplied the years of life lost by 260 working days and the minimum wage. The study by Gani also assumed the same wage rate for all people of productive age.[21] Other studies have used more complex methods. The study by Peabody et al., for example, stratified the prevalence across age, sex, income quintiles and urban/rural, and for the daily wage rate took into account age, sex, educational attainment, urban/rural, levels of unpaid family work and decisions about whether or not to work.[29] A study by Kirigia and Muthuri used GDP to estimate productivity losses.[31] A study by Goodchild et al. used DALYs to calculate the years of life lost combined with years lost due to disability, and used a measure of VSL, which takes into account loss of satisfaction (such as due to pain), to calculate the economic burden.[36]

Our intention was to keep the modeling simple for easy replicability of results, as it is important to conduct research to see what available, existing data can be used together with simple methodologies to improve the quality of key data, and in particular estimates of productivity losses. However, it should be noted that the purpose of estimating the economic impact of TB is to guide further investment in prevention, detection and treatment. The cost-effectiveness of this investment is already well-known and should not require very accurate data that require high levels of skills and resources for research.

In conclusion, our study shows that the economic burden of TB is very high in Indonesia, and that the detection and treatment of more cases would result in not only major reductions in suffering but also greater savings to society.

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RESUME

CONTEXTE : L'Indonésie a une prévalence élevée de tuberculose (TB) et fait partie des 22 pays les plus affectés par la TB dans le monde.

OBJECTIF : Comprendre le poids économique de la TB en Indonésie.

SCHÉMA : Les données de 2015 relatives à la TB ont été combinées avec des données de coût à l'aide d'une simple analyse coût bénéfice dans un modèle d'arbre de décision afin de mettre en évidence le poids économique de la TB dans différents scénarios.

RÉSULTATS : En 2015, il y a eu en Indonésie environ 1 017 378 nouveaux cas de TB active, incluant les cas de TB multirésistante. On estime que 417 976 de ces cas auraient été traités et guéris, 160 830 auraient été traités sans succès et mourraient, 131 571 n'auraient pas été traités et guériraient spontanément et 307 000 n'auraient pas été traités et seraient morts. Le poids économique total lié aux cas traités et non traités serait d'environ 6,9 milliards de $US. La perte de productivité due à un décès prématuré en serait de loin l'élément le plus important, soit 6,0 milliards de $US (escompté), c'est-à-dire 86,6% du coût total. La perte de productivité due à une incapacité serait de 700 millions de $US (10,1%), les coûts de prestations de soins médicaux seraient de 156 millions de $US (2,2%) et les coûts directs non médicaux supportés par les patients et leurs foyers seraient de 74 millions de $US (1,1%).

CONCLUSION : Le poids économique de la TB en Indonésie est extrêmement élevé et la détection et le traitement de davantage de cas aboutirait non seulement à une diminution considérable des souffrances mais également à des économies majeures pour la société.

RESUMEN

MARCO DE REFERENCIA: Indonesia tiene una alta prevalencia de tuberculosis (TB) y es uno de los 22 países con mayor carga de morbilidad por esta enfermedad en el mundo.

OBJETIVO: Comprender la carga económica que impone la TB en Indonesia.

MÉTODOS: Los datos de la TB en el 2015 se combinaron con los datos de los costos, mediante un análisis sencillo de beneficios y costos, en un modelo de árbol decisional, con el fin de poner en evidencia la carga económica según diferentes hipótesis.

RESULTADOS: Se calcula que en Indonesia se presentaron 1 017 378 casos nuevos de TB activa en el 2015, incluidos los casos de TB multirresistente. Se estimó que 417 976 de estos casos recibirían tratamiento y se curarían, en 160 830 fracasaría el tratamiento y fallecerían, 131 571 no recibirían tratamiento y presentarían curación espontánea y 307 000 no recibirían tratamiento y fallecerían. La carga económica total impuesta por los casos tratados y no tratados sería cercana a USD 6900 mil millones. La pérdida de productividad debida a la muerte prematura constituiría, con mucho, el elemento de mayor cuantía equivalente a USD 6000 millones (descontados), es decir el 86,6% del costo total. La pérdida de productividad por discapacidad seria de USD 700 millones (10,1%), los costos médicos por prestación de servicios serían 156 millones (2,2%) y los costos directos asumidos por los pacientes y sus hogares, aparte de los costos médicos, serían de USD 74 millones (1,1%).

CONCLUSIÓN: La carga económica de la TB en Indonesia es sumamente alta; la detección y el tratamiento de un mayor número de casos tendrían como resultado una disminución considerable del sufrimiento de los pacientes, además de una economía notable para la sociedad.

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Tuberculosis along the continuum of HIV care in a cohort of adolescents living with HIV in Ethiopia

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SUMMARY

SETTING: Eight health facilities in Ethiopia.

OBJECTIVE: To determine tuberculosis (TB) incidence rates and associated factors among adolescents living with the human immunodeficiency virus (ALHIV).

DESIGN: This was a retrospective cohort study. Adolescents enrolled in HIV care between January 2005 and 31 December 2013 constituted the study population. The main outcome variable was TB diagnosis during follow-up. Baseline World Health Organization (WHO) clinical stage, CD4 count, previous history of TB and use of isoniazid preventive therapy (IPT) were the main independent variables. We estimated TB incidence rates as incident cases per 100 person-years of observation (PYO). Cox regression analysis was used to control for confounders.

RESULTS: Of the 1221 adolescents screened, 1072 were studied; 60.1% were girls. TB incidence rate was 16.32 per 100 PYO during pre-antiretroviral therapy (pre-ART) follow-up but declined to 2.25 per 100 PYO after initiation of ART. Advanced WHO clinical stage (adjusted hazard ratio [aHR] 2.71, 95%CI 1.69–4.33) and CD4 count <350 cells/μl (aHR 2.28, 95%CI 1.10–4.81) predicted TB incidence in the pre-ART cohort. IPT use was associated with a significant reduction in TB incidence in the ART cohort, but not in the pre-ART group.

CONCLUSION: Although TB was a significant problem in ALHIV, timely administration of ART and IPT had a significant protective effect.

KEY WORDS: TB incidence; INH preventive therapy; pre-ART

TUBERCULOSIS (TB) is a global public health problem, with about 9 million new infections and 1.5 million deaths annually.[1] People living with the human immunodeficiency virus (PLHIV) comprise 13% of all TB deaths. However, data on the contribution of TB in adolescents to the global TB burden are limited. Lack of adolescent-specific health data is a global challenge.[2] Older epidemiological data suggest increased TB incidence during adolescence,[3,4] with the risk of TB being highest during infancy and adolescence.[5–7] More recent data suggested high TB prevalence among adolescents aged 12–18 years.[8]

As adolescents are socially active, and risk factors such as smoking, substance use and stress are more common in this group, their potential to transmit to their peers is high.[9–11] Furthermore, with increasing numbers of perinatally HIV-infected children reaching adolescence, it is important to have a clearer understanding of both the magnitude and factors contributing to TB incidence in this age group to be able to plan appropriate preventive measures.[10,11]

Data on the magnitude and determinants of TB among adolescents are scarce, and when they are reported they do not generally focus on adolescents living with HIV (ALHIV) or report separately on the 10–19 years age group.[8,12–14]

Our objective was to determine the magnitude of TB among adolescents at each phase of the HIV care cascade in an ALHIV cohort treated and followed at selected public health facilities in Ethiopia.[15]

METHODS

Study setting

This study was conducted in eight health facilities in Addis Ababa and Southern Nations', Nationalities' and Peoples' Regional State (SNNPR) regions of Ethiopia. Addis Ababa is the capital city of Ethiopia, whereas SNNPR is a predominantly rural region;

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however, most HIV patients were concentrated in urban areas even in SNNPR. The eight health facilities were selected based on the high ALHIV population, according to the investigators' prior knowledge about the sites. Despite the considerable progress made in preventing and controlling HIV and TB, Ethiopia remains a high HIV and TB burden country.[1,16]

Study design

We used a retrospective cohort study design. The study population constituted adolescents (age 10–19 years inclusive) enrolled for chronic HIV care between January 2005 and 31 December 2013. Participants included in the study had at least one documented clinic visit and were antiretroviral therapy (ART) naïve at the time of enrolment for chronic HIV care at the study clinic.

In accordance with national guidelines, all ALHIV were screened for TB symptoms at baseline and then at each clinic visit. Symptomatic patients underwent further clinical evaluation and diagnostic tests. The first-line diagnostic test during the cohort period was conventional sputum microscopy. Selected cases underwent chest radiography on physician recommendation. Rapid TB diagnostic tests were not part of the national guidelines at the time of enrolment.[17]

To calculate sample size, we used the baseline World Health Organization (WHO) clinical stage as main predictor of TB; those in stages III–IV were considered 'exposed' groups. Assuming a two-sided α of 0.05, a power of 0.8, TB in the exposed group as 10%, and TB in the unexposed group as 5%, we estimated the minimum sample size to be 948. Our assumptions were based on preliminary analyses of data from an ongoing larger cohort study at the study site. Using an electronic access database maintained at each ART clinic, we generated an age-stratified list of patients as a sampling frame. As the number of eligible adolescents was close to the estimated sample size, we included all eligible adolescents in the study.

Data collection and management

Patient charts and registers were used as data sources. At each site, two study nurses, assisted by data clerks, retrieved information using a data abstraction form. At the end of each work week, the site study nurses submitted all completed data abstraction forms to the co-investigator in the respective region. The co-investigator, a paediatrician with specialist level training in HIV, checked for errors and omissions and forwarded the paper data forms to the centrally based research assistant for further quality checking and secure storage. A centrally based data clerk entered data from the checked, approved data abstraction forms into Statistical Package for the Social Sciences, version 22.0 (IBM Corp, Armonk, NY, USA). Electronic data were stored in a password-protected data storage device and the paper data forms were kept in a lockable shelf. No patient identifiers were included in the electronic data.

The data abstraction tool was piloted in a few sites before starting actual data abstraction. All staff involved in data management were trained in the standard operating procedures of the study protocol. The principal author performed random checks of the completed data abstraction forms at regular intervals.

Definitions

The main outcome variable was TB diagnosis during follow-up as confirmed and recorded in patient registers according to the national guidelines by the treating clinician.[18] Patients in whom TB diagnosis was confirmed at least 4 weeks after the patient was in pre-ART care, but before the ART start date, were defined as having pre-ART TB. Patients who developed TB after 4 weeks of ART initiation were considered to have TB during ART.

We determined completion rates for isoniazid preventive therapy (IPT) from patient registers. Those who completed a 6-month course of IPT and were confirmed by clinicians as such were considered 'completed', those who received IPT for <6 months were categorised under 'did not complete', and those with missing information were recorded as 'no information'.

Information on adherence to cotrimoxazole therapy (CPT) was also retrieved from patient registers. Clinicians recorded either 'good' or 'poor' based on patient self-report. We determined adherence status as per the clinician's record at the time of the patient's last visit.

Data analysis

Data analysis was performed using SPSS version 22. TB incidence rate was calculated as the number of new episodes of TB per 100 person-years of observation (PYO). We checked for patterns of missing data and used list-wise deletion method for missing variables. A Cox regression survival analysis was used to control for potential confounders. TB diagnosis (as defined above) was the main outcome variable. Other variables included were baseline WHO clinical stage, CD4 count (categorised as <350 vs. $\geqslant 350$ cells/μl for the pre-ART cohort and <200 vs. $\geqslant 200$ cells/μl for the ART cohort), history of cough of >2 weeks, and IPT (ever used or not). Covariates included sex and address (as urban or rural) in the Cox model. Covariates with a P value of <0.25 in the univariate model were included in the multivariate model. Two-sided $P < 0.05$ was considered statistically significant.

Ethics

The National Research Ethics Review Committee, Addis Ababa, the Regional Health Bureau Ethical

Table 1 Baseline characteristics of adolescents enrolled in chronic HIV care at eight selected health facilities, Ethiopia, 2005–2013

Characteristic	*n* (%)
Region	
SNNPR	582 (54.3)
Addis Ababa	490 (45.7)
Total	1072 (100)
Median age, years	13
Female sex	644 (60.1)
WHO stage	
I–II	501 (46.7)
III–IV	544 (50.7)
Missing	27 (2.5)
Total	1072 (100)
CD4 count cells/μl, median [IQR]	228 [106–410]

HIV = human immunodeficiency virus; SNNPR = Southern Nations', Nationalities' and Peoples' Region; WHO = World Health Organization; IQR = interquartile range.

Review Committee, Hawassa, and the Institutional review Board of the College of Health Sciences, Addis Ababa University, Addis Ababa, approved the protocol. All research staff were trained in the ethical conduct of human subjects research. Measures to protect data security and confidentiality are described above.

RESULTS

Baseline characteristics

Of 1221 adolescents screened, 1072 who fulfilled the eligibility criteria were included in the analysis; 60.1% were girls and 87% came from urban areas. Half (50.7%) presented at an advanced WHO stage. Baseline CD4 values were available for 95.3% of patients, and the median CD4 count was 228 cells/μl. Table 1 gives the baseline characteristics of the participants. Only 142 (13.2%) of the patients received IPT during the entire follow-up (57 during pre-ART follow-up and 85 at or after ART initiation). Of these, 103 (72.5%) completed a full course of IPT, 22 (15.5%) did not complete IPT, and information was missing for 17 (12%); 84.5% of adolescents received CPT, 68.9% of whom were reported as having a good CPT adherence rate at their last visit.

Tuberculosis during pre-ART follow-up

Previous history of TB was present in 171 (16%) of the participants. A further 149 (13.9%) had history of TB at enrolment, 50.3% of whom had smear-positive pulmonary TB, 28.8% smear-negative pulmonary TB, 14.1% extra-pulmonary TB, and type of TB was not recorded in 6.7%. The total pre-ART follow-up period was 870.03 PYO, during which 142 adolescents were diagnosed with active TB, 46% of whom had a previous history of TB at baseline. TB incidence was 16.32/100 PYO (95% confidence interval [CI] 13.75–19.24).

Having advanced WHO clinical stage (adjusted hazard ratio [aHR] 5.68, 95%CI 3.72–8.68), CD4 count <350 cells/μl at baseline (aHR 1.85, 95%CI 1.21–2.84), previous history of TB (aHR 2.22, 95%CI 1.51–3.26) and history of cough of >2 weeks (aHR 4.25, 95%CI 2.81–6.44) were predictive of TB.

Table 2 Cox regression analyses of predictors of pre-ART TB incidence in adolescents living with HIV, Ethiopia, 2005–2013

Variable	Incident TB case	PY	Incidence/100 PYO	HR (95%CI)	aHR (95%CI)
Region					
Addis Ababa	69	437.51	15.77 (12.27–19.96)	Reference	Reference
SNNPR	73	432.53	16.88 (13.23–21.22)	1.09 (0.79–1.52)	1.14 (0.80–1.62)
Sex					
Female	85	531.11	16.00 (12.78–19.79)	Reference	Reference
Male	57	336.31	16.95 (12.84–21.96)	1.02 (0.73–1.43)	1.07 (0.75–1.52)
Cough*					
No	49	712.90	6.87 (5.08–9.09)	Reference	Reference
Yes	91	119.32	76.27(61.40–93.64)	9.51 (6.72–13.45)	1.85 (1.21–2.84)
WHO stage*					
I–II	30	640.84	4.68 (3.22–6.59)	Reference	Reference
III–IV	108	217.73	49.6 (40.9–59.6)	6.78 (4.48–10.23)	2.71 (1.69–4.33)
CD 4 count, cells/μl*					
⩾350	42	573.36	7.32 (5.35–9.81)	Reference	Reference
<350	96	270.77	35.45 (28.72–43.30)	2.81 (1.92–4.12)	1.85 (1.21–2.84)
Pre-ART IPT					
No	139	715.97	19.41 (16.38–22.85)	Reference	Reference
Yes	3	154.06	1.95 (0.49–5.30)	0.16 (0.05–0.50)	0.57 (0.17–1.86)
Previous history of TB					
No	76	870.04	8.73 (6.88–10.93)	Reference	Reference
Yes	66	84.84	77.78 (60.16–98.97)	6.23 (4.45–8.69)	2.22 (1.51–3.26)

* Numbers do not total 142 because of missing data.
ART = antiretroviral therapy; TB = tuberculosis; HIV = human immunodeficiency virus; PY = person-years; PYO = PY of observation; HR = hazard ratio; CI = confidence interval; aHR = adjusted HR; SNNPR = Southern Nations, Nationalities, and Peoples' Region; WHO = World Health Organization; IPT = isoniazid preventive therapy.

Table 3 Cox regression analyses of factors associated with TB incidence rate after ART, Ethiopia, 2005–2013

Variable	Incident TB case	PY	Incidence/100 PYO	HR (95%CI)	aHR (95%CI)
Region					
Addis Ababa	40	2009.76	1.99 (1.44–2.68)	Reference	Reference
SNNPR	24	833.77	2.88 (1.89–4.22)	1.96 (1.16–3.32)	2.69 (1.52–4.78)
Sex					
Female	25	1638.70	1.53 (1.01–2.22)	Reference	Reference
Male	39	1202.75	3.24 (2.24–4.39)	1.01 (0.61–1.67)	1.09 (0.65–1.84)
Cough					
Yes	12	557.39	2.15 (1.17–3.66)	Reference	Reference
No	52	2070.83	2.51 (1.89–3.27)	1.09 (0.58–2.05)	1.11 (0.55–2.21)
WHO stage*					
I–II	12	785.00	1.53 (0.83–2.59)	Reference	Reference
III–IV	51	2039.84	2.50 (1.88–3.26)	1.21 (0.64–2.31)	1.23 (0.63–2.38)
CD4 count, cells/μl					
⩾200	16	1034.02	0.9 (0.51–1.46)	Reference	Reference
<200	48	1776.82	4.64 (3.42–6.15)	1.73 (0.98–3.05)	1.92 (1.07–3.44)
Ever used IPT					
No	63	2387.82	2.64 (2.04–3.35)	Reference	Reference
Yes	1	455.71	0.22 (0.01–1.08)	0.08 (0.01–0.57)	0.06 (0.01–0.45)
Previous history of TB					
No	53	2202.88	2.41 (1.80–3.15)	Reference	Reference
Yes	11	635.26	1.73 (0.86–3.09)	0.57 (0.29–1.10)	0.64 (0.32–1.28)

* Numbers do not total 64 because of missing data.
TB = tuberculosis; ART = antiretroviral therapy; PY = person-years; PYO = PY of observation; HR = hazard ratio; CI = confidence interval; aHR = adjusted HR; SNNPR = Southern Nations', Nationalities', and Peoples' Region; WHO = World Health Organization; IPT = isoniazid preventive therapy.

IPT was associated with a reduction in TB incidence, but this was not statistically significant (aHR 0.55, 95%CI 0.16–1.91; Table 2).

Tuberculosis after ART initiation

Of 816 patients placed on ART, 98 were on anti-tuberculosis treatment at ART initiation, including 58 in the intensive and 40 in the continuation phases of treatment. Furthermore, 64 patients developed TB during 2843.53 PYO, yielding a TB incidence rate of 2.25/100 PYO (95%CI 1.78–2.86) after ART initiation. Incidence rate was highest during the first year of ART (16.7/100 PYO) compared with 2.3 and 1.6/100 PYO at between 1 and 5 years and >5 years, respectively. Being in advanced WHO clinical stage (aHR 1.23, 95%CI 0.63–2.38), having a CD4 count <200 cells/μl at baseline (aHR 1.92, 95%CI 1.07–3.43) and being from SNNPR (aHR 2.69, 95%CI 1.52–4.78) predicted higher TB rates. IPT use was associated with significantly lower TB incidence rate (aHR 0.06, 95%CI 0.01–0.45). Table 3 summarises the results for the ART cohort.

DISCUSSION

This is the first report of ALHIV-specific TB data from Ethiopia and one of perhaps only a few globally. We found a high TB incidence rate among ALHIV, especially during pre-ART and the first year of ART, which declined sharply after the first year of ART. Low baseline CD4 values, advanced clinical disease stage, previous history of TB and the presence of prolonged cough at baseline predicted TB occurrence. IPT was associated with a 94% reduction in TB incidence rate in the ART cohort. Our findings suggest the need to prioritise ALHIV for TB prevention, and highlight the need to be watchful for specific risk factors during the clinical care of adolescents.

Both the pre-ART and the after ART TB rates in our cohort are at least 10 times higher than those reported among non-HIV-infected adolescents. In rural Uganda, for example, TB incidence among adolescents aged 12–18 years was 0.235/100 PYO,[13] while among adolescents in a South African school, incidence was 0.45/100 PYO.[19]

Pre-ART TB incidence in our study was higher than that reported in adult cohorts from similar settings. In two reports from southern Ethiopia, pre-ART TB incidence ranged from 9.9 to 11.1/100 PYO.[20,21] However, overall TB incidence of 2.25/100 PYO in adolescents who received ART in our study was lower than the rate of 3.7/100 PYO in an adult cohort reported from southern Ethiopia.[21] In Addis Ababa, TB incidence was 3.1/100 PYO in an adult cohort of patients on ART.[22] In a South African adult cohort, incidence declined from 3.5 in the first year to 1.01/100 PYO in the fifth year.[23] The heightened risk of TB among adolescents in the current study despite improved TB prevention and control efforts in Ethiopia is a clear indication of the need to prioritise ALHIV as key populations for TB prevention.[1]

The predictive value of CD4 count and WHO clinical stage are well documented in adult cohorts.[18,24] We found similar results in the pre-ART cohort, but we did not find a significant association between TB incidence and WHO clinical stage after ART. This suggests that CD4 count may be a more reliable predictor of TB incidence in the adolescent cohort than WHO clinical stage.

Despite its proven effectiveness, IPT coverage was low in this age group. Our finding concurs with results from similar settings. This further confirms the need to strengthen IPT implementation.[18]

The higher TB incidence rate among ART patients from SNNPR was an unexpected finding. It could be a reflection of variations in the disease burden or a result of differences in case-finding efforts. Further analysis of epidemiological data is needed to better explain the regional variations.

Previous history of TB was associated with more than double the risk of TB in this cohort. Earlier studies among adult cohorts reported conflicting results,[23,28] but a more recent study from Brazil reported a two-fold risk of TB in patients with a previous history of TB; about 38% of the patients in that report had previous history of TB.[25] In our cohort, about 46% of patients who developed TB during pre-ART follow-up had a previous history of TB, which could be due to the higher overall TB burden in Ethiopia.[1] Reinfection due to weakened immune status is the underlying reason for TB recurrence in PLHIV.[26,27] As our cohort included patients from the pre-ART era over a decade before, they might have had TB and treatment for it long before starting ART. Our finding suggests the need for including previous history of TB as part of routine screening in high TB-HIV burden settings.

Our study had some limitations. TB diagnosis was based on microscopy or radiography, potentially leading to the underestimation of incident TB cases because of the low sensitivity of the diagnostic method. Due to the retrospective method of data collection, we were not able to determine the outcomes of treated TB cases, and data were missing on some key potential predictors such as smoking. Nevertheless, to our knowledge, these are the first adolescent-specific TB data among PLHIV in Ethiopia, and they will likely have broader implications with the increasing numbers of HIV-infected adolescents globally.

CONCLUSIONS

We found a high rate of TB incidence among ALHIV in public health facilities in two regions of Ethiopia. Although IPT and ART had a protective effect, IPT coverage was unacceptably low in this age group. The first year of ART was the period with the highest rates of incident TB cases, followed by the pre-ART period. TB programmes should prioritise ALHIV as a target group for TB prevention and control efforts, especially during the pre-ART period up to the first year after ART. Ensuring adequate IPT and ART coverage should be considered urgent priorities. Disaggregating routine TB data by adolescent age group can provide more information about TB in adolescents. Moreover, prospective studies with more comprehensive variables will provide further insights about the magnitude and predictors of TB in this age group.

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RESEARCH Open Access

Engagement of the private pharmaceutical sector for TB control: rhetoric or reality?

Niranjan Konduri*, Emily Delmotte and Edmund Rutta

Abstract

Background: Private-sector retail drug outlets are often the first point of contact for common health ailments, including tuberculosis (TB). Systematic reviews on public-private mix (PPM) interventions for TB did not perform in-depth reviews specifically on engaging retail drug outlets and related stakeholders in the pharmaceutical sector. Our objective was to better understand the extent to which the World Health Organization's (WHO) recommendation on engaging retail drug outlets has been translated into programmatic policy, strategy, and intervention in low- and middle-income countries.

Methods: The study included a content analysis of global-level documents from WHO and the Stop TB Partnership in five phases. A country-level content analysis from four data sources was performed. Global-level findings were tabulated based on key messages related to engaging retail drug outlets. Country-level findings were analyzed based on four factors and tabulated. National strategic plans for TB control from 14 countries with varying TB burdens and a strong private sector were reviewed.

Results: 33 global-level documents and 77 full-text articles and Union World Lung Health conference abstracts were included for review. Based on experience of engaging retail drug outlets that has emerged since the mid-2000s, in 2011 WHO and the International Pharmaceutical Federation released a joint statement on promoting the engagement of national pharmacy associations in partnership with national TB programs. Only two of 14 countries' national strategic plans had explicit statements on the need to engage their national pharmacy professional association. The success rate of referrals from retail drug outlets who visited an approved health facility for TB screening ranged from 48% in Vietnam to 86% in Myanmar. Coverage of retail drug outlets ranged from less than 5 to 9% of the universe of retail drug outlets.

Conclusions: For WHO's End TB Strategy to be successful, scaling up retail drug outlets to increase national coverage, at least in countries with a thriving private sector, will be instrumental in accelerating the early detection and referral of the 3 million missing TB cases. The proposed PPM pharmacy model is applicable not only for TB control but also to tackle the antimicrobial resistance crisis in these countries.

Keywords: Public-private mix, Tuberculosis, Pharmacists, Retail drug outlets, Private sector, Pharmacy associations

Background

There is no shortage of evidence that both regulated and unregulated private-sector retail drug outlets, also known as pharmacies, chemists, drug shops, drug sellers, drug vendors, or informal drug sellers, are often the preferred first point of contact for common health ailments due to their inexpensive services, ease of access, and lack of waiting times compared to public health facilities [1, 2],. There is substantial evidence regarding the health-seeking behavior of consumers, caregivers, and patients [3] related to childhood illnesses, malaria [4], sexually transmitted diseases [5], cough-like symptoms [6], prolonged cough [7], and tuberculosis (TB) [8, 9],. Systematic reviews on the role of private-sector retail drug outlets in the provision of health care [10] and their quality of services [11] and regulatory aspects [12] have examined this body of knowledge.

While 43 million lives were saved by TB treatment and care between 2000 and 2014, TB remains a scourge

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worldwide, and 9.6 million people contracted the disease in 2014 [13]. To end the TB epidemic by 2035, the World Health Organization's (WHO) End TB Strategy emphasizes tapping the full benefits of health policies and systems by engaging a much wider set of collaborators across government, communities, and the private sector. In 2013, WHO reported that 3 million people fail to get a quality-assured TB diagnosis each year and often seek care from multiple private-sector providers in their search for TB treatment. Private-sector retail drug outlets are a key ally in ensuring that patients are referred to appropriate and high-quality treatment providers in their neighborhood. WHO's first guideline on public-private mix (PPM) approaches for tuberculosis clearly spells out the range of interventions specifically needed for non-physicians, such as private-sector retail drug outlets, pharmacists, and traditional healers [14]. However, the extent to which this specific recommendation has been translated into programmatic policy, strategy, and intervention in low- and middle-income countries is unclear.

A WHO review of PPM interventions found that TB detection increased between 10 and 36% with the successful treatment of 90% of new smear-positive pulmonary TB cases [15]. One systematic assessment examined the concept and practice of PPM and concluded that national TB programs (NTPs) need guidelines to make decisions on which type of provider to engage to meet the Stop TB Partnership's global objectives [16]. A recent systematic review evaluated the performance of PPM programs against six health system themes [17]. Given the broader PPM focus, these studies did not perform in-depth reviews specifically on engaging private-sector retail drug outlets in TB control. The latter represent a particular challenge for PPM interventions because they exist in large numbers and are often staffed by low-skilled employees whose clients are looking for a quick remedy. Meanwhile, the PPM schemes ask the retail drug outlets to focus on referrals that bring no inherent benefit to the drug seller and sometimes resistance from the client.

To better understand the evolution of the recommendations concerning the engagement of private-sector retail drug outlets in TB control, we performed a content analysis of documentation from global agencies. We also reviewed and examined whether retail drug outlet engagement in TB control is merely rhetoric reflected in global guidelines and practiced in a handful of settings or reality reflected in country policy and practice. We examined whether NTPs, at least in countries with a large private sector, have embraced retail drug outlets and implemented interventions to engage them as part of their PPM strategy.

Methods

Global-level content analysis

We conducted the search in five phases. First, we reviewed all resources, tools, and publications available on WHO's PPM web page. We also reviewed relevant documents from WHO's Global TB program and Stop TB Partnership web pages. We performed a content analysis of all relevant documents for recommendations and manually scanned all documents to verify statements related to the purpose of this review. Second, we reviewed the publicly available WHO and Stop TB Partnership PPM subgroup meeting notes, or the agendas in the absence of meeting notes, from 2002 to 2015. We applied the search terms "pharmacy" and "pharmacist." Third, we reviewed WHO's annual global TB reports from 2000 to 2015 for the search terms "PPM", "public-private partnerships", "pharmacy", "pharmacist", "chemist", and "private sector." Fourth, we reviewed annual reports, strategic plans, and key Stop TB Partnership documents sourced from WHO's website from 2003 to 2015. Fifth, we reviewed 15 meeting reports and recommendations from WHO's Strategic and Technical Advisory Group for Tuberculosis from 2001 to 2015. In all instances, we hand searched additional documents mentioned or described in these documents and added them for review as appropriate.

Country-level content analysis

We searched PubMed and Google Scholar using free words at the time of this review (see Additional file 1 for search terms). For PubMed, an advanced search was used to find additional articles with the terms included in the title or abstract. We hand searched the bibliographies of relevant articles and contacted study authors for additional clarification. All articles were screened by one reviewer (ED) and verified by another (NK). Article inclusion criteria were those articles related to retail drug outlets and could be a commentary, an assessment of the situation, or an intervention. All other articles that had other PPM components or described such things as health-seeking behavior or diagnostic delays were excluded. Because we anticipated that there would be very few studies or articles that focused on retail drug outlets and TB control or included them as part of a broader PPM intervention, we expanded our search through three sources. First, we searched the abstract books of the Union World Conference on Lung Health published by the *International Journal of Tuberculosis and Lung Disease* from 2004 to 2014. We searched abstracts for the following terms: "pharmacy", "pharmacist", "chemist", "shops", and "seller". Second, we collected available national TB strategic plans or action plans specifically from countries with high TB burden and focused on 14 such countries where the private expenditure for health

was at least 45% or more of the total health expenditure and assessed country policy on PPM in relation to private pharmacy engagement [18]. Third, we retrieved the estimated number of licensed and unlicensed retail drug outlets relative to the country population against the TB burden for 13 of 14 countries (excluding India) to permit comparisons. The latter analysis was performed to assess public health implications of the relative level of scaling up PPM interventions involving retail drug outlets.

In this review, we consistently use the term "retail drug outlets" to reflect the various terms used in the literature, including drug seller, drug shop, medicine store, private pharmacy, chemist, informal drug seller, patent drug vendor, patent medicine vendor, and accredited drug dispensing outlet. However, during the multistage search process, we used these varying terms to identify relevant documents. From a regulatory standpoint, in the majority of the countries, outlets are generally classified into two categories. Category I includes those outlets that are legally allowed to sell only nonprescription medicine, also known as over-the-counter drugs, while Category II includes those outlets that are legally allowed to sell prescription medicines. In practice, there may often be no distinction in terms of what is being sold, but many other legal requirements are maintained.

Results

Global documentation: WHO and the Stop TB Partnership

A total of 33 global-level documents were reviewed. The content analysis of 16 key documents from the WHO and Stop TB Partnership websites is presented in Table 1. Pharmacists were first included as part of the formal definition of private providers in WHO's 2001 emerging policy framework to involve private practitioners [19]. A summary of the notes and presentations from eight Stop TB Partnership PPM meetings is shown in Table 2. Aspects of private pharmacy engagement were addressed in 2002, 2006, and from 2010 to 2014 in 11 Stop TB PPM subgroup meetings. The PPM subgroup dedicated significant time during the 2011 subgroup meeting to discussing and sharing experiences on anti-TB drugs and the private sector and engaging pharmacists. This meeting resulted in a concrete recommendation to the Directly Observed Treatment Short Course (DOTS) Expansion Working Group and the Stop TB Coordinating Board to disseminate widely the WHO/International Pharmaceutical Federation (FIP) joint statement on promoting the engagement of pharmacy associations and drug regulatory bodies in national partnerships to stop TB.

A summary of related information from WHO's nine annual Global TB reports is shown in Table 3. The momentum on overall PPM approaches gained traction between 2005 and 2010, and emerging results were shown in the 2011 and 2012 reports. No annual reports from the Stop TB Partnership, including those from TB REACH grants, had any information or statements that were significantly related to the purpose of this review.

Country-level findings

PubMed identified 32 unique articles for the search terms that were used, and seven articles that had a retail drug outlet component were included for review. The Google Scholar search identified 62 unique articles related to TB in the private sector, and five relevant articles were included for review. Among the Union World Conference on Lung Health abstracts between 2004 and 2014, we found 65 relevant abstracts for review. Including the 12 full-text articles sourced from PubMed and Google Scholar and 65 Union abstracts, a total of 77 relevant articles and abstracts representing 18 countries were analyzed based on four factors and tabulated (Additional file 2). Of the 18 represented countries, 11 were in Asia, five in Africa, and two in Latin America. India (17) had the most articles and abstracts included in this review, followed by Cambodia (9). Among the 77 articles and abstracts, 52 were interventions involving retail drug outlets, and 24 were assessments concerning any aspect of retail drug outlets, such as sales of anti-TB drugs and knowledge of providers. Only one abstract described a regulatory component concerning the restriction of anti-TB drugs involving key stakeholders, including the national medicines regulatory authority.

Only 15 of the 52 intervention-related articles and abstracts reviewed explicitly documented the specific number or percentage of referrals of presumptive TB cases from retail drug outlets or resulting smear-positive TB cases (Table 4). All other articles and abstracts had grouped numbers or percentages of referrals among all private providers in their overarching PPM interventions, making it difficult to obtain data on the contribution of referrals specifically among retail drug outlets. Between 2003 and 2014, there was no substantial progression or variation in the number of referrals regardless of the country setting. The success rate of referred patients who visited an approved health facility for TB screening varied from 48% in Vietnam in 2003 to 86% in Myanmar in 2014.

Of the 14 selected high-burden TB countries where the private expenditure for health was at least 45% of the total health expenditure, the most recent versions of national strategic plans for TB control were available for all but two. Of the 14 countries reviewed, the national strategic plans of 12 formally included retail drug outlet engagement primarily for referral of persons suspected of having TB (Table 5). Only Bangladesh and Indonesia had explicit statements on the need to engage their local

Table 1 Key Documents from the WHO and Stop TB Partnership Websites

Key documents	Key messages related to engaging private-sector retail drug outlets	Gaps
TB patients and private providers in India (1997) [44]	Exclude anti-TB drugs from private channels. Prescriber-oriented education in private drug-distribution channels. Delegation of TB control responsibilities to non-governmental organizations. Public-private collaboration for the delivery of documented TB cures.	No recommendation of engaging "drug retailers" despite documenting evidence of their TB drug dispensing practices.
Global Plan to Stop TB (2001–2005) [45]	DOTS strategy implementation specified for private practitioners, non-governmental organizations, hospitals, clinics, prisons, industry, and military.	No explicit mention of engaging private pharmacies.
Legislation and Regulation for TB Control (2001) [46]	Create an effective partnership with private-sector physicians to implement national guidelines on TB control. Envisage the regulation of a drug supply for TB exclusively through the public health system.	No mention of engaging private pharmacies.
Emerging policy framework for involving private practitioners (2001) [19]	First WHO document to include "private pharmacists" as part of the formal definition of private providers to be engaged in TB control. Global assessment in 23 countries focused on private physicians. Captured evidence on patient health-seeking behavior in pharmacies and unrestricted availability of anti-TB drugs.	Options for engagement prioritized only for physicians. Restriction on TB drug availability in the private sector specified without engagement of wholesalers and private pharmacies.
Improving TB Drug Management. Accelerating DOTS Expansion (2002) [47]	In the context of analyzing TB drug management practices and to inform decision-making, recommendations were made to monitor private pharmacies or private clinics if they are an important source of anti-TB drugs.	None
Expanded DOTS Framework (2002) [48]	Involve private-sector health providers for case detection and DOTS implementation.	No specification of private pharmacies as part of the private sector.
Expanding DOTS in a changing health system (2003) [49]	Considerations on how best to ensure standardized, high-quality, affordable drugs through all providers, including private pharmacies, will be necessary.	Engaging private pharmacies to ensure an uninterrupted supply of high-quality drugs was briefly considered in the context of the role of private providers. There was no mention of engaging private pharmacies from the perspective of patient case detection and referral.
PPM DOTS Practical Tool (2003) [50]	"Pharmacists" was mentioned several times throughout the document, including considerations on how to engage them. A sample referral form for non-physicians was included to encourage adaptation and use depending on the local context.	None
PPM Guidelines (2006) [51]	The guideline clearly lists the importance of engaging pharmacists, drug shops and non-physicians so that the poor and vulnerable can receive appropriate care and referrals. Interventions include identifying persons suspected of having TB, collecting sputum samples, making referrals, notifying/recording cases, and supervising treatment. Pharmacy associations were listed among various PPM stakeholders for engagement at the national level.	None

Table 1 Key Documents from the WHO and Stop TB Partnership Websites *(Continued)*

DOTS Expansion Working Group Strategic Plan (2006) [52]	The term "PPM DOTS" has evolved to represent a comprehensive approach to involve all relevant health care providers in DOTS. PPM-DOTS targets a wide range of audiences as well as private health care providers not yet sufficiently linked to NTPs. Private pharmacies were included among a variety of private providers.	None
Second Global Plan to Stop TB (2006) [53]	Promotes the wider and more strategic use of existing strategies for TB control with an explicit mention of engaging "private pharmacies" and the "informal health sector" for introducing or scaling up PPM-DOTS.	None
9th WHO STAG-TB Meeting (2009) [54]	Special session on policy change for improved quality and rational use of anti-TB drugs. Recommended to schedule anti-TB drugs as restricted with special reporting requirements for pharmacies and prescribers. WHO must develop approaches to engage pharmaceutical companies, professional associations, and pharmacies to curb unethical practices and promote rational use of anti-TB drugs.	None
PPM Scale up (2010) [55]	Non-physicians and private pharmacies were included as part of a PPM task-mix strategy. Pharmacists may be able to identify persons with TB-like symptoms, collect sputum samples, refer suspects, notify or record cases, and supervise treatment.	None
Third Global Plan to Stop TB (2011) [56]	There is good evidence that PPM approaches can increase the percentage of people who are diagnosed and receive high-quality treatment by between one-quarter and one-third, with health care providers, such as pharmacists, traditional healers, and private practitioners, often serving as the first point of contact for people with TB symptoms.	None
Role of pharmacists in TB care and control (2011) [57]	The WHO/FIP joint statement recommended engaging pharmacists and national pharmacy associations in TB control.	None
Engaging all providers for drug-resistant TB (DR-TB) (2015) [58]	Non-physicians, such as private pharmacists, are currently engaging in PPM for TB care and control. They can be similarly engaged in patient-centered care for DR-TB, such as by providing DOTS and identifying and reporting side-effects of second-line drugs. Pharmacists can also provide education to family members on infection control and strategies to prevent and manage stigma.	None

pharmacy professional association. This review found that, over the last two decades, the role of retail drug outlets has evolved from pilot projects and guidance in global documents to formal incorporation into country plans.

None of the 14 countries' national strategic plans explicitly establish targets for engaging private-sector retail drug outlets or necessarily prioritize urban or rural outlets. The public health contribution of retail drug outlets to TB case finding depends on the number of retail drug outlets in the country, the population, the relative TB burden, the percentage of engaged pharmacists who refer patients, and the percentage of clients with symptoms who are successfully counseled for

Table 2 Stop TB PPM Subgroup Meetings

Year	Aspects related to private-sector retail drug outlets
2002	Involvement of pharmacies was listed as an innovative approach. Incentives for pharmacy involvement in referrals and treatment.
2006	Pilot experience on engaging private pharmacies in Cambodia and drug vendors in Vietnam was mentioned.
2008	WHO Activities in the Americas Region: The experience of NTPs in engaging private pharmacies and traditional medicine is scarce. Mexico has an agreement with the national pharmacy association. Constraints in the Americas include limited knowledge of the role and coverage of the private sector, including private pharmacies. Donor perspective: USAID supported the following activities Cambodia: pharmacy staff and traditional healer training and referral systems. Ethiopia: training and referral systems for private pharmacies.
2010	Cambodia reported progress on engaging private doctors and pharmacists: 12,577 suspects were referred, 6,403 were evaluated, and 1,418 TB cases were identified (2005–2008). An analysis of patient health-seeking behavior helped to design the intervention. Ghana reported progress on working with regulatory authorities to restrict access to anti-TB drugs and to require private pharmacies to refer all persons suspected of having TB to the NTP.
2011	The terms "pharmacy" and "pharmacist" were mentioned 19 times in the meeting report and discussed frequently, as reflected in numerous presentations. The PPM secretariat was recommended to support the documentation and dissemination of innovative approaches, such as engaging pharmacists in TB care and control. NTPs and Ministries of Health were recommended to work with national pharmacy associations to tap the role of pharmacists in early case detection and improving TB treatment and care.
2012	One of the expected outcomes of the subgroup meeting was to produce practical tools on social franchising for and engaging pharmacies in TB care.
2013	Reported progress made on designing guidance and tools to engage private pharmacies.
2014	The meeting provided recommendations to address the knowledge gap on income sources and amounts for chemists to inform the types of incentives that might work. PPM programs must enforce regulation for the rational use of anti-TB drugs and accreditation systems for collaborating providers.

Table 3 WHO Annual Global TB Reports

Year	Private-sector pharmacy aspects
2005	Cambodia: Based on the findings of a 2002 study on the prevalence of health care-seeking behavior in the private-sector, Cambodia launched a pilot project to engage private practitioners and pharmacies. Kenya: Diagnostic and treatment services projects to engage all providers, including pharmacies, are ongoing.
2007	Cambodia: Planned activities include mapping the locations of private pharmacies and recording the training of non-NTP staff. The Philippines: Achievements include initiating operational research projects in PPM, including collaboration with pharmacies. South Africa: Achievements include engaging pharmacists, private-sector general medical practitioners, traditional health practitioners, community care givers, and community-based organizations in the referral and support of TB patients.
2008	Afghanistan: Achievements include conducting a study on the role of private pharmacies in the treatment of TB in the central region of Afghanistan. Planned activities include developing training modules for private practitioners and private pharmacies to engage all care providers. Kenya: Achievements include sensitizing pharmacists and additional private practitioners on TB to encourage the referral of TB suspects for diagnosis.
2010	Countries have prioritized different types of care providers, including pharmacies in Cambodia, private hospitals in Nigeria, public hospitals in China and Indonesia, social security organizations in Mexico, and prison services in Kazakhstan.
2011	In 20 countries for which data were available, PPM contributed approximately 20 to 40% of all notifications in 2010 in the geographical areas in which PPM was implemented *(no specific data for pharmacies)*. The role of pharmacists in TB care and control was discussed, including a box summary outlining the WHO/FIP joint statement.
2012	Intensified efforts by NTPs to engage the full range of care providers using PPM initiatives are also important; in most of the 21 countries that provided data, 10 to 40% of national notifications were from non-NTP care providers (*no specific data for pharmacies)*.
2013	No specific information pertaining to private-sector pharmacy engagement.
2014	No specific information pertaining to private-sector pharmacy engagement.
2015	In India, patients receive e-vouchers for standardized medications to be redeemed at no charge from private chemists.

referral by the pharmacist. Figure 1 compares 13 of 14 countries of comparable size (excluding India) for the first three of these factors (see Additional file 3 for data sources). This figure highlights different situations within countries. Cambodia, for example has a relatively low incidence of TB cases compared to other countries but very high per capita TB burden, with one retail drug outlet serving an average of 2,225 people. Consequently, based on the 77 articles and abstracts reviewed (Additional file 2), the coverage of retail drug outlets ranged from less than 5 to 9% of the universe of retail drug outlets in a given country.

Discussion

The findings from this review demonstrate one aspect of the evolution of PPM in TB diagnosis, care, and treatment over time. Despite the inclusion of private pharmacists in the 2001 WHO document, "*Involving private practitioners in tuberculosis control: Issues, interventions and emerging policy framework*," evidence of the engagement of this cadre of private-sector health providers appeared slowly over the following decade. For example, in 2004, the Union World Conference on Lung Health contained no abstracts that met the inclusion criteria for this review; however, by 2014, there were 14 qualifying abstracts. A similar trend was observed in global guidance documents. The term "private sector" was mentioned in the first WHO annual TB report in 2000; however, it wasn't until 2003 that the terms "public-private mix" and "public-private partnership" first appeared in WHO's annual TB report. Notably, 2003 was also the first year that the annual report included the term

Table 4 Number of Referrals or Smear-positive Cases from Retail Drug Outlets over Time

Country	Year	Number of retail drug outlets	Number of referrals	% screened among referrals	Smear-positive cases
Vietnam	2003	150	310	48% (149)	10
Bolivia	2005	70	41	27% (11)	3
Philippines	2005	no data	2,334	no data	no data
Philippines	2005	no data	1,550	37% (575)	83
Cambodia	2008	683	4,230	79% (3,356)	1,769
India (Tamil Nadu)	2010	402	101	no data	no data
Philippines	2011	119	942	11% (99)	14
India (2 cities)	2012	80	23	No data	8
Burkina Faso	2013	131	821	44% (361)	17
India (Andhra Pradesh)	2013	60	117	89% (104)	6
Myanmar	2013	99	224	65% (145)	18
India (Tamil Nadu)	2014	550	382	66% (252)	130
India (Andhra Pradesh)	2014	177	871	91% (792)	90
Myanmar	2014	212	no data	no data	53
Myanmar	2014	263	2,335	86% (2,013)	395

"pharmacies." The PPM subgroup meetings of the Stop TB Partnership showed a similar trend. While the first subgroup meeting took place in 2002, it was not until 2006 that "pharmacies/pharmacists," "chemists," and "seller" were included. Since that first inclusion, at least one of these terms has been in every meeting report or related document.

Need for tailored strategies to increase national coverage

The findings of this review have several implications for the potential role of retail drug outlets in TB diagnosis, care, and treatment. The primary finding is that a variety of articles and abstracts in varying geographic locations have demonstrated that retail drug outlets are willing and able to contribute to TB control efforts, as shown by the number of referrals (Table 4). However, given the diversity of the private sector in high-TB-burden countries and the reality that NTP budgets are stretched across competing priorities, a number of considerations are warranted as countries decide whether to scale up the engagement of retail drug outlets nationwide. None of the 77 reviewed articles and abstracts mentioned or described attempts to scale up retail drug outlet

Table 5 NTP Strategy or Action Plans

	% of private expenditure on health[a]	National strategic plan version	Private retail drug outlet engagement in strategy	Professional pharmacy association engagement in strategy[b]
Cambodia	79.5	2014–2020	X	
Afghanistan	78.8	2013–2017	X	
Nigeria	76.1	2015–2020	X	
Myanmar	72.8	2016–2020	X	
Philippines	68.4	2013–2016	X	
India	67.8	2012–2017	X	
Bangladesh	64.7	2015–2020	X	X
United Republic of Tanzania	63.7	2010–2015	X	
Pakistan	63.2	2015-2020	X	
Indonesia	61.0	2015–2019	X	X
Kenya	58.3	2015–2018	X	
Vietnam	58.1	2011–2015	X	
Uganda	55.6	2015–2020		
Democratic Republic of the Congo	46.9	2014–2017		

[a]Private expenditure on health as a percentage of total expenditure on health. WHO (2013) [18]
[b]Only if 'pharmacy association' was explicitly mentioned in the strategy instead of the generic term 'professional association'

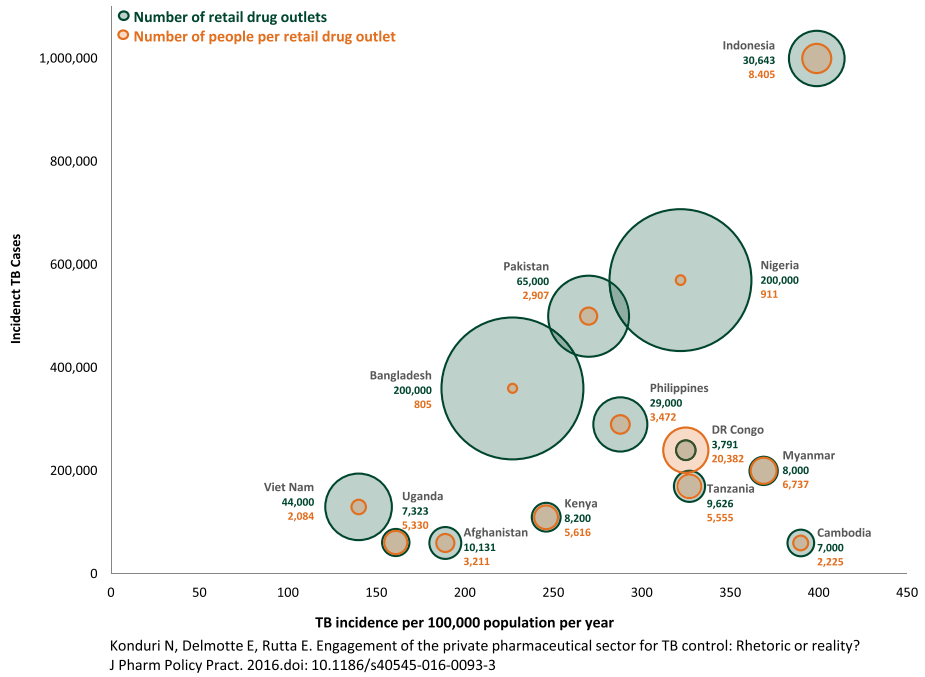

Fig. 1 Disease burden and estimated number of retail drug outlets in 13 countries [59]

engagement to increase national coverage. Pakistan had established progressive annual targets not only for engaging retail drug outlets but also for referrals and smear-positive TB cases to be detected [20].

For example, even if staff at between 10,000 and 20,000 of the drug outlets in Bangladesh or Nigeria are trained in rational antimicrobial dispensing and the referral of persons suspected of having TB, it is unlikely to have the desired public health effect, given that this comprises only 5 to 10% of the total universe of outlets. However, in most of the countries reviewed (appendix 2), the number of retail drug outlets engaged tend to be several hundred or over a thousand, which is a more manageable number to engage for quality improvement and regulatory efforts. Therefore, in Fig. 1, a large green circle (large number of outlets) means the retail drug outlet intervention is somewhat daunting and may need to rely on changing structures and incentives rather than on individual engagement, while a large brown circle (large number of clients per outlet) means that there are some useful economies of scale in engaging individual outlets. Figure 1 illustrates the reality not only for TB but also for the public health implications of irrational dispensing of antibiotics and the threat of antimicrobial resistance. Indonesia, which has a very high relative TB burden compared to Bangladesh, Nigeria, and Pakistan, has comparatively fewer retail drug outlets (30,643) that serve an average of 8,405 people per outlet, illustrating a different scenario that requires tailored strategies for maximum impact. India has an estimated 850,000 retail drug outlets. Through a public-private partnership with various entities, approximately 9% of the outlets ($n = 75{,}000$) in 12 selected districts across four states of India were engaged over a four-year period and accounted for nearly one-third of India's 1.2 billion people and one-third of its smear-positive TB cases [21, 22],. This partnership reported that approximately 10 to 15% of suspected cases referred by 7,000 pharmacists over two years were found to be positive and placed on treatment. Clearly, this example illustrates not only the success of engaging retail drug outlets but also the need for steady scale up to increase national coverage. Figure 1 highlights the numbers problem that is common for PPM interventions in general but most acute for retail drug outlet interventions [23].

Need for data on costs and number of unique referrals

This review also highlighted current gaps among the 77 articles and abstracts reviewed. For example, while many of the articles and abstracts described the potential returns of engaging retail drug outlets, none of the 12 full-text articles described the necessary inputs in terms of cost. TB programs that may need to prioritize among various PPM interventions must have an understanding of the estimated costs and cost effectiveness of each intervention [24, 25],. Such estimates, if modeled from pilot or small-scale initiatives, would allow TB programs to use a set amount of funding to determine which intervention would return the greatest output in terms of presumptive TB cases referred and

ultimately confirmed. For example, one program estimated an implementation cost of $176,635 related to engaging retail drug outlets in two regions of Tanzania to inform the NTP on a scale up strategy [26]. Another factor that may impact the cost effectiveness of such an engagement is the extent to which retail drug outlets serve as the first point of care for individuals with TB-like symptoms in a given country [27, 28],. While in some countries these providers are a first point of contact for communities, in others, different points of private care may be more common, such as private clinics or hospitals. For NTPs to better prioritize interventions, an estimate of the expected cost and return is needed. At a minimum, data on the costs to engage the retail drug outlet and the resulting additional yield in new cases are needed.

As shown in Table 4, there is a great need for data on the number of unique referrals (i.e., persons suspected of having TB or TB-like symptoms) provided by retail drug outlets as opposed to an aggregate number of referrals provided by all PPM providers. Such data would allow countries to compare the relative potential and benefit of engaging various actors within the realm of PPM. Data on periods of longer than two years on the number of referred persons who eventually visited an approved diagnostic clinic and were confirmed as smear-positive TB are also needed. Further studies are needed to examine the affordability and sustainability of incentive mechanisms, such as phone credit, compared to moral persuasion [29, 30].

Role of national pharmaceutical associations

Retail drug outlets do not operate in isolation and have linkages with wholesalers, distributors, and retail associations. While the majority of the 52 reviewed interventions primarily trained retail drug outlets to provide referrals, there are opportunities to engage other stakeholders as part of a multi-pronged intervention. A country's national pharmaceutical association must be engaged to tap into its network of pharmacy professionals and provide policy guidance to identify educational, managerial, and regulatory approaches to engage retail drug outlets. Cambodia, India, and the Philippines, for example, have involved their local pharmacy associations significantly in advocacy and mobilization among their member networks of retail drug outlets [21, 31, 32]. In our review of the national strategic plans of selected countries, only Bangladesh and Indonesia explicitly made statements of intent to engage professional pharmacy associations. While Cambodia, India, and the Philippines have engaged professional pharmacy and retail drug outlet associations, an explicit statement was not found in any of their updated 2015–2020 national strategic plans. It cannot be assumed that the engagement of professional associations is automatic because changes in program leadership and/or fluctuations in funding levels can influence priorities. Major knowledge gaps often found among retail drug outlets, such as the etiology of the disease, awareness of public-sector programs, and referrals to accredited private clinics, can be addressed by leveraging partnerships with the national pharmacy association.

For PPM interventions involving retail drug outlets, the intervention design needs to consider the different players and their roles and align incentives for each stakeholder (Fig. 2). In the short term, the focus may be to train staff at retail drug outlets to identify common presenting signs and symptoms of TB and refer patients to facilities where they can be properly diagnosed and managed. However, in the long term, more stakeholders need to be sensitized to exert their role. A country's national pharmaceutical association can work with pharmacy schools to revise their curricula to ensure that pharmacy assistants and pharmacists have the requisite knowledge on TB and the rational use of antimicrobials. Pharmacy schools are a major resource not only for any baseline assessments and evaluation activities but also for engaging pharmacy students to collect data, monitor retail drug outlet performance, recognize real-world challenges and stimulate thinking on options for policy and practice [33]. None of the 77 articles and abstracts reviewed explicitly mentioned engagement with pharmacy schools. Although there is paucity of such documented experiences, the Philippines Pharmacy Association produced an instructors' manual for revising pharmacy school curricula to incorporate content on TB control and the role of pharmacy professionals and retail drug outlets [34]. In addition, the Indian Pharmaceutical Association involved pharmacy students to act as TB community educators [35].

Role of national medicines regulatory authority

Among the 77 articles and abstracts reviewed, only one from Ghana documented a restriction on sales of anti-TB drugs without a formal legal ban. In countries with a large presence of local anti-TB drug manufacturers and where sales of anti-TB drugs are not legally prohibited, reaching and engaging these manufacturers and their wholesalers and distributors is a key to success. In collaboration with the national medicines regulatory authority, the NTP can work with local TB drug manufacturers to engage their sales representatives to promote the recommended WHO first-line medicines instead of loose, single TB tablets, to encourage dispensers to screen and refer those patients who present with persistent cough, and to not sell antimicrobials or anti-TB drugs until a proper diagnosis is made. Given the influence that wholesalers and distributors have on the retail sector, these actions could have a tremendous effect, particularly in countries with a large private-sector market [36]. For example, in Mumbai, India, certain retail drug outlets were

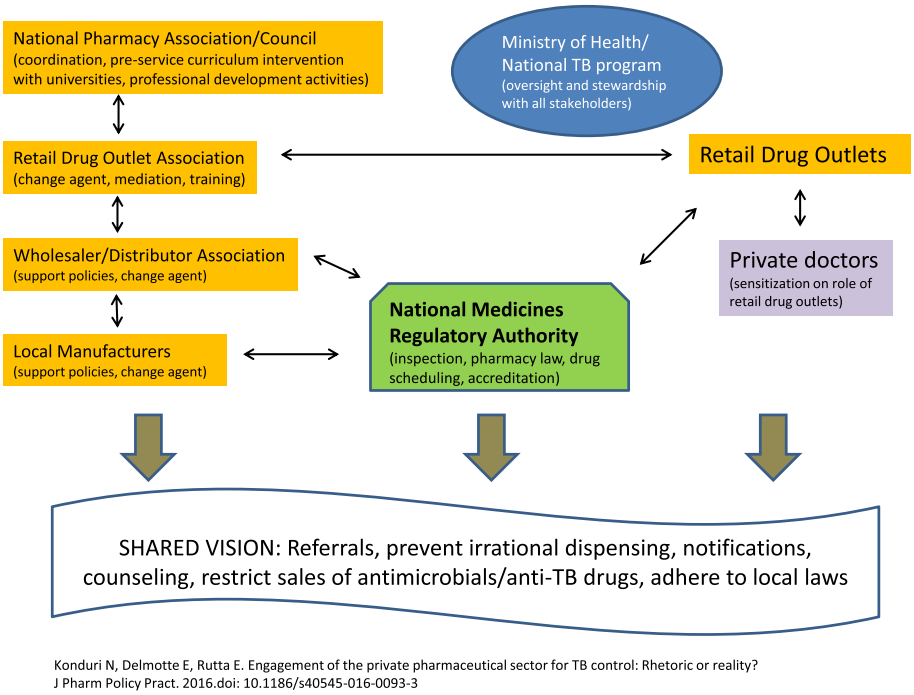

Fig. 2 A generic PPM Pharmacy Model [59]

accredited and recognized to serve as DOTS providers rather than perceiving this engagement as a loss of business.

The national medicines regulatory authority must be involved in relevant stakeholders meetings and training sessions involving retail drug outlets and related professional associations. Presenting a unified approach will ensure that all key stakeholders share a vision of improved early case identification and referral, reduced inappropriate antimicrobial and TB medicine sales, better contributions to overall TB notifications, and adherence to regulations and laws. In countries where an outright regulatory ban on the import and sale of anti-TB drugs is possible, consistent enforcement is key to preventing a recurrence because of the availability of anti-TB drugs in retail drug outlets [37]. In other settings, such as India, which issued a regulation in 2014 to limit over-the-counter sales of not only anti-TB drugs but also specific antimicrobials, enforcement is not sufficient, and incentives among all stakeholders must be aligned [38]. Recent systematic reviews of retail drug outlets and of the quality of pharmacy services in Asia found limited evidence of interventions related to regulatory enforcement and profit motives among private retail drug outlets [39, 40],. Therefore, it is important to place the PPM pharmacy model intervention within the larger PPM intervention package, particularly in countries with a high to moderate TB burden and a large proportion of the population receiving private-sector care [41]. It may be appropriate for referrals to be organized within private-sector providers, such as doctors, general practitioners, chest physicians, specialists, or clinics/hospitals, which may be where patients prefer to seek treatment. In most cases, the NTP may already be working with private-sector providers, such as general practitioners and hospitals.

Given the limited resources and competing priorities within the NTP, a long-term strategy could be for the Ministry of Health, particularly in countries with a large private sector to address other disease programs and invest in the PPM pharmacy model with links to the primary care system. Interventions that are comprehensive, such as Tanzania's accredited drug dispensing outlet model, could be a good investment in the long run for TB and other diseases, such as diarrhea and malaria, and for family planning services [42].

Limitations of this review

This review primarily focused on the role of private-sector retail drug outlets in TB control. It is possible that we may have missed some papers that did not use the terms in our search methodology. For example, community pharmacies in Bangladesh are called "village doctors" and are sensitized to refer patients suspected of having TB [43]. Because we excluded studies that were primarily focused on health-seeking behaviors of patients, we may have missed content related to the situation assessment of retail drug outlets and possible information on referrals. In addition, the relative scarcity of full-text articles on this topic compared to conference abstracts may have induced bias in the interpretation of past work involving retail drug outlets and the

referral of persons suspected of having TB. The content of the abstracts varied widely in the extent of information available, and we did not have access to posters or presentations that may contain some detail on the content. The primary authors attempted to contact at least 20 selected authors of the 65 reviewed abstracts for further clarification and to seek posters or presentation files but heard back only from 6 authors. We did not perform any formative review of other Union regional conference materials or of grey literature from international development partners working with NTPs. We may have also missed presentations made at other conferences related to private-sector health care. Finally, we excluded other studies that may have documented experiences of retail drug outlets for other health conditions, such as malaria, family planning and reproductive health, and HIV. Despite these limitations, our paper has value in blending information from global and country documentation related to the objectives of this review.

Conclusion

For the End TB Strategy to be successful, prioritizing and harnessing the power of private-sector retail drug outlets will be instrumental in accelerating the early detection and referral of the 3 million missing cases. The proposed PPM pharmacy model could become a scalable reality and make a significant contribution by harnessing both short-term solutions such as systematically engaging retail drug outlet dispensers and long-term solutions like partnerships with pharmacy schools and pharmacy associations that is long overdue in many countries. For decades, we have known about the potential of retail drug outlets but their level of engagement has not been commensurate with the TB burden and rapid growth of the private health sector. To successfully scale up PPM pharmacy models and reach ambitious targets, the international TB community must tailor interventions to the size and reach of each country's retail drug outlet network, particularly in settings with a thriving private sector.

In addition, from a public health and pharmaceutical policy perspective, the crisis of antimicrobial resistance is unlikely to be adequately addressed through a disease-specific framework. Country authorities must recognize the community's well-documented preference for seeking services from retail drug outlets and make a concerted effort to increase coverage of retail drug outlet engagement across the health system.

Additional files

Additional file 1: Search terms used. (PDF 187 kb)

Additional file 2: Summary of country-level studies or interventions involving retail drug outlets. (PDF 501 kb)

Additional file 3: Data sources for Fig. 1 – comparison of retail drug outlets with corresponding TB burden and population size. (PDF 113 kb)

Abbreviations

DOTS: Directly observed treatment short course; FIP: International Pharmaceutical Federation; NTP: National TB programs; PPM: Public-private mix; TB: Tuberculosis; USAID: United States Agency for International Development; WHO: World Health Organization

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Availability of data and materials

Data supporting the manuscript findings are available as additional files.

Authors' contributions

NK conceived of, designed, and led the review. NK and ED contributed substantially to the development and implementation of study methods, literature review and content analysis. NK and ED jointly prepared the first draft of the manuscript. ER contributed to analysis and interpretation of study findings, writing of the manuscript and synthesizing key messages. All authors read and approved the final version.

Authors' information

Emily Delmotte and Edmund Rutta were employed with Management Sciences for Health at the time of manuscript development.

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The authors declare that they have no competing interests.

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ORIGINAL ARTICLE
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User experience analysis of e-TB Manager, a nationwide electronic tuberculosis recording and reporting system in Ukraine

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ABSTRACT Ukraine has successfully implemented e-TB Manager nationwide as its mandatory national tuberculosis registry after first introducing it in 2009. Our objective was to perform an end-of-programme evaluation after formal handover of the registry administration to Ukraine's Centre for Disease Control in 2015.

We conducted a nationwide, cross-sectional, anonymous, 18-point user experience survey, and stratified the registry's transaction statistics to demonstrate usability.

Contrary to initial implementation experience, older users (aged >50 years), often with limited or no computer proficiency prior to using the registry, had significantly better user experience scores for at least six of the 12 measures compared to younger users (aged 18–29 years). Using the registry for >3 years was associated with significantly higher scores for having capacity, adequacy of training received and satisfaction with the registry. Of the 5.9 million transactions over a 4-year period, nine out of 24 oblasts (regions) and Kiev city accounted for 62.5% of all transactions, and corresponded to 59% of Ukraine's tuberculosis burden. There were 437 unique active users in 486 rayons (districts) of Ukraine, demonstrating extensive reach.

Our key findings complement the World Health Organization and European Respiratory Society's agenda for action on digital health to help implement the End TB Strategy.

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Introduction

The agenda for action of the World Health Organization (WHO) and the European Respiratory Society (ERS) for the End TB Strategy seeks digital health solutions to help advance patient care and improve surveillance and completeness of reporting on treatment outcomes [1]. Digital or electronic health applications to manage multidrug resistant tuberculosis (MDR-TB) can contribute to large-scale implementation of new diagnostics and novel medicines, particularly in resource-constrained countries [2]. One such electronic, web-based system is e-TB Manager, which manages much of the information needed by a country's national TB control programme. Developed by Management Sciences for Health (MSH, Arlington, VA, USA) with funding from the United States Agency for International Development (USAID), e-TB Manager integrates data across all aspects of TB control, including information on presumptive cases, patients, medicines, laboratory testing, diagnosis, treatment and outcome [3]. First developed and implemented in Brazil in 2004, e-TB Manager has been steadily implemented in more than a dozen resource-constrained countries including Ukraine, which is among the 30 high-burden MDR-TB countries worldwide, and the second highest in the European region [4]. After the institutionalisation of e-TB Manager following the end of international and south-to-south technical support in a given country, the source code and technical documentation is handed over to local authorities.

In 2008, as Ukraine confronted its growing TB and MDR-TB burden, it had no electronic system for its vast TB programmes, which were managed by various government agencies, including the state penitentiary system. The quality of the existing paper-based information systems varied. TB control was hampered by weak information, tracking and reporting systems. In response to a request from Ukraine's Ministry of Health, the USAID-funded Strengthening Pharmaceutical Systems programme, implemented by MSH, conducted an initial assessment of customisation needs for e-TB Manager and developed a version suitable for Ukraine. In 2009, e-TB Manager was piloted in six oblasts (regions). A 2010 WHO review of Ukraine's TB programme acknowledged e-TB Manager's beneficial role in supporting management decisions on improving programme performance, including information on case notification and treatment outcomes [5]. In 2010 and 2011, MSH continued to refine e-TB Manager based on user and Ministry of Health feedback, stabilised the platform to ensure continuous access, and trained pilot oblast users in data entry and use. In 2012, in accordance with Ukrainian law on patient confidentiality and information security, the state service of special communication and information protection issued a security certificate for e-TB Manager. With certification complete, the Ministry of Health designated e-TB Manager as the official "national TB registry". A companion Ministry of Health order specified official adoption, authorisation and requirements for use as well as reports to be produced.

Despite the Euromaidan revolution and socioeconomic crisis, the registry was implemented in all 24 oblasts of Ukraine and the city of Kiev by 2014. In October 2015, following >7 years of international assistance and partnership, the USAID-funded Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Programme, implemented by MSH, handed over the administration of the registry to the Ministry of Health's Ukrainian Centre for Disease Control (UCDC) [6]. The operation and maintenance of the registry is now funded partially by the government of Ukraine and partially by the Global Fund to Fight AIDS, Tuberculosis and Malaria. The objective of this article is to present key findings from our end-of-programme evaluation and share lessons learned from an implementer perspective, sought by the WHO/ERS task force statement, and for donors alike [7–10].

Methods

Our end-of-programme evaluation, part of the institutionally approved work plan and conducted according to the principles of the Declaration of Helsinki [11], drew upon selected usability methods [12]. We retrieved data to demonstrate the usability of the registry through a stratified analysis of geographical and anonymous TB health unit transaction statistics. No patient-related data were analysed. In addition, we retrieved and translated cross-sectional data from the UCDC that measured completeness of reporting by comparing paper-based records with those from the registry. A cross-sectional, anonymous, nationwide survey was conducted to assess the overall user experience of the registry. Our adapted questionnaire had six items on user characteristics, 12 core questions with a 0–7 scale (strongly disagree to strongly agree), and an open text box for comments (see online supplementary material) [13]. The UCDC administered the user experience survey in September and October 2015 and provided the survey's hyperlink to all active users.

Data analysis

Our hypothesis was that years of experience using the registry and years of experience working in the TB programme could influence user experience positively, as reflected in mean scores for the dependent variables (12 core questions). If a user is not knowledgeable about programmatic and clinical management of MDR-TB and its associated recording and reporting procedures necessary for both paper-based systems

and electronic applications, the job can be difficult [14, 15]. During the registry's initial implementation, older physicians and health workers resisted using the registry, had limited or no computer proficiency or preferred paper-based systems. During nationwide implementation, the UCDC expected better quality and timeliness of reporting from the rayons (cities and districts of administration) of Ukraine. Therefore, we compared the mean scores of the core questions among user groups based on years of experience using the registry, years working in a TB programme, age and location. We used t-tests to compare the mean scores among two groups of users and ANOVA to compare more than two groups using Tukey's *post hoc* test [16]. We also investigated three-way interactions and provided effect size values [17]. Statistical analysis was performed using SPSS (version 22.0; SPSS, Chicago, IL, USA). Only completed responses for all required questions were analysed. Anonymous, open-text comments were coded and analysed based on frequency and correlation of paired themes using NVivo 11 (QSR International, Melbourne, Australia) and presented visually [18].

Results

Survey findings

We received 329 responses from 565 active users (58.2% initial response rate), of which 303 included completed responses to all required questions (53.6% usable response rate). Cronbach's α was 0.81 for all 12 questions, and 0.85 for the 10 questions without the two reverse-worded questions, which indicated the questionnaire's high internal consistency. Table 1 provides demographic data of the respondents. Users with >3 years of experience using the registry generally had higher scores than those with <2.5 years of experience, and significance was detected for six out of 12 questions (table 2). Users with <2 years of experience working in the TB programme had relatively lower mean scores for all questions than those with more experience (table 3). For the two reverse-worded questions (Q9 and Q10), where lower scores are better and indicate the level of disagreement, those with 5–10 years of experience had the lowest scores and differed significantly from those with <2 years of experience.

Users aged >50 years had higher scores for at least eight questions and differed significantly from users aged 18–29 years for six out of the 12 questions (table 4). Users aged 30–39 years differed from their peers in their opinion that the registry does not help identify errors or inaccuracies in patient files (Q10), and the difference from users aged 18–29 years was significant. The comparison of mean scores between users at the oblast and rayon levels is presented in the online supplementary material. Significant findings for the three-way ANOVA examining the effects of years using the registry and years working in a TB programme, each with age and location, are presented in table 5. While there were main effects for years

TABLE 1 Demographic characteristics of respondents

Subjects	303
Sex	
Female	247 (81.5)
Male	56 (18.5)
Age group years	
18–29	32 (10.6)
30–39	96 (31.7)
40–49	87 (28.7)
⩾50	88 (29.0)
Location[#]	
National	2 (0.7)
Oblasts	79 (26.7)
Rayons	215 (72.6)
Years working in the TB programme	
Median	4
Mean±SD	7.1±6.7
Years using national TB registry	
Median	3
Mean±SD	2.7±1.2
Frequently used modules in the national TB registry	
Cases	293 (96.7)
Medicines	88 (29.0)
Management	177 (58.4)
Administration	26 (8.6)

Data are presented as n or n (%), unless otherwise stated. TB: tuberculosis. [#]: n=296.

TABLE 2 Comparison of responses by number of years using the national tuberculosis (TB) registry

	Total	Use of TB registry years		p-value
		<2.5	>3	
Subjects n	303	129	174	
Q1: I am satisfied with the national TB registry	5.55±1.41	5.32±1.54	5.72±1.28	0.018*
Q2: I have the required capacity to use all features of the national TB registry linked to my responsibilities	5.66±1.35	5.43±1.48	5.84±1.22	0.011*
Q3: I do not need more training on the national TB registry	3.93±2.40	3.94±2.36	3.92±2.44	0.94
Q4: I am happy with the available support and infrastructure for the national TB registry	4.91±1.88	4.75±1.94	5.02±1.84	0.22
Q5: It does not take me long to enter or find information in the national TB registry	5.16±1.88	4.97±2.04	5.30±1.75	0.13
Q6: The national TB registry helps me to improve case management	6.14±1.30	5.92±1.48	6.30±1.13	0.015*
Q7: The training I received on the national TB registry is adequate	4.89±1.99	4.60±2.10	5.11±1.88	0.032*
Q8: The information needed for case management is available in the national TB registry	6.06±1.25	5.81±1.40	6.24±1.10	0.005**
Q9: Generating reports from the paper system is faster than the national TB registry#	2.59±2.51	2.89±2.55	2.37±2.47	0.075
Q10: The national TB registry does not help me identify errors or inaccuracies in patient files#	3.01±2.52	3.10±2.48	2.94±2.56	0.575
Q11: My workplace productivity has improved because of the national TB registry	5.73±1.60	5.52±1.73	5.89±1.49	0.055
Q12: The national TB registry is reliable	5.82±1.41	5.60±1.50	5.99±1.31	0.019*

Data are presented as mean±SD, unless otherwise stated. A scale of 0–7 was used, where 0=strongly disagree and 7=strongly agree. Respondents were shown two ends of the scale for each question and were asked to rate their responses accordingly. #: reverse-worded questions; *: p<0.05, **: p<0.01.

TABLE 3 Comparison of responses by number of years worked in the national tuberculosis (TB) programme

	Total	Work in TB programme years				*Post hoc* test
		① <2	② 3–4	③ 5–10	④ >11	
Subjects n	303	78	85	72	68	
Q1: I am satisfied with the national TB registry	5.55±1.41	5.28±1.70	5.64±1.38	5.76±1.25	5.51±1.21	
Q2: I have the required capacity to use all features of the national TB registry linked to my responsibilities	5.66±1.35	5.10±1.71	5.74±1.32	6.06±1.03	5.79±1.00	②>①* p=0.011; ③>①*** p=0.000; ④>①** p=0.009
Q3: I do not need more training on the national TB registry	3.93±2.40	3.99±2.32	3.87±2.46	3.94±2.41	3.91±2.47	
Q4: I am happy with the available support and infrastructure for the national TB registry	4.91±1.88	4.62±1.95	5.11±1.76	4.94±1.89	4.96±1.95	
Q5: It does not take me long to enter or find information in the national TB registry	5.16±1.88	4.87±1.91	5.22±1.94	5.21±1.98	5.37±1.67	
Q6: The national TB registry helps me to improve case management	6.14±1.30	5.65±1.77	6.28±1.15	6.35±1.03	6.31±0.95	②>①** p=0.010; ③>①** p=0.006; ④>①** p=0.012
Q7: The training I received on the national TB registry is adequate	4.89±1.99	4.60±1.93	4.99±2.08	5.32±1.60	4.66±2.24	
Q8: The information needed for case management is available in the national TB registry	6.06±1.25	5.79±1.45	6.21±1.08	6.22±0.96	6.00±1.43	
Q9: Generating reports from the paper system is faster than the national TB registry#	2.59±2.51	3.29±2.64	2.54±2.54	2.13±2.34	2.34±2.38	③<①* p=0.023
Q10: The national TB registry does not help me identify errors or inaccuracies in patient files#	3.01±2.52	3.59±2.54	3.14±2.65	2.51±2.36	2.69±2.40	③<①* p=0.044
Q11: My workplace productivity has improved because of the national TB registry	5.73±1.60	5.41±1.81	5.67±1.76	6.07±1.24	5.81±1.43	
Q12: The national TB registry is reliable	5.82±1.41	5.54±1.51	6.06±1.15	5.90±1.46	5.76±1.48	

Data are presented as mean±SD, unless otherwise stated. A scale of 0–7 was used, where 0=strongly disagree and 7=strongly agree. Respondents were shown two ends of the scale for each question and were asked to rate their responses accordingly. #: reverse-worded questions. *: p<0.05, **: p<0.01; ***: p<0.001 (Tukey's honest significant difference).

TABLE 4 Comparison of responses by age categories

	Total	Age categories years				*Post hoc* test
		① 18–29	② 30–39	③ 40–49	④ >50	
Subjects n	303	32	96	87	88	
Q1: I am satisfied with the national TB registry	5.55±1.41	4.88±2.21	5.52±1.35	5.57±1.19	5.80±1.25	④>① p=0.009*
Q2: I have the required capacity to use all features of the national TB registry linked to my responsibilities	5.66±1.35	5.69±1.59	5.59±1.30	5.71±1.21	5.68±1.45	
Q3: I do not need more training on the national TB registry	3.93±2.40	3.56±2.46	3.68±2.40	4.07±2.43	4.19±2.35	
Q4: I am happy with the available support and infrastructure for the national TB registry	4.91±1.88	4.13±2.18	4.82±1.81	5.00±1.77	5.19±1.91	④>① p=0.031*
Q5: It does not take me long to enter or find information in the national TB registry	5.16±1.88	4.44±2.36	5.15±1.89	5.16±1.75	5.44±1.76	④>① p=0.048*
Q6: The national TB registry helps me to improve case management	6.14±1.30	5.53±1.79	6.08±1.19	6.17±1.29	6.40±1.16	④>① p=0.007**
Q7: The training I received on the national TB registry is adequate	4.89±1.99	4.78±2.13	4.60±2.09	5.08±1.93	5.07±1.88	
Q8: The information needed for case management is available in the national TB registry	6.06±1.25	5.53±1.81	6.05±1.17	6.06±1.26	6.26±1.03	④>① p=0.024*
Q9: Generating reports from the paper system is faster than the national TB registry#	2.59±2.51	1.78±2.39	2.91±2.64	2.31±2.23	2.82±2.62	
Q10: The national TB registry does not help me identify errors or inaccuracies in patient files#	3.01±2.52	2.13±2.39	3.56±2.62	3.08±2.43	2.65±2.43	②>① p=0.026*
Q11: My workplace productivity has improved because of the national TB registry	5.73±1.60	5.13±2.24	5.56±1.72	5.78±1.47	6.08±1.21	④>① p=0.020*
Q12: The national TB registry is reliable	5.82±1.41	5.50±1.93	5.68±1.49	5.85±1.22	6.07±1.23	

Data are presented as mean±SD, unless otherwise stated. A scale of 0–7 was used, where 0=strongly disagree and 7=strongly agree. Respondents were shown two ends of the scale for each question and were asked to rate their responses accordingly. #: reverse-worded questions. *: p<0.05, **: p<0.01 (Tukey's honest significant difference).

of experience using the registry with the selected variables and predominantly significant two-way interactions, the effect size, as expressed in η^2, was small. There was a medium effect size for age with years working in the TB programme concerning the belief that generating reports using a paper system is faster than the registry. Figures 1–3 and table 6 present the qualitative analysis of the relationship between major themes based on feedback from 74 out of 303 respondents.

Stratified usability analysis

Figure 4 presents the distribution of active users and average transactions per active user for each oblast stratified by TB burden. For example, the Lviv oblast with 91 active users had an average transaction of 3000 per active user, compared to the Mykolaiv oblast with half as many active users with an average transaction of 10 000 per active user. Nine out of 24 oblasts and Kiev city accounted for 62.5% of user transactions and 59% of Ukraine's TB burden. Online supplementary table S4 lists anonymous usability statistics among active registry users since inception for all 24 oblasts and Kiev (5.90 million cumulative transactions). As of June 2016, there were nearly 2000 registered users across 722 registered TB units nationwide. However, only 1319 users across 647 active TB units are considered active, because they logged at least one transaction in the previous 12 months. The highest average transactions per TB unit occurred in the Donetsk oblast (27 110), followed by Kiev city (19 037). Online supplementary table S4 highlights the extent of the registry's nationwide user coverage beyond oblast and city administration, particularly in rayons, towns and other cities. Figure 5 illustrates cumulative usability statistics for selected data fields from the registry's case module among the top 10 TB units by transaction volume. The UCDC-monitored, -analysed and -reported data on correspondence of paper-based records with the registry is provided in the online supplementary material.

Discussion

Our study sheds light on several factors associated with overall user experience and usability of the registry. Users gave high ratings to the registry's ability to help improve case management. Upon entering the registry, a dashboard presents real-time data for the patients being managed at that facility in areas such as case notification, treatment progress, medicines adherence, status of medicines and diagnostic

TABLE 5 Significant findings of three-way ANOVA

	Years using registry*age*location	Years working in TB programme*age*location
Q2: I have the required capacity to use all features of the national TB registry linked to my responsibilities	Main effect for years using registry: F (1, 279)=4.32, p<0.05, η^2=.01 No two-way interaction was significant	Main effect for years working in TB programme: F (3, 274)=5.07, p<0.01, η^2=.05 No two-way interaction was significant
Q3: I do not need more training on the national TB registry	Two-way interaction for years using registry*location: F (1, 279)=4.98, p<0.05, η^2=.02	
Q4: I am happy with the available support and infrastructure for the national TB registry	Main effect for age: F (3, 279)=2.74, p=0.04, η^2=.03 Two-way interaction for age*location: F (3, 279)=2.75, p<0.05, η^2=.03	
Q6: The national TB registry helps me to improve case management	Main effect for age: F (3, 279)=3.39, p<0.05, η^2=.03 Two-way interaction for age*location: F (3, 279)=3.87, p<0.05, η^2=.04	Main effect for years working in TB programme: F (3, 265)=4.78, p<0.01 η^2=.05 No two-way interaction was significant
Q8: The information needed for case management is available in the national TB registry	Two-way interaction for age*location: F (3, 279)=3.76, p<0.05, η^2=.04	
Q9: Generating reports from the paper system is faster than the national TB registry#	Main effect for location: F (2, 279)=4.85, p<0.01, η^2=.03 Three-way interaction for years using registry*age*location: F (3, 279)=4.35, p<0.01. η^2=.04	Main effect for location: F (2, 265)=3.58, p=0.02, η^2=.02 Two-way interaction for age*years in TB programme: F (8, 265)=2.74, p<0.01, η^2=.08
Q10: The national TB registry does not help me identify errors or inaccuracies in patient files#	Main effect for age: F (3, 279)=2.86, p<0.05, η^2=.03 Main effect for location: F (2, 279)=5.50, p<0.01, η^2=.04 Two-way interaction for age*location: F (3, 279)=2.97, p<0.05, η^2=.03	Main effect for age: F (3, 265)=3.03, p=0.03, η^2=.03 Main effect for location: F (2, 265)=4.48, p<0.01, η^2=.03 No two-way interaction was significant
Q11: My workplace productivity has improved because of the national TB registry	Main effect for age: F (3, 279)=3.61, p<0.01, η^2=.03 Two-way interaction for age*location: F (3, 279)=4.72, p<0.01, η^2=.04	
Q12: The national TB registry is reliable	Two-way interaction for age*location: F (3, 279)=3.28, p<0.05, η^2=.03	

TB: tuberculosis. #: reverse-worded questions.

supplies and tags to flag data quality issues. From an oblast administrator perspective, the chief TB doctor responsible for validating treatment protocols can easily review individual cases and laboratory results, validate the treatment regimen, remotely monitor adherence to clinical guidelines and take corrective action by using alerts embedded in the registry. Users strongly agreed that the information needed for case management is available in the registry. This is not surprising, given that the number of cases entered in the registry substantially increased from 120 472 in 2014 to 227 657 in 2016. A WHO assessment found that the proportion of missing information in the registry did not exceed 10% [19]. Complemented by the UCDC's analysis of data correspondence of paper-based reports with that of the registry (online supplementary material) and the usability statistics, the survey findings confirm that changes in the human element and behaviour change over time were important factors in users embracing the registry. Users with >3 years of experience with the registry at the rayon level, or aged >50 years had significantly higher mean scores for agreeing that information is available in the registry. By contrast, oblast-level users had significantly lower scores, possibly because these users are generally supervisors or administrators responsible for aggregating data, and are more likely to detect data quality issues such as for accuracy or completeness.

Users with >3 years of registry experience had significantly higher scores than users with less experience for satisfaction, capacity, adequacy of training received and perceived reliability of the registry; this finding is associated with longer use of electronic applications [20]. There was also a main effect on having capacity for number of years using the registry and number of years working in a TB programme,



FIGURE 1 Most frequent words and phrases based on user comments about the registry. Word cloud representing the most frequent words based on 74 user comments about the registry. The font size represents how frequently the terms occur. Only stemmed words were utilised, with a minimum length of three words; the word "registry" was not included in this analysis.

suggesting that with more use and experience, regardless of age, the user eventually gets comfortable with the registry and understands UCDC recording and reporting expectations. Contrary to the finding of another study [21], we found that older users generally had a positive user experience according to many of the variables and differed significantly from users aged 18–29 years, while another study reported no effect for age [22]. The WHO has promoted electronic TB recording and reporting to improve surveillance and support meaningful decision making based on access to accurate, timely and useful information [23]. Consequently, there was generally a high rating for improved workplace productivity due to the registry, particularly among older users. Management and clinical decisions can be made easily, reducing time to decision, as was briefly described in one oblast of Ukraine [24]. One chief TB doctor reported that the time taken to initiate antiretroviral therapy among TB patients dropped from 104 days to 48 days due to the registry.

With system issues (*e.g.* slow server or too many registry updates) being the dominant theme among user comments (figures 1–3), younger users probably have unmet expectations, including the need for more computers to minimise sharing. Compared to users aged 18–29 years, older users probably have lower expectations and have experienced tougher working conditions [25]. The USAID SIAPS programme and

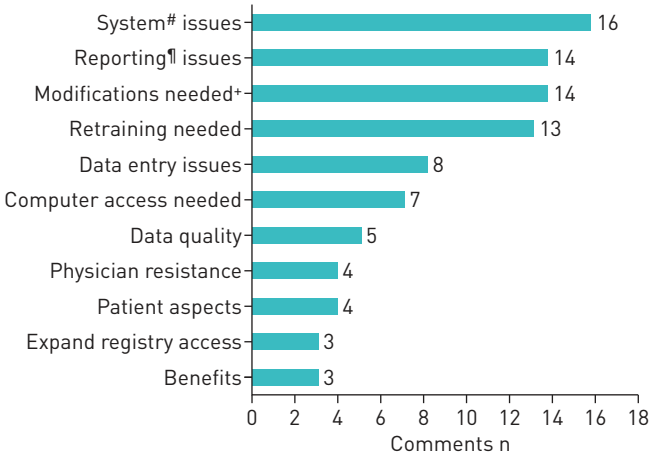

FIGURE 2 Major themes from the user comments. Comments from 74 users were coded into 11 major themes. #: server or registry platform; ¶: paper-based reports and registry data fields; +: suggestions on registry structure.

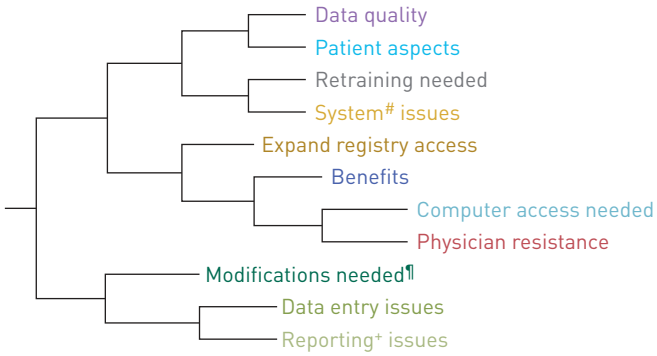

FIGURE 3 Dendrogram: themes clustered by word similarity. Themes clustered by word similarity: the dendogram is the result of a cluster analysis of user comments that clustered selected themes together if they have many words in common. Similar items are clustered together on the same branch and different items are positioned further apart. #: server or registry platform; ¶: suggestions on registry structure; +: paper-based reports and registry data fields.

the Global Fund to Fight AIDS, Tuberculosis and Malaria initially supported the purchase of 534 computers, but our survey found a moderate correlation between physician resistance and computer access (figures 1–3 and online supplementary material), which is consistent with previous studies [26]. Over the years, the UCDC has kept pace with necessary programmatic changes based on WHO guidelines and updated reporting requirements and upgraded the registry based on user feedback. From 2012 to 2016, 137 system updates were made for continuous quality improvement of the registry. The 10 most recent registry updates with pictorial instructions is a good example of e-learning methodologies promoted by the WHO and ERS [27]. A dedicated staff at the UCDC's national helpdesk fields on average 150 phone calls and emails a week, and after updates are released, this can jump to >1200 calls and emails each week. Yet, regardless of user characteristics, the overall mean scores on support and infrastructure were low. Additionally, there was a high level of user disagreement, as expressed in low mean scores on not needing more training and the moderate correlation of retraining needs with physician resistance, system issues and data quality (figures 1–3 and online supplementary table S3). Despite a relatively high score on having capacity, users expect annual training that can also serve to share experiences and improve data quality and reporting. However, training budgets in resource-constrained public-sector settings are limited. Increasing usage presents new challenges in the provision of user support. On-the-job mentoring, refresher training and supportive supervision contribute to a better user experience.

Our study findings have implications for other implementers interested in applying digital health applications in resource-constrained settings. In our experience, building sustained user (individual) and

TABLE 6 Correlation of key themes

Theme A	Theme B	Pearson's correlation coefficient
Patient aspects	Data quality	0.57
Physician resistance	Computer access needed	0.53
Physician resistance	Data quality	0.52
Retraining needed	Physician resistance	0.50
System issues	Retraining needed	0.48
System issues	Physician resistance	0.45
Retraining needed	Data quality	0.43
Physician resistance	Patient aspects	0.43
Data quality	Benefits	0.43
System issues	Data quality	0.42
Physician resistance	Expand registry access	0.41
Retraining needed	Expand registry access	0.39
Reporting issues	Data quality	0.37
Data quality	Data entry issues	0.37

There were 55 possible correlations of various themes that ranged from 0.08 to 0.57. This table represents the first 14 paired themes in rank order of correlation.

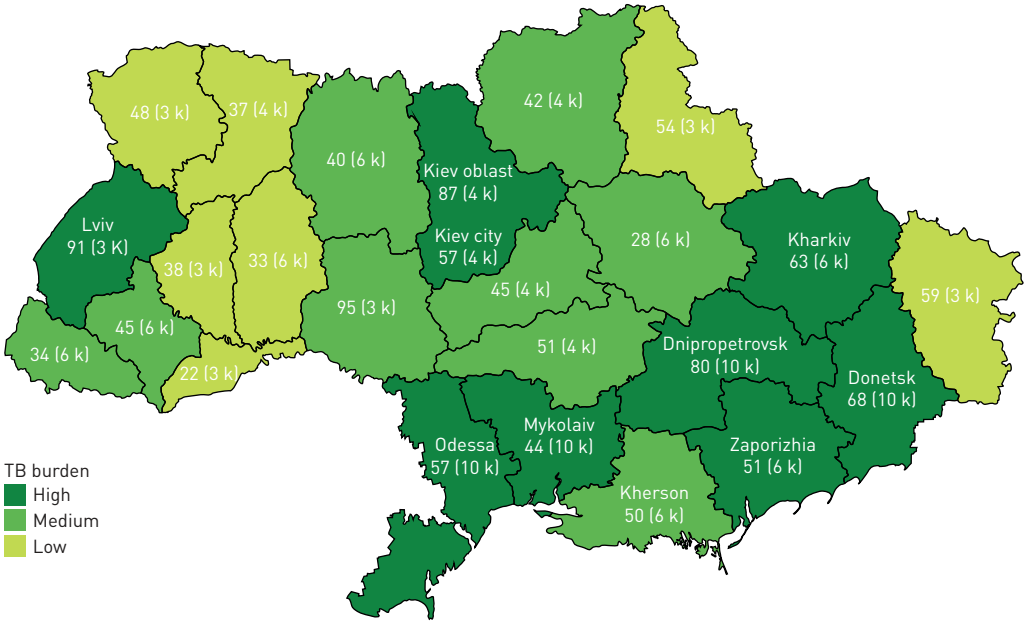

FIGURE 4 Usability statistics among active users of the national tuberculosis (TB) registry by TB burden. Each oblast (region) lists the number of active registry users in June 2016. Numbers in parentheses indicate average transactions per user in thousands (k). For example, the Kherson oblast with a medium TB burden has 50 active users with an average of 6000 transactions per user. Registry transactions are cumulative, from 2011 to June 2016 (online supplementary material). Nine out of 24 oblasts and Kiev accounted for 62.5% of cumulative transactions and 59% of the TB burden.

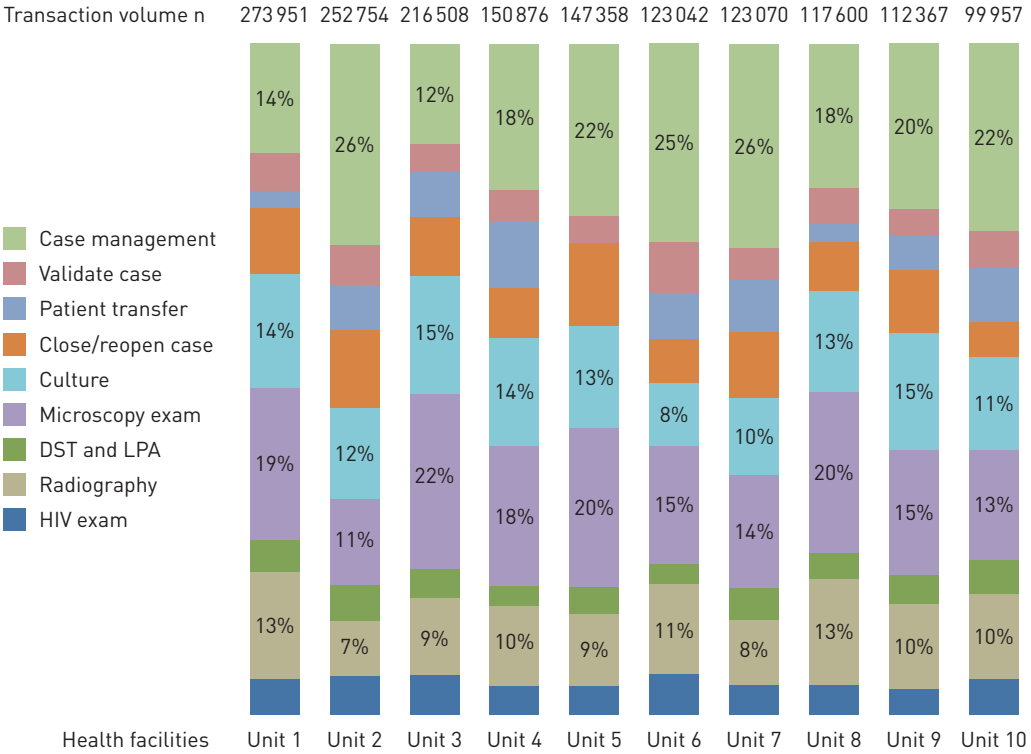

FIGURE 5 Usability statistics among top 10 tuberculosis (TB) units by transaction type for key data fields. This figure presents anonymous cumulative transaction statistics for selected data fields from the registry's case module from January 2012 to May 2016. The top 10 out of 647 active TB health units, accounting for nearly a third of the total cumulative transaction volume (5.9 million) are presented (online supplementary material). DST: drug susceptibility testing; LPA: line probe assay.

institutional capacity took >5 years, particularly when dealing with poor computer literacy, resistance to change and infrastructure challenges, among others. More research must be undertaken to investigate the root cause of persistent physician resistance. Future studies must compare differences between nurses, laboratory technicians, statisticians/data analysts, pharmacists and administrators. Such analysis could contribute to the development of an implementation model based on workflow design and job responsibilities for digital health application in other resource-constrained settings.

As with any observational study, our findings must be interpreted with caution (online supplementary material). Some or many of the findings presented here may have been addressed by the UCDC in the months following the cross-sectional survey. Although 66% of nearly 2000 registered users (June 2016 data) were considered active based on at least one transaction in the previous 12 months, a limitation of the usability statistics is that we do not account for passive users. We are unable to determine the registered passive users who could be senior ministry personnel who occasionally view the data, supervisors who only generate reports, university staff or researchers, who do not perform transactions, but were nevertheless granted access to the registry.

This is the first elaborate country-level study on user experience and usability of e-TB Manager in resource-constrained settings, and, to our knowledge, the first from Ukraine in the English language. Our end-of-programme findings are significant, given that Ukraine's global ranking on overall government usage of information communication technologies (ICTs) declined from 56 in 2009 to 124 in 2015 [28]. Ukraine's global ranking for political and regulatory environment for ICTs also declined from 95 in 2009 to 122 in 2015 (the same years as the nationwide scale-up of the registry). Notably, at the time of the survey, there were 565 active users, and this increased to 1319 active users over the following 9 months, illustrating the expansion of the registry to more TB units and rayons of Ukraine and increasing usage. The UCDC, now part of the public health centre, provided strong leadership and commitment to implementing the national TB registry despite political unrest, military conflict and socioeconomic challenges while confronting the MDR-TB burden [29–31]. In conclusion, Ukraine's experience and resilience in implementing its national TB registry using the e-TB Manager platform is testament to the WHO/ERS's digital health agenda to help implement the End TB Strategy and a model for other resource-constrained countries.

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User experience analysis of an eHealth system for tuberculosis in resource-constrained settings: A nine-country comparison

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ABSTRACT

Background: e-TB Manager, a web-based eHealth system has been successfully institutionalized in 10 resource-constrained countries that account for one-third of the world's tuberculosis (TB) burden, but user experience has never been evaluated.
Methods: A cross-sectional, anonymous survey in eight unique languages based on the targeted countries. e-TB Manager users included nurses, doctors, pharmacists, statisticians/data officers, laboratory professionals/assistants, health workers, and administrators.
Results: With an 86.3% completion rate for all required questions, 1,511 completed responses were analyzed. Users had worked in TB programs for a median of five years and had used e-TB Manager for a median of two years. Overall, 60.2% of respondents were female, 65% were clustered in the age groups of 30–39 and 40–49 years old, and nearly half (49%) were using e-TB Manager at the district and sub-district levels of a country's health system. Older respondents aged over 50, regardless of location and with at least 6 or more years of experience in public-sector TB programs, had higher mean satisfaction scores than did their younger counterparts. Overall, those who had used e-TB Manager for more than two years had significantly higher mean scores for the majority of the survey statements than did those who had used e-TB Manager for less than two years. Ukraine had significantly higher mean scores for finding patient information available in e-TB Manager and in its benefit in improving patient care compared to Brazil, Armenia, Nigeria, and Indonesia. Brazil and Ukraine differed significantly from five other countries in that they did not need additional training, thereby demonstrating their institutional capacity after more than five years of using e-TB Manager.
Conclusion: Although users gave high ratings to e-TB Manager in terms of helping to improve patient care, found it to be reliable, and were generally satisfied, there is need for a combination of refresher training and e-learning methodologies to keep pace with programmatic changes
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1. Introduction

The 2016 World Health Assembly's high-level, inter-ministerial roundtable acknowledged that digital health technologies, such as eHealth and mHealth are important to help achieve sustainable development goals including universal health coverage [1]. Digital health technologies are resource intensive and require a combination of capital, trained human resources, infrastructure upgrades, and funding for their maintenance [2]. A systematic review of electronic health record implementation in resource-constrained settings found that technical aspects, training programs, and infrastructure support all influence the effective use of the system, particularly in the more than half of reviewed projects that were donor funded [3]. Donors such as the United States Government and the Global Fund to fight AIDS, Tuberculosis and Malaria (Global Fund) are committed to funding digital health technologies and quality information systems that will promote better patient care and build resilient and sustainable health systems [4,5]. The Sustainable Development Goal 3 call for ending the tuberculosis (TB) epidemic by 2030, and the Global Plan to Stop TB makes the case for investing in digital patient information systems in various country and regional settings [6]. The World Health Organization's (WHO) digital health for the End TB strategy calls for applying digital health solutions to help advance patient care and improve surveillance and

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program management [7]. In particular, the use of digital health applications to manage multi-drug resistant TB (MDR-TB), a public health crisis is needed to help improve the accuracy of reporting on treatment outcomes [8]. Of the 30 high-burden MDR-TB countries, 23 reported using national electronic databases, and all TB patients were covered in 16 of those countries [9].

One web-based electronic database is e-TB Manager, which manages all information needed by public-sector national TB control programs under the authority of a country's Ministry of Health. It integrates data across all aspects of TB control, including information on suspects, patients, medicines, laboratory testing, diagnosis, treatment, and outcome [10]. First developed and implemented in Brazil in 2004, e-TB Manager is currently operating in over 1,600 active sites in 10 countries and managing more than half a million TB cases, MDR-TB cases, and presumptive TB individuals. e-TB Manager was implemented through multi-year serial global projects with seed funding from the United States Agency for International Development (USAID). Subsequently, country authorities sought additional funding from the Global Fund and mobilized resources from country health budgets for the continued implementation or expansion of e-TB Manager. At the country level, several stakeholders and partners were involved during piloting and implementation, particularly in the areas of user training programs, infrastructure support, and technology updates, while scaling up WHO recommended programmatic management of MDR-TB. e-TB Manager has been formally handed over to government authorities in nine of the 10 implementing countries and is used as part of TB surveillance, patient care from diagnosis to medication adherence, monitor treatment outcomes and manage medicines and diagnostics supplies.

While our project obtained serial feedback from users and national decision makers on their experience during e-TB Manager adoption and pilot phase to inform implementation strategies, no systematic user experience evaluation has been performed in any country after e-TB Manager's nationwide implementation. Some of the implementing countries are characterized by high turnover of trained users; the gradual withdrawal of donor funding and/or international technical assistance; and continued challenges in infrastructure support, such as need for computer upgrades, sporadic internet access, and interrupted electricity. In addition, e-TB Manager has not yet entirely replaced paper-based recording and reporting systems. An evaluation of the e-TB Manager user experience was deemed important to inform national authorities, donors and international technical agencies on future directions for e-TB Manager as a digital health application for WHO's End TB strategy [11,12]. The goal was to assess user experience with e-TB Manager as part of users' responsibilities in national TB control programs (NTPs) in 10 implemented countries. The specific objectives were to compare user experience: 1) by years of experience working in an NTP and using e-TB Manager; 2) by age and location; and 3) among individual countries.

2. Methods

2.1. Survey development

An adapted version of a survey to evaluate the Open Medical Record System (MRS) was utilized due to the instrument's suitability for resource-constrained settings [13]. The adapted 12-item survey was prepared by NK for internal team review for content and face validity. A multi-stage Delphi consensus method was applied to produce the final version of the survey. Two e-TB Manager subject matter experts provided feedback on the choice of words for clarity, particularly because the survey was to be administered in eight unique languages in eight countries and in English for two countries. We changed the Likert scale from the original survey to range from strongly disagree to strongly agree but retained the 0–7 scale. Over the last 10 years, our predecessor projects, international technical partners, and country TB programs have conducted training programs and orientation efforts to ensure that users and decision makers at varying levels of the health system have both knowledge and skills on the various features of e-TB Manager, such as case management, medicine supply management, report generation, and administration. To assess this, we introduced a new question, "*I have the required capacity to use all features of e-TB Manager linked to my responsibilities*" and made adjustments to five questions relevant to e-TB Manager. In addition, we ensured that the adapted English version was sufficiently clear for ease of translation into other languages for non-English speaking countries. We created six questions on user characteristics and demographics and added an open text box to enable users to share any feedback or suggestions (Appendix A).

Because e-TB Manager users such as nurses, doctors, pharmacists, statisticians/data officers, laboratory professionals/assistants, health workers and administrators in our target countries tend to have high workloads and significant data entry burdens, our intent was to have users complete the survey in the range of 5–10 min. We went through a second round of questionnaire review that included three additional colleagues who had provided technical assistance on e-TB Manager in resource-constrained countries. Further modifications were made to the wording, sequence of questions, and verification for face and content validity, and the survey was shortened until consensus was achieved. Subsequently, we invited our e-TB Manager focal project staff based in Namibia to review the revised questionnaire for content validity, clarity of wording, and length of time needed to complete the survey. No further changes were made based on this review.

2.2. Survey administration portal

Because we intended to administer the survey through an online mechanism, KS reviewed the comparative features and benefits of Google Forms, Survey Monkey, and Survey Gizmo. We selected Survey Gizmo's paid service due to its ability to efficiently create and administer the survey, its data management features and data analysis capabilities, and its reporting functions. Moreover, this portal had an excellent interface to administer non-English language surveys, which was one of our main requirements. Survey Gizmo is compatible with any device (e.g., smartphones, tablets, computers), which allows users to complete the survey from any platform. After learning that we could use Survey Gizmo's logic features to probe why a respondent chose a particular response, we further modified our adapted 12-item questionnaire. We added logic for the questions on perceived satisfaction with and reliability of e-TB Manager and on the adequacy of e-TB Manager training. If a respondent chose 0, 1, or 2 on the left end of the scale for the range of disagreement, Survey Gizmo would show an additional question only to this subset of respondents. In the additional question, we asked the respondent to explain why a low rating was chosen and offered a list of choices based on our programmatic experience (Appendix A). With six demographic and user characteristic questions and 12 core questions, the total length of the survey was a minimum of 18 questions and could increase to 21 questions if the user chose a rating of 0, 1, or 2 for the three logic-based questions.

The survey was designed to be anonymous, and no respondent identifiers, such as the name of the health facility or the user's email addresses, were tracked or collected. Initially, responses to all survey questions were required, and if a user skipped a question and clicked the next page button, Survey Gizmo would prompt the user to complete the required question. We eliminated this requirement for the question on e-TB Manager level of use and location of the

Table 1
Participating countries.

Country	e-TB Manager year of introduction[a]	Survey language	Supporting project for survey	Approval provided by
Armenia	2009	Armenian	USAID-funded Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program, administered by Management Sciences for Health (MSH)	NTP Director
Azerbaijan	2008	Azeri	USAID SIAPS Program, MSH	N/A
Bangladesh	2010	Bangla	USAID SIAPS Program, MSH	NTP Director
Brazil	2004	Portuguese	USAID SIAPS Program, MSH	Health Surveillance Secretariat, NTP
Cambodia	2011	Khmer	USAID Health Information Policy and Advocacy Project, Palladium Group	NTP Director
Indonesia	2009	Bahasa Indonesia	USAID Challenge TB Project, KNCV Tuberculosis Foundation	NTP Director
Namibia	2010	English	USAID SIAPS Program, MSH	MDR-TB Advisor
Nigeria	2011	English	USAID SIAPS Program, MSH, and USAID Challenge TB Project, KNCV Tuberculosis Foundation	Assistant NTP Director
Ukraine	2009	Ukrainian	USAID SIAPS Program, MSH	NTP Director
Vietnam	2011	Vietnamese	USAID SIAPS Program, MSH, and USAID Challenge TB Project, KNCV Tuberculosis Foundation	NTP Director

[a] After a year of introduction, there was a pilot phase of at least two years, depending on each country context, before the scale-up process began.

user (i.e., central/national, province/state, or district/sub-district) in case the respondent did not wish to indicate his or her primary work location. This meant there were 17 required questions and one optional demographic question.

2.3. Institutional permission

The anonymous user experience survey was part of our ongoing programmatic monitoring and evaluation efforts of existing donor-approved e-TB Manager-related project workplans, which are conducted in collaboration with country government authorities and their local technical partners. We sought formal permission from the relevant government authority in a country's NTP either directly or through our partner project in-country (Table 1) and was conducted according to principles of the Declaration of Helsinki [14].

Of the 10 countries using e-TB Manager, we obtained approval from all except Azerbaijan, which opted out of the survey. Each NTP director received the request in writing along with a copy of the survey. In some cases, the survey needed to be translated before beginning the approval process. The written request explained the survey administration methodology and how user experience feedback could inform ongoing quality improvement efforts. Any subsequent questions or clarification needed by the country authority were addressed through either face-to-face meetings with our personnel or project partners on the ground.

2.4. Survey translation verification and administration process

As shown in Table 1, seven of the nine participating countries required that the survey be translated into the local language. The translation was primarily performed by either the project staff or NTP program staff. Any questions related to an English word or phrase during translation were resolved via email, phone calls, or in person, depending on the country. For each of the seven countries where the survey was to be administered in a local language, we sought translation verification by at least two persons familiar with both English and use of e-TB Manager in the given country. Any needed modifications to the translated text were made, and the final version was sent back to the survey team lead (NK). The translated survey was then loaded into Survey Gizmo for the given country. The dedicated country web hyperlink of the survey was sent to the country focal person to verify that the translated survey was loaded accurately. Each country was asked to test the web survey version using dummy data and report back if there were any errors. A sample cover note was provided for adaptation and translation for the NTP Director or designate at the country level to disseminate the survey invitation, which assured users of the anonymity of their response.

The survey administration period varied depending on when approval was received, with all surveys conducted between September 2015 and July 2016. In collaboration with the country NTP, we used a range of methods to disseminate the survey, starting with email dissemination (Appendix B, table B1). In some countries, email was not effective, and we subsequently sent the survey invitation through e-TB Manager's system dialogue box, which is seen after the user logs into the system. At least one reminder was sent in each country, and additional follow-up phone calls to state or regional supervisors in some countries were made. All responses were recorded in Survey Gizmo and only one author (NK) had access to maintain the anonymity and confidentiality of the responses.

2.5. Data analysis

Our hypothesis was that years of experience using e-TB Manager and years of experience working in the NTP could influence user experience as reflected in mean scores for the dependent variables (12 core questions). If one is not knowledgeable with programmatic and clinical management of MDR-TB and its associated recording and reporting procedures necessary for both paper-based systems and electronic applications, the job can be difficult [15,16]. Therefore, we compared the mean scores of the core questions among user groups by categories based on years of experience using e-TB Manager, years working in the NTP, age, and location. We used *t*-test to compare the mean scores among two groups of users and analysis of variance (ANOVA) to compare more than two groups with Tukey's post-hoc test. We also investigated three-way interactions and provided effect size values [17]. For the third objective on comparing mean scores for all nine countries, ANOVA was performed using Scheffe's procedure, the conservative post-hoc test [18]. Statistical analysis was performed using SPSS package, version 22 (SPSS Inc., Chicago, IL, USA). Only completed responses for all required questions were utilized for the statistical analysis.

Table 2
Years working in National TB Program and Years using e-TB Manager.

	Armenia (n = 68)	Bangladesh (n = 220)	Brazil (n = 431)	Cambodia (n = 32)	Indonesia (n = 176)	Namibia (n = 38)	Nigeria (n = 150)	Ukraine (n = 303)	Vietnam (n = 93)	All countries (n = 1,511)
Number of years working in National TB Program										
Mean	9.1	10.5	8.3	8.8	4.6	5.9	8.0	7.1	7.7	7.8
Median	7.0	8.0	5.0	2.5	4.0	5.0	6.0	4.0	5.0	5.0
Std Dev	8.4	8.4	7.7	10.1	3.7	3.6	6.3	6.7	7.4	7.3
Min	1.0	0.5	0.5	1.0	0.3	0.5	1.0	1.0	1.0	0.3
Max	44	37	44	34	22	14	30	37	33	44
Number of years using e-TB Manager										
Mean	2.3	2.3	2.8	1.6	2.1	2.1	2.0	2.7	2.0	2.4
Median	2.0	2.0	2.0	1.0	2.0	2.0	2.0	3.0	2.0	2.0
Std Dev	0.8	1.3	1.8	0.9	1.3	1.4	1.3	1.2	1.2	1.4
Min	0.5	0.5	0.5	1.0	0.3	0.5	0.5	0.5	1.0	0.3
Max	4.0	6.0	8.0	4.0	7.0	6.0	6.0	6.0	6.0	8.0

3. Results

3.1. Response rates

We received 1,751 responses from 2,146 individuals who were active users of e-TB Manager at the time the cross-sectional survey was conducted, representing an initial response rate of 81.6%. Of the 1,751 responses, there were 240 partial responses, resulting in an 86.3% completion rate (n = 1,511) for all required questions. Among the nine countries, the median effective response rate was 77.1%, and the average was 73.3%. Appendix B lists the methods for calculating the response rate and the specific duration of the survey administration in each country [19]. The cronbach's alpha for our 12 core questions was 0.82, indicating high internal consistency of our adapted questionnaire. Without the two reverse worded questions, the cronbach's alpha was 0.86 for the remaining ten questions.

3.2. Characteristics of respondents

Among the nine countries, users reported working in the NTP for a median of five years (M = 7.8 years, SD = 7.3). Table 2 provides similar information for each country along with a box-and-whisker diagram (Fig. 1). Overall, users reported using e-TB Manager for a median of two years (M = 2.4 years, SD = 1.4). Females comprised at least 60% of the proportion of respondents in Armenia, Brazil, Indonesia, Namibia, and Ukraine (Fig. 2). Vietnam and Indonesia had the highest proportions (70% or more) of respondents under the age of 40. In Armenia, Brazil, Namibia, and Nigeria, at least 60% of users were over the age of 40 (Fig. 3). Across the nine countries, nearly half (49%) of respondents were at the district or sub-district level, followed by 40.8% at the state, province, or regional level and 8% at the central or national level (Fig. 4). Thirty-three respondents (2.2%) did not answer this optional question. The proportion of users at the district or sub-district level in a country's health system was highest in Bangladesh (89.5%), followed by Ukraine (71%) and Namibia (68.4%). The highest proportions of respondents at the province level were in Armenia (70.6%) and Vietnam (67.7%).

3.3. Comparison of responses by user characteristics

3.3.1. Years of experience using e-TB Manager and working in NTP

Overall, those who had used e-TB Manager for more than two years had significantly higher mean scores for all but two reverse-worded questions than did those who had used e-TB Manager for two years or less (Table 3). Respondents with less than three years of experience had significantly lower mean scores for perceived capacity of using all features of e-TB Manager linked to their specific responsibilities and adequacy of training received compared to all other users with progressively more years of experience working in an NTP (Table 4). Users with more than 11 years of experience working in an NTP had significantly higher mean scores for nine of twelve questions compared to users with less than three years of experience. Regardless of years of experience working in the NTP, there was no significant difference in mean scores for improved workplace productivity associated with using e-TB Manager.

3.3.2. Age

There were no significant differences among age groups on the perceived capacity of using e-TB Manager (Table 5). However, younger users (18–29) had significantly lower mean scores for the statement, "I do not need more training on e-TB Manager" compared to users aged 30–39 ($p < 0.05$), 40–49 ($p < 0.05$), and over 50 ($p < 0.00$). Users aged over 50 showed significant differences compared to their younger counterparts in the three age categories. They had significantly higher mean scores compared to users aged 18–29 ($p < 0.00$) and 40–49 ($p < 0.01$) regarding adequacy of training received and significantly higher mean scores compared to users aged 18–29 regarding the support and infrastructure received for e-TB Manager ($p < 0.05$). They also differed significantly from users aged 30–39 ($p < 0.05$) on the statement, "e-TB Manager does not help me identify errors or inaccuracies in patient's files."

3.3.3. Location

There were variations in mean scores for the 12 core questions depending on the user-reported location (Table 6). Users at the district level differed significantly from those at the central ($p < 0.05$) and province ($p < 0.00$) levels in their belief that the information needed for case management is available in e-TB Manager. Compared to province-level users, those at the district level had significantly higher satisfaction ($p < 0.05$), workplace productivity ($p < 0.05$), and perceived reliability ($p < 0.00$). While there were no significant differences for user location on perceived capacity and adequacy of training received, both province- ($p < 0.00$) and district-level ($p < 0.01$) users differed significantly from central-level users on the statement, "I do not need more training on e-TB Manager."

3.3.4. Three-way interaction

3.3.4.1. Years using e-TB Manager, age and location. While there were main effects for the dependent variables and predominantly significant two-way interactions, the effect size, as expressed in η^2, was small (Table 7). There was a three-way interaction for age*location*years using e-TB Manager on the belief that generating reports from paper systems is faster than e-TB Manager. No other three-way interaction was significant. There were significant two-way interactions for location*years using e-TB Manager for satisfaction (Q1), not needing more training (Q3), not taking long to

Table 3
Comparison of responses by years using e-TB Manager (Mean, SD).

	Total (n = 1,511)	2 years or less (n = 860)	More than 2 years (n = 651)	p value
Q1: I am satisfied with e-TB Manager	5.43 (1.55)	5.31 (1.61)	5.58 (1.47)**	p = 0.001
Q2: I have the required capacity to use all features of e-TB Manager linked to my responsibilities	5.35 (1.62)	5.08 (1.71)	5.71 (1.43)***	p = 0.000
Q3: I do not need more training on e-TB Manager	3.15 (2.45)	2.86 (2.41)***	3.53 (2.44)	p = 0.000
Q4: I am happy with the available support and infrastructure for e-TB Manager	4.84 (1.88)	4.76 (1.90)	4.96 (1.85)*	p = 0.037
Q5: It does not take me long to enter or find information in e-TB Manager	5.17 (1.79)	5.02 (1.86)	5.36 (1.67)***	p = 0.000
Q6: e-TB Manager helps me to improve case management	5.70 (1.55)	5.59 (1.57)	5.84 (1.51)**	p = 0.003
Q7: The training I received on e-TB Manager is adequate	4.22 (2.25)	3.82 (2.31)	4.75 (2.06)***	p = 0.000
Q8: The information needed for case management is available in e-TB Manager	5.47 (1.50)	5.34 (1.51)	5.65 (1.45)***	p = 0.000
Q9: Generating reports from the paper system is faster than e-TB Manager[a]	2.54 (2.39)	2.60 (2.37)	2.46 (2.41)	
Q10: e-TB Manager does not help me identify errors or inaccuracies in patient files[a]	2.72 (2.32)	2.70 (2.29)	2.75 (2.37)	
Q11: My workplace productivity has improved because of e-TB Manager	5.08 (1.85)	4.95 (1.85)	5.25 (1.83)**	p = 0.002
Q12: e-TB Manager is reliable	5.62 (1.55)	5.50 (1.60)	5.79 (1.47)***	p = 0.000

*p < 0.05.
**p < 0.01.
***p < 0.00.
[a] Reverse worded questions.

Table 4
Comparison of responses by number of years worked in National TB program (Mean, SD).

	Total (n = 1,511)	① Less than 3 years (n = 365)	② 3–5 years (n = 443)	③ 6–10 years (n = 323)	④ Over 11 years (n = 380)	Post-hoc test
Q1: Satisfaction	5.43 (1.55)	5.20 (1.65)	5.38 (1.61)	5.44 (1.55)	5.68 (1.35)	④ > ①***, p = 0.000
Q2: Have capacity	5.35 (1.62)	4.93 (1.77)	5.45 (1.60)	5.51 (1.55)	5.50 (1.52)	② > ①***, p = 0.000 ③ > ①***, p = 0.000 ④ > ①***, p = 0.000
Q3: Do not need more training	3.15 (2.45)	2.83 (2.44)	3.13 (2.43)	3.25 (2.43)	3.39 (2.47)	④ > ①*, p = 0.011
Q4: Support and infrastructure	4.84 (1.88)	4.62 (1.88)	4.73 (1.90)	4.94 (1.89)	5.11 (1.83)	④ > ①**, p = 0.002 ④ > ②*, p = 0.019
Q5: Enter or find information	5.17 (1.79)	4.99 (1.79)	5.14 (1.82)	5.22 (1.79)	5.34 (1.74)	④ > ①*, p = 0.04
Q6: Case management	5.70 (1.55)	5.46 (1.680	5.66 (1.58)	5.78 (1.55)	5.90 (1.34)	④ > ①**, p = 0.001 ③ > ①*, p = 0.032
Q7: Training is adequate	4.22 (2.25)	3.55 (2.29)	4.40 (2.14)	4.76 (2.07)	4.20 (2.33)	② > ①***, p = 0.000 ③ > ①***, p = 0.000 ④ > ①***, p = 0.000
Q8: Information is available	5.47 (1.50)	5.30 (1.52)	5.49 (1.51)	5.47 (1.50)	5.63 (1.44)	④ > ①*, p = 0.013
Q9: Paper system is faster [a]	2.54 (2.39)	2.77 (2.41)	2.58 (2.38)	2.44 (2.27)	2.36 (2.47)	
Q10: Errors or inaccuracies [a]	2.72 (2.32)	3.04 (2.34)	2.80 (2.36)	2.62 (2.17)	2.40 (2.36)	④ < ①**, p = 0.001
Q11: Workplace productivity	5.08 (1.85)	4.91 (1.80)	5.09 (1.88)	5.05 (1.88)	5.25 (1.83)	
Q12: Reliable	5.62 (1.55)	5.49 (1.480	5.63 (1.51)	5.58 (1.66)	5.78 (1.58)	④ > ①*, p = 0.049

*p < 0.05.
**p < 0.01.
***p < 0.00; Tukey's HSD.
[a] Reverse worded question.

Table 5
Comparison of responses by age categories (Mean, SD).

	Total (n = 1,511)	① 18–29 years (n = 187)	② 30–39 years (n = 502)	③ 40–49 years (n = 496)	④ 50+ years (n = 326)	Post-hoc test
Q1: Satisfaction	5.43 (1.55)	5.29 (1.74)	5.35 (1.51)	5.49 (1.55)	5.52 (1.51)	
Q2: Have capacity	5.35 (1.62)	5.22 (1.78)	5.29 (1.57)	5.39 (1.67)	5.45 (1.55)	
Q3: Do not need more training	3.15 (2.45)	2.56 (2.37)	3.20 (2.44)	3.13 (2.51)	3.45 (2.35)	② > ①*, p = 0.012 ③ > ①*, p = 0.036 ④ > ①***, p = 0.000
Q4: Support and infrastructure	4.84 (1.88)	4.61 (2.03)	4.75 (1.75)	4.88 (1.97)	5.07 (1.83)	④ > ①*, p = 0.04
Q5: Enter or find information	5.17 (1.79)	5.08 (1.94)	5.14 (1.75)	5.14 (1.83)	5.31 (1.68)	
Q6: Case management	5.70 (1.55)	5.68 (1.64)	5.60 (1.51)	5.75 (1.52)	5.78 (1.59)	
Q7: Training is adequate	4.22 (2.25)	3.71 (2.35)	4.28 (2.17)	4.06 (2.32)	4.67 (2.10)	④ > ①***, p = 0.000 ④ > ③**, p = 0.001 ② > ①*, p = 0.016
Q8: Information is available	5.47 (1.50)	5.41 (1.62)	5.42 (1.40)	5.53 (1.54)	5.51 (1.50)	
Q9: Paper system is faster [a]	2.54 (2.39)	2.67 (2.56)	2.68 (2.31)	2.30 (2.35)	2.60 (2.45)	
Q10: Errors or inaccuracies [a]	2.72 (2.32)	2.71 (2.40)	2.93 (2.27)	2.66 (2.38)	2.49 (2.24)	④ < ②*, p = 0.043
Q11: Workplace productivity	5.08 (1.85)	5.12 (1.84)	4.97 (1.80)	5.14 (1.91)	5.13 (1.83)	
Q12: Reliable	5.62 (1.55)	5.53 (1.63)	5.48 (1.55)	5.73 (1.52)	5.73 (1.54)	

*p < 0.05.
**p < 0.01.
***p < 0.00; Tukey's HSD.
[a] Reverse worded questions.

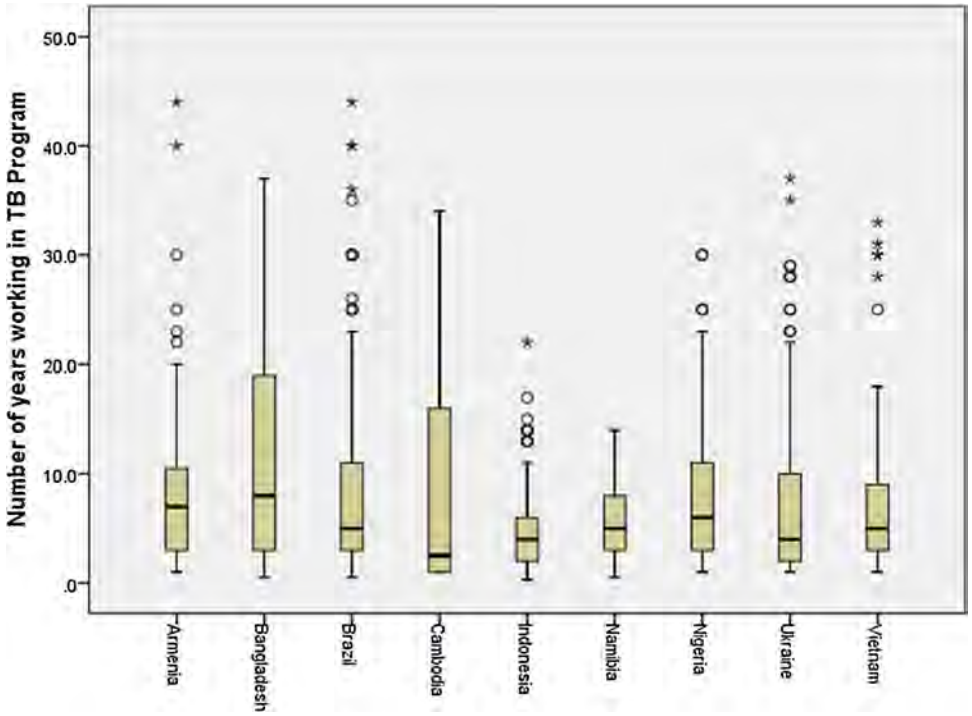

Fig. 1. Number of years working in TB program.

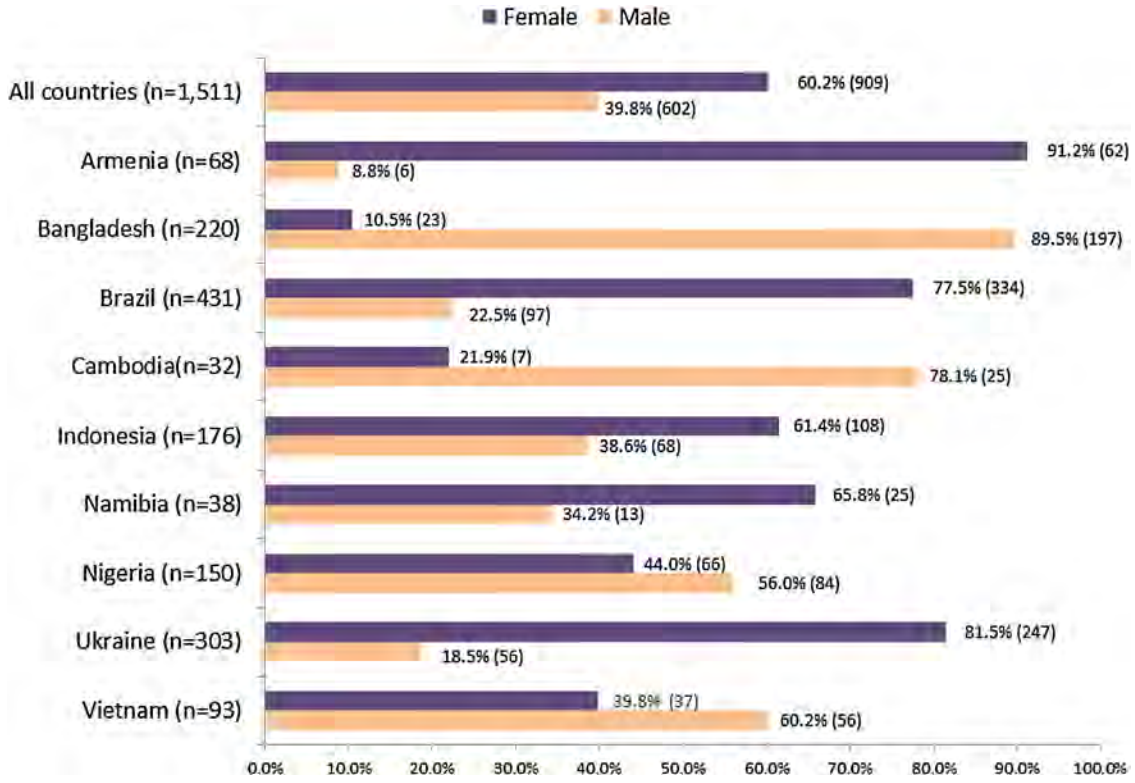

Fig. 2. Gender of e-TB Manager users.

enter or find information in e-TB Manager (Q5) and improved case management due to e-TB Manager (Q6). Respondents who had used e-TB Manager for two years or less and were at the district level had relatively higher satisfaction scores (M = 5.41, SD = 1.67) than did users located at the province (M = 5.28, SD = 1.46) and central (M = 4.78, SD = 1.95) levels who had also used e-TB Manager for less than two years. Respondents who had used e-TB Manager for more than two years and were located at the central (M = 5.88, SD = 1.14) and district (M = 5.52, SD = 1.57) levels had relatively higher mean scores for not taking long to enter or find information compared to province-level users (M = 5.09, SD = 1.81). Within the central level, respondents who had used e-TB Manager for more than two years



Fig. 3. Age of e-TB Manager users.

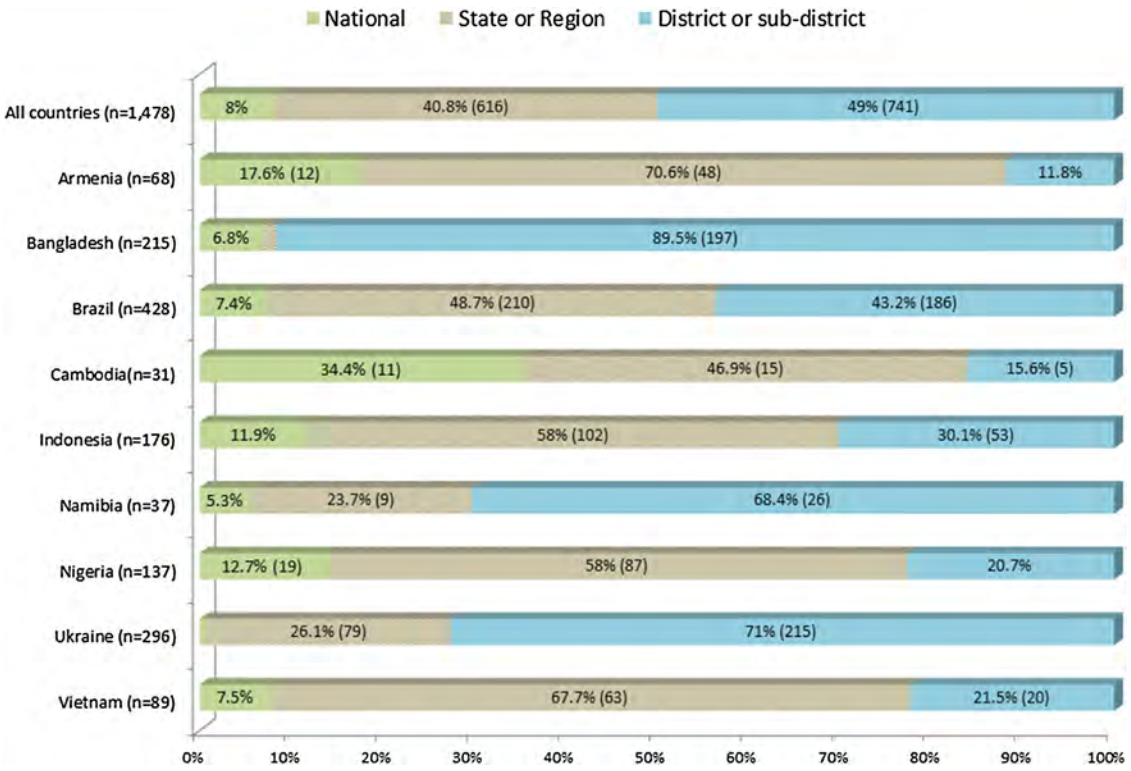

Fig. 4. Location of e-TB Manager users.

had higher mean scores (M = 6.29, SD = 0.93) than those who had used it for less than two years (M = 5.33, SD = 1.51) for e-TB Manager's help in improving case management.

3.3.4.2. Years working in NTP, age and location. There were main effects for all but three questions (except Q1, Q9, Q11) with small effect size. There was a three-way interaction for

Table 6
Comparison of responses by location of user (Mean, SD).

	Total (n = 1,478)	① Central (n = 121)	② Province/ Region/State (n = 616)	③ District and sub-district (n = 741)	Post-hoc test
Q1: Satisfaction	5.43 (1.55)	5.31 (1.68)	5.31 (1.53)	5.54 (1.56)	③ > ②, $p^{*} = 0.021$
Q2: Have capacity	5.37 (1.61)	5.55 (1.41)	5.34 (1.57)	5.37 (1.68)	
Q3: Do not need more training	3.16 (2.45)	3.92 (2.29)	2.96 (2.37)	3.19 (2.51)	① > ②, $p^{***} = 0.000$ ① > ③, $p^{**} = 0.007$
Q4: Support and infrastructure	4.85 (1.89)	5.07 (1.68)	4.71 (1.88)	4.92 (1.92)	
Q5: Enter or find information	5.18 (1.78)	5.45 (1.58)	5.05 (1.75)	5.24 (1.84)	
Q6: Case management	5.70 (1.55)	5.79 (1.35)	5.58 (1.56)	5.78 (1.56)	
Q7: Training is adequate	4.23 (2.25)	4.57 (1.86)	4.32 (2.16)	4.10 (2.38)	
Q8: Information is available	5.48 (1.50)	5.28 (1.47)	5.31 (1.47)	5.65 (1.50)	③ > ①, $p^{*} = 0.033$ ③ > ②, $p^{***} = 0.000$
Q9: Paper system is faster [a]	2.54 (2.39)	2.18 (2.22)	2.58 (2.34)	2.57 (2.47)	
Q10: Errors or inaccuracies [a]	2.71 (2.32)	2.19 (2.06)	2.70 (2.23)	2.81 (2.42)	③ < ①, $p^{*} = 0.017$
Q11: Workplace productivity	5.07 (1.86)	5.22 (1.74)	4.89 (1.81)	5.19 (1.90)	③ > ②, $p^{*} = 0.011$
Q12: Reliable	5.62 (1.56)	5.49 (1.53)	5.45 (1.62)	5.78 (1.50)	③ > ②, $p^{***} = 0.000$

$^{*}p < 0.05$.
$^{**}p < 0.01$.
$^{***}p < 0.00$; Tukey's HSD.
[a] Reverse worded questions.

Table 7
Findings of three-way ANOVA for years using e-TB Manager and years working in NTP, each with age and location.

Item	Years using e-TB Manager*age*location	Years working in NTP*age*location
Q1: Satisfaction	Main effect for years using e-TB Manager $F(1, 1454) = 14.22$, $p < 0.00$, $\eta^2 = 0.01$ age*location: $F(6, 1454) = 2.41$, $p < 0.05$, $\eta^2 = 0.01$ location*e-TB Manager: $F(2, 1454) = 4.38$, $p < 0.05$, $\eta^2 = 0.01$	age*location: $F(6, 1433) = 2.19$, $p < 0.05$, $\eta^2 = 0.01$ age*NTP: $F(9, 1433) = 2.11$, $p < 0.05$, $\eta^2 = 0.01$ age*location*NTP: $F(15, 1433) = 1.68$, $p < 0.05$, $\eta^2 = 0.02$
Q2: Have capacity	Main effect for years using e-TB Manager $F(1, 1454) = 45.57$, $p < 0.00$, $\eta^2 = 0.03$	Main effect for years working in NTP $F(3, 1433) = 4.29$, $p < 0.01$, $\eta^2 = 0.01$
Q3: Do not need more training	Main effect for location: $F(2, 1454) = 6.22$, $p < 0.01$, $\eta^2 = 0.01$ Main effect for years using e-TB Manager: $F(1, 1454) = 20.99$, $p < 0.00$, $\eta^2 = 0.01$ location*e-TB Manager: $F(2, 1454) = 5.95$, $p < 0.01$, $\eta^2 = 0.01$	Main effect for location: $F(2, 1433) = 8.15$, $p < 0.00$, $\eta^2 = 0.01$
Q4: Support and infrastructure	Main effect for location $F(2, 1454) = 5.93$, $p < 0.01$, $\eta^2 = 0.01$	Main effect for location: $F(2, 1433) = 3.95$, $p < 0.05$, $\eta^2 = 0.01$
Q5: enter or find information	Main effect for location: $F(2, 1454) = 5.35$, $p < 0.01$, $\eta^2 = 0.01$ Main effect for years using e-TB Manager: $F(1, 1454) = 7.85$, $p < 0.01$, $\eta^2 = 0.01$ location*e-TB Manager: $F(2, 1454) = 4.46$, $p < 0.05$, $\eta^2 = 0.01$	Main effect for location $F(2, 1433) = 5.12$, $p < 0.01$, $\eta^2 = 0.01$
Q6: Case management	Main effect for years using e-TB Manager: $F(1, 1454) = 12.75$, $p < 0.00$, $\eta^2 = 0.01$ age*location: $F(6, 1454) = 2.17$, $p < 0.05$, $\eta^2 = 0.01$ location*e-TB Manager: $F(2, 1454) = 4.52$, $p < 0.05$, $\eta^2 = 0.01$	Main effect for years working in NTP: $F(3, 1433) = 3.11$, $p < 0.05$, $\eta^2 = 0.01$
Q7: Training is adequate	Main effect for location: $F(2, 1454) = 3.89$, $p < 0.05$, $\eta^2 = 0.01$ Main effect for years using e-TB Manager: $F(1, 1454) = 30.55$, $p < 0.00$, $\eta^2 = 0.02$	Main effect for years working in NTP: $F(3, 1433) = 5.90$, $p < 0.01$, $\eta^2 = 0.01$
Q8: Information is available	Main effect for location: $F(2, 1454) = 5.90$, $p < 0.01$, $\eta^2 = 0.01$ Main effect for years using e-TB Manager: $F(1, 1454) = 10.64$, $p < 0.01$, $\eta^2 = 0.01$	Main effect for location: $F(2, 1433) = 7.90$, $p < 0.00$, $\eta^2 = 0.01$ age*NTP: $F(9, 1433) = 2.87$, $p < 0.01$, $\eta^2 = 0.02$ age*location*NTP: $F(15, 1433) = 1.67$, $p < 0.05$, $\eta^2 = 0.02$
Q9: Paper system is faster [a]	age*location*e-TB Manager: $F(6, 1454) = 5.10$, $p < 0.00$, $\eta^2 = 0.02$	age*location*NTP: $F(15, 1433) = 1.69$, $p < 0.05$, $\eta^2 = 0.02$
Q10: Errors or inaccuracies [a]	Main effect for location: $F(2, 1454) = 4.42$, $p < 0.05$, $\eta^2 = 0.01$ age*location: $F(6, 1454) = 2.10$, $p < 0.05$, $\eta^2 = 0.01$	Main effect for location: $F(2, 1433) = 3.02$, $p < 0.05$, $\eta^2 = 0.00$
Q11: Workplace productivity	Main effect for years using e-TB Manager $F(1, 1454) = 8.79$, $p < 0.01$, $\eta^2 = 0.01$	age*NTP $F(9, 1433) = 2.87$, $p < 0.01$, $\eta^2 = 0.02$
Q12: Reliable	Main effect for location: $F(2, 1454) = 3.85$, $p < 0.05$, $\eta^2 = 0.01$ Main effect for years using e-TB Manager: $F(1, 1454) = 7.48$, $p < 0.01$, $\eta^2 = 0.00$ Age*location: $F(6, 1454) = 2.36$, $p < 0.05$, $\eta^2 = 0.01$	Main effect for location $F(2, 1433) = 5.23$, $p < 0.01$, $\eta^2 = 0.01$

[a] Reverse worded questions.

age*location*years working with NTP for satisfaction (Q1), information is available for case management (Q8) and that paper system is faster than e-TB Manager (Q9) (Table 7). No other three-way interaction was significant. Older respondents aged over 50, regardless of location and with at least 6 or more years of experience in NTP, had higher mean satisfaction scores than did their younger counterparts. There was a significant two-way interaction for age*years working in a TB program for both patient information being avail-

able in e-TB Manager and improved workplace productivity due to e-TB Manager. Regardless of location and among users with more than 11 years of experience, users aged 40–49 had higher mean scores (M = 5.67, SD = 1.67) than users aged over 50 (M = 4.84, SD = 1.93) for workplace productivity.

3.4. Comparison of aggregate country responses

Appendix C provides the mean scores for the 12 core questions in each country with corresponding results from Scheffe's post-hoc tests. This section only provides an overview of the results, and p values are shown in Appendix C. Bangladesh had significantly higher mean scores for satisfaction with e-TB Manager than did Armenia, Nigeria, and Indonesia. For the question, "I have the required capacity to use all features of e-TB Manager linked to my responsibilities", only Ukraine had a significantly higher mean score than Indonesia. However, for "the training I received on e-TB Manager is adequate," Ukraine, Brazil, and Vietnam had significantly higher mean scores than Bangladesh, Cambodia, and Indonesia. Nigeria had a significantly higher mean score than Bangladesh for adequacy of training received.

Bangladesh had a significantly higher mean score than Nigeria or Armenia concerning the length of time needed to enter or find information in e-TB Manager. Compared to Brazil, Armenia, Nigeria, and Indonesia, Ukraine had significantly higher mean scores for the belief that e-TB Manager helps improve patient case management and for the statement, "The information needed for case management is available in e-TB Manager." Indonesia had a significantly lower mean score than Brazil, Vietnam, Bangladesh, or Cambodia in the level of agreement for e-TB Manager's help in improving patient case management. Bangladesh and Ukraine had significantly higher mean scores for perceived workplace productivity compared to Brazil, Nigeria, and Indonesia. For perceived reliability of e-TB Manager, Armenia had a significantly lower score than all countries except Indonesia, which also had a significantly lower mean score compared to five other countries. Generally, respondents who disagreed with the specific statements on satisfaction, adequacy of training received, and perceived reliability of e-TB Manager provided justifications for their responses (Appendix D, table D1).

4. Discussion

This was the first large-scale, cross-sectional, anonymous user experience survey of a wide range of e-TB Manager users from nine diverse resource-constrained countries that bear nearly one-third of the world's TB burden [9]. The 86.3% completion rate among responses received for all required questions exceeds the recommended 80% completion rate even in a possible situation of a low average response rate of 25% in survey research [20,21]. However, our survey had a high average response rate of 73.3% among completed responses, which substantially exceeds that of comparable digital health-related surveys in both high-income and developing countries [22,23]. Our survey, therefore, indicates very high engagement of e-TB Manager users from the national decision making level to the health facility level and the validity of our results to all users of the system. While our findings from the e-TB Manager user experience survey may not be generalizable, they offer implications for other eHealth systems in resource-constrained countries.

Implementing eHealth systems in resource-constrained settings is often beset with challenges, including limited infrastructure, poor internet connectivity, and interrupted maintenance of technology [3]. Although our surveyed countries are experiencing these challenges at various levels, the relatively high mean scores from our survey regardless of user characteristics, affirm overall user satisfaction, perceived reliability, and that e-TB Manager helps improve patient case management. With real-time access to patient information, physicians can share their knowledge, for example, from possible special cases they have treated with specific regimens. This information is accessible to other assigned users and permits them to learn from other colleagues' experience and thereby contribute to improved treatment outcomes. Contrary to popular belief and experience in other settings in which older users are likely to resist eHealth systems, our survey of e-TB Manager users found no significant differences for older users [24,25]. The mean scores for satisfaction, having capacity, and e-TB Manager's help in case management increased progressively from younger to older users. This finding is noteworthy particularly among older users aged over 50 and with at least 6 or more years of experience working in the NTP. Regardless of age, having 11 or more years of experience in a NTP, using e-TB Manager for more than two years, and working at the district level than the province level led to significantly higher satisfaction levels and perceived reliability of e-TB Manager.

District-based users tend to utilize e-TB Manager more through entering patient data, updating various data fields, tracking patient adherence, and entering laboratory results, among other tasks. In most high TB-burden countries, there has been steady decentralization of programmatic management of MDR-TB since 2012, which means that it is the responsibility of district-level users to routinely update e-TB Manager with patient adherence data, treatment outcomes, and medicine supply information. Therefore, it is not surprising to find significant differences in mean scores for district-level users' satisfaction and reliability compared to province-level users. Consequently, district-level users differ significantly from province- and central-level staff in their belief that the patient information needed for case management is available. Routine data entry is often the responsibility of district staff, while province- and/or central-level staff aggregate information for surveillance and report generation purposes. If there is missing information in certain fields in e-TB Manager, central and provincial officials reach out to district staff and fill in the gaps because they expect better data quality and completeness; this is similar to experience in other resource-constrained settings [26]. This could also explain why central level staff relies on e-TB Manager to detect errors or inaccuracies in patient files based on their significantly different mean score compared to district level staff.

There were no significant differences in mean scores for age group or location for the perceived capacity of using all e-TB Manager features linked to user responsibilities. However, when asked about the need for additional training and adequacy of training received, users aged 18–29 had significantly lower scores than did users in other age categories. Donors in all surveyed countries financially supported the initial core training for NTPs and national referral hospitals, with the expectation that the NTP would budget for cascade training whether from the Global Fund or from domestic resources. However, frequent turnover of trained public-sector staff common in resource-constrained countries likely hampered this effort either due to low public-sector salaries or job dissatisfaction among other reasons [27,28]. Public-sector health workers and particularly those new to eHealth systems such as e-TB Manager expect to be trained and are disappointed if they do not receiving formal training, but they nevertheless adapt and learn on the job [29,30]. Overall, regardless of age, working in an NTP for less than three years and using e-TB Manager for less than two years are indicators that these users are likely less knowledgeable about the complexities of MDR-TB diagnosis and treatment and the corresponding recording and reporting features in both e-TB Manager and a country's paper-based reporting systems. This finding aligns with other studies measuring health worker knowl-

edge of MDR-TB diagnosis and treatment [31,32]. When an NTP changes or updates MDR-TB clinical guidelines and disseminates them, mass training is usually not given, and clinicians and users alike are expected to keep abreast of new developments and adapt to new changes in TB recording and reporting systems. Even if existing users have received training but MDR-TB guidelines have changed with corresponding updates in e-TB Manager reporting fields, there is typically a user expectation for additional training. From the NTP perspective, limited budgets and competing priorities make refresher training difficult in terms of both cost and time for personnel involved.

Providing routine technical support and infrastructure, such as computers and uninterrupted internet connectivity, is the responsibility of the national-level team and, depending on the country's health system, the government's provincial office. One or more dedicated staff member, usually from the MDR-TB team, oversees data quality and completeness issues, and he or she is available to field calls or emails from users if there are any issues or challenges with e-TB Manager. In some countries, even if computers are provided in a health facility as a precondition for e-TB Manager use, internet connectivity may be unreliable, or there may be two to three users who are expected to share the only available computer. For the question on available support and infrastructure, the mean score was generally low compared to other questions (mean = 4.84, SD = 1.88). However, there were significant differences between older (aged over 50) and younger (aged 18–29) workers, and between those with more than 11 years and less than five years of NTP experience. We note that older public-sector users and those with more than 11 years of experience in NTP (regardless of age) tend to be more tolerant of infrastructure challenges and limited technical support than are younger or less experienced users.

When comparing countries, regardless of user characteristics, we expected Brazil and Ukraine to have relatively high scores for most questions. With more than five years of e-TB Manager use in both countries, institutional capacity has been built. Their NTPs have the ability to adapt to changes and absorb new updates in e-TB Manager, even with turnover of staff and key leaders who have championed e-TB Manager in both countries. Moreover, our project had long-term country presence, a greater number of local staff for technical assistance, and dedicated programming support to respond rapidly to customization requests and adaptations. This could help explain why these two countries generally had higher scores for key measures than other countries where local programmers learned to code e-TB Manager on the job for periodic updates and to fix IT problems. Only Ukraine has a government-authorized law that mandates the use of e-TB Manager as the country's national TB registry [33]. Therefore, users in Ukraine are expected to routinely update e-TB Manager, and the central-level supervision team conducts periodic data quality checks [34]. This explains why Ukraine has the highest score among all countries for information being available in e-TB Manager to help improve case management and having the capacity to use e-TB Manager. Brazil, however, recently had challenges in data quality and infrequent updates in their version of e-TB Manager, as demonstrated by comparatively lower ratings for the same measures. Besides the survey, many users in Brazil provided comments in the open text box related to poor data quality, particularly in e-TB Manager's medicines management module.

Beyond the pilot phase, Indonesia has more years of institutional experience with the nationwide implementation of e-TB Manager than does Bangladesh, which began expansion in 2012. However, Indonesia scored lower than all other countries, while Bangladesh had the highest score for perceived satisfaction and reliability for e-TB Manager. We believe that Indonesia's experience with other eHealth systems suggest that users expected significantly more from e-TB Manager also evidenced by the volume of user comments received (Appendix D, table D2). By contrast, users in Bangladesh's NTP were comparatively new to an eHealth system such as e-TB Manager and therefore had a generally more positive opinion. In addition, Indonesia has two parallel electronic systems in its TB programs and one general health information system, and data are not exchanged among the systems. This could explain user frustration from dealing with one eHealth system for first-line TB diagnoses and treatment and with e-TB Manager for MDR-TB diagnoses and treatment. The new version of e-TB Manager has interoperability features that could address this challenge [35]. However, despite the highest user satisfaction in Bangladesh, these users still expect refreshers and frequent training programs on e-TB Manager, as indicated by lower scores relative to other countries.

The TB burden is higher in Bangladesh and Ukraine than in other countries, and both rated e-TB Manager highly in terms of improving their workplace productivity compared to other countries where users have a lower data-entry burden. With better workplace productivity due to e-TB Manager, nurses can investigate TB patient's contacts, follow-up with patients who are not adhering to treatment, spend more time with patients, and focus on other tasks. By contrast, Namibia, which has a relatively low TB burden, had the highest mean scores among all countries, but the differences were not significant for perceived reliability and workplace productivity. Frequently slow technology and brief system crashes that require data re-entry can undermine user confidence. That could explain Armenia's low scores for the perceived reliability of e-TB Manager and for satisfaction compared to other countries. While the brief episode of system slowness and subsequent data re-entry was fixed in Armenia at least one year prior to the survey, users tend to remember the problem, despite it being a server issue and not a problem with e-TB Manager itself.

5. Strengths and limitations of the study

To our knowledge, this is the first cross-country user experience study in resource-constrained countries of a successfully adopted and institutionalized eHealth system, and it sheds light on many of the factors presented in this paper rather than simply evaluating a pilot project. Evaluations of Open MRS, an eHealth system that is widely used in resource-constrained countries, have been published [13,36,37]. However, our contribution to the existing knowledge base is that our study had a very high response rate for a multi-country, public-sector survey; was conducted in the local language in seven of nine countries; analyzes key user characteristics of an institutionalized eHealth system; and presents the comparable country context of our findings. We strove to implement best practices outlined in survey research as reflected in our methods, and we have provided additional data in Appendix B [19,38]. The translated questionnaire can easily be replicated at a low cost to compare the initial benchmarks established in this study. For example, research in one high-income country evaluated eHealth usability by repeating a previous survey to draw rich comparisons over time [39]. Even before preparation and publication of this paper, a country level report with key survey findings and user comments were promptly channeled back to each country authority for decision making, thereby meeting some of the principles for digital development [40]. For example, based on user comments in the survey, authorities in Ukraine took action to conduct refresher training and addressed specific reporting and infrastructure issues. In Nigeria, the survey findings strengthened the interim decision of authorities to expand use of e-TB Manager to more districts and took into account the resources needed to make it happen. In Brazil, the survey findings and user comments prompted authorities to upgrade the medicines management feature of e-TB

Manager. Our study findings contribute to the growing knowledge base of the eHealth user experience in resource-constrained countries and have implications for other eHealth systems.

There are some limitations to our study. Due to the anonymous nature of the survey, we were unable to compare differences among non-respondents with those who responded to the survey to address non-response bias. We also did not compare early responders with late responders to assess whether there was any influence in the results within a country. For example, we received at least 50% more responses from Bangladesh and Brazil after trying different methods to increase the response rate because users in these countries often lack a valid or updated email address. Long periods of holiday due to Carnival and Easter in Brazil also hampered the initial response rate. In Ukraine, we only had permission to conduct the survey over an eight-week period, which resulted in a country-level response rate of 52%, despite Ukraine having significantly better email outreach and a larger user base compared to other countries. Therefore, comparing early versus late responders within a country is unlikely to have significantly changed our findings. Despite our best efforts to make the survey as clear as possible either in local language for seven countries or in English for two countries, it is likely that some users may have misunderstood the question. The two reverse worded questions (Q9, Q 10) and one negatively worded question (Q 3) may have caught users off guard and affected their response.

Summary points
What was already known on the topic?

- Multi-drug resistant tuberculosis (TB) is a public health crisis.
- Strong electronic recording and reporting systems are fundamental to advance the WHO End TB strategy and meet the Sustainable Development Goal 3 related to health
- After multi-year and nationwide implementation of e-TB Manager, a web-based eHealth system in 10 resource-constrained countries, no user experience evaluation has been performed

What this study added to our knowledge?

- Older respondents aged over 50 generally had higher user experience scores compared to younger counterparts
- More than two years of experience with e-TB Manager resulted in higher user satisfaction, perceived reliability, workplace productivity, and capacity to use e-TB Manager to help in patient care
- Depending on the country context and disease burden, future interventions must take into account unmet learning expectations of younger users by age and inexperienced users in a TB program, regardless of age
- Beyond the pilot phase, after a five-year period with gradual scale-up, institutional capacity was built in Brazil and Ukraine compared to other countries.

6. Conclusions

The WHO's digital health for End TB strategy cited e-TB Manager as an example in contributing to quality patient-centered care and TB program management [7]. Our findings demonstrated that across diverse country health systems with varying TB burdens, users are satisfied with e-TB Manager, find it to be reliable, have the capacity to use e-TB Manager linked to their responsibilities and confirm that it helps improve patient care and improved workplace productivity. Implementing an eHealth system such as e-TB Manager, particularly in large and complex, resource-constrained, high TB-burden settings, requires multi-stakeholder partnerships and organizational agility. There must be committed financial, infrastructural, technical and trained human resources to ensure its sustained use to help improve patient care. After the gradual withdrawal of donor funding, country authorities need to allocate resources for both refresher training and establish e-learning methodologies to keep pace with periodic programmatic changes and improve overall user experience. A digital health technology such as e-TB Manager has the potential to contribute to countries' aspiration to meet the Sustainable Development Goal 3 and end the TB epidemic by 2030.

Authors' contributions

NK conceived of, designed and led the implementation and analysis of the multi-country study. All authors participated in the survey adaptation and finalization. NK, LGVB, and LFAR contributed to country-specific implementation methods and strategy. KS analyzed various survey platforms and performed the statistical analysis. NK, KS, LGVB performed the primary interpretation of the study findings. LFAR validated primary study findings. NK wrote and finalized the manuscript. LGVB provided critical intellectual input for the analysis and interpretation of the study findings. All authors reviewed and approved the manuscript.

Statement on conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijmedinf.2017.03.017.

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The experience of scaling up a decentralized, ambulatory model of care for management of multidrug-resistant tuberculosis in two regions of Ethiopia

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ABSTRACT

Strong strategies, including proven service delivery models, are needed to address the growing global threat of multidrug-resistant tuberculosis (MDR-TB) in low- and middle-income settings. The objective of this study was to assess the feasibility and effectiveness of the nationally approved ambulatory service delivery model for MDR-TB treatment in two regions of Ethiopia. We used routinely reported data to describe the process and outcomes of implementing an ambulatory model for MDR-TB services in a resource-limited setting. We compared percentage improvements in the number of MDR-TB diagnostic and treatment facilities, number of MDR-TB sputum samples processed per year, and MDR-TB cases ever enrolled in care between baseline and 2015. We also calculated interim and final treatment outcomes for patients who had completed at least 12 and 24 months of follow-up, respectively. Between 2012 and 2015, the number of MDR-TB treatment-initiating centers increased from 1 to 23. The number of sputum samples tested for MDR-TB increased 20-fold, from 662 to 14,361 per year. The backlog of patients on waiting lists was cleared. The cumulative number of MDR-TB patients put on treatment increased from 56 to 790, and the treatment success rate was 75%. Rapid expansion of the ambulatory model of MDR-TB care was feasible and achieved a high treatment success rate in two regions of Ethiopia. More effort is needed to sustain the gains and further decentralize services to the community level.

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Introduction

Multidrug resistant tuberculosis (MDR-TB) is a global public health challenge. In 2015, of over half a million people estimated to have developed MDR-TB, national TB control programs (NTPs) notified only 20% [1]. Moreover, only 52% of those treated successfully completed the recommended regimen .While these data suggest the presence of critical challenges in the scale-up of MDR-TB services, they also highlight a tripling in case detection and enrollment in care compared with the 2009 baseline [1].

Further scale-up of MDR-TB services in resource-limited settings requires consensus on the best model of service delivery, since the hospitalized model of care used in developed settings is not sustainable [2]. Cost-effectiveness studies suggest that MDR-TB treatment can be cost-effective, but the model of care is the main influencer of costs, with ambulatory care being more cost-effective [3]. There is also clear evidence from other infectious disease programs that decentralized service delivery improves treatment outcomes. Lessons from decentralized management of HIV programs are particularly relevant for scale-up of MDR-TB services, although important differences between the care needs of MDR-TB patients and those of HIV patients should be taken into consideration [4-6].

Earlier experience from resource-limited settings in Asia, Eastern Europe, and Latin America demonstrated the effectiveness of

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standardized MDR-TB treatment approaches, but treatment outcomes varied significantly among countries because of differences in the mode of service delivery. Higher loss-to-follow-up rates, for example, were reported from countries that provided services at a single centralized site compared with countries that implemented a more decentralized approach [7]. The degree of decentralization also varied considerably across countries and regions, with varying degrees of success in treatment outcomes [8-12]. More data are needed, especially from sub-Saharan Africa, to support the ongoing efforts to strengthen the decentralized ambulatory model of care for low- and middle-income settings.

Ethiopia is among the MDR-TB high-burden countries that have achieved an MDR-TB treatment success rate (TSR) exceeding 70% [13]. However, there is limited data on the TSR following the rapid expansion and decentralization of services. In this paper, we describe the processes and outcomes of a decentralized, ambulatory approach to MDR-TB treatment in two large regions of Ethiopia. The two regions cover over half of the country's population. Also, more than 50% of the country's MDR-TB treatment centers are located in these two regions. Our objective was therefore to describe how a decentralized, ambulatory model of MDR-TB treatment, if coupled with appropriate quality assurance strategies, could improve access to and quality of MDR-TB services without compromising treatment outcomes in a setting with limited resources. We also highlighted some of the challenges encountered during this progress and suggested practical solutions based on field-level implementation experience.

Methods

The setting

Ethiopia is located in the horn of Africa. The country is subdivided into nine administrative regional states and two city councils. Each regional state is further subdivided into administrative zones, which in turn comprise woredas (equivalent to districts). Oromia is the largest regional state, with an estimated population of over 34 million, followed by Amhara Region, which has a population of over 20 million [14]. The current national TB incidence and prevalence estimates per 100,000 population are 200 and 207, respectively [1]. The proportion of MDR-TB cases among new and previously treated cases is estimated to be 1.6% and 11.8%, respectively [15].

Under the guidance of the Ministry of Health of Ethiopia (FMOH) and the Regional Health Bureaus of Amhara and Oromia regions, the Help Ethiopia Address the Low Tuberculosis Performance (HEAL-TB) Project has provided comprehensive TB program support to the two regions since July 2011. HEAL-TB, funded by the United States Agency for International Development (USAID) and implemented by Management Sciences for Health, prioritized. MDR-TB was one of the key technical areas for support. We selected the two HEAL-TB-supported regions for this analysis because we were able to obtain complete data through project activities, which allowed us to thoroughly document the processes and outcomes of the program.

Service delivery models

FMOH recommends two models of care for management of MDR TB patients [16,17]. In the **inpatient model of care**, all eligible patients that are ready to start treatment with second line drugs (SLDs) are admitted to treatment initiating centers (TICs) with designated MDRTB wards for four to eight weeks till the patient turns sputum smear negative. Upon discharge from the TICs, patients are referred to treatment follow up centers (TFCs) for outpatient follow up. Prior to 2011, only two tertiary hospitals provided MDR TB treatment to patients from all over the country using the inpatient model of care (Fig. 1). However, with the growing need to improve access to MDR-TB services, the FMOH developed a decentralized, ambulatory model of care for rapid expansion of the services [16].

In the **ambulatory model of care**, patients are treated at outpatient level at TFCs from day one. The multidisciplinary panel team at TICs may recommend temporary admission at TICs based on clinical or social criteria. At TFCs, patients received daily injections six times per week for the initial 8–9 months (intensive phase) and attended daily follow up during the continuation phase. The patients received their medications under direct observation and strict follow up by health workers both at TICs and TFCs. Table 1 describes the roles and responsibilities of TICs and TFCs in the ambulatory model of care.

All newly diagnosed MDR-TB patients received a standardized treatment regimen, per the national guidelines [18]. Accordingly, the recommended regimen of choice was eight months of Pyrazinamide (Z)- Capreomycin (Cm)- Levofloxacin (Lfx)-Prothionamide (Pto)-Cycloserine (Cs) for the intensive phase followed by 12 months of Pyrazinamide (Z)-Levofloxacin (Lfx)-Cycloserine (Cs) abbreviated as ***8 Z-Cm$_6$-Lfx-Pto-Cs, 12 Z-Lfx-****Cs.*

Interventions and innovative approaches

Some of the challenges identified at baseline and anticipated to be encountered in the longer-term necessitated prompt innovative interventions. Less organized clinic appointment systems and consequent poor adherence to treatment and follow up; limited experience of the clinical team; and irregularities in laboratory monitoring systems were some of the key challenges identified at baseline.

Strengthening the national and regional level program coordination capacity was the initial step in enabling the operationalization of the decentralized, ambulatory model of care. This was followed by specific capacity building efforts for health care providers and program managers through trainings on clinical and programmatic management of MDR-TB. To ensure ongoing learning and skills improvement we prepared, printed and distributed provider support tools including pocket guides, clinician desk references, cohort monitoring charts, and wall charts adapted from national guidelines. Since most health facilities did not have adequate space and were not infection control friendly, we supported renovation of three major MDR-TB treatment centers, and improved the functionality of facilities renovated through other projects by providing furniture and equipment. Strengthening the laboratory capacity was another area which required significant investment. This included supplying laboratory equipment and consumables and building human resource capacity on their use through training, on-site demonstration, and by providing job aids.

While clearing the backlog of patients in waiting list, we focused on improving case finding. As part of this effort and in addition to strengthening the overall human resource and laboratory capacity, we sensitized the community through mass communication by organizing orientation sessions for health program managers and community workers, with a focus on presumptive case identification and contact investigation.

Strengthening the monitoring and evaluation of the MDR TB program performance was a key component of the interventions. We supported the design and implementation of specific indicators for MDR-TB standards of care, for quarterly monitoring and reporting, and trained clinic staff on recording and reporting of MDR-TB data. To support more efficient recording and reporting, we provided desktop computers, an electronic patient data monitoring system, and access to mobile internet services.

At each TIC, MDR-TB panel teams, composed of a multidisciplinary group of personnel, guided patient-level decisions. Typi-

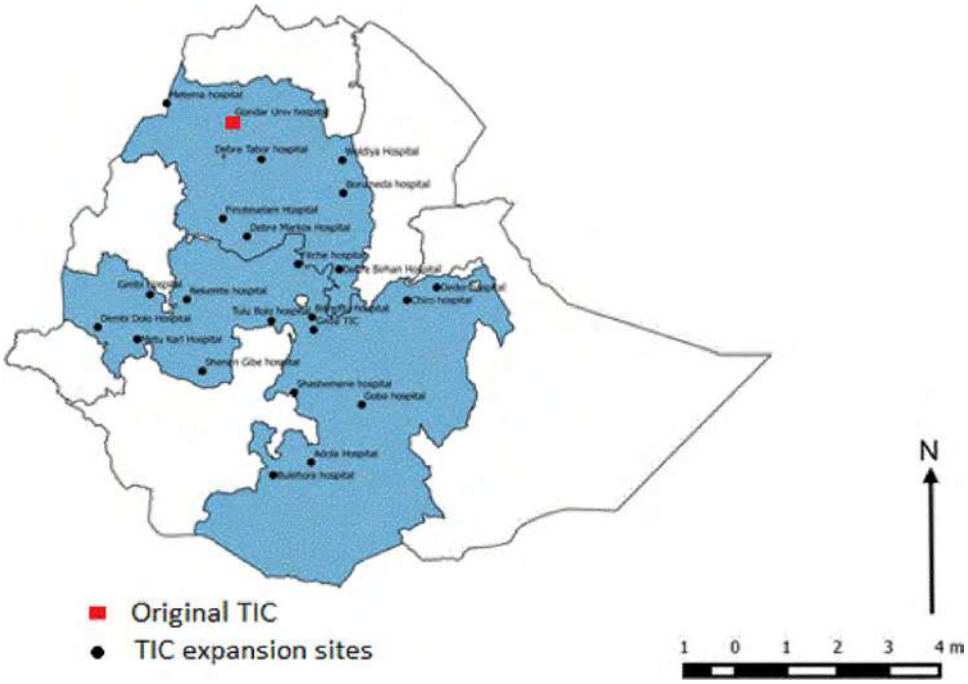

Fig 1. Map of Ethiopia showing the location of TICs in Amhara and Oromia Regions, Ethiopia, as of August 2015.

Table 1
Roles and Responsibilities of TICs and TFCs, per FMOH Guidelines.

Treatment initiating centers	Treatment follow-up centers
Identify patients eligible for ambulatory or in-patient MDR TB treatment care	Administer medications; under DOT
Initiate patients on treatment	Provide adherence support
Arrange referral of stable patients to TFCs	Screen, identify, and manage minor side effects
Record activities and report quarterly	Refer patients with serious side effects to TICs
Conduct clinical and laboratory monitoring	Trace and screening contacts
Determine final treatment outcomes	Record and report activities to TICs
Support the distribution of second-line drugs to TFCs	
Monitor patient progress on monthly bases.	
Patients at TFCs visit TICs monthly for check up	

cally, members of a panel team included hospital administrators (Chief Executive Officer, Medical Director, and Matron), MDR-TB clinicians (doctors and nurses), pharmacists, laboratory technologists, social workers, and representatives from the local health office. Representatives from the relevant TFC and technical partners participated in the meetings as needed. The team discussed and made decisions about patient care at critical phases, including treatment initiation (regimen and mode of treatment), the end of intensive phase, arrangement of social support (for eligible patients), transfer to TFCs, and determination of treatment outcomes.

To improve patient follow-up and coordination, monthly follow-up days for MDR-TB patients (known as MDR-TB clinic days) were designated so that patients could receive comprehensive support services during one visit. On the MDR-TB clinic day, the entire hospital MDR-TB treatment team, program experts, and mentors dedicate the day to receiving all patients at the TIC for treatment monitoring (clinical check-ups, laboratory monitoring testing including sample collection, nutrition and psychosocial support). Patients are reimbursed for transportation costs to and from the clinic and receive food items support enough for a month. To promptly detect and address the underlying and immediate causes of high mortality rates, the treatment sites organized mortality audits. Moreover, continuing medical education sessions were organized for clinicians working in MDR-TB clinics.

Data sources

We used routinely collected and reported data in this analysis. We obtained quarterly reports from each TIC using FMOH-approved data capturing and reporting tools. Regularly reported key variables included the number of TICs and TFCs, new and cumulative numbers of presumptive and confirmed MDR-TB patients enrolled, and treatment outcomes for each cohort, per national guidelines. TFCs sent monthly patient status report to TICs. Six month interim outcomes are reported for patients who had at least 6 months of treatment follow up while final outcome was reported for those who had completed 24 months. Patient's treatment outcome is determined based on the 24 month report. This is the standard approach for the conventional regimen used in Ethiopia.

Ethical considerations

We received ethical approval from the ethics committees of Amhara and Oromia Regional Health Bureaus to analyze the routine data and disseminate the findings. We used aggregate program-level reports for this analysis with the consent of the reporting institutions. No patient identifiers were included in the routine report.

Table 2
Key MDR-TB service expansion indicators, 2012–2015, Amhara and Oromia Regions, Ethiopia.

Indicator	Baseline (2012)	Current (2015)	Percentage Increase
Cumulative number of TICs ever established	1	23	2100%
MDR-TB sputum samples processed per year	662	14,361	1969%
Cumulative number of MDR-TB patients ever enrolled	56	790	1211%

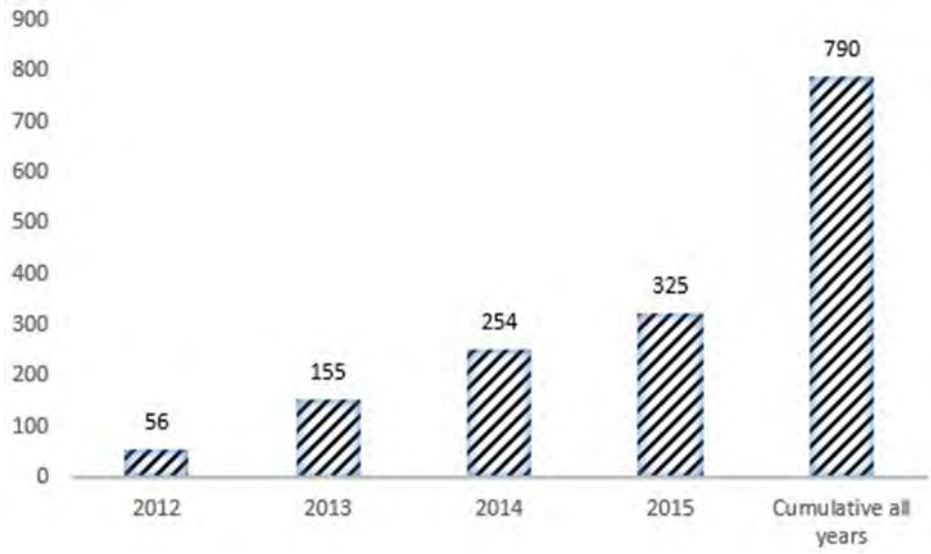

Fig. 2. Cumulative and new MDR TB patients enrolled per year, 2012–2015, Amhara and Oromia Regions, Ethiopia.

Results

Improvements in service accessibility

Before 2012, MDR-TB service delivery was limited to a single tertiary hospital in one of the regions. In the two regions, the number of TICs had increased from one in 2011 to 23 by the end of September 2015. Similarly, there were only two MDR-TB culture centers and no GeneXpert machine at the beginning of the project. By September 2015, the number of GeneXpert centers had reached 49. There were no liquid culture and DST service at baseline but by the end of August 2015 five labs were equipped. Moreover, the number of MDR-TB sputum samples tested had increased from 662 per year in 2012 to 14, 361 by September 2015. The number of MDR-TB cases identified and put on treatment increased from 56 in the first year to 790 by the end of September 2015, and no patient was on the waiting list (Table 2 describes key indicators of service expansion and Fig. 2 shows annual enrollment rates).

Treatment outcomes

Of 790 patients ever enrolled in care by the end of September 2015, six-month interim results were available for 469 patients enrolled between July 2012 and December 2014, and final results were available for 178 patients enrolled during July 2012–September 2013. Of 469 patients assessed for interim treatment outcomes, 65% had negative culture results at six months.

For 178 patients who completed at least 24 months of follow up, final treatment success rate was 75%, with a cure rate of 65% (**Table 3** summarizes interim and final treatment outcomes).

Table 3
Six month interim outcome of MDR-TB patients, July 2012–September 2014, Oromia and Amhara Regions, Ethiopia.

Six month interim outcome, July 2012–June 2014 (N = 464)	Number (%)
Culture negative	289 (62)
Culture positive	9 (2)
Died	47 (10)
Lost	27 (6)
Not evaluated	97 (21)
Final outcome, July 2012–September 2013 (N = 178)	
Cured	115(65)
Completed	17 (10)
Died	27 (15)
Failed	2 (1)
LTFU	15 (8)
Not evaluated	2 (1)

Discussion

This is the first large scale implementation experience of the ambulatory MDR TB treatment model in Ethiopia, through which it was possible to achieve rapid expansion of MDR-TB services. Between 2012 and 2015, patient enrollment rate increased twelvefold while at the same time achieving treatment success rate of 75% and cure rate of 65%. These findings suggest that if adequate resources and robust technical support are put in place, the ambulatory model of care can be implemented successfully in settings with limited resources.

Treatment success rate of 75% and cure rate of 65% in our cohort exceeded those reported in recent systematic reviews, and was comparable with results from two tertiary hospitals from Ethiopia which used a predominantly inpatient model of care [18]. In a systematic review conducted in 2009, the treatment success rate for programs that used standardized treatment regimen was 54%, and 64% in individualized treatment models [10]. The treatment success rate was 62% in a study that summarized findings from 36 studies that reported treatment outcomes from 21 countries [9]. A recent review of studies from programs implementing community-based MDR-TB treatment approaches reported a treat-

ment success rate of 65%. No specific factor was associated with successful treatment outcomes in this more recent review [12].

The higher treatment success rate in our cohort could be attributed to the robust technical support provided and the actions taken to address challenges encountered early in the course of service roll-out. Strengthening the technical and infrastructure capacity for early detection and management of patients was a critical step in ensuring a higher treatment success rate. The MDR-TB clinic day was a useful mechanism to improve adherence to clinical appointments and medications.

Ambulatory models of MDR-TB care have been implemented in several countries, but the specific modalities of care have varied considerably across regions and countries. In a poor district in South Africa, for example, a decentralized, home-based care model for MDR-TB and HIV patients, about 77% were reported to have cured or still on follow up but the proportion cured was not clearly described [19]. Analysis of programmatic management of MDR-TB in three different continents suggested the feasibility of a decentralized approach in diverse settings [20]. However, the extent of decentralization varied considerably among countries. In Peru, for example, the initial locus of care was the community; in Russia, a prison/hospital combination was used; and Lesotho followed the combined hospital/community approach. A more recent report from Uganda suggests the acceptability of home-based care [21].

Ethiopia's MDR-TB treatment experience is relatively recent and builds on global experience from similar settings. However, it differs from experiences in other resource-poor settings in several major respects. Treatment and follow up was not yet decentralized to community level as follow up was organized at health center or hospital levels. Decentralization to the community level should be considered as the program matures, and Ethiopia's extensive network of Health Extension Workers (HEWs) could be tapped into to further decentralize MDR-TB services. These HEWs s can play a larger role, not only in contact tracing and suspect referral but also in treatment observation and psychosocial support.

Despite considerable progress made in improving access to MDR-TB services, further concerted effort is needed to strengthen the program [22]. The current results were achieved through significant external support. Further technical assistance and close collaboration with the National TB Program should be maintained until the MDR-TB program is fully integrated within the existing TB program at all levels of the health care system. The continuing medical education begun under the current program needs to be continued until a critical mass of national expertise is established. Addressing broader structural barriers such as TB-associated stigma, which, according to anecdotal data, appear to contribute to high rates of loss to follow-up, should be considered a priority. Moreover, the ongoing psychosocial support schemes should be strengthened and more innovative counseling approaches should be devised.

Our results should be interpreted cautiously because of important limitations. Because our report relied on programmatic data reported through routine project management systems, we were not able to do in depth analysis of factors affecting treatment outcomes. Since this relatively high treatment outcome was achieved in the context of strong technical assistance through external funding, it cannot be generalized to settings where such external support does not exist. Moreover, whether such high treatment outcome will be sustained as the program expands to more sites remains to be determined. In conclusion, rapid expansion of an ambulatory model of MDR care was feasible in the Ethiopian setting. The treatment success rate was far better than the recently reported global average of 52% [1]. This was achieved in the context of good collaborative efforts between the National TB Program and robust external technical assistance and program support. More effort is needed to sustain the gains made through this collaboration. Further analysis of data is required to understand individual factors contributing to treatment outcomes. The impact of further decentralization of services to the community level should be evaluated through implementation research.

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RESEARCH

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Vitamin D deficiency among smear positive pulmonary tuberculosis patients and their tuberculosis negative household contacts in Northwest Ethiopia: a case–control study

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Abstract

Background: Vitamin D is a fat-soluble vitamin that increases the immunity against tuberculosis (TB), decreases the re-activation of latent TB and reduces the severity of active TB disease. Epidemiological studies on the prevalence of vitamin D deficiency, and its association with TB showed inconsistent results in different countries. This study was aimed to determine the prevalence of vitamin D deficiency and its association with TB in Northwest Ethiopia.

Methods: A case–control study was conducted among smear positive pulmonary tuberculosis patients and their household contacts without symptoms suggestive of TB. Study participants were recruited at 11 TB diagnostic health facilities in North and South Gondar zones of Amhara region between May 2013 and April 2015. The spot-morning-spot sputum samples and 5 ml blood sample were collected prior to commencing TB treatment for the diagnosis of TB and serum vitamin D assay, respectively. The diagnosis of TB was performed using smear microscopy and GeneXpert. Serum vitamin D level was analyzed using VIDAS 25 OH Vitamin D Total testing kits (Biomerieux, Marcy l'Etoile, France) on mini VIDAS automated immunoassay platform. Vitamin D status was interpreted as deficient (<20 ng/ml), insufficient (20–29 ng/ml), sufficient (30–100 ng/ml) and potential toxicity (>100 ng/ml).

Results: Of the total study participants, 134 (46.2%) were vitamin D deficient, and only 56 (19.3%) had sufficient vitamin D level. A total of 59 (61.5%) TB patients and 75 (38.7%) non TB controls were vitamin D deficient. Results of multivariate logistic regression analyses showed a significantly higher vitamin D deficiency among tuberculosis cases ($p < 0.001$), females ($p = 0.002$), and urban residents ($p < 0.001$) than their respective comparison groups. Moreover, age groups of 35–44 ($p = 0.001$), 45–54 ($p = 0.003$) and ≥55 ($p = 0.001$) years had significantly higher vitamin D deficiency compared with age group <15 years.

Conclusions: Vitamin D deficiency is highly prevalent among TB patients and non TB controls in Ethiopia where there is year round abundant sunshine. Study participants with tuberculosis, females, older age groups, and urban residents had significantly higher prevalence of vitamin D deficiency. These findings warrant further studies to investigate the role of vitamin D supplementation in the prevention and treatment of tuberculosis in high TB burden countries like Ethiopia.

Keywords: Vitamin D deficiency, Tuberculosis, Household contacts

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Background

Tuberculosis (TB) remains one of the deadliest communicable diseases in the world. According to World Health Organization (WHO) global TB report 2014, Ethiopia ranked 7th among the 22 high TB burden countries and 15th among the 27 high Multi-Drug Resistant Tuberculosis (MDR-TB) burden countries in the world. Ethiopia had an estimated 211 prevalent TB case per 100,000 population and a total of 30,000 TB related deaths. Among patients with notified pulmonary TB cases in the year 2013, there was an estimated 1400 MDR-TB cases in the country [1].

Vitamin D is a fat-soluble vitamin that plays important role against infectious diseases including tuberculosis [2]. The two most likely ways by which vitamin D controls the immune system in the fight against *M. tuberculosis* are: (1) Vitamin D decreases the viability of *M. tuberculosis* by increasing the fusion of the phagosome and lysosome in infected macrophages [3]; (2) It may improve the production of LL-37, an antimicrobial peptide of the cathelicidin family [3–6]. Defensin and cathelicidin are some of the antimicrobial peptides that involve as a first line of defenses in the inhibition of infections with infectious diseases such as TB. The vitamin D in neutrophils and macrophages controls the hCAP-18 gene that codes for LL-37, hence, vitamin D may increase the host body defenses to control TB [3–7]. The use of vitamin D to treat TB patients has a long history even before Robert Koch discovered the etiologic agent of TB [3].

Vitamin D can be present naturally in very few foods, as dietary supplements, and produced endogenously when ultraviolet rays from sunlight strike the skin and trigger vitamin D synthesis, however, vitamin D deficiency has been shown to be common in low-income countries, including those in equatorial Africa [8–10].

Inadequate vitamin D level, vitamin D insufficiency or deficiency, is a global problem. It was estimated that one billion people globally have inadequate level of vitamin D [11]. Previous studies have shown that vitamin D deficiency is a problem in Africa [12–16]. Higher prevalence of vitamin D deficiency was observed among untreated pulmonary TB patients compared to the non-TB healthy controls [17]. Vitamin D deficiency among TB patients have been reported in different African countries with the prevalence ranging from 8.5 to 62.7% [8, 10, 14–16]. A study conducted in the central part of Ethiopia showed a prevalence of 42% vitamin D deficiency among school children [18]. Another study conducted in Israel among adult Ethiopian women immigrants showed that all women (five) with hypocalcaemia were also vitamin D deficient [19].

Previous reports showed that inadequate vitamin D status is a public health problem globally. However, there are discrepancies in the prevalence of vitamin D deficiency, and the association between vitamin D deficiency and TB among studies conducted in different countries. The lack of consistency of results may be due to the fact that the level of vitamin D in human is affected by several factors such as race, latitude, exposure to sunlight, socioeconomic status, nutrition, and traditional/cultural traits [20]. As far as our knowledge is concerned, there are quite few reports, one on the prevalence of vitamin D deficiency among children and the other on Ethiopian women immigrants, but no data on the association between vitamin D deficiency and tuberculosis in Ethiopia. Therefore, this study was aimed to determine the prevalence of vitamin D deficiency and the association between vitamin D deficiency and tuberculosis among smear positive pulmonary tuberculosis patients and their household contacts without symptoms suggestive of TB in Northwest Ethiopia.

Methods

Study design, settings and study period

A prospective case–control study was conducted among smear positive pulmonary tuberculosis patients and their household contacts without symptoms suggestive of TB (controls). A total of 290 study participants were included in this study. Of them, 96 participants are TB patients and 194 are non TB controls. Study participants were recruited at 11 TB diagnostic health facilities in North and South Gondar zones of Amhara region between May 2013 and April 2015. The 11 TB diagnostic health facilities included in this study are Gondar Health Center (HC), Marakie HC, Woleka HC, Gebriel HC, Azezo HC, Kola Duba HC, Tseda HC, Maksegnit HC, Enferanze HC, Addis Zemen HC, and Woreta HC.

Based on the 2007 census conducted by the central statistical agency of Ethiopia (CSA) [21], Amhara region has a total population of 17,221,976, of whom, 8,641,580 are males and 8,580,396 are females. It is the second populous region in the country. The Amhara region extends from 9° to 13° 45′ N and 36° to 40° 30′ E. It covers approximately 161,828.4 sq km in area. This is 11% of Ethiopia's total area. This land consists of three major geographical zones. These are highlands (above 2300 m above sea level), semi-highlands (1500–2300 m above sea level) and lowlands (below 1500 m above sea level) accounting 20, 44 and 28%, respectively. The Amhara region, like the rest of the country, is located within the tropics where there is no significant variation in day length and the angle of the sun throughout the year. As a result, the average annual temperatures in the region are high. The region has three climatic zones such as hot dry tropical (800–1830 m above sea level), sub tropical (1830–2440 m above sea level), cool temperature (over 2440 m above

sea level) with average annual temperatures 27, 22 and 16 °C, respectively. In all climatic zones there is sunshine throughout the year.

Recruitment of the study participants

All smear positive TB patients diagnosed during the study period and their household contacts without symptoms suggestive of TB, volunteered to participate were enrolled in this study. Clinical screening of contacts was conducted using the WHO screening criteria [22] in 2 weeks time after the index case diagnosed. For all study subjects, information on the socio-demographic data was collected using structured questionnaire. The spot-morning-spot sputum samples and 5 ml venous blood sample were collected prior to commencing TB treatment. Sputum and serum specimens were stored at −20 °C until transported to University of Gondar and Felege Hiwot hospitals using cold box. Sputum samples transported to University of Gondar Hospital for GeneXpert testing while serum samples transported to Felege Hiwot Hospital, Bahir Dar for serum Vitamin D assay.

Laboratory diagnosis of tuberculosis

The spot- morning-spot sputum samples collected from presumptive TB patients were examined using either Zihel Neelsen microscopy or light emitting diode (LED) fluorescence microscopy (FM) for acid fast bacilli (AFB) at respective health facilities following the manufacturer's procedures (Zeiss, Germany). Split sputum samples of all smear positive TB patients were further examined using the Gene Xpert MTB/RIF (Cepheid, USA) following the standard procedure to confirm TB positive study participants.

Study participants were considered TB positive, if their sputum samples are positive for TB by GeneXpert or both GeneXpert and smear microscopy. Study subjects were considered TB negative controls, if household contacts of smear positive TB cases had no symptoms suggestive of TB. TB negative study participants were included in this study as a control to compare the association between TB and vitamin D deficiency.

Measurement of serum vitamin D concentration

Serum samples were separated by centrifugation and frozen immediately at −20 °C. Serum 25 OH Vitamin D levels were measured using a VIDAS 25 OH Vitamin D Total testing kits (Biomerieux, Marcy I'Etoile, France) on mini VIDAS automated immunoassay platform. VIDAS 25 OH Vitamin D Total is a quantitative test using Enzyme Linked Fluorescent Assay (ELFA) technology. The vitamin D status of study participants was interpreted based on the serum 25-(OH) Vitamin D concentration following the manufacturer's instructions as deficient (<20 ng/ml), insufficient (20–29 ng/ml), sufficient (30–100 ng/ml) and potential toxicity (>100 ng/ml). The VIDAS 25-OH Vitamin D Total assay showed excellent performance with correlation of $r = 0.93$ compared with the reference standard liquid chromatography/mass spectrometry methods (LC–MS/MS) [23].

Quality control of laboratory methods

The reliability of the study findings was guaranteed by implementing quality control measures throughout the whole process of the laboratory work. All materials, equipment and procedures were adequately controlled.

Statistical analysis

The data analysis was made using SPSS version 16 software (SPSS Inc., Chicago, IL) after the data was entered and properly cleared. The Chi square test was used to compare the categorical variables. The two important outcome variables assessed using logistic regression analysis model were TB and Vitamin D deficiency. The odds ratios (OR) and 95% confidence intervals (CI) were calculated for demographic and epidemiologic variables by using logistic regression analysis. A multivariate binary logistic regression analysis was used to identify independent risk factors associated with TB and vitamin D deficiency in the study participants. P value <0.05 was considered statistically significant.

Results

General characteristics of study participants

A total of 290 study participants (141 males and 149 females) were included in this study. The study included 96 TB patients (57 males and 39 females) and 194 non TB controls (84 males and 110 females). Majority, 180 (62.1%) of the study participants were urban residents. Eighty one of the study participants (27.9%) were children, <15 years of age. The proportion of children among controls was 35.1% compared to the 13.5% children among TB cases. The mean age (SD) of the study subjects was 27.1 (16.7) years (Table 1).

Serum vitamin D levels

Of the total study participants, 134 (46.2%) were vitamin D deficient, 100 (34.5%) had insufficient vitamin D and only 56 (19.3%) study participants had sufficient vitamin D level. In the TB positive cases, 59 patients (61.5%) were vitamin D deficient and 20 (20.8%) had insufficient vitamin D. While, 75 study participants (38.7%) in the non TB controls were vitamin D deficient and 80 (41.2%) had insufficient vitamin D (Table 2).

Table 1 Socio-demographic and clinical characteristics of study participants (N = 290)

Characteristics	TB patients (N = 96) N (%)	Non TB controls (N = 194) N (%)	Total (N = 290)
Gender			
Male	57 (59.4)	84 (43.3)	141 (48.6)
Female	39 (40.6)	110 (56.7)	149 (51.4)
Residence			
Rural	34 (35.4)	76 (39.2)	110 (37.9)
Urban	62 (64.6)	118 (60.8)	180 (62.1)
Age group in years			
<15	13 (13.5)	68 (35.1)	81 (27.9)
15–24	27 (28.1)	33 (17.0)	60 (20.7)
25–34	30 (31.2)	33 (17.0)	63 (21.7)
35–44	10 (10.4)	27 (13.9)	37 (12.8)
45–54	6 (6.2)	17 (8.8)	23 (7.9)
55+	10 (10.4)	16 (8.2)	26 (9.0)

N number, *TB* tuberculosis

Risk factors associated with tuberculosis

As shown in Table 3, tuberculosis cases had significantly higher rate of vitamin D deficiency (AOR 3.3; 95% CI 1.8–6.0; p < 0.001) than non TB controls. Significantly higher number of males had active TB compared with females (AOR 2.5; 95% CI 1.4–4.3; p = 0.001). Furthermore, study participants in the age groups of 15–24 (AOR 4.5; 95% CI 2.0–10.2; p < 0.001) and 25–34 (AOR 4.3; 95% CI 1.9–96; p < 0.001) years had significantly higher proportion of active TB compared with age group <15 years of age.

Risk factors associated with vitamin D deficiency

Results of multivariate logistic regression analyses showed that females had significantly higher prevalence of vitamin D deficiency than males (AOR 2.3; 95% CI 1.3–3.9; p = 0.002). Urban residents had significantly higher proportion of vitamin D deficiency compared with rural residents (AOR 3.0; 95% CI 1.7–5.3; p < 0.001). Moreover, study subjects in the age groups of 35–44 (AOR 4.5; 95% CI p = 0.001), 45–54 (AOR 5.8; 95% CI 0 1.8–18.6; p = 0.003) and ≥55 (AOR 7.5; 95% CI 2.3–24.2; p = 0.001) years had significantly higher proportion of vitamin D deficiency compared with age group <15 years of age (Table 4).

Discussion

In this study, a high prevalence of vitamin D deficiency, 46.2% was observed among the total study participants. This finding is in agreement with a previous report from the central part of Ethiopia with the total prevalence of 42% vitamin D deficiency among school children [18]. This finding shows that vitamin D deficiency is highly prevalent among the general community in Ethiopia.

Table 2 Vitamin D levels among study participants (n = 290)

Characteristics	Vitamin D levels			Total N
	Deficient (<20 ng/ml) N (%)	Insufficient (20–29 ng/ml) N (%)	Sufficient (30–100 ng/ml) N (%)	
Total	134 (46.2)	100 (34.5)	56 (19.3)	290
TB status				
Positive	59 (61.5)	20 (20.8)	17 (17.7)	96
Negative	75 (38.7)	80 (41.2)	39 (20.1)	194
Gender				
Male	56 (39.7)	49 (34.8)	36 (25.5)	141
Female	78 (52.3)	51 (34.2)	20 (13.4)	149
Residence				
Rural	36 (32.7)	42 (38.2)	32 (29.1)	110
Urban	98 (54.4)	58 (32.2)	24 (13.3)	180
Age group				
<15	25 (30.9)	37 (45.7)	19 (23.5)	81
15–24	22 (36.7)	21 (35.0)	17 (28.3)	60
25–34	32 (50.8)	19 (30.2)	12 (19.0)	63
35–44	20 (54.1)	14 (37.8)	3 (8.1)	37
45–54	15 (65.2)	5 (21.7)	3 (13.0)	23
55+	20 (76.9)	4 (15.4)	2 (7.7)	26

N number, *TB* tuberculosis

Table 3 Risk factors associated with tuberculosis (n = 290)

Characteristics	Total	TB status		Univariate analysis		Multivariate analysis	
		TB patients (N = 96) N (%)	Controls (N = 194) N (%)	COR (95% CI)	p values	AOR (95% CI)	p values
Vit D deficient							
Yes	96	59 (61.5)	37 (38.5)	2.5 (1.5–4.2)	<0.001	3.3 (1.8–6.0)	<0.001
No	194	75 (38.7)	119 (61.3)	1			
Gender							
Male	141	57 (40.4)	84 (59.6)	1.9 (1.2–3.2)	0.010	2.5 (1.4–4.3)	0.001
Female	149	39 (26.2)	110 (73.8)	1			
Residence							
Rural	110	34 (30.9)	76 (69.1)	1			
Urban	180	62 (34.4)	118 (65.6)	1.2 (0.7–2.0)	0.535	0.8 (0.4–1.4)	0.427
Age group							
<15	81	13 (16.0)	68 (84.0)	1			
15–24	60	27 (45.0)	33 (55.0)	4.3 (2.0–9.4)	<0.001	4.5 (2.0–10.2)	<0.001
25–34	63	30 (47.6)	33 (52.4)	4.8 (2.2–10.3)	<0.001	4.3 (1.9–9.6)	<0.001
35–44	37	10 (27.0)	27 (73.0)	1.9 (0.8–4.9)	0.167	1.4 (0.5–3.8)	0.475
45–54	23	6 (26.1)	17 (73.9)	1.8 (0.6–5.6)	0.276	1.3 (0.4–4.2)	0.662
55+	26	10 (38.5)	16 (61.5)	3.3 (1.2–8.8)	0.019	2.0 (0.7–5.6)	0.203

N number, *TB* tuberculosis, *COR* crude odds ratio, *AOR* adjusted odds ratio, *Vit D* vitamin D, *CI* confidence interval

The prevalence of vitamin D deficiency among TB patients (61.5%) reported in our study is comparable to that reported in South Africa (62.7%) [16]. On the contrary, lower prevalence of vitamin D deficiency was reported in Tanzania (10.6%) [8], Guinea Bissau (8.5%) [10] and Uganda (7%) [14] compared to our study. These discrepancies among different reports might be due to the differences in the laboratory assay methods used to measure vitamin D level, definition of vitamin D deficiency, dietary habits of the study population, latitude of the study sites and frequencies of co-morbidities in the study population of different studies. The different

Table 4 Risk factors associated with vitamin D deficiency (n = 290)

Characteristics	Total	Vit D deficiency		Univariate analysis		Multivariate analysis	
		Deficient (<20 ng/ml) N (%)	Not deficient (20–100 ng/ml) N (%)	COR (95% CI)	p values	AOR (95% CI)	p values
Total	290	134 (46.2)	156 (53.8)				
Gender							
Male	141	56 (39.7)	85 (60.3)	1			
Female	149	78 (52.3)	71 (47.7)	1.7 (1.0–2.7)	0.03	2.3 (1.3–3.9)	0.002
Residence							
Rural	110	36 (32.7)	74 (67.3)	1			
Urban	180	98 (54.4)	82 (45.6)	2.5 (1.5–4.0)	<0.001	3.0 (1.7–5.3)	<0.001
Age group							
<15	81	25 (30.9)	56 (69.1)	1			
15–24	60	22 (36.7)	38 (63.3)	1.5 (0.8–2.9)	0.227	1.0 (0.5–2.1)	0.995
25–34	63	32 (50.8)	31 (45.2)	2.0 (1.0–4.1)	0.054	1.6 (0.7–3.4)	0.252
35–44	37	20 (54.1)	17 (45.9)	3.9 (1.7–9.2)	0.002	4.5 (1.8–11.3)	0.001
45–54	23	15 (65.2)	8 (34.8)	4.9 (1.7–14.2)	0.004	5.8 (1.8–18.6)	0.003
55+	26	20 (76.9)	6 (23.1)	7.6 (2.5–22.9)	<0.001	7.5 (2.3–24.2)	0.001

N number, *COR* crude odds ratio, *AOR* adjusted odds ratio, *Vit D* vitamin D, *CI* confidence interval

techniques used to measure serum vitamin D concentrations in the studies done in Uganda [14], Guinea Bissau [10] and Tanzania [8] were a semi-automated solid phase extraction reverse phase high performance liquid chromatography assay, isotope-dilution liquid chromatography–tandem mass spectrometry on an API3000 mass spectrometer and Radio Immuno Assay (RIA) with ^{125}I-labeled 25(OH) D [^{125}I-25(OH)D] as tracer using a kit from Immunodiagnostic-Systems, respectively.

In this study, multivariate logistic regression analysis showed a significant association between vitamin D deficiency and tuberculosis ($p < 0.001$). The possible association between vitamin D deficiency and active tuberculosis was first reported more than 20 years ago [24], however, several studies reported conflicting results. Similar to our study, many studies have reported a significant association between vitamin D deficiency and TB. Studies in West Africa [10], Australia [12], Kenya [17], Vietnam [25], Tanzania [26] and India [27] have reported higher levels of vitamin D deficiency in patients with TB compared with non TB controls. A meta-analysis by Nnoaham et al. also showed that serum vitamin D levels were 0.68 standard deviation lower in TB patients compared to controls [20]. However, studies from Indonesia [28], China [29], Hong Kong [30] and Korea [31] have reported no significant difference in serum vitamin D levels between TB patients and controls. The discrepancies between these studies may be due to differences in cultural characteristics, ethnic, sunlight exposure, skin color or dietary practices. Although there is good evidence to suggest that a decrease in serum vitamin D levels compromises immunity and leads to the re-activation of latent tuberculosis [32], the low serum vitamin D levels may also result from tuberculosis itself.

In the present study, it was noted that a significantly higher level of vitamin D deficiency was observed among females compared with males ($p = 0.002$). Similarly, a report from Pakistan showed that vitamin D deficiency was significantly higher in females than males [33]. Possible reasons for this female preponderance might be due to poorer nutritional status than their male counterparts, inadequate exposure to sunlight because of the culture of most females to stay at home, and pregnancy experiences.

Increasing age was found to be significantly associated with vitamin D deficiency in our study. Similar findings have also been observed in reports from Uganda [34], and in the USA [35]. Older people are prone to develop vitamin D deficiency because of various risk factors: decreased dietary intake, diminished sunlight exposure, reduced skin thickness, impaired intestinal absorption, and impaired hydroxylation in the liver and kidneys [36–38].

In this study, urban residence was found to be a significant risk factor for vitamin D deficiency compared with rural residence. Our finding was in agreement with the findings of the previous studies in the central part of Ethiopia [18] and in Peru [39] that showed significant association between vitamin D deficiency and urban environment. This might be due to lifestyle changes associated with urbanization that may lead to less time spent outdoors which in turn can be associated with being vitamin D deficient.

The major limitations of our study include dietary intake, biochemical variables (calcium, parathyroid hormone), HIV status and latent TB infections, all of which could affect vitamin D deficiency, were not considered in this study. However, the effect of these factors on the level of vitamin D among TB patients was controlled using tight control groups from the same household who did not have TB diseases. As the cases and controls shared similar environment and household, the cases and controls are likely to have similar risk factors exposures including dietary intake.

Conclusions

Vitamin D deficiency is highly prevalent among TB patients and non TB controls in Ethiopia where there is year round abundant sunshine. This study confirms a significant association between vitamin D deficiency and tuberculosis in Ethiopia. Vitamin D deficiency was also significantly higher in females, older age groups, and urban residents. The findings of this study warrant further studies first to resolve the chicken–egg dilemma of the association between vitamin D deficiency and TB using cohort study and then to determine whether vitamin D supplementation can have a role in the prevention and treatment of tuberculosis in high TB burden countries like Ethiopia.

Authors' contributions

BT conceived the study, involved in proposal writing and design, data collection, analysis, interpretation and draft manuscript writing. FM, BG and MM involved in proposal writing and design and reviewed the manuscript. DH, NH and SY involved in data analysis, interpretation of results and reviewed the manuscript. KM, YK and PGS reviewed the manuscript. All authors read and approved the final manuscript.

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Competing interests
The authors declare that they have no competing interests.

Availability of data and materials
The authors declare that the data supporting the findings of this study are available within the article.

Consent for publication
All authors read and approved the final manuscript for submission for publication.

Ethics approval and consent to participate
The ethical approval of the study was obtained from institutional ethical review board of University of Gondar, Ethiopia. Written informed consent was obtained from all eligible study participants or from parents/legal guardians of any participants under 18 years of age. Moreover, oral consent was also obtained from under 18 years of age study participants. Tuberculosis positive study participants received the standard anti-TB treatment regimens based on the national treatment guideline without delay. Information obtained in each course of the study was kept confidential.

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Trend and outcome of notified children with tuberculosis during 2011-2015 in Kampala, Uganda

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Abstract

Background: The road map for childhood tuberculosis launched in 2013 provided strong renewed efforts focused towards zero deaths due to tuberculosis in children. From 2010, there were efforts to improve childhood tuberculosis diagnosis in Kampala and this study aimed to document the trend and outcome of tuberculosis in children over the period.

Methods: This was a retrospective study of tuberculosis data for Kampala city for the period 2011–2015. We extracted data from the unit TB registers in the 52 Diagnostic and treatment units (DTUs) in the Kampala. We report on data for children 0 to 14 years.

Results: We accessed 33,221 TB patient records of which 2333 (7.0% 95% CI 6.7 to 7.3) were children. The proportion of children with pulmonary TB was 80% (1870/2333) (95% CI 76.7 to 83.7 and extra-pulmonary TB accounted for 20% (463/2333) (CI 18.3 to 21.5). Among pulmonary TB cases, the clinically diagnosed were 82% (1530/1870) (95% CI 80.0 to 83.5) while the bacteriologically confirmed were 18% (340/1870) (95% CI 16.5 to 20.0). Among the bacteriologically confirmed, 45% (154/340) (95% CI 40.1 to 50.6) were smear positive. During the study period 2011 through 2015, the childhood TB notification rate declined as follows; 105, 76, 72, 88, and 74 per 100,000 respectively. The treatment success rate increased from 78% in 2011 to 83% in 2015.

Conclusions: The TB notification rate among children in Kampala city showed a large decline during the period 2011 to 2015. There was a slight improvement in the treatment success rate among the children.

Background

The Millennium Development Goal (MDG) VI set in 2000 targeted to halve the global tuberculosis (TB) prevalence of 331/100,000 in 1990 by 2015 [1]. The World Health Organization (WHO) global TB reports since 1990 have referenced some of these bench marks to assess progress. The global TB incidence rate declined by 2% each year between 2000 and 2016. The better reporting of cases mainly in India largely explains the increase in notification rates since 2013 [2]. Although the decline in TB deaths by 24% between 2000 and 2016 is significant, it remains the ninth cause of mortality worldwide [2]. The TB associated deaths among HIV negatives reduced from 1.7 Million in 2000 to 1.3 Million in 2016 [2].

The proportion of children notified with TB has progressively increased from 6% in 2012 to the current 10% of the total in 2016 [2, 3]. Reports have also shown a drop in global treatment success rate from 87% in 2013 to 83% in the 2015 cohort largely credited to the large number of "not evaluated" patients [2, 4]. There were 110,000 TB deaths among the HIV negative children, representing 8.5% of all TB deaths in 2016 [2] . Despite the WHO recommendation to start all child TB contacts on isoniazid preventive therapy (IPT), only 13% of child contacts received IPT in 2016 [2]. Reports have shown a decline in childhood notification rates on the background of doubt about the true burden of TB in children with many cases underdiagnosed or under reported. The road map for childhood TB launched in 2013 provided

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strong renewed efforts focused towards zero deaths due to TB in the <15 years age group [5].

In Uganda, the TB notification rate declined from 209 per 100,000 in 2010 to 161 per 100,000 in 2014 [6]. The treatment success rate improved from 67% in 2009 to 75% in 2013 among new and relapse cases [6–8]. The estimated case detection rate improved from 61% in 2010 to 72% in 2014 [6–8]. HIV testing among diagnosed TB patients improved from 81% in 2010 to 95% in 2014 [6–8], antiretroviral therapy (ART) coverage from 24% in 2010 to 81% in 2014 [6]. Cotrimoxazole preventive therapy (CPT) coverage improved from 90% in 2010 to 98% in 2014 [7, 8]. Data on TB contact investigation in Uganda at the writing of this paper was not available while IPT rolled out at the beginning of 2015. Uganda is one of the countries that achieved a remarkable decline in the prevalence of TB and met the MDG target [9].

Data reported in Uganda so far does not show trend of childhood TB to track progress of TB control in this age group. Projections for childhood TB progress in Uganda are on the background of under reporting and underdiagnosis of TB in children. Over the years, there has been a steady shift from reporting only smear positive cases to all cases including the clinically diagnosed potentially leading to an increase in the reported child TB cases. Even with these improved reporting strategies, the available evidence suggests the true burden of TB disease in children is an underestimate [10]. This reflects the implementation challenges in the diagnosis and reporting of TB in children by the National TB & Leprosy program (NTLP). We showed in our previous report that 7% of the reported TB in 2009 and 2010 in Kampala city were in children [11]. The WHO report covering the same period reported children TB cases represented 1.5% of all smear positive TB cases reported in Uganda [12]. The proportion increased to 7.5% of all the TB cases in Uganda among children in 2013 [6].

From 2013, the NTLP heightened efforts towards improvement of childhood TB diagnosis in Uganda. Such efforts included appointment of a national pediatric TB focal person at the NTLP and mentorships in childhood TB care, recording and reporting. The objective of these interventions was to improve case notification and outcomes of childhood TB. This study therefore aimed to document the trend and describe outcome of child TB cases reported in Kampala city from 2011 to 2015.

Methods

Study design

This was a retrospective study of TB records for Kampala city for the period 2011–2015.

Study setting and data generation

We conducted this study in Kampala city, Uganda's capital city. Kampala has 5 administrative divisions (Central, Nakawa, Kawempe, Rubaga, and Makindye). Wakiso district, from where much of the Kampala city day population lives, surrounds the city. Children below 15 years in Kampala city for 2011, 2012, 2013 and 2015 were 478,075, 487,830, 497,785 and 518,307 respectively using a baseline population of 507, 942 reported in the 2014 census [13]. We used the simple share population projection formula; baseline population x EXP (growth rate x t) where t is projection time in years from the baseline time point. The census of 2014 showed 2.02% Kampala population increase each year between 2002 and 2014 [13]. The population growth rate for each division is difficult to estimate since in-migrations are not uniform. For this study, we assumed a uniform increase of 2.02% for each division.

This report covers data collected from all the 52 TB diagnostic and treatment units (DTUs) in the Kampala city. Each of the DTUs records TB cases in the Unit TB registers. Health workers complete the unit TB registers at the start of treatment. All the TB medicines are free and testing for HIV is part of the TB and HIV integrated services. The division supervisors transfer information from the Unit TB registers into the division TB registers (both paper and electronic) monthly. The division supervisor files quarterly reports by the 7th of the following month after the end of the quarter to the Kampala city health office for onward transmission to the NTLP. A TB case is a patient in whom a clinician has made a diagnosis of TB either as bacteriologically (smear or Xpert® MTB/RIF or culture positive) or clinically [14].

We included all records of children aged less than 15 years reported with TB in Kampala for the period 2011 to 2015 in the analysis. The data extracted included; age, sex, address, HIV status, ART uptake, CPT uptake, TB classification and outcome.

Data management and statistical analysis

We extracted data from an electronic TB database. We used Stata transfer v9 to export the relevant extraction from the electronic data to a Stata format and analyzed using STATA v12. We cleaned, coded and explored all the eligible captured records and used descriptive statistics to explore the study population characteristics such as sex, age, HIV status, ART, TB classification, and outcome. Treatment success rate was the proportion of cured plus completed among all childhood TB notifications. We performed exploratory analysis to recognize trends and outcomes of TB in children. We used Chi square for trend test to assess the trend of the reported proportions.

Results

Descriptive statistics

We accessed 33,221 patient TB records of which 2333 (7.0% (CI 6.7 to 7.3)) were for children. Of the 2333 children, 53% were males. The median age was 4 years (IQR 9 i.e. 1, 10). Children 0 to 4 years contributed 53% (1241/2333). The proportion with PTB and EPTB among all cases was 80% (1870/2333) (95% CI 78.1 to 81.7) and 20% (463/2333) (95% CI 18.3 to 22.0) respectively. Among pulmonary TB cases the clinically diagnosed were 82% (1530/1870) (95% CI 81.9 to 85.6). The bacteriologically confirmed were 18% (340/1870) (95% CI 14.4 to 18.1) of whom 45% (154/340) (95% CI 41.6 to 54.4) were smear positive. Only 8.7% (162/1870) (95% CI 7.5 to 10.0) of PTB cases had a baseline smear microscopy.

Trend of TB in children over the study period

There was a general increase in the total TB notifications for all ages but a relative decline in the proportion of children with TB. See other details in the Table 1.

Overall there was a 34% decline in the childhood TB notification rate over the study period with a significant decline observed among the 0 to 4 years' age group. See the other details in Table 2.

HIV and ART uptake over the study period

The proportion tested for HIV was 79% (1926/2333) and 100% (1925/1926) received their results of whom 35% (673/1926) were HIV-positive. Of those 91% (610/673) were on ART and 97% (654/673) were on CPT. Details of HIV and ART uptake over the study duration are in Table 3.

Outcomes of notified children TB cases over the study period

The average treatment success rate (TSR) was 77% during the study period, a rate below the national target of 80% and there was no significant increase over the study period. The average TSR was lowest in children 0 to 4 years and adolescents 10 to 14 years at 76% compared with 79% in 5 to 9 years. Overall, we noted the highest decline in loss to follow up in adolescents 10 to 14 years. The details of treatment outcomes during the study period are in Table 4.

Discussion

We undertook to document the trend in notification and outcome of children TB cases in Kampala city. Our findings show a non-significant declining trend of TB notification rate over the study period. The outcomes of TB varied over the study period with no significant increase in the treatment success rate and the average treatment success rate not reaching the national target of 80%. The average mortality rate was highest among the under-fives at 9% almost double the ≤5% WHO acceptable case fatality ratio to achieve the 2025 milestone for reduction of TB deaths [2] .

Our results show a modest declining trend in TB notification rate among children reported in Kampala. We noted that this decrease was not uniform with children under 5 years showing a significant decline in notification rate but a stable trend in the 5 to 14 years. This finding is consistent with what we earlier reported for the 2009 and 2010 [11]. Our results are also comparable to the reported global trend in world TB report 2017 that shows a modest overall decline [2]. We note the higher proportionate TB notification in age group 0 to 4 years over the study period attributable to the increased focus by the national program on TB diagnosis in the under-fives. Since appointing of a paediatric TB focal person at the NTLP, there has been greater impetus in TB case notification among children. A Paediatric TB curriculum was developed and systematic training and mentorships undertaken. A cluster randomized study showed that systematic training increased TB notification in children by three times from the baseline [15]. We note the documented steady decrease of notified TB cases among adults [2]. The decrease in the number of adults with TB represents a lower transmission chance most especially in the home environment [16] and this best reflects in the under-fives that have the highest risk of infection. In this report, we show that children represent about 7% of reported TB in Kampala city but also observe a decrease in the proportion of children over the years though the numbers increased. Compared to the projected estimate of 15% of all TB among children, the current performance remains below the expected [10]. The value addition of this paper above our previous work [11] is demonstration of trend of outcome of TB in children. Our previous work had 2-time points that could not allow us to show trend. This work also covers a period in which several interventions to increase TB case finding in children took place as opposed to of our previous work where minimal took place.

Most of the TB in children (80%) was pulmonary of which the clinically diagnosed represented 82%. This observation might be because of to the extra efforts to train health workers in childhood TB diagnosis and the emphasis on using algorithms to make a clinical diagnosis. Only about 7% of pulmonary bacteriologically confirmed cases had smear microscopy done of whom many (45%) were smear positive. We can speculate this to have resulted from the limited ability of health workers to collect sputum samples. The higher smear positivity rate

Table 1 Trend of TB notifications in children in Kampala district divisions 2011–2015

Age group	Division		2011	2012	2013	2014	2015	*p* value for trend
Overall (adults and children)	Central		626	256	597	1128	1199	
	Kawempe		4054	2440	2866	3475	3040	
	Nakawa		878	457	753	1000	1151	
	Rubaga		1339	533	901	1048	1152	
	Makindye		979	443	788	1448	670	
Proportion of children			7.2%	10%	6.9%	6.3%	6%	0.35
0–4 years	Central	notified	0	0	0	20	18	
		rate[b]	0	0	0	232	204	0.17
	Kawempe	notified	194	147	130	191	117	
		rate[b]	410	304	264	380	228	0.0003***
	Nakawa	notified	0	0	4	7	21	
		rate[b]	0	0	9	17	50	0.004**
	Lubaga	notified	86	47	50	36	36	
		rate[b]	155	83	86	61	60	<0.0001****
	Makindye	notified	33	37	25	27	15	
		rate[b]	64	70	46	49	26	0.0002***
5–14 years	Central	notified	0	0	0	25	33	
		rate[b]	0	0	0	217	281	0.004**
	Kawempe	notified	153	95	105	120	107	
		rate[b]	239	145	157	176	154	0.0009***
	Nakawa	notified	0	0	11	13	37	
		rate[b]	0	0	17	19	55	0.007**
	Lubaga	notified	54	56	56	38	34	
		rate[b]	68	49	33	40	19	<0.0001****
	Makindye	notified	48	35	24	30	15	
		rate[b]	67	47	32	39	19	<0.0001****

[b]notification per 100,000
*$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$, ****$P \leq 0.0001$

suggests a selection bias towards older children who are more likely to provide a sputum sample with higher bacillary load. This low sputum collection rate implies the Xpert® MTB/RIF which is the recommended first test for TB has low uptake. We note that even with emphasis on Xpert® MTB/RIF as first test, the bacteriologically confirmed constituted 18% of the PTB cases. This compares with 15% reported in our previous work when the Xpert® MTB/RIF was not readily available [11]. This small difference may suggest underutilization of the Xpert® MTB/RIF in children whose underlying reasons are outside the scope of this work.

The average proportion tested for HIV was still low at 79% over the study period compared to the national target of 100%. There was however a significant increase from 56% in 2011 to 100% in 2015 and all the tested children received their results. This suggests the efforts over the study period in TB and HIV integration were yielding results. The average TB and HIV co-infection was 35% and remained in the same range over the study period with greatest decline seen in the 5–9 years. Data on the prevalence of HIV in children with TB are rare but available literature shows 5 to 56% in different settings [17]. Previous work in our setting reported an HIV prevalence of up to 49% among children with TB [11, 18] therefore our findings show a significant decline in HIV burden among children registered for TB treatment. This could be a reflection of reduced mother to child HIV transmission that has reduced new infections in children from 27,660 in 2011 to 9629 in 2013 [19]. Alternatively, it could be HIV positive children with TB die before diagnosis since they have a higher hospital related mortality [20]. Recent work by Dodd et al. showed the odds of HIV in cohorts of children with TB compared to that of children without TB was 7 times [21]. We found good CPT uptake above 95% and ART uptake increasing from 24% in our previous work [11] to the reported 91%. This is a good sign of integrated TB and

Table 2 The trend of paediatric TB notification rates in Kampala 2011–2015

		2011	2012	2013	2014	2015	*p* value for trend
All children	notified	568	417	401	507	433	
	confirmed[b]	49	28	57	112	94	
	population	478,075	487,830	497,785	507,942	518,307	
	rate[a]	119	85	81	100	84	0.07
0–4 years	notified	313	231	209	281	207	
	confirmed[b]	11	4	7	42	8	
	population	200,684	204,780	208,958	213,222	217,573	
	rate[a]	155	112	100	131	95	0.003**
5–14 years	notified	255	186	196	226	226	
	confirmed[b]	38	24	50	70	86	
	population	277,390	283,051	288,826	294,720	300,734	
	rate[a]	81	65	67	76	75	0.97

[a]notification per 100,000
*$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$, ****$P \leq 0.0001$
[b]bacteriologically confirmed either smear, Xpert MTB/RIF or culture

Table 3 Trend of HIV testing, ART and CPT uptake among children with TB in Kampala 2011–2015

Age group	variable	2011	2012	2013	2014	2015	*P* value for trend
	Notified cases	568	417	401	507	433	
	Tested for HIV	333	264	387	508	433	
Overall	% tested for HIV	59	63	96.5	99.8	100	<0.0001***
	Received results	333	264	387	508	433	
	HIV + ve (%)	126 (38)	114 (43)	100 (26)	182 (36)	151 (35)	0.39
	CPT (%)	121 (96)	111 (97)	97 (97)	175 (96)	150 (99)	0.35
	ART (%)	107 (85)	102 (90)	86 (86)	167 (92)	148 (98)	0.003**
	Tested for HIV	180	135	197	280	207	
0–4 years	Received results	180	135	197	280	207	
	HIV + ve (%)	57 (32)	53 (39)	37 (19)	98 (35)	62 (30)	0.58
	CPT (%)	55 (96.5)	51 (96.2)	35 (94.6)	94 (95.9)	61 (99)	0.48
	ART (%)	48 (84)	48 (91)	26 (70)	87 (89)	60 (97)	0.58
	Tested for HIV	54	71	81	97	93	
5–9 years	Received results	54	71	81	97	93	
	HIV + ve (%)	36 (67)	41 (58)	26 (32)	38 (39)	42 (45)	0.0001***
	CPT (%)	34 (94.4)	40 (97.6)	25 (96.2)	36 (94.7)	42 (100)	0.11
	ART (%)	30 (83)	35 (85)	24 (92)	36 (95)	42 (100)	<0.0001****
	Tested for HIV	99	58	109	131	133	
10–14 years	Received results	99	58	109	131	133	
	HIV + ve (%)	33 (33)	20 (34)	37 (34)	46 (35)	47 (35)	0.73
	CPT (%)	32 (97)	20 (100)	37 (100)	45 (97.8)	46 (99)	0.56
	ART (%)	29 (88)	19 (95)	36 (97)	44 (96)	46 (98)	0.0028**

*$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$, ****$P \leq 0.0001$

Table 4 Distribution of the treatment outcomes by age group in children notified with TB in Kampala district 2011–2015

Age group	Outcome	2011 (%)	2012 (%)	2013 (%)	2014 (%)	2015 (%)	*P* value for trend
Overall	[a]Cured	39	50	44	56	77	<0.0001****
	[b]TSR	78	70	70	83	83	0.084
	[b]LFU	7	16	5	5	3	0.02*
	[b]Died	4	5	10	9	11	0.027*
	[b]Not Evaluated	11	9	15	3	3	0.016*
0–4 years	[a]Cured	27	25	14	24	63	<0.0001
	[b]TSR	80	71	70	79	82	0.37
	[b]LFU	7	12	4	5	3	0.049*
	[b]Died	5	6	10	12	12	0.027*
	[b]Not Evaluated	9	11	16	4	2	0.016*
5–9 years	[a]Cured	40	60	0	50	80	<0.0001****
	[b]TSR	87	66	65	91	84	0.14
	[b]LFU	3	21	10	3	2	0.018*
	[b]Died	4	5	8	5	11	0.074
	[b]Not Evaluated	6	8	17	1	3	0.107
10–14 years	[a]Cured	42	53	56	83	77	<0.0001****
	[b]TSR	67	72	73	86	84	0.0004***
	[b]LFU	10	19	4	7	2	0.0014**
	[b]Died	1	4	12	6	9	0.02*
	[b]Not Evaluated	22	6	11	2	3	<0.0001****

[a]% of PBC cases only; [b]% of all cases; TSR combines cure and completed cases
*$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$, ****$P \leq 0.0001$

HIV care services in accordance to with the Uganda national guidelines.

The average treatment success rate over the study period was 77%. We noted variations in all age groups but 0 to 4 years and 5 to 9 years had declining treatment success rate over the study period. A report from Malawian hospital TB records in 1998 showed poor treatment success rate of less than 43% in children below 5 years and 54% in those above 5 years [22]. In our study, we noted the direct linkage between many cases of loss to follow, high mortality and treatment success rate. We hypothesize this results from the drive to diagnose many more children without satisfactory human resources to support adherence leading to high loss to follow up and poor completion rates. The 10 to 14 years showed the highest loss to follow up in the earlier years of the study period. In most children, diagnosis is made on clinical grounds and where parents do not agree, adherence to treatment remains a challenge. We noted a significant decline in loss to follow up over the study period. The explanation for this significant decline in loss to follow is beyond the scope of this study. Our results show that mortality in the 0 to 4 years age-group increased as the notifications increased. Most of these deaths are likely from the hospital setting where TB diagnosis in children is commonly made late. There is evidence that many children die either as a result or with underlying undiagnosed TB [23]. Since we document a high death rate, we hypothesize that TB in this 0 to 4 years age-group is more likely to be severe and diagnosed late usually at the referral health unit. There is evidence that children with TB present with other conditions most especially severe pneumonia where TB is an afterthought leading to late diagnosis of TB [24, 25]. Harries A et al. reported a higher mortality in the under 1-year and those below 4 years compared to other age groups [22]. A recent systematic review by Jenkins et al. [26] showed a low mortality rate of 0.9% in children with TB in the context of available TB medicines. This may confirm our suggestion that most of deaths are due to late diagnosis of TB rather than failure of TB medicines. The Adolescent age group had a high average mortality rate of about 6%. This high mortality in adolescents has largely gone unnoticed whose causes our study could not find out. The adolescents commonly have adult type disease and are less likely to be compliant to chronic treatment [27]. The poor TB treatment outcomes among children needs further exploration and there is need to examine the time points of these deaths on the path of care and other co-morbidities in the adolescents.

Strengths and limitations

In this paper, we showed a trend over a five-year study period. This report follows a previous study with similar methods and therefore allows for a fair assessment of the progress of childhood TB services. We admit the inherent weaknesses of retrospective data that includes missing and inability to verify the records. Our inability to report data on Xpert ® MTB/RIF use in the diagnosis of TB in children is a drawback. The routine reporting tools to the NTLP were not capturing this data during the period covered by this study. We are however confident that our results are a representation of the true picture of the trend of childhood TB notification and outcomes in Kampala city. The weakness of notification rate is that it does not reflect the prevailing TB incidence unless there are few numbers of undetected, unreported or retreatment cases alongside good access to health services. Besides, the denominator projected population assumed a uniform growth rate despite the migrations in the urban setting, limiting accurate measurement of TB notification rates. We are also aware that some of the patients registered in Kampala are nonresidents and that some registered in one division may be residing in another division. Nevertheless, for purposes of showing a trend, our paper still makes an important contribution.

Implications for practice and program implementation

The focused efforts by the NTLP to look for TB among the under 15 years age group did show good results. The declining trend of notification rates in children mirrored declining adult TB notifications. This study cannot explain drivers of the noted trend for which we recommend further study. The low proportion of children among the notified TB cases in Kampala is likely due to a weak case finding system. Weak household contact tracing, TB screening and diagnostic skills lead to under diagnosis and under reporting TB in children. The high loss to follow up may suggest weaknesses in the support services such as adherence counseling and human resources for health leading to inadequate quality of care. We hypothesize the high mortality rate is mainly among previously hospitalized children. There is high mortality of up to 11% among children diagnosed with TB after hospitalization with delays of up to 16 days to make a TB diagnosis [28]. Thus, many children started on TB treatment while on the wards are commonly sicker.

Conclusion

There was a minimal decline in the trend of childhood TB notification rates from our report. The increase in the treatment success rate over the study period was not significant and its average did not reach the national target. The adolescents had the worst proportionate treatment outcomes. The average mortality over the study period of about 5% is still high with under-fives having a consistently higher relative mortality.

Abbreviations

ART: Anti-retroviral therapy; CPT: Cotrimoxazole preventive therapy; DTU: Diagnostic and treatment unit; EPTB: Extra-pulmonary tuberculosis; HIV: Human immune-deficiency virus; MDG: Millenium development goal; MoH: Ministry of Health; MREC: Mulago Research and Ethics Committee; NTLP: National Tuberculosis and Leprosy Program; PTB: Pulmonary tuberculosis; TB: Tuberculosis; TSR: Treatment success rate; WHO: World Health Organization

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Availability of data and materials

The dataset used and/or analysed during the current study is available from the corresponding author on reasonable request.

Authors' contributions

EW and DL formed the idea. They designed the study and the collected data. DL and DK performed the data analysis. EW wrote the manuscript draft. MS contributed to interpretation of results and reviewing the scientific content of the manuscript. FM reviewed the manuscript. All the authors contributed to data interpretation. All the authors read and approved the manuscript.

Ethics approval and consent to participate

We got ethical approval from Mulago Research and Ethics Committee (Reference number: MREC 966). We ensured confidentiality of patient information by not extracting unique personal identifiers such as patient's name.

Consent for publication

Not Applicable.

Competing interests

The authors declare that they have no competing interests.

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Delays to treatment initiation is associated with tuberculosis treatment outcomes among patients on directly observed treatment short course in Southwest Ethiopia: a follow-up study

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Abstract

Background: Despite reported long delays to initiate anti-TB treatment and poor outcomes in different parts of Ethiopia and elsewhere, evidences on association between the delay and treatment outcomes are scanty.

Methods: A follow up study among 735 new TB cases registered at health facilities in districts of southwest Ethiopia was conducted from January 2015 to June 2016. Patients reported days elapsed between onset of illness and treatment commencement of 30 days cutoff was considered to ascertain exposure. Thus, those elapsed beyond 30 days to initiate anti-TB treatment since onset of illness were exposed and otherwise non-exposed. The cases were followed until earliest outcome was observed. Treatment outcomes was ascertained as per the World Health Organization standard definitions and dichotomized into 'successful' when cured or treatment completed and 'unsuccessful' when lost to follow-up or died or treatment failure. Bivariate and multiple log-binomial models were fitted to identify predictors of unsuccessful outcomes.

Results: The overall treatment success among the treatment cohort was 89.7% (88.4% vs. 94.2%, $p = 0.01$ respectively among those initiated treatment beyond and within of 30 days of onset of illness. Higher risk of unsuccessful outcome was predicted by treatment initiation beyond 30 days of onset [Adjusted Relative Risk (ARR) = 1.92, 95%CI:1.30, 2.81], HIV co-infection (ARR = 2.18, 95%CI:1.47, 3.25) and received treatment at hospital (ARR = 3.73, 95%CI:2.23, 6.25). On the other hand, lower risk of unsuccessful outcome was predicted by weight gain (ARR = 0.40, 95%CI:0.19, 0.83) and sputum smear negative conversion (ARR = 0.17,95% CI:0.09, 0.33) at the end of second month treatment.

Conclusion: Higher risk of unsuccessful outcome is associated with prolonged days elapsed between onset of illness and treatment commencement. Hence, promotion of early care seeking, improving diagnostic and case holding efficiencies of health facilities and TB/HIV collaborative interventions can reduce risk of unsuccessful outcome.

Keywords: TB, Delay, Follow-up, Log-binomial, Ethiopia

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Background

Despite the fact that nearly all cases can be cured, tuberculosis (TB) remained to be among the major global public health problems. Globally, 10.4 million incident cases, of whom 6.1million notified and 1.4 million deaths were estimated to occur in 2015 [1]. Thus, the latest strategy, "End TB" has been designed in line with the sustainable development goals (SDG). The strategy aimed at reaching 90% case detection and treatment success by 2025 [2].

Tuberculosis has been recognized as a major public health problem in Ethiopia and efforts to control the disease has begun since early 1960s [3]. Nonetheless, TB has remained among the major public health problems in the country [4]. Accordingly, Ethiopia has been listed among the 14 TB, TB/HIV (Human Immunodeficiency Virus) and Multi-Drug Resistant TB (MDR TB) High Burden Countries (HBC) [1]. The first national TB prevalence survey conducted in 2011 revealed smear positive pulmonary TB(PTB) prevalence of 108/100,000; of which 55% were not detected before the survey [5] . In 2015, about 205,463 new cases [6] and 29,000 deaths were estimated to occur in the country [1] when only 125,801 (61%) were notified to National TB control Program (NTP) [6].

The ultimate goal of any TB control program is reduction of morbidity and mortality among patients and stop transmission through curing infectious cases [7]. Hence early detection and treatment of cases have been a pillar for the end TB strategy [2]. Nonetheless, studies from different parts of Ethiopia reported patients elapse too long time to initiate care seeking and treatment. TB patients elapse median of 30 [8, 9] in Northern Ethiopia and 63 days in Bale [10] to initiate care seeking and median of six in Addis Ababa [11] and 34 days in Bale [10] to commence treatment.

Delays to diagnosis and treatment of TB result in more serious illness, increased length of infectiousness and poor treatment outcomes including mortality and drug resistance [12–16]. It is also reported that the high mortality rate among people living with HIV is also partly explained by delays to TB treatment [16, 17]. In contrast, a study in Tel Aviv reported no association between treatment success and delay in treatment initiation [18].

Achieving high cure rates help to reduce transmission of TB and attract the great majority of existing cases to seek treatment [19]. As a result, treatment of TB is beyond treating an individual patient, rather it is considered as a public health intervention. Globally, 83% of cases successfully completed their treatment in 2015,and effective diagnosis and treatment of TB saved an estimated 49 million lives between 2000 through 2015 [1]. In Ethiopia, 89% (range: 69%–95%)of treatment cohort in different regions attained successful TB treatment [6]. However, cure rates of 81% (range: 38% to 92%) [4] across regions of the country have been reported.

Studies uncovered that patient demographics, clinical, bacteriologic and HIV co morbidity were associated with unsuccessful TB treatment outcomes [20–23]. Despite the prevailing long delays to initiate anti-TB treatment and poor outcomes in different parts of Ethiopia and elsewhere, evidences on effect of the delay on treatment outcomes are scanty. Hence, this study assessed effect of delayed treatment initiation on outcomes of TB. Evidences on the association between treatment delay and outcome is crucial to realize the targets of ending TB epidemic [2].

Methods

Study setting

The study was conducted in 14 health facilities (three hospitals and 11 health centers) in three zones of Southern Nation, Nationalities, and Peoples Region (SNNPR) of Ethiopia. The SNNPR is one of the nine Regional States in the country with an estimated 15.7million population in 2017 [24]. The three study Zones (Bench Maji, Kaffa and Sheka) are located at the southwestern part of Ethiopia bordering South Sudan and harbor an estimated 1.8million peoples [24]. The zones (an administrative unit that liaison *woredas* with the region) are organized into four town administrations and 26 *woredas*(administrative unit equivalent to districts). At the time of the study, three hospitals and 65 health centers were providing TB Directly Observed Treatment Short course (DOTS) services. However, all the hospitals and only 25 health centers were providing TB/HIV collaborative interventions [25].

Diagnosis and treatment of all forms of TB across Ethiopia has been based on national TB control guidelines that specify case definitions, diagnostic and treatment standards [26]. Thus all TB cases enrolled for this study were diagnosed using either sputum smear microcopy or clinical signs aided with x-ray. Those cases with sputum smear positive were labeled as smear positive pulmonary TB and negatives were smear negative pulmonary TB. Diagnosis of smear negative and extrapulmonary TB were made using diagnostic algorithm recommended by the national guideline [26]. Detail definitions for each cases presented in definition of terms section. Previously, TB diagnosis and treatment had been limited to public hospitals and health centers, but public private mix (PPM) DOTS and community DOTS to public health posts have been recently introduced. Thus, in 2011, 92% of public hospitals and 95% of health centers, 2100 health posts and 317 PPM–DOTS centers were providing DOTS based diagnosis and/or treatment of TB in the country [27].

Study design and sampling

A prospective cohort study among new TB cases was carried out from January 2015 through June 2016. The treatment cohorts were recruited from baseline survey designed to determine delays to initiate treatment. Since no standard cutoff point for delay to treatment, a clinical sound cutoff of 30 days was used to ascertain exposure. Thus TB cases who elapsed beyond 30 days to initiate treatment since onset of illness were labeled as exposed and those started treatment within 30 days of onset of illness were non exposed. Then the cases were followed until earliest treatment outcome. The sample size was computed using StatCalc program of EpiInfo at 95% significance level, 80% power, expected outcome (unsuccessful of 3% [15] among those delayed beyond 30 days) to detect a difference of 7% with those initiated treatment earlier and considering design effect of 1.5 and 10% lost to follow up a total of 640 cases were required., However, the sample size for assessing predictors of delaycomputed using the same procedure provided a total of 802 new cases . Hence, the same cases were followed for the outcome; the larger sample of 802 was taken the final sample size.

The sample was proportionally allocated to the zones, *woredas* and health facilities based on TB cases reported during the year preceding the study. Finally, consecutive consenting cases from were prospectively enrolled until the required sample was reached and followed until completion of the six-month treatment or earliest outcome. During the enrollment those new cases, older than 18 years of age, on intensive phase treatment were included and those transferred out and died before the interview were excluded from the study.

Data collection

A structured questionnaire adapted from tools used elsewhere [5, 28] and standard TB register book [26] was used to gather the data. Besides, data abstraction checklist was prepared to draw clinical, bacteriologic and treatment outcomes of the patients from TB register. The questionnaire was translated into national language (*Amharic*) spoken by almost all residents in the study area. Ten diploma graduate nurse data collectors and three public health specialist supervisors were recruited and trained for 3 days. The training included description of questionnaire, interviewing techniques and pretest among TB cases on DOTS at nearby health facilities not included in the study. Finally, eligible cases were traced from the unit TB register and interviewed for sociodemographic, health care seeking, and treatment practices.

Exposure ascertainment

The main exposure variable was delays to treatment measured by days elapsed between onsets of illness to initiation of anti-TB treatment (total delay). The total delay comprises both patient and provider delays. Patient delay was assessed by asking patients to recall and estimate date or number of days elapsed between onset of TB constitutional symptoms such as cough, fever, night sweats, chest pain, weight loss and loss of appetite until formal care seeking. Similarly, provider delay was estimated by asking date or number of days elapsed between first formal health care facility visits to anti-TB treatment initiation. Finally, total delay was computed as a sum of patient and provider delay or number of days elapsed between onsets of illness to initiation of anti-TB treatment. Since no standard cut off for delay, a clinically sound cut off of 30 days delay was taken to define exposure status. Therefore, cases who delayed beyond 30 days were categorized as exposed and those initiated within 30 days were grouped as non-exposed.

Outcome ascertainment

The main outcome variable was treatment outcome which was ascertained based on standard definitions [26, 29]. Accordingly, outcomes were categorized into successful when the TB patient completed treatment with or without evidence of cure and unsuccessful when died or lost to follow-up or treatment failure. So that, coding was made as unsuccessful outcomes = 1 and successful = 0.

Data processing

Data were entered in to Epi-Data V 3.5 and processed on SPSS version 21 and/or STATA version 13. The data were described using frequencies, proportions, mean, median, inter-quartile range and standard deviation as appropriate. Both the baseline and follow-up data were described and compared across the exposed and non-exposed groups. Categorical variables were compared using chi square test and numeric variables using independent and paired t tests as appropriate.

Information provision adequacy during treatment initiation was assessed based on 15 items constructed from TB treatment guidelines. The internal consistency of the items was checked by Cronbach's Alpha (α) =0.87). A score of one is given for proper information and zero otherwise. So that information adequacy index was computed and labeled adequate when above median and inadequate when below median scores.

Association between the exposure (exposed vs, non-exposed) and outcome (unsuccessful vs. successful) was determined by log-binomial regression. Accordingly, bivariate and multiple log-binomial regression models were fitted to estimate crude and adjusted relative risk (RR) of unsuccessful outcome. In all the statistical tests, significance was judged at p value < 0.05.

Ethical issues

The study was ethically approved by the Institutional Review Board (IRB) of college of Health Sciences at Addis Ababa University. Informed written consent was sought from patients before the two interviews, during the intensive phase and end of treatment.

Definition of terms

- New case those never been treated for TB or have taken anti-TB drugs for less than 1 month.
- Smear positive PTB is a patient with at least two sputum smear examinations positive for Acid Fast Bacilli (AFB) by direct microscopy.
- Smear negative pulmonary TB is a patient having symptoms suggestive of TB with at least three initial smear examinations negative for AFB by direct microscopy, and no response to a course of broad-spectrum antibiotics, and again three negative smear examinations by direct microscopy and radiological abnormalities consistent with pulmonary tuberculosis, and decision by a clinician to treat with a full course of anti- tuberculosis
- Extra pulmonary TB is TB in organs other than the lungs, proven by histo-pathological evidence from a biopsy, Or based on strong clinical evidence consistent with active EPTB and the decision by a physician to treat with a full course of anti-TB therapy.
- Cured: A bacteriologically confirmed pulmonary TB case at the beginning of treatment who was smear or culture-negative at last month of treatment and on at least one previous occasion.
- Treatment completed: A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative
- Treatment failure: TB patient whose sputum smear or culture is positive at month 5 or later during treatment.
- Died: TB patient who dies for any reason during the course of treatment.
- Lost to follow up: TB patient interrupted treatment for 2 or more consecutive months.
- Treatment outcome not evaluated TB patient for whom no treatment outcome is assigned including cases “transferred out” to another treatment unit.

Results

Profile of study participants

A total of 735 (91.6%) of TB cases required were enrolled from 11 health centers and 3 hospitals. The rest of cases 67(8.4%) were not retrieved due to refusals (9), inability to respond (3) and end of the survey time (55). Of the cases 574 (78.4%) and 161(21.9%) had initiated anti-TB treatment within and above 30 days of onset of illness, respectively. Of the cases enrolled, 699 (95.1%) had documented treatment outcome and analyzed (Fig. 1).

Baseline sociodemographic characteristics of study participants

The median age [inter-quartile range (IQR)] and of the cases was 27(20–37) years. Among the cases, 52.9% and 29.4% had completed elementary school and involved in subsistence farming respectively (Table 1).

Care seeking and treatment practices

Patients initially presented to healthcare facility after a median (IQR) 25(15–36) days (patient delay) since the onset of illness. Diagnosis of 623(84.7%) of the cases were made after an average (±SD) of 3.6(±2.4) visits to an average (±SD) of 2.2(±1.2) healthcare facilities at which time the patients had been treated with different medicines. The rest of the cases, 112(15.3%) were diagnosed at their first visit to the first health facilities. Thus diagnosis and initiation of anti-TB treatment took a median (IQR) of 22(9–48) days (provider delay) since the first visit to health care facilities. Generally, a median (IQR) 55(32–100) days (total delay) had been elapsed to initiate treatment since the onset of illness. Of the total cases, 373(50.7% were smear positive pulmonary in whom diagnosis was bacteriologicaly confirmed using sputum smear microscopy. All of the cases were offered HIV screening test, of whom 68 (9.3%) tested positive (95% CI: 7.2%–11.3%)). Of those TB/HIV co infected cases, 27(39.7%) and 32(47.1%) were respectively receiving antiretroviral therapy (ART) and Cotrimoxazole Prophylactic Therapy (CPT)(Table 2).

Follow-up and treatment outcomes

After initiation of treatment, patients had undergone weight and sputum smear monitoring as per the recommended schedules. Accordingly, 501(68.2%), 266(36.2%) and 239(32.5%) of the cases had documented weight at end of second, fifth and sixth months of treatment respectively. Thus, a statistically significant difference in mean weights were observed between baseline and end of second month ($t_{df=500} = 13.94$, $p < 0.001$), between sixth month and baseline weight ($t_{238} = 11.81$, $P < 0.001$). On the other hand, among those smear positive pulmonary TB cases (373(50.7%)) eligible for monitoring of sputum smear, 231(61.9%), 200(53.6%) and 178(47.5%) had documented sputum smear result at end of second, fifth and sixth months of treatment respectively. So, among those with documented follow-up sputum result, 225 (97.4%) from both groups converted to negatives at the end of second month treatment $p = 0.5$) (Table 3).

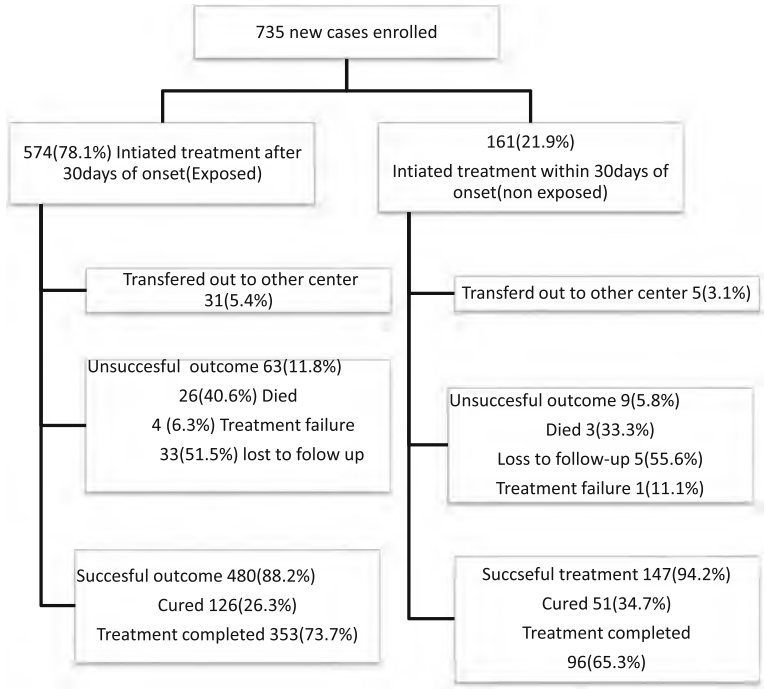

Fig. 1 Flow chart of exposure and outcome ascertainment of TB cases Southwest Ethiopia,January 2015 to June 2016

Table 1 Socidemographic characteristics and delays to treatment in southwest Ethiopia January to December 2015

Variable		Total delay(days)		*P* value	Total N(%)
		> 30 (Exposed) *N* = 574 n(%)	<=30 (Non exposed) *N* = 161 n(%)		
Gender	Male	345(60.1)	102(63.4)	0.6	447(60.8)
	Female	229(39.9)	59(36.6)		288(39.2)
Age group (years)	18–34	389(67.8)	114(70.8)	0.04	503(68.4)
	35–65	173(30.1)	43(26.7)		216(29.4)
	> 65	12(2.1)	4(2.5)		16(2.2)
Residence	Urban	280(48.9)	88(54.7)	0.7	368(50.1)
	Rural	294(51.1)	73(45.3)		367(49.9)
Marital status	Never married	208(36.2)	67(41.6)	0.3	275(37.4)
	Currently married	315(54.8)	89(55.3)		404(55.0)
	Divorced/widowed	51(9)	5(3.1)		56(7.6)
Educational status	Illiterate	168(29.3)	44(27.3)	0.2	212(28.8)
	Completed primary	309(53.8)	80(49.7)		389(52.9)
	Secondary & above	97(16.9)	37(23.0)		134(18.2)
Occupation	Employed	134(23.3)	38(23.6)	0.01	172(23.4)
	Farming	163(28.4)	53(32.9)		216(29.4)
	Unskilled work [a]	42(7.3)	9(5.6)		51(6.9)
	Dependents [b]	235(40.9)	61(37.9)		296(40.3)

[a]housemaid, daily laborer, [b]students, housewife

Table 2 Patient characteristics and time delays to treatment southwest Ethiopia January to December 2015

Variable		Total delay(days)			Total
		> 30 (Exposed) *N* = 574	<=30(non exposed) *N* = 161		
		n(%)	n(%)	*P* value	n(%)
Type of TB	Pulmonary positive	277(48.3)	96(59.6)	0.02	373(50.7)
	Pulmonary negative	167(29.1)	46(28.6)		213(29.0)
	Extra pulmonary	130(22.6)	19(11.8)		149(20.3)
HIV status	Positive	57(9.9)	11(6.8)	0.4	68(9.3)
	Negative	517(90.1)	150(93.2)		667(90.7)
Mode of TB diagnosis	Bacteriological	277(48.3)	96(59.6)	0.04	373(50.6)
	Clinical	297(51.7)	65(40.4)		363(49.4)
Treatment center	Hospital	206(35.9)	60(37.3)	0.02	266(36.2)
	Health center	368(64.1)	101(62.7)		469(63.8)
Action before HCF[a] visit	None	440(76.7)	146(90.7)	0.04	586(79.7)
	Took actions[b]	134(23.3)	15(9.3)		149(20.3)
Place TB diagnosis made	Public	493(85.9)	143(88.8)	0.09	636(86.5)
	Private	81(14.1)	18(11.2)		99(13.5)
Hospitalized for TB illness	Yes	15(2.6)	4(2.5)	0.5	19(2.6)
Knowledge about TB	Poor	159(27.7)	31(19.3)	0.8	190(25.8)
	Good	415(72.3)	130(80.7)		545(74.2)
Patient delay	Median(IQR)days	30(16–57)	14(10–17)	< 0.001	25(15–36)
Provider delay	Median (IQR)days	31(16–64)	7(3–10)	< 0.001	22(9–48)
Pre-diagnosis cost	Median(IQR) US$[c]	119.1(74.0–221.6)	48.2(36.3–66.8)	< 0.001	
Post-diagnosis cost	Median(IQR) US$[c]	93.7(56.9–141.3)	78.8(41.5–113.7)	< 0.001	
Treatment information adequate	Yes	279(48.6)	78(48.4)	0.04	357(48.6)
	No	295(51.4)	83(51.6)		378(51.4)
Initial weight	Mean(±SD) Kg	49.0(8.6)	47.7(8.5)	0.9	48.7(± 8.6)

[a]Healthcare Facility, [b]self treatment, traditional healer, holy water, [c](1US$ = 20.56Birr)

At the end of follow-up, 699(95.1%) TB patients had documented treatment outcome of whom 627(89.7%, 95%CI:87.2–91.7%) had successfully completed their treatment. However, among those smear positive TB cases, only 177(47.5%) were declared cured. The treatment success is significantly different among cases initiated treatment beyond and within 30 days of onset of illness (88.4% vs 94.2%, $P = 0.01$), respectively. Thus, significant difference in proportions of death (4.8% Vs 1. 9%), treatment failure (0.7% Vs 0.6%) and loss to follow-up (6.1% vs. 3.2%), respectively, among those initiated treatments beyond and within 30 days of onset $p = 0.04$. The treatment success across HIV positive and negatives respectively was 75.8% vs 91.1%, $p < 0.001$. Disaggregation of the treatment success among bacteriologicaly confirmed (smear positive pulmonary) and clinically diagnosed cases respectively revealed 90.1% vs 89.3%, $p = 0.7$. Furthermore, we found no statistically significant differences in treatment success among smear positive pulmonary (90.1%), smear negative pulmonary (88.0%) and extra pulmonary cases (91.1%) ($p = 0.6$).

Predictors of unsuccessful treatment outcomes

Treatment outcome of the study patients varied significantly across time elapsed for initiation of treatment. Patients delayed for > 30 days to initiate treatment had more than twice higher risk of having unsuccessful outcome Adjusted relative risk [(ARR) = 2.02, 95% confidence interval (CI); 1.03,3.95). Moreover, being older than 65 years, (ARR = 3.83,95% CI; 2.04,6.1), HIV co infection (ARR = 1.93,95% CI; 1.23,3.01) and treatment center being hospital (ARR = 3.78, 95% CI;2.25,6.36) independently predicted higher risk of unsuccessful outcomes. On the other hand, weight gain at the end of second month treatment (ARR = 0.45,95% CI;0.22,0.91) predicted lower risk of unsuccessful outcome. Those patients gained weight at the end of two-month treatment compared to the baseline had about 60% lower risk of having unsuccessful outcome (Table 4).

Subgroup analysis among smear positive pulmonary cases revealed delays to initiate treatment (ARR = 1. 56,95%CI;1.46,1.65), HIV co infection (ARR = 3.73,95%CI: 1.68,5.97), treatment center being hospital (ARR = 1.

Table 3 Follow-up characteristics and outcomes across delays to treatment southwest Ethiopia January 2015 to june 2016

Variable		Total delay(days)			
		> 30(exposed) *N* = 574	<=30 (non exposed) *N* = 161		Total
		n(%)	n(%)	*P* value	n(%)
Sputum smear end of 2nd month(*n* = 373)	Positive	3(1.1)	3(3.0)	0.5	6(1.6)
	Negative	158(57.9)	67(67.0)		225(60.3)
	Not available	112(41.0)	30(30.0)		142(38.1)
Sputum smear end of 5th month(*n* = 373)	Positive	4(1.5)	1(1.0)	0.4	5(1.3)
	Negative	137(50.1)	58(58.0)		195(52.3)
	Not available	132(48.4)	41(41.0)		173(46.4)
Sputum smear end of 6th month(*n* = 373)	Negative	127(46.5)	51(51.0)	0.3	178(47.7)
	Not available	146(53.5)	49(49)		195(52.3)
Sputum check up after diagnosis(*n* = 373)	None	112 (41.0)	30(30.0)	0.3	142(38.1)
	At least once	161(59.0)	70(70.0)		231(61.9)
Weight end of 2ndmonth	Mean(SD)	51.2(8.6)	50.2(8.6)	0.9	51.3(8.6)
Weight change end of 2nd month	Unchanged/lost	93(16.2)	30(18.6)	0.2	123(16.7)
	Gained	298(52.0)	80(49.7)		378(51.5)
	Unknown	183(31.8)	51(31.7)		234(31.8)
Weight end of 5thmonth	Mean(SD)	54.2(8.7)	51.8(9.5)	0.5	53.6(8.9)
Weight end of 6th month	Mean(SD)	54.2(10.3)	52.9(9.0)	0.1	53.9(9.9)
Treatment out come	Cured	126(21.9)	51(31.7)	0.04	177(24.2)
	Treatment complete	354(61.5)	96(59.6)		450(61.1)
	Loss to follow-up	33(5.7)	5(3.1)		38(5.2)
	Died	26(4.5)	3(1.9)		29(3.9)
	Treatment failure	4(0.7)	1(0.6)		5(0.7)
	Not evaluated[a]	31(5.4)	5(3.1)		36(4.9)
Treatment success (*n* = 699)	Unsuccessful	63(11.6)	9(5.8)	0.01	72(10.3)
	Successful	480(88.4)	147(94.2)		627(89.7)

[a]cases transferred out to other treatment centers

89,95%CI:1.04,3.45) and age older than 65 years (ARR = 6.49,95%CI:3.60,11.70) as independent predictors of unsuccessful outcomes. Similarly analysis among clinically diagnosed cases showed delayed treatment, HIV co-infection, treatment center being hospital and older than 65 years independently predicted higher risk of unsuccessful outcome. Weight gain at the end of second month (ARR = 0.16,95%CI: 0.05, 0.53) predicted higher risk of unsuccessful outcome among clinically diagnosed cases and having at least one sputum checkup after diagnosis (ARR = 0.17, 95%CI:0.09, 0.33) predicted higher risk of unsuccessful outcomes among smear positive cases. Analysis of treatment outcomes among HIV negatives showed initiated treatment after 30 days of onset (ARR = 2.52,95%CI:1. 55, 4.10), weight gain at the end of second month treatment (ARR = 0.27,95%CI:0.12, 0.64) and treatment center being hospital (ARR = 2.33,95%CI:1.33, 4.09) independently predicted unsuccessful treatment outcome (Additional file 1: Tables S1-S3).

Discussion

This follow-up study revealed patients elapse too long time (median of 55 days) to initiate anti-TB treatment since onset of the illness. Subsequently, we found statistically significant differences in treatment success (94.2% vs 88.4%) respectively among those who initiated treatment within and beyond 55 days of onset. Those patients initiated anti-TB treatment beyond 30 days of onset had higher risk of unsuccessful outcomes including death, lost to follow up and treatment failure. Patients initiated treatment within and beyond 30 days of onset had undergone significantly diverse healthcare seeking practices, patient and provider delays. However, both groups of patients had no significant differences in sputum smear conversion and weight changes at end of second month treatment. The longer delays to initiate treatment accompanied by higher risk of unsuccessful outcomes depict increased morbidity and mortality to patients and prolonged period of transmission to the community. The finding suggests need for prompt

Table 4 Predictors of TB treatment outcome in districts of southwest Ethiopia January 2015 to June 2016

Variable		Treatment success		Crude Relative Risk (CRR) (95%CI)	Adjusted relative risk (ARR) (95% CI)
		Unsuccessful n(%)	Successful n(%)		
Gender	Male	44(10.3)	382(89.7)	Ref.	Ref.
	Female	28(10.3)	245(89.7)	0.9(0.63,1.56)	0.87(0.61,1.25)
Age group(years)	18–34	48(10.0)	433(90.0)	Ref.	Ref.
	35–65	20(9.9)	183(90.1)	0.9(0.60,.62)	0.88(0.68,1.12)
	> 65	4(26.7)	11(73.3)	2.67(1.11,6.45)	3.82(2.4,6.10)*
Educational status	Illiterate	25(12.3)	178(87.7)	Ref.	Ref.
	Completed primary	37(9.9)	338(90.1)	0.8(0.50,1.29)	0.93(0.61,1.41)
	Secondary & above	10(8.3)	111(91.7	0.67(0.33,1.35)	1.00(0.64,1.56)
Treatment center	Hospital	31(12.6)	215(87.4)	1.39(0.9,2.16)	3.78(2.4,6.35)*
	Health center	41(9.1)	412(90.9)	Ref.	Ref.
Action before HCF [a]visit	None	57(10.3)	498(89.7)	Ref.	Ref.
	Took action	15(10.4)	129(89.6)	1.01(0.59,1.74)	0.81(0.50,1.30)
Mode of TB diagnosis	Bacteriological	35(9.9)	320(90.1)	Ref.	Ref.
	Clinical	37(10.7)	308(89.3)	1.09(0.7,1.7)	0.86(0.67,1.10)
HIV status	Positive	15(24.2)	47(75.8)	2.7(1.63,4.5)	1.93(1.23,3.01)*
	Negative	57(8.9)	580(91.1)	Ref.	Ref.
Weight change end of 2nd month	No change/lost	13(11.2)	103(88.8)	Ref.	Ref.
	Gained	15(4.1)	354(95.9)	0.36(0.18,0.74)	0.45(0.22,0.91)
	Unknown	44(20.6)	170(79.4)	1.83(1.03,3.26)	4.34(2.47.7.65)*
Total delay(days)	<=30	9(5.8)	147(94.2)	Ref.	Ref.
	> 30	63(11.6)	480(88.4)	2.01(1.02,3.95)	2.02(1.03,3.95)*
Treatment information provided	Inadequate	39(11.0)	314(89.0)	0.86(0.56,1.34)	1.06(0.70,1.63)
	Adequate	33(9.5)	313(90.5)	Ref.	Ref.

*statistically significant at $p < 0.05$ [a] Healthcare facility

detection and treatment of cases to ensure better outcomes among patients and reduce burden in community.

The higher risk of unsuccessful outcome among those patients delayed to initiate anti-TB treatment had been consistently reported in studies from Ethiopia [30] and elsewhere [15]. The increased risk of unsuccessful outcome among patients delayed treatment initiation could be explained by various factors. First, delayed initiation of treatment had been reported to be associated with severe clinical presentation [14, 31] which predict unsuccessful outcomes [32]. In this study, patients delayed to initiate treatment had relatively higher rate of hospitalization (3% vs 2.1%) that would be proxy measure of severe presentation. Second, a delay to treatment is associated with both prescribed and self-treatment those lead to poor treatment outcome [33–35]. In the current study, the majority (84.7%) of the cases had visited an average of 2.2 HCFs until diagnosis of TB at which time both self and prescribed medicines had been used. Third, delays to treatment often accompanied by higher direct and indirect costs that impoverish households [36, 37] and ultimately lead to poor treatment compliance and outcome [36]. In our study we observed significantly higher median pre diagnosis (US$119.1 vs 48.2, $p = 0.001$)and post diagnosis (US$93.7vs.98.8, $p < 0.001$) costs among those delayed to initiate treatment which could explain the increased risk of unsuccessful outcome.

Consistent with studies in Ethiopia [30, 38] and elsewhere [39–42], the current study revealed that HIV comorbidity increase risk of unsuccessful outcome. Hence, significantly lower (75.8% vs 91.1%, $p < 0.001$) treatment success with higher deaths (12.9% vs. 3.3%, $p = 0.002$) were observed among HIV co infected compared to negatives. The observed lower treatment success among HIV co infected is far below the targeted 90% success to be met by 2020 [2]. The increased risk of unsuccessful outcome among the HIV co infected could be due to significantly prolonged time to initiate care seeking (median of 29 vs.

24 days, $P = 0.04$) among HIV co infected patients. Thus HIV co morbidity had been reported to delay anti-TB treatment initiation [13, 43]that explain the high mortality among HIV co infected TB patients [16, 17]. In addition, HIV co infection independently increases risk of unsuccessful outcome due the complex and overlapping drug interactions and toxicities and TB-associated immune reconstitution inflammatory syndrome [44]. Furthermore the increased risk could also be explained by the low uptake of TB/HIV collaborative interventions (39.7% and 47.1% on ART and CPT, respectively) those proved to bring better outcome [45]and predict worse outcome in their absence [40].

We found patients took anti-TB treatment at hospital had higher risk of unsuccessful outcome compared to those treated at health center. This could be due to significantly higher proportion of delays to initiate anti-TB treatment (55.6% Vs46.3%, $p = 0.02$), HIV co infection (14.3% Vs 6.4%, $p < 0.001$) and hospitalization (5.3% Vs 1.1%, $p = 0.001$) among patients treated at hospitals. Studies reported HIV co infection [39, 40], hospitalization [32] and delays to treatment [15, 30] to predict higher risk of unsuccessful outcomes. Moreover, patients treated at hospitals were more of pulmonary negative (36.5% vs 24.7%, $p < 0.001$) and extra pulmonary (21.8% vs 19.4%, $p < 0.001$) those had been reported to predict unsuccessful outcome [46].

Regular monitoring of TB patients during treatment is among standard of TB care, which is used to assess response to therapy and facilitates treatment completion. Accordingly regular sputum and weight monitoring have been recommended TB patients on treatment [47]. Despite low sensitivity and modest specificity of sputum results at the end of intensive phase to predict failure and relapse [48], sputum conversion to negative among those positive at initiation of treatment had been taken as one of the indicator TB control program performance [47]. In the current study no significant differences was observed in sputum smear conversion at end of second month treatment in both patients initiated treatment within and beyond 30 days of onset. Consistent with studies in Ethiopia [46]and elsewhere [49] smear conversion to negative at the end of second month treatment had lower risk of unsuccessful outcome. In this study, 3/6(50%) of those treatment failure cases had positive smear at the end of second month treatment. The higher risk among those positives could be due to possible poor quality of initial therapy and co morbid conditions that interfere with adherence or response [47]. Similarly, weight gain at the end of second month treatment predicted lower risk of unsuccessful outcomes which is in line with reports from Vietnam [50].

This study has some limitations. First, exposure assessment relied upon patient recall of the onset of illness that might be subjected to recall bias and ultimate misclassification bias. But efforts had been made to minimize the bias through use of local and national event listing. The second limitation was inability to measure treatment adherence that could have effect on treatment outcome. Third, we did not test for drug susceptibility so that we could not associate delay with resistance. Lastly, we studied only new adult TB cases so that the findings will not apply to all TB cases. On the other hand, relatively large sample and geographic coverage, reduced selection bias through consecutive enrolment, being prospective design, direct estimation of risk and use of standard outcome ascertainment could be mentioned as strength of the study. Therefore, the study is valid and applies to new TB cases in similar settings.

Conclusion

TB patients in the study area elapse too long time to initiate anti-TB treatment. The delayed treatment initiation was associated with higher risk of unsuccessful outcome including death, treatment failure and lost to follow-up. Apart from the delayed treatment, HIV co infection, treatment center being hospital, weight change and sputum conversion at the end of second month treatment independently predicted unsuccessful outcomes. Therefore, promotion of early care seeking within community, improving diagnostic, and case holding efficiencies of HCF and TB/HIV collaborative interventions could enhance the TB treatment success. Time delays to TB diagnosis can be reduced by raising community level awareness on TB suggestive symptoms, involving traditional healer, religious and private healthcare institutions in TB case finding, equipping healthcare facilities with rapid diagnostic tests and building capacities of healthcare providers to suspect and diagnose TB.

Additional file

Additional file 1: Table S1. Predictors of unsuccessful outcomes among new smear positive pulmonary TB cases in districts southwest Ethiopia January 2015 to June 2016 ($n = 355$). Table S2 Predictors of unsuccessful outcomes among new clinically diagnosed TB cases in districts southwest Ethiopia January 2015 to June 2016 ($n = 344$). Table S3 Predictors of unsuccessful outcomes among not HIV coinfected TB cases in districts of southwest Ethiopia January 2015 to June 2016. (DOCX 20 kb)

Abbreviations

ARR: Adjusted relative risk; ART: Antiretroviral therapy; CI: Confidence Interval; CPT: Cotrimoxazole prophylactic therapy; DOTS: Directly Observed Treatment Short course; HCF: Healthcare Facility; HIV: Human Immunodeficiency Virus; IQR: Inter-quartile Range; SD: Standard deviation; TB: Tuberculosis; US$: United States dollar

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
AA conceived and designed the study, collected and analyzed data, prepared manuscript:
WD and DJ critically reviewed for intellectual content of the study protocol and manuscript as primary and co-supervisors respectively. All authors approved the final version of the manuscript for submission.

Ethics approval and consent to participate
The study was ethically approved by Institutional Review Board (IRB) of the College of Health Sciences at Addis Ababa University (protocol number: 045/14/sph). Written informed consent was sought from each study participant before the interview. Patient clinical profile from records and unit register was retrieved upon permission from respective health care facilities.

Competing interests
The authors declare that they have no competing interests.

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RESEARCH ARTICLE Open Access

Pre- and post-diagnosis costs of tuberculosis to patients on Directly Observed Treatment Short course in districts of southwestern Ethiopia: a longitudinal study

Abyot Asres[1,3*], Degu Jerene[2] and Wakgari Deressa[3]

Abstract

Background: Financial burden on tuberculosis (TB) patients results in delayed treatment and poor compliance. We assessed pre- and post-diagnosis costs to TB patients.

Methods: A longitudinal study among 735 new TB cases was conducted from January 2015 through June 2016 in 10 woredas (districts) of southwestern Ethiopia. Direct out-of-pocket, payments, and lost income (indirect cost) were solicited from patients during the first 2 months and at the end of treatment. Thus, we ascertained direct medical, nonmedical, and indirect costs incurred by patients during pre- and post-diagnosis periods. We categorized costs incurred from onset of illness until TB diagnosis as pre-diagnosis and that incurred after diagnosis through treatment completion as post-diagnosis. Pre- and post-diagnosis costs constitute total cost incurred by the patients. We fitted linear regression model to identify predictors of cost.

Results: Between onset of illness and anti-TB treatment course, patients incurred a median (inter-quartile range (IQR)) of US$201.48 (136.7–318.94). Of the total cost, the indirect and direct costs respectively constituted 70.6 and 29.4%. TB patients incurred a median (IQR) of US$97.62 (6.43–184.22) and US$93.75 (56.91–141.54) during the pre- and post-diagnosis periods, respectively. Thus, patients incurred 53.6% of the total cost during the pre-diagnosis period. Direct out-of-pocket expenses during the pre- and post-diagnosis periods respectively amount to median (IQR) of US$21.64 (10.23–48.31) and US$35.02 (0–70.04). Patient delay days ($p < 0.001$), provider delay days ($p < 0.001$), number of healthcare facilities visited until TB diagnosis ($p < 0.001$), and TB diagnosis at private facilities ($p = 0.02$) independently predicted increased pre-diagnosis cost. Similarly, rural residence ($p < 0.001$), hospitalization during anti-TB treatment ($p < 0.001$), patient delay days ($p < 0.001$), and provider delay days ($p < 0.001$) predicted increased post-diagnosis costs.

Conclusion: TB patients incur substantial cost for care seeking and treatment despite "free service" for TB. Therefore, promoting early care seeking, decentralizing efficient diagnosis, and treatment services within reach of peoples, and introducing reimbursement system for direct costs can help minimize financial burden to the patient.

Keywords: TB, Direct cost, Indirect cost, Longitudinal, Pre-diagnosis, Post-diagnosis, Ethiopia

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Background

Tuberculosis (TB) remained among the major global public health problems. In 2015, an estimated 10.4 million cases and 1.4 million deaths occurred globally. The African Region constitutes 28% of the global cases and the most severe burden relative to population (281 cases per 100,000 people) [1]. TB morbidity and mortality pose an enormous economic burden to patients, household, and society. Each year, a TB patient loses on average 3 to 4 months of work and up to 30% of household earnings [2].

Efforts to control TB have three distinct, but overlapping humanitarian, public health, and economic dimensions. The efforts imply timely diagnosis and treatment of patients and reduction of costs due to TB [3]. The latest TB control strategy, End TB, underlined the need for universal access to health services without financial hardship, social protection for income replacement, and support in the event of illness [4]. Accordingly, a global target has been set to have no TB-affected family facing catastrophic costs due to TB by 2020 [4, 5]. Costs incurred by a TB patient include either direct or indirect costs. The direct costs comprise out-of-pocket expenses for medical and nonmedical services whereas the indirect costs constitute foregone income because of lost workdays [6].

Despite the free TB diagnosis and treatment, TB patients and families incur high direct and indirect costs due to TB illness [5]. Systematic reviews across low- and middle-income countries showed mean total costs of TB ranging from fewer than I$1 to I$8198 [5, 7]. The review further reported indirect and direct costs incurred for TB care respectively constituted 60 and 40% of the total cost [5]. Studies also reported that seeking care and treatment of TB costs a median of United States of America Dollar (US$) 592 in Nigeria [8] and mean cost of US$108.4 in Yemen [9] per household. The high cost of TB care seeking and treatment result in delays to diagnoses [10, 11] and poor outcome [12, 13]. The poor outcome lead to development of drug resistant TB [14] that require much higher cost of care [15].

Implementation of global TB control strategies in Ethiopia have led to improvements in access to TB care, decline in TB morbidity, and mortality [16]. Nonetheless, Ethiopia belongs to the 14 TB, TB/human immunodeficiency virus (HIV), and multi-drug resistant (MDR) TB high-burden countries [1]. Out of a total US$47.8 million spent for TB control in 2008, household out-of-pocket expenses constituted 62% [17]. A cost and epidemiological modelling in Ethiopia, showed out-of-pocket medical cost for TB amounted to US$49 per patient that led households to fall below poverty line [18]. A study in Tigray, Northern Ethiopia from patient perspective reported median cost incurred for care seeking to be US$16 [19]. A community randomized trial using societal perspective in southern Ethiopia revealed a successful treatment of a smear-positive patient costs US$158.9 at a health facility compared to that within the community (US$61.7) [20].

It is important to understand the financial burden of TB patients to adapt and realize a global target of having no households incurring catastrophic costs because of TB [1]. However, only few studies exist in Ethiopia, those dealt on the financial burden of TB patients. The few studies dealt on cost of care seeking and diagnosis [19] or cost of treatment [20] but not both. The studies were conducted during the 8 months of treatment regimen. However, the current 6-month regimen requires frequent visits (daily to weekly) to health facilities throughout the course of treatment [21]. Furthermore, none of the studies analyzed cost predictors across the continuum of care. Generally, evidences on financial burden posed to TB patients across the pathways to treatment are limited in Ethiopia. Therefore, we studied costs incurred by TB patients across the pre- and post-diagnosis periods including cost drivers in districts of southwestern Ethiopia.

Methods

Study setting and design

A longitudinal study among new TB cases on Directly Observed Treatment Short course (DOTS) was carried out from January 2015 through June 2016. We included 14 public healthcare facilities (three hospitals and 11 health centers) from 10 *woredas* (an administrative unit equivalent to district) in three zones (an administrative structure that oversees woredas and report to regional states). The zones, Bench Maji, Kaffa, and Sheka, are among the 15 zones in Southern Nations Nationalities and Peoples Region (SNNPR). The zones are located at the southwestern border of the region where an estimated 2,064,102 people reside [22]. The zones are organized into four town administrations and 26 woredas. During the study, three hospitals and 65 health centers were providing TB DOTS [23].

Diagnosis and treatment for all forms of TB in Ethiopia is according to a national guidelines [21, 24] that specify case definitions, diagnostic, and treatment standards. Diagnosis based on sputum microscopy, sputum follow-up test, and anti-TB drugs are free of charge in all public and selected private facilities. Since the end of 2011, all forms of new TB cases are treated for 6 months with combination of rifampicin (R), isoniazid (H), pyramidal (Z), and ethambutol (E) for the first 2 months (intensive phase) (2RHZE) followed by rifampicin (R) and isoniazid (H) for 4 months (4RH). Thus, patients need to visit a DOTS center daily and weekly during intensive and continuation phase treatments, respectively.

Sample size and sampling

The sample size needed for the study was calculated using STATA V13 considering a mean (SD) patient cost of care seeking of US$29(14) [19] to detect a US$5 difference which revealed 250 cases. This study is part of a doctoral dissertation aimed at assessing time delays, cost, and outcomes of TB patients on DOTS. Thus, among the sample sizes calculated for each objective of the dissertation, which required for assessing predictors of delay, 802 cases was the largest. Since similar cases were studied for all the objectives, the largest sample, 802 cases was used for this study.

We selected the region (SNNPR) and zones (Bench Maji, Kaffa, and Sheka) conveniently. Considering the available resources and representativeness, we decided to study 10 woredas of the three zones. Thus, through proportional allocation, we determined the number of woredas from each zone. Considering the number of TB cases notified in the preceding year to the study time, we selected the woredas from each zones. Then, all public health facilities providing diagnosis and treatment of TB in the selected woredas were included for the study. We included 14 health facilities (three hospitals and 11 health centers). Therefore, we allocated the 802 cases proportionally to the zones, woredas, and health facilities based on their preceding year TB case notification. Finally, successive consenting cases were enrolled until the required sample reaches. Those new cases, older than 18 years and on intensive phase treatment, were included and those on continuation phase, transferred to other treatment center, lost to follow-up, and died before the enrollment were excluded from study.

Data collection

Data were collected using structured questionnaire (Additional file 1) adapted from the tool to estimate TB patients' cost developed by the WHO and other partners [6]. Similarly, data abstraction checklist was prepared to extract data from the standard unit TB register. The questionnaire was translated in to the national language (Amharic) to ease the understanding among both the data collectors and participants. Then, 10 diploma graduate nurse data collectors and three master holder supervisors were recruited and trained for 3 days. The training included the basics of TB control, details of questionnaire, data abstraction, interviewing techniques, and pretest of the tool at health facilities not included in the study. Finally, eligible cases were traced from the unit TB register, and face-to-face interview was held within the intensive phase and end of treatment. The first interview-included patients' sociodemographic, healthcare-seeking practices, and costs incurred until TB diagnosis (pre-diagnosis cost). The follow-up interview inquired costs incurred after the diagnosis of TB through completion of the treatment (post-diagnosis cost).

Cost ascertainment

Cost data were ascertained from patient perspective using prevalent approach that estimate financial burden of an illness to patients at specified period of time [25]. So costs incurred by patients for care seeking and treatment of TB were collected at two-time points, during the first 2 months of treatment and at the end of the treatment. Both direct out-of-pocket expenses (for medical and nonmedical services) and indirect costs were measured. Direct costs consisted of out-of-pocket charges for medical services (consultation, drugs, laboratory tests, X-ray, and hospitalization) and nonmedical services (transportation, meal, and accommodation) while visiting healthcare facilities.

Direct out-of-pocket patient expenses during the pre-diagnosis period (incurred from onset of illness to treatment initiation) were determined by asking patient expense at each visit for consultation, laboratory tests, drugs, transportation, meals, and lodging. In the same way, post-diagnosis direct costs (incurred from initiation to completion of the prescribed treatment) were measured by inquiring patients' medical and nonmedical expenses during visits for anti-TB treatment. The number of visits for the pre-diagnosis period was solicited from patients, and post-diagnosis visits were taken from attendance records on a unit register. Thus, transportation cost was calculated by multiplying the number of visits with the fee per trip.

The indirect costs were estimated using the human capital approach. Patients were requested to estimate time lost due to sickness and visits for consultation, hospitalization, drug collection, and trip journey. The time spent second or minute were converted to hours and then to days at an average of eight working hours in a day (8 h = 1 day). Finally, the number of days was multiplied by an average daily wage rate of US$2.43 = 50 Ethiopian Birr for those unemployed and daily rate calculated from their gross monthly salary for those formally employed. Monthly income of formally employed cases was inquired from patients by asking their monthly salary. For self-employed, self-estimated average monthly earning was used to calculate daily rate. An average wage rate estimated by the social affair offices was used for unemployed cases.

For cost items with no charge, it was recorded as zero. All the costs were inquired in local currency, Ethiopian Birr (ETB), and then converted into US dollars (US$) using the average exchange rate of (US$1 = 20.56 ETB) during January through December 2015 [26].

Data management

Data were entered into EpiData v3.1 then exported to SPSS version 21 for cleaning and then to STATA 13 for analysis. The data were described using frequency, proportions, mean (standard deviation), and median (inter-quartile range), and normality of the cost data were checked using plots (Q-Q plots and/or histograms) or Kolmogorov-Smirnov test. The cost data were right skewed and became log normal upon log transformation to base 10. Hence, all the statistical tests were done with the lognormal data and reported by back transforming to its anti-log.

Proportion and mean differences across categorical variables were tested using chi-square and independent *t* tests respectively. Associations between continuous variables were tested with simple correlation. Mean difference between pre- and post-diagnosis costs were tested with paired *t* test. Finally, simple and multiple linear regression models were fitted to identify predictors of pre- and post-TB diagnosis costs. Assumptions and fitness for the linear regression model were assessed and ensured. In all the statistical tests, significance was judged at $p < 0.05$.

Ethical issues

The Institutional Review Board of the College of Health Sciences at Addis Ababa University approved the study protocol. Therefore, patients consented in written for the interview and clinical records of patients were retrieved upon permission from the respective health facilities.

Operational definitions

Patient delay is days elapsed between onsets of illness to the first formal healthcare seeking.

Health system/provider delay is the number of days spent between the first consultations to initiation of treatments.

Total delay is the number of days elapsed since onset of illness to anti-TB treatment initiation.

Medical cost is costs incurred for medical services including consultation, laboratory tests, drugs other than anti-TB, X-ray, and related services.

Nonmedical cost is costs incurred for transportation, accommodation, meal, and related services while seeking care for TB and visiting to collect anti-TB drugs.

Direct cost is out-of-pocket patient expenses for medical or nonmedical services while seeking care, diagnosis, and treatment for TB.

Indirect cost is lost earning because of inability to work or lost workdays while traveling to seek care, diagnosis, and treatment for TB.

Pre-diagnosis cost is the cost incurred since onset of illness until anti-TB treatment initiation.

Post-diagnosis cost is the cost incurred since the beginning up to the completion of anti-TB treatment.

Total cost is both direct and indirect costs incurred for care seeking, diagnosis, and treatment of TB.

Results

A total of 735 TB cases were enrolled of which 627(85.3%) completed the follow-up. Those lost included 29(3.9%) deaths, 36(4.9%) transferred to other treatment centers, 5(0.7%) treatment failure, and 38(5.2%) lost to follow-up. Nonetheless, there were no statistical significant differences with the proportions of the attributes across the baseline and end line surveys (Table 1). The median age (inter-quartile range (IQR)) of the cases during enrollment (baseline) was 27(20–37) years. Of the cases enrolled, 53 and 29.4% completed elementary school and are involved in farming, respectively. The mean (+ SD) of size and median annual income of the households were 4.3(+ 2.1) and US$466.93, respectively.

Care-seeking pathways

TB patients first visited a healthcare facility after a median of 25 days from onset of illness (patient delay). Thus, 35.4 and 32.4% of the cases first visited private clinics and public health centers, respectively (Table 2). The rest of the cases first visited hospitals (30.1%) and health posts (2.1%). TB diagnosis of 448(61%) cases was made at a hospital, and for 244(33.2%), the diagnosis was made at the first visited health facility. Diagnosis of 491(66.8%) were reached after an average (+SD) of 3.6(+ 2.4) visits to an average (+SD) of 2.2(+ 1.2) healthcare facilities (HCF). Since the first consultation, a median of 22 days had been elapsed to initiate anti-TB treatment. Among the cases, 586(79.7%) had pulmonary TB and 362(49.3%) were diagnosed clinically. All of the cases were offered HIV screening test of whom 68 (9.3%) tested positive, 95% CI (7.2–11.3%).

Pre-diagnosis cost

Until diagnosis of TB, patients incurred a median (IQR) cost of US$97.6 (56.4–184.2) (Table 3). Direct cost amount to median (IQR) US$21.64 (10.23–48.31) and constitute 25.6% (Fig. 1) of the total pre-diagnosis costs. Patients had lost median (IQR) of 24.7(15.1–48.4) workdays until diagnosis of TB that corresponded to median (IQR) US$64.45 (39.8–128.8) income loss.

The pre-diagnosis cost was positively correlated with patient ($\gamma = 0.32$, $p < 0.001$), provider ($\gamma = 0.64$, $p < 0.001$) and total delays ($\gamma = 0.68$, $p < 0.001$), and the number of HCF visited until diagnosis ($\gamma = 0.42$, $p < 0.001$). The mean pre-diagnosis cost was significantly different across the types of TB ($F = 10.03$, $p < 0.00$), type of first visited HCF ($p = 0.002$), HCF where diagnosis was made ($p < 0.001$), and mode of diagnosis ($p = 0.001$) (Additional file 2: Table S1).

Table 1 Sociodemographic characteristics of TB cases in districts of southwestern Ethiopia, January to December 2015

Variable		Baseline ($n = 735$) n(%)	End line ($n = 627$) n(%)	P value
Gender	Female	288(39.2)	244(38.9)	0.9
Age(years)	18–34	503(68.4)	431(68.7)	0.9
	35–65	216 (29.4)	183(29.1)	0.8
	> 65	16(2.2)	13(2.1)	0.89
Marital status	Never married	275(37.4)	235(37.5)	0.97
	Currently married	404(55)	342(54.5)	0.85
	Widowed/divorced	56(7.6)	50(8)	0.78
Educational status	No formal education	212(28.8)	176(28.1)	0.77
	Completed elementary	389(53)	340(54.2)	0.66
	Secondary and above	134(18.2)	111(17.7)	0.8
Occupation	Employed	172(23.4)	147(23.4)	1.00
	Farming	216(29.4)	188(30.0)	0.81
	Unskilled work[a]	51(6.9)	43(6.9)	1.00
	Dependents[b]	296(40.3)	249(39.7)	0.82
Residence	Urban	369(50.2)	313(49.9)	0.94
	Rural	367(49.9)	314(50.1)	0.74
Household main income earner	Self	370(50.3)	310(49.4)	0.74
	Other[c]	365(49.7)	317(50.6)	0.8
Household income	≤ US$466.93	288(50.6)	242(50.3)	0.9
	> US$466.93	281(49.4)	239(49.7)	0.9

[a]Housemaid, daily laborer
[b]Students, housewife
[c]Father/mother/husband/wife/brother/sister/employer

In a multiple regression patient and provider delays, being clinically diagnosed, TB diagnosis at private facilities and the number of visited healthcare facilities independently predicted higher mean pre-diagnosis costs (Table 4). Every single patient and provider delay days each increased the mean pre-diagnosis cost by 0.5%. Those patients' diagnosed clinically incurred 11% higher mean pre-diagnosis costs compared to those diagnosed bacteriologically. Similarly, patients diagnosed at private HCFs incurred 18% higher mean pre-diagnosis cost compared to those diagnosed at public HCFs.

Post-diagnosis cost

After the diagnosis of TB, patients incurred a total median (IQR) of US$93.75 (56.9–141.54) until the completion of the treatment (Table 3). The direct cost amounted to a median (IQR) of US$35.02 (0–70.04) and constitutes 35.9% (Fig. 1) of the total post-diagnosis cost. During the treatment, TB patients had lost a median (IQR) of 21(13–35.3) workdays that corresponded to a median (IQR) of US$51.0 (34.6–97.0) income loss (indirect cost). Thus, significantly lower medical and indirect costs and higher nonmedical costs were incurred during the post-diagnosis period compared to the pre-diagnosis. The post-diagnosis cost was positively correlated with patient ($\gamma = 0.20$, $p < 0.001$) and provider ($\gamma = 0.23$, $p < 0.001$) delays.

In the multiple regression analysis, being a rural resident, having a travel time beyond 1 h to the treatment center, being admitted for anti-TB treatment, patient and provider delays independently predicted higher mean post-diagnosis cost. On the other hand, completing primary and higher educational status and being treated at a hospital predicted lower mean post-diagnosis costs (Table 5). Thus, being a rural resident was associated with an increase in mean post-diagnosis cost by 48% compared to those being urban residents. Every patient and provider delay days increases the mean post-diagnosis cost by 0.3 and 0.2%, respectively. Those patients hospitalized for anti-TB treatment had more than twofold higher mean post-diagnosis cost compared to those patients never hospitalized for anti-TB treatment. Patients who followed their course of anti-TB treatment at hospitals had about 18% lower mean post-diagnosis cost compared to those who received the anti-TB treatment at health centers.

Table 2 Care-seeking pathways and clinical characteristics of TB cases on treatment in districts of southwestern Ethiopia, January to December 2015

Variable		Baseline ($n = 735$)	End line ($n = 627$)	*P* value
		n(%)	*n*(%)	
Action to illness before visiting HCF	None	586(79.7)	497(79.3)	0.85
	Took action[a]	149(20.3)	130(20.7)	0.85
First visited HCF	DOTS center	459(62.5)	387(61.7)	0.85
	Non-DOTS	276 (37.5)	240(38.3)	0.76
Diagnosis made HCF	Public	636(86.5)	537(85.6)	0.76
	Private	99(13.5)	90(14.4)	0.70
Type of TB	Pulmonary positive	373(50.7)	320(51.0))	0.90
	Pulmonary negative	213(29.0)	176(28.1)	0.70
	Extra pulmonary	149(20.3)	131(20.9)	0.70
Mode of diagnosis	Bacteriological	373(50.7)	319(50.9)	0.90
	Clinical	362(49.3)	308(49.1)	0.90
Treatment center	Health center	469(36.2)	408(65.1)	0.70
	Hospital	266(63.8)	219(34.9)	0.70
Travel time to treatment center	≤ 1 h	437(59.5)	373(59.5)	1.00
	> 1 h	298(40.5)	254(40.5)	1.00
Hospitalized for treatment	Yes	19(2.6)	15(2.4)	0.40
HIV co-infection	Yes	68(9.3)	46(7.3)	0.10
Patient delay	Median (IQR) days	25((15–36)	23(14–34)	0.20
Provider delay	Median (IQR) days	22(9–48)	20(8–48)	0.40
Total delay	Median (IQR) days	55(32–100)	52(31–93)	0.50

[a]Self-treatment, consult traditional healer, used holy water

Total cost of TB care seeking and treatment

Total costs incurred by patients for care seeking, diagnosis, and treatment amount to a median (IQR) of US$201.48 (136.70–318.94) (Table 3). Pre- and post-diagnosis costs respectively constituted 53.6 and 46.4% of the total cost. Total direct cost constituted 29.4% (Fig. 1) of the total cost and amounted to a median (IQR) of US$59.58 (29.43–113.81). Drugs other than anti-TB and diagnostic tests (laboratory or imaging tests) corresponded to 49.7 and 44.6% of the total medical costs, respectively. During the care seeking and treatment visits, patients had totally lost a median (IQR) 51.7 (32.0–80.8) workdays that corresponded to a median (IQR) of US$127.68 (78.43–201.85) income loss (indirect cost). Out of the total forgone income due to the TB illness, the loss due to lost workdays following care-seeking visits amounted to a median (IQR) of US$18.02

Table 3 Distribution of TB patient costs across cost categories and periods in districts of southwestern Ethiopia, January to December 2015

Cost category		Cost period		
		Pre-diagnosis (US$)	Post-diagnosis (US$)	Total (US$)
Medical	Mean (95% CI)	8.56 (7.68, 9.54)	4.4 (3.23, 6.0)	8.75 (7.85, 9.75)
	Median (IQR)	10.72 (4.58, 23.76)	0 (0)	11.19 (4.73–24.08)
Nonmedical	Mean (95% CI)	10.08 (8.99, 11.30)	43.27 (38.32, 48.23))	64.1 (58.34, 69.9)
	Median (IQR)	8.27 (1.61, 24.32)	35.02 (0–70.04)	37.11 (14.35, 85.12)
Total direct	Mean (95% CI)	21.46 (19.65, 23.43)	43.80 (38.82, 48.78)	84.82 (77.92, 91.72)
	Median (IQR)	21.64 (10.23, 48.31)	35.02 (0–70.04)	59.58 (29.43, 113.81)
Indirect	Mean (95% CI)	75.62 (70.68, 80.90)	75.20 (69.14, 81.26))	140.31 (132.35, 148.74)
	Median (IQR)	64.45 (39.82, 128.80)	51.07 (34.65, 93.02)	127.68 (78.43, 201.85)
Total	Mean (95% CI)	108.0 (101.31, 115.11)	117.0 (110.47, 123.87)	244.71 (229.45, 260.98)
	Median (IQR)	97.62 (56.43, 184.22)	93.75 (56.91, 141.54)	201.48 (136.7, 318.94)

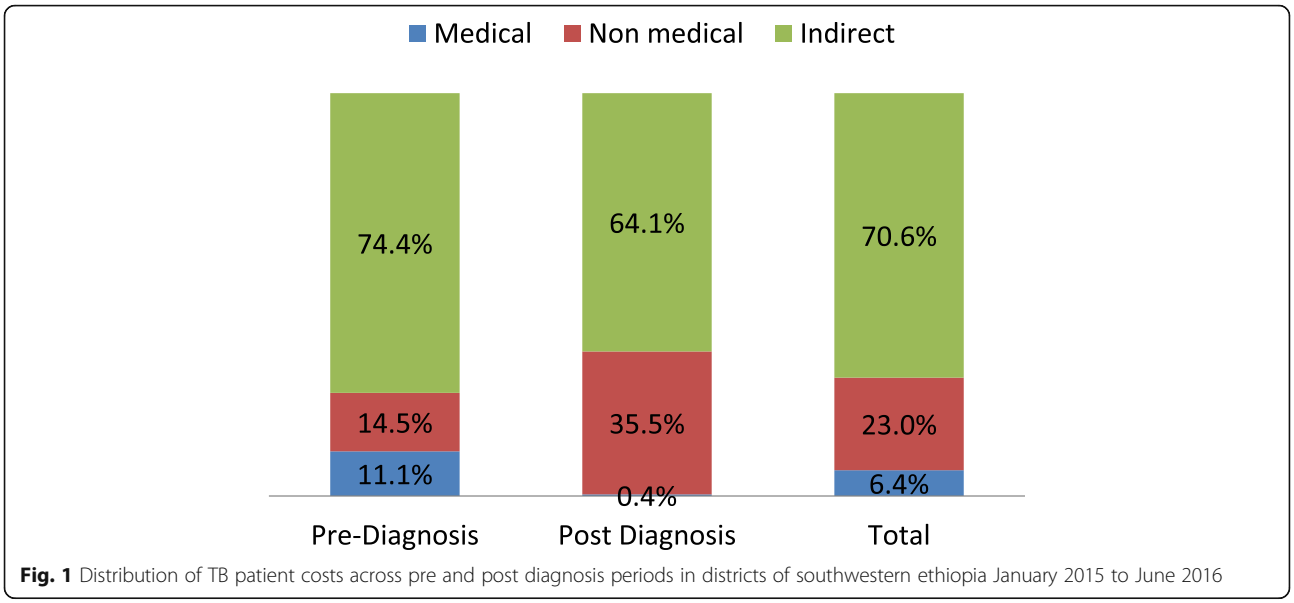

Fig. 1 Distribution of TB patient costs across pre and post diagnosis periods in districts of southwestern ethiopia January 2015 to June 2016

(11.35–30.85) that constitutes 28.4% of the total indirect cost. For 471/569 (82.8%) of the cases, the total cost represents more than 10% of their estimated household annual income.

The mean total cost is significantly different across the types of TB (F = 3.68, $p = 0.03$), action taken before HCF visit ($p = 0.01$), travel time to treatment center ($p = 0.001$), and hospitalization for anti-TB treatment ($p = 0.005$) (Additional file 2: Table S1). In multiple regression, rural residence, travel time to treatment center beyond 1 h, action taken before HCF visit, hospitalized for anti-TB treatment, number of visited HCF, and patient and

Table 4 Predictors of pre-diagnosis cost among TB cases on treatment in districts of southwestern Ethiopia January to December 2015

Variable		Mean(SD) (US$)	Unadjusted exp.[a] coefficient (95% CI)	*P* value	Adjusted exp.[b] coefficient (95% CI)	*P* value
Gender	Male	112.62(0.12)	Ref.		Ref.	
	Female	101.25(0.11)	0.90(0.79, 1.02)	0.1	0.94(0.86, 1.03)	0.20
HIV result	Positive	131.2(0.13)	1.24(0.98, 1.55)	0.07	1.16(0.99, 1.36)	0.06
	Negative	106.02(0.11)	Ref.		Ref.	
Mode of diagnosis	Bacteriological	97.00(0.11)	Ref.		Ref.	
	Clinical	121.08(0.12)	1.25(1.10, 1.42)	0.001	1.08(0.99, 1.18)	0.09
Residence	Urban	114.61(0.12)	Ref.		Ref.	
	Rural	102.13(0.1)	0.89(0.78, 1.01)	0.07		
Patient delay[c](days)			1.006(1.005, 1.006)	< 0.001	1.005(1.004, 1.01)	< 0.001*
Provider delay[c](days)			1.006(1.005, 1.01)	< 0.001	1.005(1.004, 1.01)	< 0.001*
Action before HCF visit	None	106.72(0.12)	Ref.		Ref.	
	Took action[d]	113.41(0.11)	1.23(1.07, 1.41)	0.03	1.15(1.03, 1.28)	0.01
First visited HCF	DOTS center	99.97(0.11)	Ref.		Ref.	
	Non-DOTS center	122.57(0.11)	1.23(1.07, 1.40)	0.002	1.01(0.91, 1.11)	0.8
TB diagnosed HCF	Public	101.78(0.11)	Ref.		Ref.	
	Private	153.88(0.13)	1.5(1.26, 1.81)	< 0.001	1.18(1.03, 1.34)	0.02*
Number of HCF visited until diagnosis[b]			1.40(1.34, 1.47)	< 0.001	1.18(1.13, 1.23)	< 0.001*

*Statistically significant at $p < 0.05$
[a]Exponent to the power of 10
[b]Adjusted for all the variables listed in the table
[c]Variable treated as continuous
[d]Self-treatment, used holy water, consult traditional healer

Table 5 Predictors of post-diagnosis cost among TB cases on treatment in districts of southwestern Ethiopia January to December 2015

Variable		Mean(SD)	Unadjusted exp[a] coefficient (95% CI)	*P* value	Adjusted exp[b] coefficient (95% CI)	*P* value
Gender	Male	119.73(0.1)	Ref.		Ref.	
	Female	112.51(0.1)	0.94(0.83, 1.06)	0.3	0.92(0.83, 1.02)	0.07
Residence	Urban	94.02(0.11)				
	Rural	154.7(0.08)	1.64(1.48, 1.83)	< 0.001	1.48(1.34, 1.64)	< 0.001*
Educational status	Illiterate	137.15(0.09)	Ref		Ref	
	Primary	117.35(0.09)	0.86(0.74, 0.98)	0.03	0.87(0.77, 0.97)	0.02*
	Secondary and above	97.79(0.08)	0.71(0.60, 0.84)	< 0.001	0.83(0.72, 0.95)	0.01*
HIV result	Positive	123.52(0.1)	1.06(0.88, 1.28)	0.5	1.13(0.97, 1.30)	0.1
	Negative	116.20(0.1)	Ref.		Ref.	
Mode of diagnosis	Bacteriological	118.25(0.1)	Ref.		Ref.	
	Clinical	115.82(0.1)	0.98(0.87, 1.10)	0.7	0.96(0.87, 1.05)	0.3
Treatment center	Hospital	103.05(0.1)	0.78(0.70, 0.88)	< 0.001	0.82(0.74, 0.90)	< 0.001*
	Health center	131.43(0.1)				
Travel time to treatment center	> 1 h	105.7(0.08)	1.37(1.22, 1.55)	< 0.001	1.09(1.02, 1.21)	0.03*
	≤ 1 h	145.14(0.09)	Ref.		Ref.	
Patient delay[c]			1.003(1.002, 1.004)	< 0.001	1.003(1.001, 1.003)	< 0.001*
Provider delay[c]			1.002(1.001, 1.003)	< 0.001	1.002(1.001, 1.002)	< 0.001*
Action before HCF visit	None	111.85(0.11)	Ref.		Ref.	
	Took action[d]	137.34(0.1)	1.23(1.07, 1.41)	0.003	1.08(0.98, 1.28)	0.1
TB diagnosed HCF	Public	116.37(0.1)	Ref.			
	Private	121.27(0.1)	1.04(0.87, 1.24)	0.5	0.95(0.83, 1.09)	0.5
Hospitalized for treatment	Yes	240.82(0.1)	2.13(1.61, 2.80)	< 0.001	2.3(1.84, 2.88)	< 0.001*
	No	113.3(0.1)	Ref.		Ref.	

*Statistically significant at $p < 0.05$
[a]Exponent to the power of 10
[b]Adjusted for variables in the table
[c]Variable treated as continuous
[d]Self-treatment, used holy water, consult traditional healer

provider delays all independently predicted increased mean total patient cost of TB care (Additional file 2: Table S2). The mean total cost incurred by patients who are rural residents is about 24% higher than that by urban residents, adjusted exp. coefficient (AeC) (95% CI) 1.24 (1.13, 1.4). Similarly, every patient and provider delay day predicts about 0.3% each AeC (95% CI) 1.003(1.002–1.004) increment in mean total patient cost. Those patients who took action before initiating HCF visits had incurred 17% higher mean total cost compared to those who did not took action. Hospitalization during anti-TB treatment increase the total mean patient cost by 97% compared to those not hospitalized.

Discussion

This follow-up study of new TB cases on DOTS revealed patients incurred substantial cost across pathways to TB treatment. Thus, the median out-of-pocket payment for an episode of TB illness amounted to US$59.58 that constitutes more than a quarter (29.4%) of the total cost. More than half (53.6%) of the total cost were incurred before diagnosis of TB, and majority (70.6%) of the total cost were attributed to nearly 52 lost workdays per patient. Compared to the post-diagnosis, patients incurred significantly higher medical and indirect costs and lower nonmedical costs during the pre-diagnosis period. Increased pre-diagnosis costs were attributed to patient and provider delays, taking informal treatment before HCF visit, diagnosis at private facilities, being clinically diagnosed, and the number of visited health facilities. On the other hand, rural residence, hospitalization for anti-TB treatment, and following anti-TB treatment at a health center predicted increased post-diagnosis patient costs.

The total cost incurred across the care-seeking and treatment pathways are significantly correlated with both patient and provider delays. The increased pre-diagnosis

cost with patient delay could be due to increased risks of severe manifestation [27] that lead to hospitalization and companion during care seeking and treatment. Besides, the patient delay is associated with informal care including self-treatment and traditional cares [28, 29] that pose costs to patients. The patient delays are accompanied by longer lost workdays that reduced patient income. On the other hand, the delay at health system (provider delay) is associated with repeated visits to different HCF when patients incur for both medical and nonmedical services.

Those patients diagnosed clinically incur significantly higher pre-diagnosis cost. This could be due to national diagnostic algorithm that respectively requires 2–4 and 4–8 weeks follow-up for the clinical diagnosis of smear negative and extra pulmonary TB [21]. The higher costs for the clinical diagnosis could be due to the requirement of experienced clinician decisions guided by better diagnostic facilities. Such experts and facilities exist at only few healthcare facilities situated in cities very far from the majority of the people that lead to higher transportation and lodging costs to patients. The repeated consultations and diagnostic tests until diagnosis of TB all incur cost to the patients. The relatively lower cost of bacteriologically confirmed diagnosis could be due to exemption of sputum smear microscopy and culture by the national TB control program. Hence, ensuring efficient diagnostic algorithms and quality bacteriological tests can reduce the financial burden of TB patients.

Consistent with other studies [8, 30] patients diagnosed at private facilities incur significantly higher pre-diagnosis cost compared to those diagnosed at public facilities. The different cost items and rates at the private facilities where every services including sputum microscopy is charged can explain the relatively higher cost at the private. Since there were no public-private mix (PPM)-DOTS in the study area at the time of study, the private HCF might not implement the proper diagnostic algorithm that might lead to delay and extra cost. Furthermore, public health facilities requirement of retesting a positive sputum result from private facilities for treatment initiation leads to delay and extra cost [31].

We found patients treated at hospitals had significantly lower post-diagnosis cost compared to those treated at health center. This could be due to the presence of full-time staff that exclusively provides TB patient care at hospitals. However, at health centers, providers are given multiple duties other than TB DOTS that increase patient waiting time and costs. In addition, health centers are situated in rural areas where there is no transport access within villages in contrast to hospitals in urban areas easily accessible to patients within the town. Thus, statistically significant difference in mean total time (71.17 vs 106. 79 min, $p < 0.001$) had been respectively spent per each patient visit to hospitals and health centers. Consistent with other studies [8, 32], we found significantly higher post-diagnosis cost incurred by patients from rural areas compared to those from urban areas. The reason could be due to significantly higher mean time spent per each visit among patients that are rural and urban residents (119.51 vs. 68.35 min, $p < 0.001$), respectively.

Our study had some limitations. First, cost measurements relied on patient recall, which was liable to recall bias. However, we did the baseline interview within the first 2 months of treatment when patients are highly likely to recall about the costs they incurred. Second, the study employed only patient perspective so that we were not able to determine costs incurred by health systems, households, and communities. Lastly, we determined the cost based on a prevalent approach that measure costs for an episode of illness so that we could not determine lifetime cost of TB illness. On the other hand, our study employed a longitudinal design involving a relatively large sample recruited consecutively. As a result, selection bias was minimized and patient costs from care seeking through treatment completion were determined. The findings in the paper are valid but need to be interpreted cautiously considering the limitations. Given the internal validity, the findings can be applied to patients in similar settings since the characteristics of patients and the health systems in similar settings might not differ significantly.

Conclusion

The study revealed TB patients on DOTS incur substantial cost across the pathways to anti-TB treatment despite the "free service." Significantly, higher cost was incurred during the pre-diagnosis period compared to the post-diagnosis period showing longer pathways of care seeking. Increased pre-diagnosis costs are attributed to patient and provider delays, informal care before consultation, seeking care at private healthcare facilities, and clinical diagnosis. Higher post-diagnosis costs are attributed to patient and provider delays, rural residence, and being treated at health center. Thus, implementation of patient-centered TB care introducing reimbursement mechanisms and scaling up of national community and social insurance initiatives to the study area are vital to reduce patients' out-of-pocket expenditures. In addition, introducing reimbursement of direct costs, promoting early care seeking, equipping healthcare facilities with the necessary equipments, and staffing with qualified health work force, and decentralizing efficient diagnosis and treatment within reach of patients can minimize the patient costs.

Additional files

Additional file 1: Consent form and questionnaire. (DOCX 112 kb)

Additional file 2: Table S1. Mean differences of pre, post, and total costs to patients among TB cases on treatment in districts of southwestern Ethiopia January to December 2015. Table S2. Predictors of total cost to patients among TB cases on treatment in districts of southwestern Ethiopia January to December 2015. (DOCX 25 kb)

Abbreviations

CI: Confidence interval; DOTS: Directly Observed Treatment Short course; ETB: Ethiopian Birr; HCF: Healthcare facility; HIV: Human immunodeficiency virus; IQR: Inter-quartile range; PPM: Public-private mix; SD: Standard deviation; TB: Tuberculosis; US$: United States of America Dollar

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Availability of data and materials

The data from which conclusion of this study was made can be available upon request from the corresponding author.

Authors' contributions

AA conceived and designed the study, collected and analyzed the data, and prepared the manuscript. WD and DJ critically reviewed the study protocol and manuscript for intellectual content as primary and co-supervisor, respectively. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study was ethically approved by the Institutional Review Board (IRB) of the College of Health Sciences at Addis Ababa University (protocol number: 045/14/sph). Written informed consent was sought from each study participant before the interview. Patient clinical profile from records and a unit register was retrieved upon permission from respective health care facilities.

Competing interests

The authors declare that they have no competing interests.

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RESEARCH ARTICLE Open Access

Improvement in tuberculosis infection control practice via technical support in two regions of Ethiopia

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Abstract

Background: Globally recommended measures for comprehensive tuberculosis (TB) infection control (IC) are inadequately practiced in most health care facilities in Ethiopia. The aim of this study was to assess the extent of implementation of TB IC measures before and after introducing a comprehensive technical support package in two regions of Ethiopia.

Methods: We used a quasi-experimental design, whereby a baseline assessment of TB IC practices in 719 health care facilities was conducted between August and October 2013. Based on the assessment findings, we supported implementation of a comprehensive package of interventions. Monitoring was done on a quarterly basis, and one-year follow-up data were collected on September 30, 2014. We used the Student's *t*-test and chi-squared tests, respectively, to examine differences before and after the interventions and to test for inter-regional and inter-facility associations.

Results: At baseline, most of the health facilities (69%) were reported to have separate TB clinics. In 55.2% of the facilities, it was also reported that window opening was practiced. Nevertheless, triaging was practiced in only 19.3% of the facilities. Availability of an IC committee and IC plan was observed in 29.11 and 4.65% of facilities, respectively. Health care workers were nearly three times as likely to develop active TB as the general population. After 12 months of implementation, availability of a separate TB room, TB IC committee, triage, and TB IC plan had increased, respectively, by 18, 32, 44, and 51% ($p < 0.001$).

Conclusions: After 1 year of intervention, the TB IC practices of the health facilities have significantly improved. However, availability of separate TB rooms and existence of TB IC committees remain suboptimal. The burden of TB among health care workers is higher than in the general population. TB IC measures must be strengthened to reduce TB transmission among health workers.

Keywords: TB infection control, TB transmission, TB prevention, Health care workers, Ethiopia

Background

Tuberculosis (TB) is one of the major infectious diseases that have tested the knowledge and wisdom of mankind. Innovations related to TB diagnosis, prevention, and treatment have lagged behind other technological advancements. After isolation of the tubercle bacillus, it took 38 years to invent a preventive vaccine and 61 years to discover the first anti-TB drug [1, 2]. The death toll from TB is enormous, and it continues to claim millions of lives throughout the world, even though simple preventive measures exist. Through airborne transmission, its favored mode of dissemination, TB has managed to sustain itself for millennia [3, 4].

Against all odds, remarkable progress has been made in recent times through formulation and implementation of effective strategies like the Directly Observed Treatment, Short course (DOTS) and Stop TB strategies,

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which greatly contributed to meeting the TB-related target of the Millennium Development Goals (MDGs) of halting and beginning to reverse the TB epidemic [5]. On one hand, between 2000 and 2015, TB mortality declined by 34% and the number of deaths averted as a result of TB treatment was estimated at 49 million. On the other hand, TB remained one of the top 10 killer diseases in 2015. Moreover, increasing TB mortality was seen in Congo and the Democratic People's Republic of Korea [6].

Ethiopia is one of the 30 high-TB-burden countries that have shown a substantial reduction in TB incidence and mortality since 2000. The estimated decline in the incidence rate as of 2010 was 6.7%. In 2015, the estimated TB incidence was 191,000, while the actual notified TB cases were 137,960. In the same year, 599 cases of drug-resistant TB (DR-TB) were notified. Of the notified TB cases, 8% were people living with the human immunodeficiency virus (HIV) [6].

In low-income countries such as Ethiopia, patients and visitors tend to congregate in health facilities' corridors and waiting areas. This congestion is due to uncontrolled population growth and an increasing number of health care seekers, on one hand, and a shortage of health care workers (HCWs) and limited number of health care facilities (HCFs), on the other hand [7]. This overcrowding, in turn, supports airborne nosocomial transmission of TB to HCWs, patients, and even visitors [8]. Highly vulnerable people, such as children, undernourished people, and immunocompromised people, are among the health service seekers in HCFs, which is an opportunity for TB to continue its spread. The emergence and rapid spread of drug-resistant mycobacterial strains, as well as its interaction with HIV, have heightened the demand for effective infection control (IC) interventions at all levels [9–11].

IC, in the TB context, aims at reducing the transmission of TB within populations and relies on a set of managerial, administrative, environmental, and personal protective interventions. When such measures are not implemented, the risk of TB (both drug susceptible and drug resistant) dramatically increases, in some circumstances to epidemic proportions. Inpatient outbreaks of DR-TB among people living with HIV have been reported in Africa and Europe [12, 13]. Implementing IC measures, however, is known to reverse the airborne threat [9]. The TB IC hierarchy of measures is so crucial that the World Health Organization (WHO) has issued a standalone policy document and implementation guidelines for member countries' action. TB IC has also been recommended in important global documents [8, 14–16].

Ethiopia developed its first national TB IC guidelines based on international recommendations in 2009—in the same year that the relevant WHO documents were published [5, 9]. The Federal Ministry of Health has trained a number of health care workers using a TB IC curriculum. Still others were trained in comprehensive TB/HIV services as well as programmatic management of DR-TB, both of which have incorporated TB IC topics [17, 18].

The Help Ethiopia Address the Low Performance of TB (HEAL TB) project led by Management Sciences for Health (MSH) implemented a comprehensive TB control program, one of the components being TB IC. Capacity building for health managers and health workers, supportive supervision, and technical and material support were among the interventions geared toward improving TB IC in HCFs. It is evident that there is little research, particularly intervention studies, about TB IC in low-income settings. The objective of this study was to compare the implementation of TB IC measures before and after introduction of a comprehensive technical support package in two regions of Ethiopia.

Methods

Setting

Ethiopia is the second most populous nation in Africa, with a population close to 99 million. It is administratively composed of nine regional states and two city administrations. Under each regional state there are a number of zonal administrations (also called zones), and under each zone are several *woredas* (districts) [19].

In 2017, there were 22,807 TB notified cases out of the 21.1 million population in Amhara, and 43,321 notified TB cases out of 35.8 million population in Oromia Region [20].

The study employed a pre- and post-intervention design built upon project implementation. All of the project HCFs were included in the study.

Funded by the United States Agency for International Development (USAID), the HEAL TB project supported the government of Ethiopia in addressing many of the major challenges posed by TB. The project began in July 2011 in two of the most populous regional states in the country: Oromia and Amhara, with a total population of 57 million. Before the intervention, HEAL TB conducted a baseline assessment in all HCFs of the selected 11 zones. Twenty-two hospitals and 697 health centers were included in the assessment, which ran from August through October 2013. Basic information on TB IC measures was collected.

Intervention

The intervention package consisted of capacity building, provision of standard operating procedures (SOPs), regular supportive supervision, and program review meetings. The project initially trained woreda TB focal persons on the basics of TB IC and on supervisory skills

so that they could provide technical support to HCWs. The woreda TB focal person supervises, on average, five HCFs under his/her catchment once every three months, using supervision checklists and TB SOC indicators. Both templates address TB IC issues. Based on the findings of the supervision, the woreda TB focal person gives on-site feedback and subsequently follows the implementation status of the action plan developed during the last visit. In addition to the woreda TB focal persons, HCWs were also trained using a TB IC curriculum. Different SOPs appropriate to the service delivery points were developed and posted on the wall, starting with the triage room continuing all the way to the laboratory. TB program review meetings were held biannually; during the meetings, woreda TB focal points presented the performance of the HCFs in their respective woredas over the previous six months. In such meetings, TB IC is a major topic that is thoroughly discussed, and improvement plans are formulated.

Data collection instruments

Two types of checklists were used, one for baseline assessment and another for quarterly monitoring. The baseline checklist is a comprehensive tool of eight pages with 171 items structured into different thematic areas, including TB IC. The TB IC questionnaire asks about the (1) availability of a separate TB room, (2) opening of windows during consultation hours, (3) presence of cough triage, (4) TB IC committee, (5) TB IC plan, and (6) number of HCWs who developed active TB in the previous year. The quarterly monitoring instrument also contains a subsection on TB IC specifically referring to the presence of a functional multidisciplinary team/infection prevention committee, revised IC plan, triage/cougher prioritization, and separate TB room. Both tools were developed based on consultation with stakeholders and adaptation of international TB standards [21, 22]. Taking into account the large number of HCFs under project support, it was decided that the number of TB IC indicators should be kept to the minimum, while ensuring robustness, for the sake of efficient resource utilization.

Data collectors and data collection procedures

For the baseline assessment, the data collectors were HEAL TB employees who were medical doctors, health officers, and specialist laboratory professionals, all with public health experience. Training on the baseline assessment tools was provided for two days, before their departure to the field. Observation, review of documents, and interviews were the approaches used to collect the baseline data. Information about the number of HCWs who developed active TB was obtained from the TB registers kept in TB rooms. For this purpose, HCWs were defined as all people working in HCFs.

For quarterly monitoring, the trained woreda TB focal persons were in charge of data collection from their respective catchment HCFs. During the visits, they used the SOC tool, which required them to interview HCF TB focal persons about the status of TB IC activities, to review documents (minutes of infection prevention/IC committees), and to observe practices (prioritization of people with cough; status of the TB room).They spent on average half a day in each HCF to collect relevant TB program data. The following four TB IC indicators were monitored every three months: existence of (1) TB IC committee, (2) triage, (3) separate TB room, and (4) revised/updated TB IC plan. Data were collected from all 719 health facilities at baseline and every quarter thereafter.

Data management and analysis

A data entry template in the Census and Survey Processing System (CSPro), version 4.1 (US Census Bureau, ORC Macro International, and Serpro SA), was prepared, and data were entered into the template immediately after data collection. We checked the data for consistency and completeness by running frequency tables and cross-tabulations.

The data entered into CSPro 4.1 were exported to Stata 11 (College Station, TX: StataCorp., LP), where data cleaning, editing, and consistency checking were performed. Frequencies and percentages were computed to describe the data and compare TB IC practices before and after the program was implemented. We used the Student's *t*-test to determine significant differences between baseline and post-intervention data. The chi-squared test (Table 1) was also utilized to test for associations between the two regions as well as between hospitals and health centers (Tables 2 and 3).

Ethical considerations

We received ethical approval from the ethics committees of Amhara and Oromia Regional Health Bureaus to analyze the routine data and disseminate the findings. We used health facility level reports for this analysis with the consent of the reporting institutions. No patient identifiers were included in the routine reports.

Table 1 Comparison of the TB IC performance before and after intervention

Variables	Before intervention % ($N = 719$)	After intervention % ($N = 719$)	*P*-value (Before after t-test)
Separate TB room	69.1	87.1	$P < 0.001$
Cough triage	19.3	63.0	$P < 0.001$
IP/TB IC committee	29.1	61.1	$P < 0.001$
TB IC Plan	4.7	56.1	$P < 0.001$

Table 2 TB IC performance at baseline and after intervention by region

Characteristics	Baseline			After Intervention		
	Region		*P*-value (Chi-square)	Region		*P*-value (Chi-square)
	Amhara (*n* = 306)	Oromia (*n* = 413)		Amhara (*n* = 306)	Oromia (*n* = 413)	
% Cough triage	17.4	21.8	0.31	84.2	46.7	< 0.01
% IP/TB IC committee	57	14.7	< 0.01	71.2	53.6	< 0.01
% TB IC Plan	2.9	6.3	0.16	67.3	48.0	< 0.01

Results

At baseline, separate TB clinics existed in the majority of health facilities (69.1%). HCWs assigned to outpatient departments were reported to be working with open windows in 55.2% of the HCFs. However, coughing patients were prioritized for TB services in only 19.41% of the health facilities. Infection prevention committees and TB IC plans existed in only 29.11 and 4.65% of the assessed HCFs, respectively. There were no statistically significant differences between Amhara and Oromia regions regarding the practice of cough triage ($p = 0.31$) and existence of a TB IC plan ($p = 0.16$).However, regional differences in existence of TB IC committees ($p < 0.01$) did attain statistical significance (Table 2). Furthermore, hospitals differed from health centers significantly in terms of cough triage, TB IC committees, and TB IC plan availability ($p < 0.01$) (Table 3).

Sixty-one of the 8667 HCWs had developed active TB in the year preceding this assessment, making the annual incidence rate 704/100,000. Using WHO's 2012 TB incidence estimation for Ethiopia, which was 247/100,000, we calculated the incidence rate ratio to be 2.85 (for all forms of drug-susceptible TB, not only new cases). The incidence risk ratio was not age standardized; the rates were compared to the general population based on the WHO estimate, which is not age standardized.

Health care workers with TB were identified according to the national diagnostic algorithms, which consisted of sputum smear microscopy (the algorithm was recently revised, so that HCWs are tested with GeneXpert assay), radiography, and cytology—as indicated.

After 12 months of implementation, the number of HCFs with TB IC committees increased to 61%, and prioritized service for coughers had been put in place in 63% of the HCFs ($p < 0.001$). Furthermore, 56% of HFs had written TB IC plans, and 87% had designated separate TB rooms, which was significantly higher than the situation before intervention ($p < 0.001$) (Table 1).

Post-intervention, statistically significant differences occurred between Amhara and Oromia regions pertaining to availability of all the TB IC measures ($p < 0.01$). Moreover, with the exception of existence of TB IC committees ($p = 0.10$), hospitals differed from health centers significantly in terms of cough triage ($p < 0.01$) and availability of TB IC plans ($p = 0.01$).

Discussion

Before the technical support and comprehensive package of interventions, the majority of the health facilities lacked basic work procedures and policies to facilitate smooth implementation of TB IC. After intervention, availability of TB IC plans and use of triage showed marked improvement, while existence of TB IC committees and separate TB rooms improved modestly.

When comparing HCFs in Amhara with those of Oromia Region, the former did well post-intervention in availability of TB IC plans and triage, whereas the latter performed better in existence of TB IC committees. In addition, hospitals performed better than health centers in all the TB IC indicators, which can be explained by a relatively good start at baseline, presence of trained HCWs in sufficient number, and extra supervisory support from different stakeholders due to hospitals' physical accessibility.

According to the WHO directive, facility-level TB IC implementation begins with assignment of a coordinating body. Health facility risk assessment, formulation of a TB IC plan, and implementation of the plan should

Table 3 TB IC performance at baseline and after intervention by type of health facility

Characteristics	Baseline			After Intervention		
	Type of Health Facility		*P*-value (Chi-square)	Type of Health Facility		*P*-value (Chi-square)
	Health Center (*n* = 697)	Hospital (*n* = 22)		Health Center (*n* = 697)	Hospital (*n* = 22)	
% Cough triage	18.8	47.8	< 0.01	61.5	91.7	< 0.01
% IP/TB IC committee	28.6	56.5	< 0.01	60.4	79.2	0.10
% TB IC Plan	3.6	34.8	< 0.01	55.2	83.3	0.01

follow in that order [9]. In our baseline assessment, however, this logical order was not evident. Only 29% of the facilities had functional IP committees, meaning that the great majority of the facilities lacked a responsible body to combat TB transmission. Without this committee, it is not possible to do facility assessments and to plan TB IC activities, in line with the guidelines. The literature is scanty regarding availability of infection prevention/TB IC committees. Ogbonnaya et al. reported that 16.7% of the assessed TB/HIV implementing health facilities in Nigeria had IC committees [23]. This figure is lower than what we found at baseline in Ethiopia. A 32% improvement was seen post-intervention.

The least-implemented TB IC measure was the facility-level IC plan, which was found in only 4.7% of the HCFs. This also brings to light that 24.3% of the HCFs reported as having IC committees failed to develop plans, bringing into question their functionality. In sub-Saharan Africa, availability of TB IC plans in health facilities ranges from none to 77% [24, 25]. In Mozambique, it was 48% [26] and in Uganda, 31% [27]. Our baseline finding lies in between and was increased to 56% after intervention. Unavailability of a TB IC plan implies poor managerial activity and attention. It is very difficult to implement what has not been planned.

Close to 80% of the assessed facilities did not provide prioritized services for presumptive TB patients. Functional triage availability is reported from Nigeria [23] and South Africa [28] as 16.7, and 26%, respectively. In a 2012 study involving nine countries in sub-Saharan Africa, it ranged from 5 to 93% [25]. At baseline, triage availability in Ethiopia was a bit higher than the reported figure from Nigeria but modestly lower than in South Africa and within the range of figures in sub-Saharan Africa. In such a situation, generation of infectious droplet nuclei and contamination of the environment are facilitated; HCWs, visitors, and other patients become highly exposed.

Screening of all health facility care-seekers for TB symptoms, with subsequent isolation and/or fast tracking for services are triage functions and an essential component of administrative control. It is generally agreed that triage is the first defense mechanism against TB transmission in HCFs. Rapid diagnosis and effective TB treatment are the hallmarks of TB IC. Establishment of triaging had increased to 63% of the HCFs by the end of the intervention year.

At baseline, HCWs in half of the assessed facilities opened window(s) during consultation hours and thereafter. This practice was indicative of individuals' precautions rather than a concerted IC effort, given the low level of availability of TB IC committees and plans. Moreover, awareness among HCWs has been raised by their attending trainings related to TB, HIV, and DR-TB. Reports of increased awareness of HCWs (clinicians) about IC were recently demonstrated in Addis Ababa and in northwest Ethiopia in a survey of knowledge, attitudes, and practices [29, 30].

In nearly 70% of the health facilities, TB rooms were standalone. This should not be counted as a strength, however, since all service delivery points are required to have separate rooms as a matter of health service standards. It also implies that the remaining one-third of HCFs are providing TB service together with other services, compromising space and ventilation. In South Africa, dedicated TB rooms were available in only 31% of HCFs [25]. Through project support in Ethiopia, it was possible to increase the level from the baseline of 69 to 87%.

Poor implementation of IC measures is reflected in HCWs' acquisition of TB disease, as this study showed. Sixty-one HCWs acquired TB in 1 year. They were about 2.85 times more likely to acquire active TB disease than the general population. Reports of TB among HCWs from sub-Saharan African countries [24] and resource-rich countries [31] show disparities. The TB case notification rate in HCWs of Malawi was 3.2% as compared to 1.8% for primary schoolteachers [32]. In South Africa, Claassens et al. stated that the standardized incidence ratio of smear-positive pulmonary TB in primary health care workers was more than double that of the general population [28]. A study in 2013 in the same country showed a 10% DR-TB rate among physicians with pulmonary TB diagnosis, which the researchers attributed to lack of effective IC work practices combined with negative attitudes of administrators [33]. A recent meta-analysis by Baussano et al. indicated that the stratified pooled estimates for annual TB incidence risk ratio for countries with high TB incidence (> 100 cases/100,000) is 3.68, whereas it is 2.42 for low-incidence (< 50 cases/100,000) and intermediate-incidence (50–99 cases/100,000) countries. The overall estimate of annual TB incidence risk ratio was 2.97, which is comparable to our finding of 2.85. They concluded that HCWs' risk of acquiring TB was higher than that of the general population across the globe and that effective TB IC measures could decrease annual TB incidence among HCWs by as much 81, 27, and 49% in countries with high, intermediate, and low TB incidence, respectively [34]. Most, if not all, countries have long recognized TB as an occupational disease [9, 35].

It is worth noting the following limitations of the study. We were not able to present data regarding the cross-ventilation status of outpatient departments and active TB disease among HCWs to make comparison with the baseline findings, since our quarterly data source did not capture these items. Furthermore, lack of randomization in quasi-experimental design makes it difficult to control for confounding variables, and hence statistical association may not necessarily imply causal

association. Similarly, we used Student's *t*- and chi-squared tests, which do not allow adjustment for confounders. Moreover, we relied on facility-level registers to collect data about the number of HCWs with TB, which might miss those being treated outside the HCF; hence there is a possibility of underreporting.

Conclusions

Building the capacity of district TB focal persons to provide supportive supervision to health facilities, together with the other comprehensive TB program support, was instrumental in improving the TB IC situation of health facilities. Huge gaps in implementation of the recommended TB IC practices at health facility level can be narrowed, if systematized basic capacity building can be provided. The burden of TB among HCWs is higher than the prevalence in the general population. There is a need to further strengthen infection prevention/TB IC committees in order to plan and implement the hierarchy of TB IC activities and reduce TB transmission among patients and HCWs.

Abbreviations

DR-TB: Drug-resistant tuberculosis; HCF: Health care facility; HCW: Health care worker; HIV: Human immunodeficiency virus; IP: Infection prevention; SOC: Standard of care; TB IC: Tuberculosis infection control; TB: Tuberculosis; USAID: United States Agency for International Development; WHO: World Health Organization

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Availability of data and materials

Raw data will be made available from the authors upon reasonable request.

Authors' contributions

AA conceived and designed the study; NH, DH, & AA participated in the acquisition, analysis, and interpretation of data; AA, DJ, and DH drafted the article; ZG, MM, TA, and PS have contributed to inception, design and implementation of the interventions. They also critically reviewed the first and subsequent drafts of the manuscript and provided critical inputs to the interpretation of the findings. IJ and GA have actively participated in the roll out and implementation of the TB IC in the study regions. Moreover, they have contributed to the drafting and subsequent revision of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

We received ethical approval from the ethics committees of Amhara and Oromia Regional Health Bureaus to analyze the routine data and disseminate the findings. We used health facility level reports for this analysis with the consent of the reporting institutions. No patient identifiers were included in the routine reports.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Can patients afford the cost of treatment for multidrug-resistant tuberculosis in Ethiopia?

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SUMMARY

SETTING: Ethiopia has a high prevalence of tuberculosis (TB) and is one of the countries with the highest burden of multidrug-resistant TB (MDR-TB).

OBJECTIVE: To understand the costs that patients incur in obtaining diagnosis and treatment for MDR-TB.

DESIGN: In March 2013, interviews were conducted with 169 MDR-TB patients at three hospitals in Ethiopia to identify the cost to patients and the impact on employment and family income.

RESULTS: The average MDR-TB patient incurred a total cost of US$1378, which represented 25 months of a mid-treatment household income of US$54. The impact on the patient's employment and on overall patient and family income was generally catastrophic: 74% of all respondents reported losing their jobs, 66% of patients lost household income, and household income was reduced by 38%. To help cover the costs, 38% of patients sold some type of property, while 7% leased out property and 41% took out loans, any of which could jeopardize their future financial situation even further.

CONCLUSION: Despite services being officially free of charge, most patients incurred catastrophic costs and suffered significant income loss as a result of obtaining diagnosis and treatment for MDR-TB.

KEY WORDS: TB; MDR-TB; patient costs; catastrophic costs

TUBERCULOSIS (TB) is one of the ten leading causes of death worldwide. It is a costly disease, with an estimated total economic burden to society of over US$8 per capita, according to a recent study conducted in Indonesia.[1] The study also found that the main reason for the high cost is the large number of untreated cases every year, including multidrug-resistant TB (MDR-TB) cases, which have higher death rates and place a greater burden on the health system and the patients' families. One reason why people with TB do not seek or complete treatment is the costs that they incur.[2–8] These costs can also drive families into poverty, and an important goal of the post-2015 global TB strategy is that no families affected by TB should face catastrophic costs.[9,10] A recent systematic review showed, however, that despite diagnosis and treatment services being officially free of charge, the financial burden to patients is often high,[10] especially for patients with MDR-TB.[11,12] Policy makers need to understand patient costs to address causes and develop mitigation policies.[13] However, data on the financial burden and cost drivers for MDR-TB diagnosis and treatment are currently limited, and more research is needed.

Ethiopia is one of the high TB and MDR-TB burden countries. According to the World Health Organization's 2016 global TB report, the TB incidence rate in 2015 was 192 per 100 000 population (including TB among people living with the human immunodeficiency virus [HIV]), and 2.7% of new and 14% of retreatment cases of TB were MDR-TB. From 2009 to June 2013, 29% of the patients diagnosed with MDR-TB in Ethiopia did not start treatment, and 3% of the 890 patients who did start treatment were lost to follow-up. Several reasons have been identified for delays in seeking, starting and continuing treatment in Ethiopia, and in some cases patient costs have been identified.[3,5,6,14–17]

The present study presents evidence on the impact of MDR-TB diagnosis and treatment on the economic status of patients and their families. The study was undertaken to inform the development of policies that could provide greater patient support, as part of a three-country study conducted by TB CARE I; the

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other two were carried out in Kazakhstan in September–October 2012 and in Indonesia in February–March 2013. Details on the methods used and the results from each country are available in the individual country reports, and in a summary report and journal article.[13,18–21]

STUDY DESIGN, POPULATION AND METHODS

At the time of the present study, in March 2013, there were only three facilities in Ethiopia that treated MDR-TB patients. These were the University of Gonder Hospital in Gonder (northern Ethiopia), Saint Peter's TB Specialized Hospital in Addis Ababa and the All Africa Leprosy, Tuberculosis and Rehabilitation Training Centre (ALERT) Hospital, also in Addis Ababa. Since starting to provide MDR-TB treatment, the Gonder, Saint Peter's and ALERT hospitals had treated accumulated totals of respectively 140, 627 and 123 cases by March 2013.

Given the challenge of collecting data for, or after, the period of MDR-TB diagnosis and treatment, which often takes as long as 2 years, a cross-sectional approach was used, under which a minimum of 50 patients would be interviewed in each of three phases: diagnosis, intensive treatment and continuation treatment. A cross-sectional approach is common for this type of study and was used in several of the studies cited here.[3,5,6,12,14–17] This approach should provide reasonable estimates of costs, data collection should be relatively inexpensive and fast, and results can be available quickly for use by policy makers and program managers to address issues in a timely way.

Interviews were conducted for 1 month starting in March 2013. Patients were interviewed consecutively as they became available—while they were in-patients or at the time that they visited as out-patients. Interviews during the diagnosis phase were conducted with patients who had been diagnosed within the previous 1 month, and there was no limit on the period of recall. During the intensive and continuation phases, the only patients interviewed were those who had been on intensive or continuation treatment for at least 3 months, and data were mainly collected for a period of 3 months before each interview.

Each patient was interviewed once at the health facility using a questionnaire adapted for MDR-TB from a tool previously used for cost interviews of drug-susceptible TB patients in other countries.[22] The questionnaire was translated from English into Amharic, adapted to the local context for some questions, and translated back into English by a different person to check for translation and interpretation consistency. The questionnaire was pretested on a few patients to check for clarity before it was finalized. The questionnaire included cross-checks, and the interviewers were trained to double-check unusually high costs reported by patients.

Data were collected on both the direct and indirect costs of seeking and obtaining diagnosis and treatment. Direct, out-of-pocket, cost data covered costs paid to service providers as well as the cost of transport, accommodation and food supplements. Indirect costs related to diagnosis were pre-treatment income losses reported by patients due to time spent seeking and receiving a diagnosis, but did not include the valuation of opportunity costs for time spent where income losses were not reported. Indirect costs related to treatment were calculated by multiplying the reported time lost by the reported mid-treatment income. The indirect costs of time spent unproductively due to illness were not included as costs, but were covered to some degree under reduction in income. To determine the cost of diagnosis, the average cost per visit was multiplied by the number of visits to obtain a total cost. To determine treatment costs, monthly average costs were developed and these were extrapolated over the complete treatment period using the internationally defined durations of the intensive and continuation treatment phases for MDR-TB patients, i.e., 8 and 12 months, respectively.[23,24] Data were also collected on companion costs but were not considered to be very reliable or significant and are not included in the figures shown in the present study.

In terms of impact, patients were asked questions about loss of employment and income, whether they were reimbursed through insurance and whether they received vouchers or other financial support. They were also asked how they financed the costs, such as by selling assets or taking out loans. These questions covered the whole period of diagnosis and treatment through the time of interview, and were not limited to the final 3 months of treatment.

We excluded patients who did not consent to the study and patients aged <21 years, assuming that they were not generally economically independent. As we interviewed patients when they visited the facilities, patients who had died, were transferred out or were lost to follow-up were not included. Not interviewing patients at home could mean that patients who were lost to follow-up were not included and that they could be among the poorest of MDR-TB patients.

Data entry clerks entered the data into EpiData Entry v 3.1 (EpiData Association, Odense, Denmark; www.epidata.dk) and used double data entry to ensure accuracy. The original analysis was done in Statistical Package for the Social Sciences v 15.0 (SPSS, Chicago, IL, USA) and a later analysis was done using Microsoft Excel™ (MicroSoft, Redmond, WA, USA). As the distributions of almost all costs were skewed toward higher values, median values with 25th and 75th percentiles (interquartile range

Table 1 Characteristics of MDR-TB patients interviewed according to hospital

	Total *n* (%)	St Peter's *n* (%)	ALERT *n* (%)	Gonder *n* (%)
Total interviews	169 (100)	93 (55)	30 (18)	46 (27)
Patient group				
Just diagnosed	27 (16)	14 (15)	7 (23)	6 (13)
Intensive phase	79 (47)	39 (42)	17 (57)	23 (50)
Continuation phase	63 (37)	40 (43)	6 (20)	17 (37)
Sex				
Male	92 (54)	45 (48)	18 (60)	29 (63)
Female	77 (46)	48 (52)	12 (40)	17 (37)
Age group, years				
18–29	97 (58)	52 (56)	18 (60)	27 (59)
30–39	43 (25)	26 (28)	8 (26)	9 (20)
40–49	16 (9)	6 (6)	2 (7)	8 (17)
⩾50	13 (8)	9 (10)	2 (7)	2 (4)
Type of MDR-TB				
Pulmonary smear-positive	160 (95)	90 (97)	28 (94)	42 (92)
Pulmonary smear-negative	2 (1)	0	1 (3)	1 (2)
Extra-pulmonary	6 (3)	3 (3)	1 (3)	2 (4)
No information	1 (1)	0	0	1 (2)
HIV				
Positive	25 (15)	13 (14)	2 (7)	10 (22)
Negative	138 (82)	76 (82)	28 (93)	34 (74)
Not tested	2 (1)	2 (2)	0	0
No information	4 (2)	2 (2)	0	2

MDR-TB = multidrug-resistant tuberculosis; ALERT = All Africa Leprosy, Tuberculosis and Rehabilitation Training Centre; HIV = human immunodeficiency virus.

[IQR]) were used for the analysis. For each type of cost we calculated four indicators: the interquartile mean (IQM), the median, IQR and the number of responses. The IQM eliminates the outliers in the bottom 25% and top 25% of the figures which, given the presence of many zeros and some abnormally high costs, makes the results more robust. Financial data were collected in Ethiopian *birrh* and were converted into US dollars using the average daily midpoint exchange rate for March 2013 (18.60 Ethiopian birrh = US$1.00). All figures shown in the present study are expressed in $US.

Approval for the study protocol was obtained from the Armauer Hansen Research Institute/ALERT Ethics Review Committee, Addis Ababa, on 10 December 2012 (Protocol PO35/12). Written informed consent was provided by patients before they were interviewed. Interviews were conducted by hospital staff, who wore N95 respirators when interviewing. Interviews were conducted in separate rooms or in a private area outside the building if such a room was not available to ensure confidentiality. Data were stored and analyzed without personal identifiers.

RESULTS

A total of 169 patients were interviewed, with 93 (55%) from Saint Peter's Hospital, 30 (18%) from ALERT Hospital and 46 (27%) from Gonder Hospital (Table 1). These figures represent the numbers of patients who were qualified and available for interview during the month and are representative of the total numbers of MDR-TB patients treated at those hospitals. A total of 27 (16%) of the interviewed patients had just been diagnosed, 79 (47%) were in the intensive phase and 63 (37%) were in the continuation phase. The aim was to interview 50 patients in each phase, but the cohort of patients who had just been diagnosed with MDR-TB was smaller than the numbers of patients in the other two phases. In terms of other characteristics, 54% were male and 46% were female, 58% were aged 18–29 years, 95% were pulmonary smear-positive, and 15% were HIV-positive.

The total cost of diagnosis and treatment incurred by a MDR-TB patient was US$1378, comprising US$83 during the pre-diagnosis period and respectively US$661 and US$634 during the intensive and continuation periods (Table 2). The total cost represented 17 months of the pre-diagnosis household income of US$81 and 25.5 months of the mid-treatment household income of US$54. Most of these costs (US$1348) were direct, out-of-pocket costs, and included US$155 paid for medical services, including follow-up tests and non-TB medicines. Median indirect costs were zero for all three phases. These figures are, however, based on reported income losses due to time spent seeking and obtaining diagnosis and treatment and do not include opportunity costs related to time lost where income loss was not reported. Of the 17 patients who reported time lost during the diagnosis phase, only five reported losing income. Of 48 intensive-phase and 63 continuation-

Table 2 Costs of diagnosis and treatment of MDR-TB patients ($US)

	MDR-TB, $US			MDR-TB Months of mid-treatment median household income
	Patients *n*	Median (range)	IQM	
Number of interviews	169	169		
Direct costs				
Direct pre-/diagnosis	21	75 (40–191)	107	
Direct intensive treatment	85	639 (259–968)	640	
Direct continuation treatment	63	634 (458–1048)	731	
Total		1348	1478	25.0
Indirect costs				
Indirect pre-/diagnosis	17	0 (0–8)	2	
Indirect intensive treatment	85	0 (0–0)	0	
Indirect continuation treatment	63	0 (0–0)	0	
Total		0	2	0
Total costs				
Total pre-/diagnosis	21	83 (40–206)	118	
Total intensive treatment	85	661 (269–968)	659	
Total continuation treatment	63	634 (458–1048)	731	
Total direct and indirect costs	169	1378	1508	25.5

MDR-TB = multidrug-resistant tuberculosis; $US = US dollar; IQM = interquartile mean.

phase patients who reported lost time, only 8 and 1, respectively, reported losing income.

There were significant differences in costs by diagnosis and treatment location, with a total direct cost of US$1634 per patient in Addis Ababa, which was 80% higher than the total of US$906 in Gonder (Table 3). The biggest difference was in patient food costs (US$392 in Addis Ababa compared with US$53 in Gonder). The costs of treatment of adverse events, patient transport, patient accommodation and supplementary food were also higher in Addis Ababa.

Direct costs were compared by income level by dividing the patients into three equal groups using pre-diagnosis household income levels (Table 4). Patients in the lower income group incurred a direct cost of US$909, those in the middle income group incurred US$1437 and those in the upper income group incurred US$2210. The poorer group spent less on most elements of TB care, for example on food, which is understandable, as they had less income. Of the patients in the lower income group, the majority (83%) were patients at Saint Peter's Hospital.

Significant time was spent in getting a diagnosis, with medians of three visits and 22 h per visit, including travel time (Table 5). The greatest time spent was in Gonder, with 156 h per visit. Significant time was also spent during hospitalization—82% of the patients were hospitalized, and each spent on average 80 days in the hospital. During the continuation phase, patients visited Saint Peter's Hospital once per month, but visited the ALERT and Gonder hospitals four times per month.

Impact on patient employment and on overall patient and family income was significant. Of the 169 patients, 74% reported losing their jobs due to the illness, 66% of patients experienced household income loss, and household income was reduced by 34% (from US$81 before TB to US$54 at the time of the interview) (Table 6).

The costs of seeking and obtaining diagnosis and treatment were financed in various ways. Health

Table 3 MDR-TB direct patient costs by city (2013 $US)

Type of cost	Addis Ababa median $US (IQM)	Gonder median $US (IQM)
Number of interviews	123	46
Health care costs: diagnosis (administrative charges, laboratory tests, X-rays, medicines)	0 (4)	1 (7)
Health care costs: hospitalization	1 (6)	9 (10)
Health care costs: adverse events and follow-up fees, tests and medicines	183 (218)	117 (129)
Patient transport	115 (205)	9 (22)
Patient food	392 (478)	53 (113)
Patient accommodation	94 (107)	4 (7)
Dietary supplements	774 (908)	619 (655)
Relocation	75 (75)	94 (132)
Other	0 (2)	0
Total*	1634 (2003)	906 (1075)

* Differences are due to rounding.
MDR-TB = multidrug-resistant tuberculosis; $US = US dollar; IQM = interquartile mean.

Table 4 Direct patient costs by household income level, 2013 ($US)

	Lower-income group (US$16–53/month) ($n = 56$) median $US (IQM)	Middle-income group (US$54–107/month) ($n = 55$) median $US (IQM)	Upper-income group (US$108–833/month) ($n = 56$) median $US (IQM)
Health services	101 (126)	134 (171)	139 (145)
Transport	47 (63)	99 (194)	91 (144)
Food	109 (138)	189 (265)	552 (677)
Accommodation	77 (84)	106 (140)	121 (124)
Dietary supplements	516 (585)	839 (894)	1,032 (1,122)
Relocation	59 (59)	67 (72)	275 (244)
Other	0 (1)	3 (2)	0
Total	909 (1055)	1437 (1739)	2210 (2455)

$US = US dollar; IQM = interquartile mean.

insurance was not generally available in Ethiopia and only one of the patients interviewed had coverage; that patient had not received any reimbursement of costs at the time of the interview (Table 6). Vouchers were received by 63% of patients, mostly for food, transport, and house rent. Each patient received an average of four vouchers, with a total value of US$33; 30% of the patients who received vouchers also sold property or took out loans, indicating that the value of the vouchers was insufficient. Property was sold by 38% of patients, while 7% leased property and 41% took out loans. Almost all of the loans were without interest, indicating that they were from family or friends.

DISCUSSION

The core findings from the study showed that, although MDR-TB diagnosis and treatment services are officially free in Ethiopia, most patients incurred catastrophic costs. Patients incurred an average cost of US$1378 over the period of diagnosis and treatment, with higher costs suffered by patients in Addis Ababa than in Gonder due to higher costs of food, transport and accommodation. Poorer patients incurred lower costs than better-off ones, for example on food, but this is not a positive finding because they had less disposable income and would have suffered more financially. Some patients suffered high indirect costs in obtaining a diagnosis due to the lengthy time spent, especially in Gonder. Significant time was also spent during hospitalization, with 82% of patients hospitalized and an average stay of 80 days. Higher numbers of patients were admitted to Saint Peter's Hospital than at the other hospitals, and they stayed in hospital longer. Some patients also spent a lot of time on out-patient treatment visits, especially at ALERT Hospital, where they made daily visits of 90 min during the intensive phase and weekly visits of the same duration during the continuation phase.

In addition to the costs incurred, most patients lost their jobs and most households lost income. While more than half the patients received financial assistance in the form of vouchers, the value of the vouchers was much smaller than the costs incurred. Without sufficient financial assistance, many patients sold or leased property and took out loans, providing further evidence that the costs were catastrophic.

The findings of the present study are comparable with the results of the two MDR-TB patient cost studies in Indonesia and Kazakhstan that used the same methodology.[13] In Indonesia, the median total cost of diagnosis and treatment was US$2342, which was 11 months of the pre-diagnosis household income of US$206 and 19 months of the household income of US$124 at the time of interview. In Kazakhstan, the total cost was US$3125, which was 9 months of the median pre-diagnosis household income of US$489 per month. In both countries, the

Table 5 Time spent seeking and receiving diagnosis and treatment for MDR-TB

	Saint Peter's *n*	ALERT *n*	Gonder *n*	Total *n*
Visits to obtain a diagnosis, median	3	3	3	3
Time spent per diagnostic visit, median h	13	5	156	22
Patients hospitalized, %	94	90	54	82
Duration of stay for patients who were hospitalized, median days	90	75	60	80
Visits per week: intensive phase	NA	7	5	NA
Hours per visit: intensive phase	NA	1.5	1.0	NA
Visits per month: continuation phase	1	4	4	2
Hours per visit: continuation phase	7	1.5	1.2	4.0

MDR-TB = multidrug-resistant tuberculosis; ALERT = All Africa Leprosy, Tuberculosis and Rehabilitation Training Centre; NA = not available.

Table 6 Financial impact of MDR-TB and coping mechanisms

Description	Saint Peter's %	ALERT %	Gonder %	Total %
Patients who lost their jobs	76	75	67	74
Patients who reported household income loss due to TB	45	85	79	66
Median monthly household income before TB, $US	54	134	74	81
Median monthly income at time of interview, $US	51	54	48	54
Patients with health insurance	0	3	0	0.5
Patients with health insurance who received reimbursements	0	0	0	0
Patients who received vouchers	53	67	83	63
Median number of vouchers per patient	1	11	6	4
Median total value of vouchers, $US	16	70	34	33
Patients who sold property	34	10	70	38
Patients who leased property	1	7	20	7
Patients who took out loans	37	37	52	41

MDR-TB = multidrug-resistant tuberculosis; ALERT = All Africa Leprosy, Tuberculosis and Rehabilitation Training Centre; $US = US dollar.

total costs were higher than in Ethiopia but represent fewer months of household income.

A systematic review of the financial burden for TB patients found three studies which detailed MDR-TB costs.[10] The total cost as a percentage of pre-diagnosis patient income was 223% in Ecuador and 76% in Cambodia, and in Brazil, the cost was 34% of reported income after TB diagnosis. Only in Ecuador was the cost burden higher than in Ethiopia. An additional study conducted in the Dominican Republic identified a total cost per MDR-TB patient of US$3557, which represented 132 months of pre-diagnosis household income for a medium-income group of patients.[25] No previous studies of MDR-TB costs were found for Ethiopia.

Several limitations should be taken into account. First, costs were probably underestimated due to the difficulty of recalling all the costs related to seeking diagnosis because: 1) treatment duration may have sometimes exceeded the normative period; and 2) some costs may have been incurred during previous treatments. Second, the number of just-diagnosed MDR-TB patients interviewed was only 27 out of the planned sample of 50 because this was a smaller cohort. Third, and perhaps most importantly, it was not feasible to interview people with TB who did not attend a facility during the period of the study, for example, patients lost to follow-up. The study population may therefore have under-represented poorer people.

Economic impact can be measured in different ways, and it is not yet clear which method constitutes best practice. We calculated total cost in terms of months of pre-diagnosis household income, and mid-treatment household income. We also calculated the same figures as percentages of annual household income to enable comparison with results from other studies, although caution should be used with comparing these figures as MDR-TB costs are generally incurred over 2 years. Using household income appears to be a better indicator of economic burden than patient income, as the burden generally falls on a family rather than an individual. Using mid-treatment income appears to provide a better indicator of the economic burden experienced by the household during the course of treatment, as the pre-diagnosis income had fallen after treatment had started.

While there is no universal definition of catastrophic costs, one proposed option is for any cost over 10% of annual household income to be considered catastrophic.[10] With an average cost of US$1378 over approximately 2 years, which is 142% of the average annual income of US$972 before TB and 213% of the average income of US$648 at the time of interview, it is clear that for most of the households with an MDR-TB patient, the costs were catastrophic.

CONCLUSIONS

Although MDR-TB diagnosis and treatment services are officially free for patients in Ethiopia, patients incur significant costs and often lose their jobs and suffer major reductions in income. If the patient is the breadwinner of the family, the combination of lost income and extra costs is generally catastrophic. A high financial burden may cause patients not to obtain a diagnosis, not to start treatment, or to stop treatment, leading to prolonged transmission of the disease to others and the development of increased drug resistance. The findings of the present study indicate the need for policies and practices that reduce the economic burden for MDR-TB patients and their families.

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RÉSUMÉ

CONTEXTE : L'Ethiopie a une prévalence élevée de tuberculose (TB) et elle est l'un des pays les plus touchés du monde par la TB multirésistante (TB-MDR).
OBJECTIF : Comprendre les coûts subis par les patients pour obtenir un diagnostic et un traitement de TB-MDR.
SCHÉMA : En mars 2013, des entretiens ont été réalisés avec 169 patients TB-MDR dans trois hôpitaux d'Ethiopie afin d'identifier les coûts subis par les patients et l'impact sur leur emploi et les revenus de la famille.
RÉSULTATS : Le patient TB-MDR moyen subit un coût total de US$1378, ce qui représente, à mi traitement, 25 mois de revenus d'un foyer de $US54 par mois. L'impact sur l'emploi des patients et sur le revenu d'ensemble du patient et de la famille a été généralement catastrophique : 74% de tous les répondants ont rapporté avoir perdu leur travail, 66% des patients ont perdu le revenu du foyer, et le revenu du foyer a été réduit de 38%. Pour contribuer à couvrir les coûts, 38% des patients ont dû vendre certains biens, tandis 7% ont loué leur propriété et 41% ont contracté des emprunts, chacune de ces stratégies pouvant compromettre encore plus leur situation financière future.
CONCLUSION : En dépit du fait que les services sont officiellement gratuits, la majorité des patients ont subi des coûts catastrophiques et une perte significative de leurs revenus à la suite du diagnostic et du traitement de la TB-MDR.

RESUMEN

MARCO DE REFERENCIA: Etiopía tiene una alta prevalencia de tuberculosis (TB) y es uno de los países con alta carga de morbilidad por tuberculosis multirresistente (TB-MDR) en el mundo.
OBJETIVO: Comprender los costos que deben sufragar los pacientes con el fin de obtener el diagnóstico y el tratamiento de la TB-MDR.
MÉTODO: En marzo del 2013, se entrevistaron 169 pacientes con TB-MDR en tres hospitales en Etiopía, con objeto de reconocer el costo que genera la enfermedad a los pacientes y su repercusión en el empleo y el ingreso familiar.
RESULTADOS: En promedio, el paciente con TB-MDR sufraga un costo total de US$1378, que corresponde a 25 meses de ingreso familiar a la mitad del tratamiento, el cual es de US$54. En general, la repercusión sobre el empleo del paciente y el ingreso global del paciente y su familia fue extremadamente grave: el 74% de todos los pacientes que respondieron refirió haber perdido el empleo, el 66% de los pacientes sufrió pérdida del ingreso familiar y el ingreso familiar se redujo un 38%. Con el propósito de cubrir los costos, el 38% de los pacientes vendió algún tipo de propiedad, el 7% arrendó propiedades y el 41% recurrió a un préstamo; en todos los casos la solución ponía aún más en peligro su futura situación económica.
CONCLUSIÓN: Pese a que oficialmente los servicios son gratuitos, la mayoría de los pacientes sufragó costos extremadamente altos y sufrió una pérdida considerable del ingreso familiar como consecuencia de la obtención del diagnóstico y el tratamiento de la TB-MDR.

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Comparison of the yield of tuberculosis among contacts of multidrug-resistant and drug-sensitive tuberculosis patients in Ethiopia using GeneXpert as a primary diagnostic test

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ABSTRACT

Objectives: This study compared the yield of tuberculosis (TB) among contacts of multidrug-resistant tuberculosis (MDR-TB) index cases with that in drug-sensitive TB (DS-TB) index cases in a program setting.
Methods: A comparative cross-sectional study was conducted among contacts of sputum smear-positive new DS-TB index cases and MDR-TB index cases. After contacts were screened, GeneXpert was used for the diagnosis of TB.
Results: The study included 111 MDR-TB and 119 DS-TB index cases. A total of 340 and 393 contacts of MDR-TB and DS-TB index cases, respectively, were traced, of whom 331 among MDR-TB contacts and 353 among DS-TB contacts were screened. There were 20 (6%) presumptive TB cases for MDR-TB contacts and 41 (11%) for DS-TB contacts. The prevalence of TB among MDR-TB contacts was 2.7% and among DS-TB contacts was 4.0%. The majority of the MDR-TB contacts diagnosed with TB had MDR-TB; the reverse was true for DS-TB.
Conclusions: The yield of TB among contacts of MDR-TB and DS-TB patients using GeneXpert was high as compared to the population-level prevalence. The likelihood of diagnosing rifampicin-resistant TB among contacts of MDR-TB index cases was higher in comparison with contacts of DS-TB index cases. The use of GeneXpert in DS-TB contact investigation has the added advantage of diagnosing rifampicin-resistant TB cases when compared to the use of the nationally recommended acid-fast bacillus (AFB) microscopy for DS-TB contact investigation.
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Introduction

In 2016, the population of Ethiopia was estimated to be 92.2 million, with more than half of the population living in the Amhara and Oromia regions: 34.6 million and 20.8 million people, respectively (Federal Democratic Republic of Ethiopia and CSA, 2013). According to the World Health Organization (WHO) Global Tuberculosis Report, Ethiopia was among the 30 high-burden countries for tuberculosis (TB). The incidence rate of all forms of TB was 192 per 100 000 population and mortality was 26 per 100 000 (excluding HIV-positive people). About 2.7% of new TB cases and 14% of previously treated TB cases are estimated to have drug-resistant TB. In 2015, the treatment success rate for multidrug-resistant (MDR)-TB cases in Ethiopia was reported to be 68% (WHO, 2016).

Studies have shown that screening contacts of TB index cases yields more cases than community-level screening for TB (Jerene et al., 2015; Otero et al., 2016). The aim of this study was to compare the yield of household contact screening of MDR-TB and drug-sensitive (DS)-TB index cases in a routine program setting, using GeneXpert as a primary diagnostic method.

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Methods

Study design

This study was conducted at TB DOT (directly observed treatment) centers and treatment initiating centers (TICs) for MDR-TB in Amhara and Oromia regions of Ethiopia. Patients with MDR-TB enrolled for treatment at 22 TIC hospitals during two quarters of 2015 were included.

TB focal persons at 11 health centers were trained on contact screening of DS-TB index cases, data collection, symptomatic screening, sputum sample collection, and referral. New acid-fast bacillus (AFB) sputum smear-positive patients diagnosed at these health centers during the study period, who had at least one household family member, were included in the study. A total of 119 consecutive smear-positive DS-TB index cases were registered in the study. All of these smear-positive index cases were either asked to bring their family members to the health center or were visited at home by the study team within 2 weeks of diagnosis. The team was composed of supervisors and community health workers, called health extension workers (HEWs).

In the same way as for DS-TB, contacts of 111 MDR-TB patients registered in the 22 TICs were screened for TB. The diagnosis of MDR-TB index cases was made either by culture and drug-susceptibility testing for isoniazid and rifampicin, or via diagnosis with GeneXpert MTB/rifampicin resistance, which is treated as MDR-TB as per the national guidelines (Federal Democratic Republic of Ethiopia and MOH, 2016). The management of MDR-TB in Ethiopia uses a mixed model of care, both ambulatory and inpatient. Patients who are critically ill or cannot start treatment on an ambulatory basis because of distance are admitted to TICs. Patients who live within walking distance of the TIC can start as ambulatory patients. After 1 or 2 months, if there are no side effects and if a patient can walk, s/he is discharged to follow-up with daily MDR-TB DOT at the health center nearest to the patient's residence, called a treatment follow-up center (TFC). Every month, patients visit the TICs for clinical and laboratory follow-up tests. By the end of June 2015, there were 22 TICs and 193 TFCs in the two regions.

MDR-TB focal persons in both the TICs and TFCs were trained on clinical management of MDR-TB and contact screening. Registration of contacts of MDR-TB index patients was introduced at the beginning of the project, which involved counseling every patient and registering his/her close contacts in the contact registration book. Patients then brought their contacts to a TIC or TFC, whichever was more convenient, for screening for TB symptoms.

Both DS-TB and MDR-TB contacts with a cough that had lasted 2 weeks or more and other constitutional symptoms were asked to provide sputum for an AFB or GeneXpert test. The national guidelines recommend GeneXpert as the primary test for presumptive cases among MDR-TB contacts and AFB for DS-TB contacts. For this study, GeneXpert was also used for contacts of DS-TB cases so that the yield of TB could be compared in the two groups of contacts. The resistance pattern here is presented only for GeneXpert, because the MDR-TB treatment decision is made on the basis of rifampicin resistance alone. In the baseline follow-up test, culture and drug-susceptibility testing for isoniazid and rifampicin was performed for the purposes of follow-up, but the data were not available for this publication.

Definitions

A TB index case was defined as a DS-TB or MDR-TB patient enrolled in treatment. A household contact was defined as a person who had shared the same enclosed living space for one or more nights a week, or for frequent or extended periods of time during the day, with the index patient during the 3 months before the current treatment episode began (Jerene et al., 2015; WHO, 2012; Fair et al., 2015).

TB diagnosis

Morning sputum was collected from all presumptive MDR-TB and DS-TB patients. Sputum samples were transported to the nearest GeneXpert testing facility using the standard infection control and cold chain system, and testing was performed using GeneXpert.

Data analysis

Data entry and analysis were performed using SPSS version 13 (SPSS Inc., Chicago, IL, USA). Frequencies, percentages, and the 95% confidence intervals of proportions were computed. The numbers needed to screen and to test were also computed. The number needed to screen is the number of contacts who have to be screened to detect a single case of active TB; the number needed to test is the number of contacts with presumptive TB who have to be investigated in the laboratory to detect a single case of active TB (Jerene et al., 2015).

Ethical considerations

Contact investigation of patients with MDR-TB and DS-TB is a routine health procedure for all patients (Federal Democratic Republic of Ethiopia and MOH, 2016); however ethical clearance was obtained from the Amhara and Oromia regional health bureaus to utilize the information for publication. Each study participant provided oral informed consent and permission for TB screening and diagnosis. Diagnosis of and treatment for all presumptive TB patients are provided free of charge (Fair et al., 2015). MDR-TB patients were also provided with an ambulance service to the TIC for the initiation of treatment, and they received reimbursement for the cost of transport for the monthly follow-up trip to a TIC.

Results

In total, 111 MDR-TB and 119 new DS-TB cases were diagnosed in the study health facilities. Three hundred and forty contacts were registered for MDR-TB index cases and 393 contacts were registered for DS-TB index cases. The contact-to-index case ratio was 3.1 for MDR-TB contacts and 3.3 for DS-TB contacts.

Of the 340 MDR-TB contacts registered, 331 (97.4%) were screened for TB, of whom 20 (6%; 95% confidence interval (CI) 3.8–9.1%) were found to be presumptive MDR-TB cases. Of the 20 presumptive MDR-TB cases, nine (45%; 95% CI 24.6–66.7%) were diagnosed with TB, and of those, eight (88.9%; 95% CI 56.1–99.4%) had rifampicin-resistant TB and one had rifampicin-sensitive TB (Figure 1).

Among the 393 DS-TB contacts, 353 (89.9%) were screened and 41 (11%; 95% CI 9.7–17.4%) were found to be presumptive TB cases. With the exception of two children under 5 years of age diagnosed with TB empirically, 39 presumptive TB cases had a sputum test done using GeneXpert. Fourteen (35.9%; 95% CI 20.9–49.5%) were diagnosed with TB, one of whom (7.1%) was found to have rifampicin-resistant TB (Figure 1).

Among the household contacts of MDR-TB patients screened, 2.7% of the contacts were diagnosed with TB, while the yield among contacts of the new DS-TB patients was 4.0% ($p > 0.05$). In the MDR-TB contacts, the yield of rifampicin-resistant TB was 2.4% (Table 1).

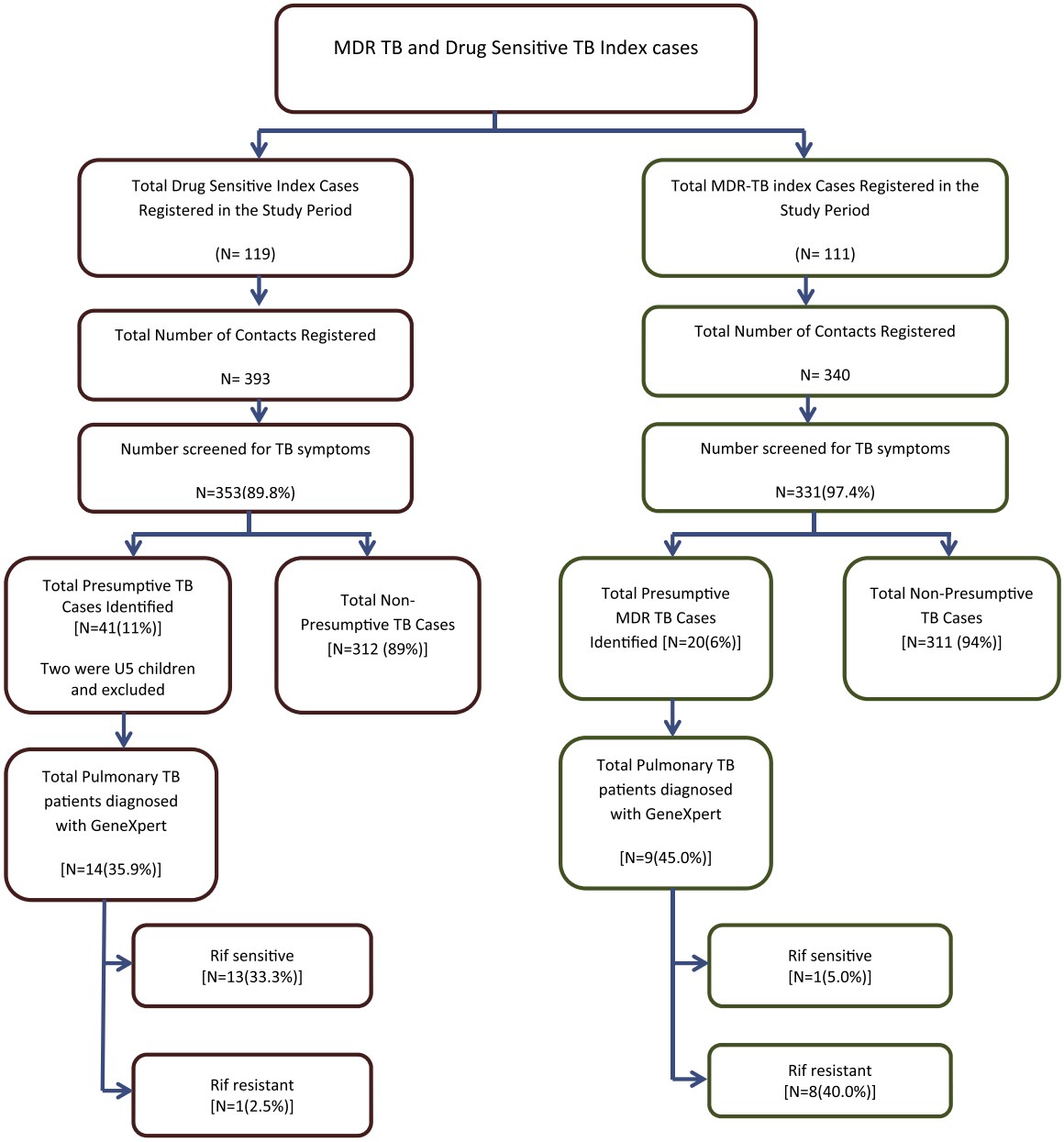

Figure 1. The procedures followed in screening and diagnosis among contacts of drug sensitive and MDR-TB index cases.

Table 1
Comparison of the prevalence of TB among contacts of DS-TB and MDR-TB index cases diagnosed with GeneXpert

Variables	DS-TB	MDR-TB/Rif	*p*-Value
Number of index cases registered	119	111	–
Number of contacts registered	393	340	–
Number of household/close contacts screened for TB	353	331	–
Number (percentage) of all TB cases diagnosed by GeneXpert	14 (4)	9 (2.7)	>0.05
Number (percentage) of rifampicin-resistant TB cases diagnosed	1 (0.3)	8 (2.4)	<0.05
Number (percentage) of rifampicin-sensitive TB cases diagnosed	13 (3.7)	1 (0.3)	<0.01

TB, tuberculosis; DS, drug-sensitive; MDR, multidrug-resistant; Rif, rifampicin.

A significant proportion of the TB cases diagnosed among contacts of DS-TB index patients were DS-TB cases (3.7% versus 0.3% for MDR-TB index contacts; $p < 0.01$). In contrast, the majority of the TB cases diagnosed among contacts of MDR-TB index cases had rifampicin-resistant TB (2.4% versus 0.3% among DS-TB index cases; $p < 0.05$) (Table 1).

The number needed to screen for DS-TB index contacts was 25, and for the MDR-TB contacts was 37. The number needed to test for

the contacts of DS-TB index cases was 2.8, while it was 2.2 for contacts of MDR-TB index cases.

Discussion

The yield of TB among contacts of DS-TB index patients was about 20 times the estimated national prevalence of TB (WHO, 2016; Federal Democratic Republic of Ethiopia et al., 2011). The TB yield among the contacts of MDR-TB index patients of 2.7% was higher than the national estimated MDR-TB prevalence of 2.3% among new TB cases (Federal Democratic Republic of Ethiopia and EPHI, 2012).

These results further confirm the need to scale up contact investigation among index patients as a high-yield strategy for identifying more missing TB cases in Ethiopia. The overall yield for DS-TB was higher than reported in previous studies from Ethiopia and elsewhere. Studies in Ethiopia and Peru showed that the yield of all forms of TB from contact investigation was 10 times higher than the national prevalence (Jerene et al., 2015; Otero et al., 2016). In another retrospective screening of contacts who had completed treatment of 6 months to 3 years, the yield was six times higher than the national prevalence (Gashu et al., 2016). In a meta-analysis of 19 studies, yields ranged from 1% to 14.1%, with a pooled estimate of 1.8% (Blok et al., 2015). Since most of the previous studies used AFB microscopy as the primary test for screening contacts, it is likely that the expanded use of GeneXpert for contact investigation will yield better results.

Another finding of this study is that 92.8% of the TB cases diagnosed among DS-TB contacts had rifampicin-sensitive TB, whereas 88.8% of the newly diagnosed TB cases among MDR-TB contacts had rifampicin-resistant TB. These findings are similar to those of two studies, which reported that 80% and 88.4% of the cases diagnosed among MDR-TB contacts had MDR-TB (Otero et al., 2016; Titiyos et al., 2015). Two other studies reported that more than 50% of secondary cases with DS-TB were concordant with the index case (Parr et al., 2014; Shah et al., 2014). This finding indicates that MDR-TB contacts, if they are diagnosed as having TB, are highly likely to have rifampicin-resistant TB. A recent DS-TB contact investigation study in Ethiopia using the nationally recommended AFB microscopy showed that 12.4% of the presumptive TB cases had smear-positive TB, who were all considered as DS-TB cases and treated with first-line drugs (Jerene et al., 2015). In the present study, the GeneXpert test was used as a diagnostic modality for DS-TB contacts, and rifampicin-resistant TB as well as rifampicin-sensitive TB cases were diagnosed. This shows the added advantage of the new diagnostics in any kind of TB contact screening.

The same high yield of TB among contacts of MDR-TB index cases has also been reported in many studies. In a study in Ethiopia, of the 155 family contacts of MDR-TB patients, 16 (10.3%) were found to have TB, all of whom had MDR-TB (Titiyos et al., 2015). In an Indian study of 302 MDR-TB contacts, 16 (5.2%) developed TB and two (0.66%) had MDR-TB (Singla et al., 2011). A study in Peru indicated that 5% of the household contacts of MDR-TB index cases developed TB, of whom 80% also had MDR-TB (Grandjean et al., 2011). In Brazil, among contacts of MDR-TB and DS-TB patients, about 4% developed TB, and five of the six diagnosed with TB among MDR-TB contacts had MDR-TB (Teixeira et al., 2001).

Some studies have shown that the yield of TB among contacts of MDR-TB and DS-TB patients is comparable (Teixeira et al., 2001; Cohn et al., 1954; Snider et al., 1985), while others have reported that TB disease among MDR-TB household contacts is half that among DS-TB contacts (Grandjean et al., 2015). Other studies have shown that the yield among MDR-TB household contacts is lower than the yield in contacts of DS-TB index cases (Teixeira et al., 2001; Cohn et al., 1954; Snider et al., 1985; Barnett et al., 1953). The possible reason for the low transmission rate of MDR-TB is mainly related to the evolutionary change of the Mycobacterium to become resistant to drugs (Van Soolingen et al., 1999; Nitta et al., 2002). However the yields of TB among close contacts of MDR-TB and DS-TB patients in this study were not statistically different, even though there was a significant difference in the type of TB diagnosed.

Earlier studies from animal models have shown that the higher the degree of resistance, the lower the virulence (Otero et al., 2016; Barnett et al., 1953; Mitchison, 1954; Windlock et al., 1955). In another study, *Mycobacterium tuberculosis* strains resistant to isoniazid resulted in fewer secondary cases, but rifampicin-resistant strains were more likely to result in a secondary case of TB (Burgos et al., 2003). A molecular epidemiological study in Mexico reported that drug-resistant strains of *M. tuberculosis* may have a diminished capacity to spread and cause disease (García-García et al., 2000).

As the data for this study came from routine program implementation, information about variables such as socio-demographic characteristics and duration of illness were lacking. The drug sensitivity pattern of the newly diagnosed DS-TB index cases was also not known, as AFB microscopy alone was used to reach the diagnosis. The results among DS-TB contacts indicate that the new cases were most likely drug-sensitive, assuming that the contacts acquired the infection from the DS-TB index cases, although this might not always be true. More molecular studies and strain typing are needed to show the link between the index cases and TB-positive contacts. The strength of this study is the use of the GeneXpert test in both DS-TB and MDR-TB contacts, which enabled plausible comparison between the two groups. The authors also recommend conducting culture and drug-susceptibility testing for all Xpert/MTB Rif resistance cases to determine the pattern of drug resistance.

Conclusions

This study further confirmed the usefulness of contact investigation as a high yield strategy for identifying missing people with TB. Moreover, the use of GeneXpert improved the yield of TB among contacts and had the added value of identifying patients with drug-resistant TB. The diagnosis of MDR-TB among contacts of MDR-TB index cases is higher than among DS-TB contacts. It is recommended that further larger scale studies be performed on the additional yield of TB if GeneXpert is used as a primary diagnostic tool for DS-TB versus the costs that would be incurred to avert the disease and achieve the End TB Strategy. Molecular epidemiological studies to understand the genetic diversity of *M. tuberculosis* and link the index cases with the secondary infection among close contacts would be valuable.

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Conflicts of interest

None.

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PLOS ONE

RESEARCH ARTICLE

Response to anti-tuberculosis treatment by people over age 60 in Kampala, Uganda

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Abstract

While old age is a known risk factor for developing active tuberculosis (TB), studies on TB in the population aged 60 years and older (considered elderly in this study) are few, especially in the developing world. Results of the TB prevalence survey in Uganda found high TB prevalence (570/100,000) in people over 65. We focused on treatment outcomes in the elderly to understand this epidemic better. We conducted a retrospective analysis of data from TB facility registers in Kampala City for the period 2014–2015. We analyzed the 2014–15 cohort with respect to age, sex, disease class, patients' human immunodeficiency virus (HIV) and directly observed therapy (DOT) status, type of facility, and treatment outcomes and compared findings in the elderly (≥60) and younger (<60) age groups. Of 15,429 records, 3.3% (514/15,429) were for elderly patients. The treatment success rate (TSR) among elderly TB patients (68.3%) was lower than that of the non-elderly (80.9%) and the overall TSR 80.5%, (12,417/15,429) in Kampala. Although the elderly were less likely to test positive for HIV than the young (AOR 0.39; 95% CI 0.33–0.48, p<0.001), they had a two-fold higher risk of unfavorable treatment outcomes (AOR 2.14; CI 1.84–2.72, p<0.001) and were more likely to die while on treatment (AOR 1.86; CI 1.27–2.73; p = 0.001). However, there was no statistically significantly difference between treatment outcomes among HIV-positive and HIV-negative elderly TB patients. Compared to the younger TB patients, elderly TB patients have markedly poorer treatment outcomes, although TB/HIV co-infection rates in this age group are lower.

Introduction

The global burden of the tuberculosis (TB) epidemic in 2016 was estimated at 10.4 million people, much higher than the previous year. Despite the availability of effective TB treatment, TB remains one of the 10 top causes of death globally [1]. Moreover, although TB is known as a disease of younger age groups in countries with high prevalence of the disease [2], its incidence

necessarily reflect the views of USAID, PEPFAR or the United States government.

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among the elderly has increased over the past three decades [3–5] and its diagnosis in this age group remains a challenge. Unlike in the young, TB in the elderly frequently presents atypically, making its diagnosis difficult; it is often unrecognized until diagnosis is made at autopsy [6], [7]. Currently, global efforts to control TB are focused mainly on key vulnerable populations, such as people living with HIV (PLHIV), people living with diabetes, women, and children, excluding the elderly [8–11]. Targets such as "zero TB deaths among children" [12], [13] are set accordingly. Globally, the elderly population is increasing [11], and old age presents health challenges due to immunosenescence [2], [14] The need to prioritize TB care in the elderly is, therefore, critical for reducing the TB burden and TB transmission to the general population, and addressing TB in the elderly will ultimately contribute to the End TB strategy [15].

Data collection tools for national programs collect TB data on age categories to meet WHO reporting requirements regarding new and relapse patients [16], but cohort data analyses on treatment outcomes involving age disaggregation are not a common practice. We aimed to establish, therefore, the contribution of the elderly (defined as those aged 60 years or more) to the TB burden [17] in Kampala and their treatment outcomes as compared to those of the younger population.

Study population and methods

Study design

We studied retrospective data collected routinely from TB registers in 62 Kampala health units during the period 2014–2015. This is routine data collected monthly by the Divisional TB/Leprosy Supervisors for program monitoring in the city. We hypothesized that there was no difference in treatment outcomes between elderly TB patients and non-elderly TB patients seeking care at health facilities in Kampala district.

Study area

The study was conducted in 62 Kampala City health facilities that report TB cases to the Kampala Capital City Authority (KCCA). Kampala's population is estimated to be 1,507,080 people [18] with 28,975 (1.9%) of the total population estimated to be people aged 60 years and above [19]. Data from January 1, 2014, to December 31, 2015, from Kampala health unit TB registers were collected and used for this study. For purposes of this study, patients aged 60 years and above were defined as elderly.

Data management and analysis

We extracted data from the unit TB electronic register [20] into Microsoft Excel (2013) and analyzed the data using Stata version 12.1 (StataCorp, Stata Statistical Software: Release 12, College Station, TX: StataCorp LP; 2011). The electronic register was a pilot electronic database aimed at keeping track of performance of TB patients within the district. It captured patient variables of interest to the TB program by health facility. The patient variables extracted were: age, sex, disease classification (PBC, PCD, EP), type of patient (New, Relapse, Previously lost to follow up, or Failure), HIV status (Positive or Negative), Co-trimoxazole preventive therapy (CPT) uptake status and Antiretroviral Therapy (ART) status for HIV patients, TB treatment model (Directly observed), TB treatment outcome (cured, completed, failed, died, lost to follow up, not evaluated). Cured and completed treatment outcomes were categorized as favorable while the rest were categorized as unfavorable treatment outcomes. The others were. Continuous data were summarized using medians with interquartile ranges, while

categorical data were computed as proportions. We presented the data in text, tables, and graphs. In calculating the incidence rate of TB among elderly people, we assumed that all patients registered in KCCA facilities were residents of Kampala District and were registered during the period considered for analysis. Results were presented at p-value = 0.05 level of significance and 95% confidence interval. All registered patients were included. Patients missing any of the variables used in the analysis were excluded from the analysis.

Ethical considerations

This study involved a review of existing routine TB program data for analysis hence, no ethics approval was sought. The review was planned and guided by KCCA's Urban Tuberculosis Control Unit, the Directorate of Public and Environmental Health. KCCA reviewed and approved the manuscript for publication in a peer-reviewed journal.

Results

Of 15,429 patients records accessed, 3.3% (514/15,429) were for TB patients aged 60 years and above, of whom 60.7% (312/514) were male. While the overall mean age was 67.5 years (± SD 7.5 years), among males and females it was 67.1 years (± SD 7.9 years) and 68.2 years (± SD 7.2 years), respectively. Results showed that 75.1% (386/514) of the patients were on DOT during the time of TB treatment (Table 1). All 514 elderly patients had HIV test results, of which 157 (30.5%) were positive. There were more females (35%) living with HIV than males (27.8%). Among PLHIV, uptake of cotrimoxazole preventive therapy (CPT) was 98.1% (154/157), while that of antiretroviral treatment (ART) was 93.0% (146/157).

The risk of HIV infection among the elderly was much lower than among their non-elderly counterparts (AOR 0.39; 95% CI 0.33–0.48), and they were less likely to be classified as pulmonary bacteriologically confirmed (PBC) TB patients (AOR 0.65; 95% CI 0.51–0.83). However, being a retreatment, pulmonary clinically diagnosed (PCD), or extra-pulmonary TB patient was not associated with elderly age. See Table 2.

The overall treatment success rate among the elderly was 68.3% (351/514), of whom only 36.8% (189/514) completed treatment and 31.5% (162/514) were cured. About 78.1% (274/351) of the elderly whose TB treatment was successful were documented to be on DOT and 29.3% (103/351) of them were HIV positive. Among the cured patients, 81.5% (132/162) had been on DOT and 28.4% (46/162) were HIV positive. Among those who completed treatment, 75.1% (142/189) had been on DOT and 30.2% (55/189) were HIV positive. Of the 163 (31.7%) patients with unfavorable outcomes, 19.8% (102/514) died, 1.6% (8/514) failed on treatment, 6.4% (33/514) were lost to follow-up, and 3.9% (20/514) were not evaluated (had been transferred out and hence no final treatment outcomes were assigned). In this category, 68.7% (112/163) were on DOT and 33.1% (54/163) were HIV positive. Compared to the non-elderly patients, unfavorable treatment outcomes were higher among the elderly (OR 1.96; CI 1.63–2.37; $p<0.001$). Of the deaths, 53.0% (35/66) occurred within the first two months of treatment, while a cumulative percentage of 75.7% (50/66) occurred within the first four months of treatment. See Table 3.

The elderly had a two-fold higher risk of death (AOR 1.86; CI 1.27–2.73; $p = 0.001$) than the non-elderly. Generally, the elderly were less likely to register a treatment success (OR 0.51; CI 0.42–0.62; $p<0.001$) and were less likely to be cured (OR 0.57; CI 0.48–0.69; $p<0.001$). See Table 4.

Results showed no statistically significantly difference between treatment outcomes among HIV-positive and HIV-negative elderly TB patients. See Table 5.

Table 1. Characteristics of elderly TB patients registered during January 2014 to December 2015.

Category	All TB Patients	Treatment Outcomes for All TB Patients			TB Patients ≥60	Treatment Outcomes for TB Patients ≥60			Proportion of Elderly TB Patients among all TB Patients
		Favorable	Unfavorable	P-value		Favorable	Unfavorable	P-value	
Total, *n*	15,429	12,417 (80.5%)	3,012 (19.5%)		514	351 (68.3%)	163 (31.7%)		3.3%
Sex									
Male	9,541 (61.8%)	7,669 (80.4%)	1,872 (19.6%)	0.708	312 (60.7%)	220 (70.5%)	92 (29.5%)	0.211	3.3%
Female	5,888 (38.2%)	4,748 (80.6%)	1,140 (19.4%)		202 (39.3%)	131 (64.9%)	71 (35.1%)		3.4%
Disease Category									
Extra-pulmonary	2,543 (16.5%)	1,863 (73.3%)	680 (26.7%)	<0.05	95 (18.5%)	52 (54.7%)	43 (45.3%)	0.004	3.7%
PBC	9,311 (60.3%)	7,802 (83.8%)	1,509 (16.2%)		267 (52.0%)	195 (73.0%)	72 (27.0)		2.8%
PCD	3,575 (23.2%)	2,752 (77.0%)	823 (23.0%)		152 (29.5%)	104 (68.4%)	48 (31.6%)		4.2%
DOT Status									
On DOT	11,120 (72.1%)	9,143 (82.2%)	1,977 (17.8%)	<0.001	386 (75.1%)	274 (71.0%)	112 (29.0%)	0.03	3.5%
Not on DOT	4,309 (27.9%)	3,274 (76.0%)	1,035 (24.0%)		128 (24.9%)	77 (60.2%)	51 (39.8%)		3.0%
HIV Results									
Positive	7,696 (49.9%)	5,806 (75.4%)	1,890 (24.6%)	<0.001	157 (30.5%)	103 (65.6%)	54 (34.4%)	0.445	2.0%
Negative	7,733 (50.1%)	6,611 (85.5%)	1,122 (14.5%)		357 (69.5%)	248 (69.5%)	109 (30.5%)		4.6%

PBC, pulmonary bacteriologically confirmed; PCD, pulmonary clinically diagnosed. 95% Confidence interval, Pearson's X^2.

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Extra-pulmonary TB patients had a higher risk of unfavorable treatment outcomes (AOR 1.78; CI 1.04–3.04; p = 0.03), compared to other patient categories such as PCD and PBC. However, the risk of unfavorable treatment outcomes was lower among elderly TB patients who were on DOT (AOR 0.61; CI 0.4–9.33; p = 0.02). See Table 6.

Table 2. Comparison of elderly and non-elderly TB patients.

Variable	<60 (%)	≥60 (%)	Crude OR (CI)	P-Value	AOR (CI)	P-Value
HIV positive	7,539 (50.5%)	157 (30.5%)	0.43 (0.36–0.52)	<0.001	0.39 (0.33–0.48)	<0.001
Retreatment	1,202 (8.1%)	38 (7.4%)	0.91 (0.65–1.27)	0.585	0.90 (0.71–1.39)	0.992
PBC	9,044 (60.6%)	267 (52.0%)	0.70 (0.59–0.84)	<0.001	0.65 (0.51–0.83)	0.001
PCD	3,423 (22.9%)	152 (29.6%)	1.41 (1.16–1.71)	<0.001	1.13 (0.87–1.47)	0.352
Extra-pulmonary	2,448 (16.4%)	95 (18.5%)	1.15 (0.92–1.45)	0.214	0.88 (0.67–1.15)	0.352
DOT	10,734(71.97%)	386 (75.1%)	1.17 (0.96–1.44)	0.120	1.19 (0.97–1.47)	0.09
TB unfavorable outcome[a]	2,849 (19.1%)	163 (31.7%)	1.96 (1.62–2.37)	<0.001	2.24 (1.84–2.72)	<0.001

[a]Unfavorable outcome = died, failed treatment, lost to follow-up, or transferred out.

95% Confidence interval. Adjusted for Sex, type of patient, CPT uptake, ART uptake.

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Table 3. Time of death during treatment.

			Month of Death during Treatment								
Age	**Total Died**	**Documented Date of Death**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
<60	1,539	969	366	196	146	93	69	45	34	14	6
≥60	102	66	25	10	7	8	7	6	3	0	0
Total	**1,641**	**1,035**	**391**	**206**	**153**	**101**	**76**	**51**	**37**	**14**	**6**

606 patient records did not have a documented date of death.

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Among the elderly, those who were HIV positive had a higher risk of death (AOR 1.62; 95% CI 1.01–2.56), however, risk of death was lower among pulmonary bacteriologically confirmed TB patients (AOR 0.42; 95% CI 0.26–0.66). See Table 7.

Discussion

Our study explored characteristics and treatment outcomes among elderly TB patients in Kampala, Uganda. TB patients aged 60 years and above accounted for nearly 3.3% of the total TB patients notified, which is comparable to the 3.7% contribution of this age group to the total population [18]. We show that the elderly had a two-fold higher risk of unfavorable treatment outcomes than younger TB patients, a finding similar to what was reported in Tamilnadu, South India [21].

Although TB is documented as a significant problem among the elderly [2], information about TB among the elderly in sub-Saharan Africa remains scanty. The data we collected for this study covered all KCCA health facilities reporting to the National TB/Leprosy Program, making our results generalizable to similar urban settings in Uganda and beyond [18]. Our study covered two years, thereby controlling for potential seasonal variations in health care-seeking patterns that might bias the findings. This study is among the few that attempt to explore TB indicators in the elderly population in a resource limited setting. It is interesting to note that, despite the shorter life expectancy of males compared to females [18], the male-to-female ratio among elderly TB patients remains higher, at 3:2, possibly indicating that more men are affected with TB than females. This finding is further confirmed by the Uganda population-based TB prevalence survey, in which the ratio of TB among males compared to females was 4:1 [5], also similar to what is observed elsewhere [21], with elderly patients showing a higher proportion of men compared to non-elderly patients[22].

Other important findings are that the treatment success rate (TSR) among elderly TB patients (68.3%) was lower than that of the non-elderly (80.9%) and significantly lower than the overall TSR (80.5%) in Kampala. In this case, TB in the elderly represents 31.7% of

Table 4. Comparison of treatment outcomes between elderly and non-elderly TB patients.

Variable	<60 n (%)	≥60 n (%)	Crude OR (CI)	P-Value	AOR (CI)	P-Value
Treatment success	12,066 (80.9%)	351 (68.3%)	0.51 (0.42–0.62)	<0.001	0.66 (0.48–0.92)	0.015
Cure (PBC only)	6,606 (44.3%)	162 (31.5%)	0.57 (0.48–0.69)	<0.001	0.74 (0.50–1.08)	0.114
Died	1,539 (10.3%)	102 (19.8%)	2.15 (1.72–2.69)	<0.001	1.86 (1.27–2.73)	0.001
Lost to follow-up	818 (5.5%)	33 (6.4%)	1.18 (0.83–1.69)	0.361	0.74 (0.33–1.64)	0.458
Not evaluated	328 (2.2%)	20 (3.9%)	1.80 (1.14–2.85)	0.012	1.36 (0.78–2.36)	0.282
Treatment failure	164 (1.1%)	8 (1.6%)	1.42 (0.69–2.91)	0.335	1.29 (0.56–2.59)	0.640

96% Confidence interval. Adjusted for Sex, disease classification, type of patient, HIV status, CPT uptake, ART status, and treatment model.

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Table 5. Treatment outcomes among elderly Hiv-positive TB patients.

Variable	HIV Positive	HIV Negative	Crude OR (CI)	P-Value	AOR (CI)	P-Value
Treatment success	103 (65.6%)	248 (69.5%)	0.84 (0.56–1.25)	0.386	0.72 (0.17–3.11)	0.660
Cure (PBC only)	46 (29.3&)	116 (32.5%)	0.86 (0.57–1.29)	0.473	0.92 (0.58–1.46)	0.718
Died	40 (25.5%)	62 (17.4%)	1.63 (1.03–2.55)	0.03	1.93 (0.65–5.74)	0.234
Lost to follow-up	6 (3.8%)	27 (7.6%)	0.48 (0.19–1.20)	0.12	0.37 (0.06–1.99)	0.247
Not evaluated	5 (3.2%)	15 (4.2%)	0.75 (0.27–2.10	0.58	0.55 (0.09–3.21)	0.511
Treatment failure	3 (1.91%)	5 (1.4%)	1.37 (0.32–5.81)	0.67	1.8 (0.31–10.3)	0.511

96% Confidence interval. Adjusted for Sex, disease classification, type of patient, HIV status, CPT uptake, ART status, and treatment model.

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unfavorable treatment outcomes. This disparity poses a special challenge to the National TB/Leprosy Program as it strives to achieve the End TB Strategy target of 75% reduction in TB deaths by 2025 [11] compared to the 2015 baseline.

Although the proportion of the population of the elderly compared with the general population in Uganda is on the decline [18], worldwide the population of the elderly is on the increase [23]. Given age-associated low immunity, the increasing elderly population, especially in high-TB-burden settings, is likely to increase the incidence and prevalence of TB [24], [25]. The persistently small population of the elderly might mean that any changes in the TB epidemic in Uganda will not be attributed to this population. Nevertheless, treatment failures and loss to follow-up among these patients have the potential to propagate the epidemic—just as in younger patients—and should be closely monitored [24].

The high death rate of 19.4% among the elderly as compared to 10.3% among non-elderly populations of TB patients is also a concern and may make the achievement of the WHO End TB Strategy aims and targets difficult in Kampala. That death occurred mainly in the first two months of initiating treatment may reflect delays in seeking health care and late diagnosis. At the moment, mortality audit data to explain this observed high mortality among the elderly are lacking. This observed high mortality might imply that those with TB stayed untreated in the community for a long time [26], thereby promoting transmission of TB to their close contacts, who may develop active TB in the future. Although death will interrupt the transmission chain, the high basic reproductive ratio of *Mycobacterium tuberculosis* will produce many latent infections, which might progress into active TB disease [27]. The high death rate can also be explained by other studies that have reported advanced age as the leading determinant of death among elderly TB patients while on treatment [28]. These deaths can be averted through active case-finding strategies, as demonstrated by recent studies in Kampala [29].

Since most of the deaths (and lower odds of having a favorable outcome) occurred among those not on DOT, this points to challenges in the quality of care provided to the diagnosed TB

Table 6. Risk of unfavorable outcomes of TB Treatment among the elderly by patient category.

Variable	Unfavorable Outcome	Favorable Outcome	OR (95% CI)	P-Value	AOR (95% CI)	P-Value
EP	43 (45.3%)	52 (54.7%)	2.06 (1.30–3.27)	0.002	1.78 (1.04–3.04)	0.034
PBC	72 (27.0%)	195 (73.0%)	0.63 (0.43–0.92)	0.016	0.79 (0.51–1.23)	0.300
PCD	48 (31.6%)	104 (68.4%)	0.99 (0.66–1.49)	0.967	1.26 (0.81–1.95)	0.300
On DOT	112 (29.0%)	274 (71%)	0.62 (0.41–0.94)	0.023	0.61 (0.4–9.33)	0.023
HIV Positive	54 (34.4%)	103 (65.6%)	1.19 (0.80–1.78)	0.387	1.11 (0.74–1.67)	0.616

95% Confidence interval. Adjusted for Sex, type of patient, CPT Uptake and ART status.

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Table 7. Risk factors associated with death among the elderly TB population.

Variable	Died	OR (95% CI)	P-Value	AOR (95% CI)	P-Value
On DOT	72 (18.7%)	0.75 (0.46–1.21)	0.241	0.76 (0.46–1.25)	0.289
PBC	36 (13.5%)	0.42 (0.27–0.67)	<0.001	0.42 (0.26–0.66)	<0.001
HIV positive	40 (25.5%)	1.62 (1.03–2.55)	0.035	1.61 (1.01–2.56)	0.046
Male	60 (19.2%)	0.91 (0.58–1.41)	0.665	0.90 (0.57–1.41)	0.659

95% Confidence interval. Adjusted for Disease classification, Type of patient, CPT Uptake and ART status.

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patients in this age group. Better approaches to diagnosis and treatment, including more emphasis on DOT among the elderly, are needed. If treatment is interrupted due to self-administered treatment, the likelihood of developing multidrug resistance remains high for both patients and their regular contacts [5]. Our findings, however, show a lower loss- to-follow-up rate (6.4%) than findings from other studies (e.g., 18.9% in India) [30], [31].

Our study also showed that elderly pulmonary TB patients are less likely to be bacteriologically confirmed. Failure and delay to confirm TB in such patients operationally contributes to continued TB transmission as well as increased morbidity and mortality. The TB/HIV co-infection rate in the elderly was considerably lower (30.5%) than in the younger population (50.5%). Consequently, we can speculate that the HIV prevalence is higher among the economically productive age group, a position that is confirmed by findings of the Uganda AIDS Indicator Survey [32]. Our findings showed no statistically significantly difference in treatment outcomes between HIV-positive and HIV-negative elderly TB patients. However, other studies have attributed high mortality among HIV-co-infected TB patients to late health care seeking and some life years lost due to HIV, especially for people who do not have access to ART [33], [34].

The study had some limitations. Since we used a record review of TB registers, it was not possible to validate data about any co-morbidities other than HIV, such as diabetes, which may be a risk factor for TB in lower-income countries [35]. Hence we could not assess the extent of the problem of co-morbidities as it relates to mortality. Furthermore, the population of the elderly was only 3.3% compared to 96.7% of the non-elderly population, which might have skewed our findings. We assumed that all the TB patients were from Kampala District, which might not be the case. Our study considered the United Nations working definition of the elderly as those aged 60 years and above[36]. This guided our age categorization for elderly versus non-elderly comparison and may have resulted into a study bias because further categorizations can be made within each of the groups. Finally, this study did not consider TB in the elderly in a rural setting, which might affect generalizability to such populations.

Implications of findings

Poor TB treatment outcomes in older adults have often been attributed to delayed diagnosis, increased rates of drug-related adverse events, co-morbidities, and overarching poverty[13], [37]. A high death rate was evidenced among the elderly in our study; however, we did not establish the causes of this high death rate from the available data. The health systems needs to confront the challenges of an ageing population and the integrated services required to address their health needs. Our study also makes a case for the need to implement a systematic regular mortality audit among the elderly and all other TB patients in Uganda using recommended TB mortality audit tools [38], the findings of which may help to increase TB case detection and case holding through early diagnosis and improved TB case management. Older adults often act as society's caregivers, community leaders, and mentors, and play an important role in

educating the younger generation [13]. Increasing focus on them as a key population in TB prevention, active case finding, and treatment interventions will not only have positive cascading effects through families, communities, and societies but also demonstrate inclusiveness in health service provision.

Conclusions

Elderly TB patients have poorer treatment outcomes than the non-elderly despite having lower TB/HIV co-infection rates and high DOT coverage. They are more likely to present with extra-pulmonary TB than the non-elderly populations. Since there was a high death rate among the elderly TB patient, there is need to understand the major causes contributing to this high rate of death, hence the need for further studies to explore the causes of mortality among this group. Such further studies should comprehensively explore the need for existing TB programs to capture additional heath information on elderly TB patients to guide TB programming; specifically, early case finding and case holding to achieve better treatment outcomes. [39]

Supporting information

S1 File. Anonymized data set.
(XLSX)

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Use of indicators of standards of care to improve tuberculosis program management in Ethiopia

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ABSTRACT

Background: Systematic monitoring of health programs and on-site mentoring of health workers are essential for the success of health care. This operations research was designed to measure the effectiveness of a new mentorship and supervisory tool for supervisors.

Methods: In 2011 the Help Ethiopia Address the Low TB Performance (HEAL TB) Project used WHO or national TB indicators as standards of care (SOC) for baseline assessment, progress monitoring, gap identification, assessment of health workers' capacity-building needs, and data quality assurance. Cut-off points were selected for poor, average, and best performers for each indicator. In this analysis we present results from 10 zones (of 28) in which 1,165 health facilities were supported from 2011 through 2015. Other zones were excluded from the analysis because they entered the project later. The data were collected by trained mentors/supervisors and entered into Microsoft Excel. We used rates and ratios to show the impact of the intervention.

Results: The improvement in the median composite score of 13 selected major indicators (out of 22) over four years was significant ($p = 0.000$). The proportion of health facilities with 100% data accuracy for all forms of TB was 55.1% at baseline and reached 96.5%. In terms of program performance, the TB cure rate improved from 71% to 91.1%, while the treatment success rate increased from 88% to 95.3%. In the laboratory area, where there was previously no external quality assurance (EQA) for sputum microscopy, 1,165 health facilities now have quarterly EQA, and 96.1% of the facilities achieved a ≥ 95% concordance rate in blinded rechecking.

Conclusion: The SOC approach for supervision was effective for measuring progress, enhancing quality of services, identifying capacity needs, and serving as a mentorship and an operational research tool.

1. Background

Tuberculosis (TB) remains a major cause of morbidity and mortality in many countries and a significant public health problem worldwide. Ethiopia is one of the 30 high-TB, TB/HIV, and MDR TB-burden countries globally and TB remains one of the leading causes of death. According to the 2017 World Health Organization (WHO) report, the incidence of all forms of TB in Ethiopia was 177 per 100,000 [1]. Major progress in global TB control followed the widespread implementation of the DOTS and later Stop TB strategies in countries with a high burden of TB. Establishing a reliable monitoring and evaluation system in TB programs, with regular communication between the central and peripheral levels of the health system, is very important [2–4].

Since good-quality data are needed to monitor the performance of TB programs and identify gaps, systematic TB program supervision should be carried out to verify the quality of information and address performance problems. Data at both the health facility and district levels can be used to monitor performance and identify gaps [3,5].

In analyzing these data, there is increasing recognition of the importance of using standard approaches to diagnose and treat TB patients, as well as to screen for and prevent TB, at all levels. A standard set of WHO-endorsed indicators captures the processes and outcomes of

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Table 1
Sample reference sheet for indicators of standards of care.

TB Standards of Care (SOC)	Code	Quarterly Measure	Numerator/Denominator	Source	Results of Quarterly Measure		
All patients should be monitored for response to therapy, best judged in patients with pulmonary TB by follow-up sputum microscopy (two specimens) at least at the time of completion of the initial phase of treatment (two months), at five months, and at the end of treatment	C8	Cure rate (new smear-positive cases)	No. of smear-positive TB cases cured during the reporting period / Total no. of smear-positive patients in registered cohort (evaluated during the last quarter)	TB register	[illegible]	80-85	[illegible]
	C9	Cure rate (re-treatment)	No. of retreatment TB patients cured in the reporting period / No. of re-treatment TB patients registered in a cohort (evaluated during the last quarter)	TB register	[illegible]	80-85	[illegible]
	C10	Sputum conversation rate at the end of intensive phase of treatment (of patients registered in the previous quarter)	No. of new smear-positive TB cases registered in the previous quarter that were smear-negative at the end of the intensive phase of Rx / Total no. of new smear-positive TB cases registered for Rx in the previous quarter	TB register	[illegible]	85-90	[illegible]
	C11	Proportion of smear-positive TB cases that were not examined at the	No. of new smear-positive TB cases registered in the previous quarter that were	TB register	[illegible]	1-4	0

TB treatment, but these are often analyzed primarily at central levels rather than at the district or facility level. Even when workers at the health facility or district level do analyze their TB data, there is typically no standard description of what indicator values would be considered a "good" or "poor" outcome in that particular setting, nor any method for prioritizing which indicator values to target for improvement in the future. The standards of care (SOC) tool was developed in Ethiopia to address these needs and is described in this paper.

Various studies have linked supervision to standards of health care, performance improvement, and subsequent quality of care [4]. But the efficacy of supervision in changing providers' practices is unclear: one study confirmed better provider performance with supervision than without supervision, while another study showed no significant difference [6,7]. Other studies reported that community health workers allocated to a supportive supervision group performed significantly better than those in the group with standard supervision [8,9]. Supervisors using an indicator-based checklist realized greater improvement in the performance of midwives as compared to standard supervision [10]. A systematic review showed that there is insufficient high-quality evidence to advocate for any particular approach of implementing supervision [7].

This intervention was designed to develop a tool for supervisors that serve as an objective tool of mentorship/supervision and at the same time helps to identify program gaps. The tool is also used to prioritize health facilities for resource allocation based on their objective performance.

2. Methods

2.1. Definition of terms

Although there is no agreed-on definition of standard of care in medical practice, for this purpose we defined SOC as the quality of care that a patient should get based on WHO or national performance indicators.

2.2. The setting

The Ethiopian health care system. The Federal Ministry of Health has overall responsibility for the health of Ethiopians, a responsibility that it carries out by designing national policies, strategies, and regulations. The country is organized into nine federal states and two city administrations, each with a Regional Health Bureau, which is responsible for planning, implementing, monitoring, and evaluating health programs. Under the region, there are zones with Zonal Health Departments. The zones are divided into *woredas* (equivalent to districts), with Woreda Health Offices. The lowest-level administrative structure is a *kebele* (community), with a population of 3,000–5,000. Each kebele has two Health Extension Workers. Ethiopia has a three-tiered health care system: at the lowest level, primary hospitals, health centers, and health posts provide primary health care; general hospitals offer secondary care; and specialized hospitals provide tertiary care [11].

2.3. Development of the indicators of standards of care

The USAID-funded HEAL TB project supported the implementation of a comprehensive TB program in the Amhara and Oromia regions of Ethiopia, with a population of 55 million, between 2011 and 2016 and in collaboration with the Amhara and Oromia Regional Health Bureaus, developed indicators of standards of care (SOC). The indicators are WHO TB indicators, indicators from the national health management information system, and indicators customized to measure specific needs. The SOC tool was designed for serving as a baseline assessment, monitoring the progress of activities, identifying gaps, mentoring staff based on the gaps, and planning to address capacity-building needs.

The SOC tool is also used to verify the quality of data, provide data for operational research, and modify implementation approaches based on results.

The indicators are categorized by case notification, including community TB; treatment outcomes; laboratory quality; drug management; TB infection control; and TB/HIV. The indicators include definitions, formulas to calculate achievements, data sources, and customized cut-off points classified as poor, moderate, or very good performance. These three levels of performance are labeled red, yellow, and green respectively (see the sample SOC indicators in Table 1). At the beginning, 28 indicators were applied, but after one year of implementation they were reduced to 22 to focus on the core indicators and decrease the load for the mentor.

2.4. Implementation of the standards of care

The SOC was implemented in 28 zones and 471 woredas and 2,180 health facilities covering 55 million population in a phased manner. The project invested in managerial, monitoring, and evaluation capacity of the zonal- and woreda-level TB managers through tailored leadership and management trainings. Quarterly the woreda TB mangers mentor every health facility. To systematize supervision and make it objective the SOC tool was developed and managers trained to use the SOC indicators and interpret the findings for each indicator. Every quarter, the woreda TB focal person applies the SOC tool in the supervision of every health facility in their catchment area. With a health facility TB focal person, the woreda TB focal person measures progress, identifies gaps, designs an improvement plan, and at the same time checks the quality of reported data. This team discusses the improvement plan with the health facility manager and documents the actions taken or to be taken in the mentorship logbook kept in the health facility (Table 2). In the next quarter, the woreda TB focal person repeats the same approach and measures progress against the previous quarterly plan.

Mechanisms to check the woreda TB focal person's performance. After completing the quarterly supervision and mentorship of the health facility's staff, the woreda TB focal person presents information about progress, including the gaps identified and improvement plans developed, to the Zonal Health Department TB manager. The woreda TB focal person also presents the actions to be taken by the Zonal Health Department, Regional Health Bureau, or partners. Then the Zonal Health Department TB manager, together with the HEAL TB zonal teams based in the zonal health department office, plans supervision of health facilities with poor performance. During the supervision visit, the respective woreda TB focal persons are also represented and use the SOC to conduct rechecking jointly. The repeat supervision has two purposes: (1) checking the capacity of the woreda TB focal person and mentoring the TB focal person and (2) supporting the poor-performing heath facility to improve its performance. The zonal team also checks a few very good performers to substantiate the findings. If all the findings reported by the woreda TB focal person are correct, then supervision by the Zonal Health Department TB manager to that specific woreda is reduced (Fig. 1).

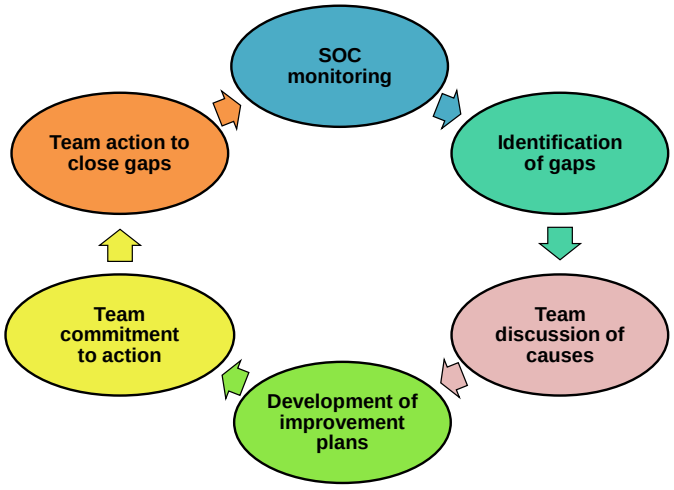

Fig. 1. The cycle of standards of care at the heath facility, woreda, zonal, and regional levels.

Semi-annually, all zonal TB focal persons, under the leadership of the Regional Health Bureaus, present the progress of their respective zonal TB implementation progress. This experience-sharing forum also serves as a mechanism to redesign implementation approaches. The

Table 2
Indicators of standards of care applied by woreda TB focal persons in health facilities.

Unit	Actions*
Outpatient departments (OPDs) The woreda TB focal person, together with the unit focal person, checks the OPD register and calculates the percentage of patients screened for TB and the linkage for diagnostic investigation.	If the result is red or yellow, they identify the cause of low performance, discuss it with the unit head, and design an improvement action plan. The agreed-on action points are documented in the logbook, and both sign beside the next steps.
Tuberculosis unit Together with the unit focal person, calculate the total case notifications for the health facility and compare it with the target for the catchment population. Calculate the interim treatment and final treatment outcomes.	In the same way as above, identify the cause of the gap and mentor staff based on the gap. Plan further training or supply management actions as needed. Design improvement plans with the unit head.
Laboratory Check if internal quality control for acid-fast bacilli reagents is done and documented per national guidelines. Verify that all sputum smear slides are properly labeled and documented in the laboratory register as well as properly stored. If all are perfect, randomize the slides per the national sample size guidelines and drop the slides off at the external quality assurance (EQA) center for reading.	The same measures as above are taken. In the microscopy aspect, if EQA finds discordant slides, an expert from the regional laboratory or higher-level expert travels to the health facility and identifies the cause of the discordance and mentors laboratory staff on-site or plans more training of the laboratory staff. If there is a microscope issue, the expert recommends a change.
TB infection control Check if triage of patients is taking place and if staff observe proper practices. Check if the rooms in the health facilities are appropriate for TB infection control and advise the health workers about how to improve infection control practices.	The woreda TB focal person assists the health facility to establish a triage system and provides advice about ventilation. The TB focal person mentors staff on proper disinfection and disposal of infectious materials.
TB drug management Check if the stock balance is updated regularly and measure the stock available.	If there was a stock-out in the quarter, identify the reason and agree on actions. The actions could be better stock monitoring and early request for refill.
Health management information systems unit The woreda TB focal person, together with the unit staff, recounts indicators and reconciles those data with those reported in the previous quarter.	If there is a discrepancy, identify the reason and design an improvement plan together.

*The woreda TB focal person then discusses all the findings in all departments with the facility manager, and they revisit the improvement plan.

project assisted in organizing meetings and mentoring the Regional Health Bureau and zonal TB managers in monitoring and use of data for program improvement and covered the logistics and workshop costs.

Data collection. The zonal and woreda supervisors use a checklist that covers both qualitative parameters and SOC indicators. The supervisor records the SOC while visiting the different units in the health facilities. Once the SOC indicators are computed, they are compared with the cut-off points for the respective indicators.

Data source and analysis. The woreda TB focal persons collect data on SOC indicators from health facilities manually and report the data to the Zonal Health Department and HEAL TB zonal team. The data are entered into Excel software by Zonal Health Offices. IBM SPSS software for Windows (Version 20.0. Armonk, NY: IBM Corp.) was used in the analysis for this paper. We assigned the values 2, 1, and 0, respectively, to the indicators in the green, yellow, and red categories for calculating the composite score of each indicator improvements across time. The data presented are for 10 zones and 1,165 health facilities that were supported for four years, but the rest of the zones, which entered the project later, were not included in this analysis.

3. Results

3.1. Capacity building of Woreda Health Offices and Zonal Health Departments

The results presented below offer evidence of this improved capacity. Although the results presented in this paper relate to measurement of SOC, other capacity building efforts, such as training of health workers, drug supply management, and provision of equipment and commodities, were also part of the intervention.

3.2. Progress in performance based on standards of care

We compared the proportion of health facilities in the green category (better performers) for each indicator at baseline versus four years after intervention. We noticed significant improvement in the proportion of health facilities in the green category for all indicators. Fig. 2 shows improvements for selected major indicators.

The composite scores for SOC were computed by adding these values of each indicator in each quarter. Fig. 3 shows the trend in the improvement of the composite SOC indicators over four years for 13 major SOC indicators in the 10 zones. There was a significant quality improvement in the median composite score over the years ($p = .000$). Fig. 4 illustrates the trend in data quality for three selected indicators in health facilities in 10 zones of Amhara and Oromia from 2011 to 2015. The accuracy of reports (reported versus recounted) in the health facilities improved significantly over the four years ($p < 0.05$).

Sputum microscopy EQA was not a practice at baseline, but by the end of the fourth year all 1,165 health facilities were implementing EQA, and 96.1% of the health facilities were achieving a ≥ 95% concordance rate in blinded rechecking [12]. As shown in Fig. 5, the TB cure rate and treatment success rate also improved in all health facilities in the 298 zones.

4. Discussion

Regular quarterly mentorship significantly improved the performance of the TB program in health facilities. Building the capacity of government TB focal persons in mentorship contributed to strengthening their sense of ownership and ensured the sustainability of the TB program support. Evidence-based mentorship, feedback, and decision-making were the hallmarks of the SOC approach, as recognized by health facility managers and health workers. This approach allowed health facilities to track the progress of TB program indicators on a quarterly basis. The advantage of objective indicator-based mentorship over subjective checklist-based supervision in improving performance has also been demonstrated in a trial setting [12]. In a case study report from Malawi, quality supervision in an HIV program significantly improved the performance of health programs and data quality [13]. Linking good performance with an award system is reported to be an effective motivational tool [14], which should be used in the future in Ethiopia's TB program.

In this project, a mentorship visit was conducted every three months, soon after the submission of the quarterly reports by health facilities. This timing helped the health care system to monitor the quarterly performance of the health facilities, identify gaps, and discuss improvement plans for the subsequent implementation period. Furthermore, the supervising team counterchecks the accuracy of the quarterly report against the health facility TB register, laboratory register, and administrative reports, which are essential inputs to improve the national health information system.

The woreda TB focal persons were effectively discharging the mentorship and capacity-building responsibility for health facilities in their catchment areas. On average, the TB focal persons mentored more

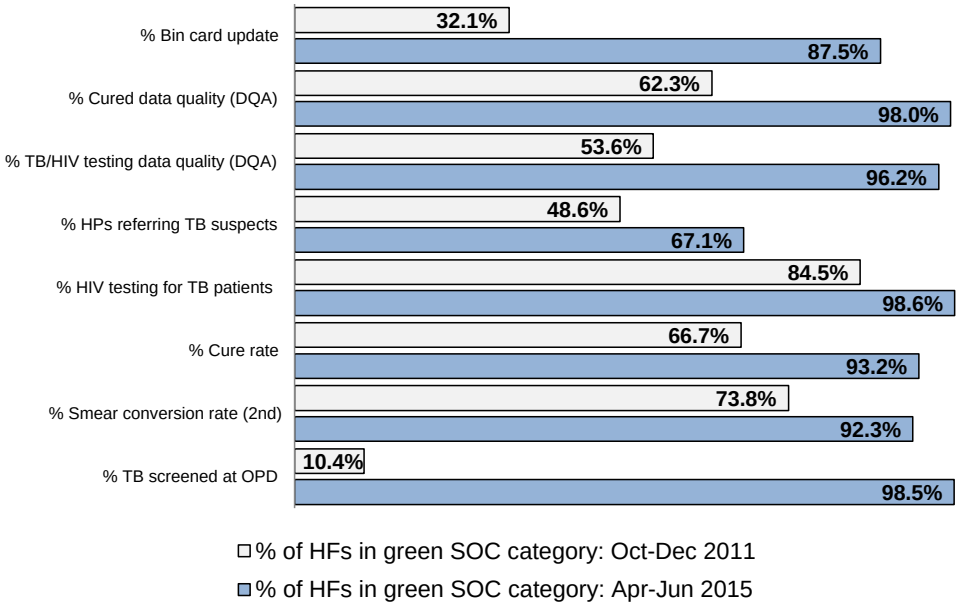

Fig. 2. Progress in the performance of selected indicators of standards of care, 2011–2015.

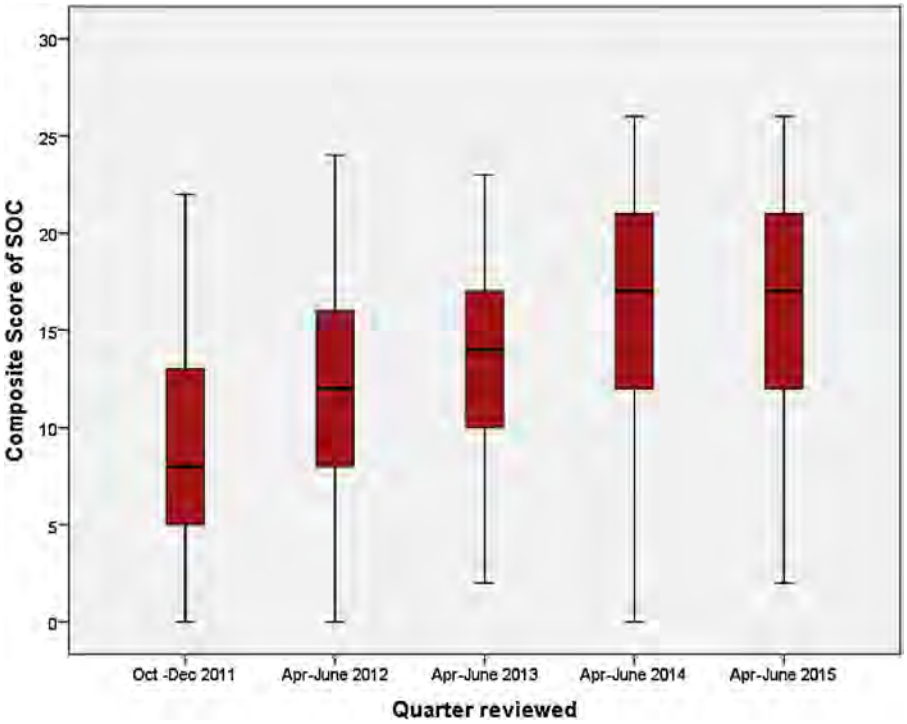

Fig. 3. Improvement in the composite score of 13 standard of care indicators in 10 zones, 2011–2015.

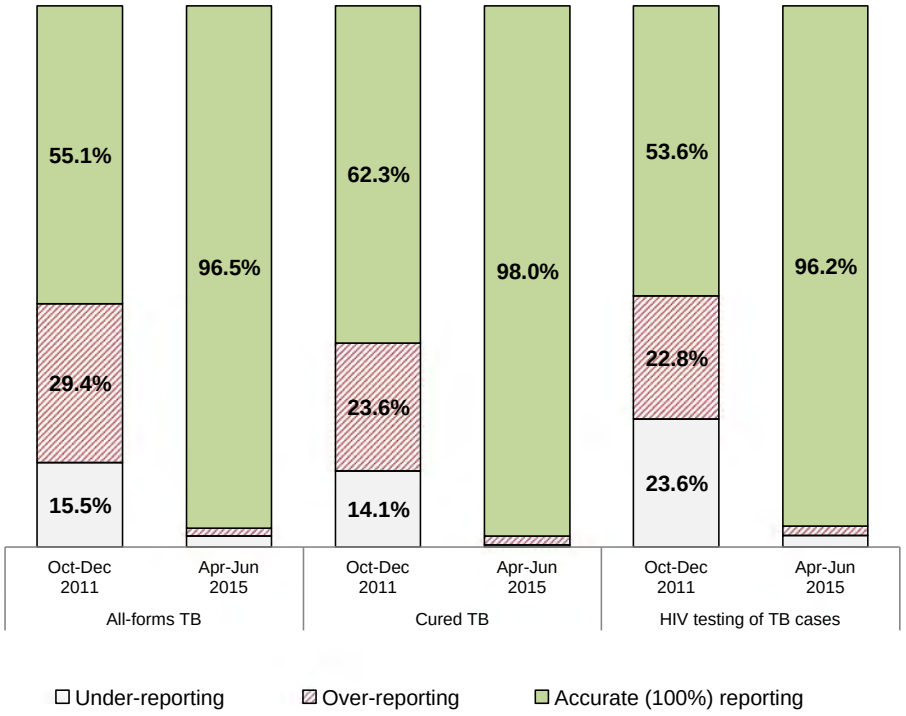

Fig. 4. Percentage improvement in the accuracy of reporting of selected TB program indicators in Ethiopia, 2011–2015.

than 90% of the health facilities each quarter. Inaccessibility of health facilities and competing priorities were among the reasons for missing some health facilities. However, the TB focal persons prioritized high-TB-burden health facilities so that they were not missed in the quarterly supportive supervision. The study by Loevinsohn et al. has shown that regular supervision is needed to sustain gains [10].

The SOC tool assesses the comprehensive package of TB interventions, most of which are not covered by the routine health information system. Drug supply management, community TB care, TB infection control, data quality, screening for TB in outpatient departments, and TB screening among contacts of TB index cases are not monitored in the government's routine health information system. Information about these variables is critical to assess the status of case finding, drug supply management, infection prevention approaches, and the accuracy of the reports submitted by health facilities.

The SOC tool is not merely a data collection tool, however; it is a tool to monitor the progress of the comprehensive interventions, identify implementation gaps, assess the capacity of health workers, and decide on the improvement plan. The SOC tool helped the supervisors to analyze the gaps with the aim of pinpointing facility-specific challenges and health system needs that must be prioritized and addressed. Supervisors themselves were responsible for computing the TB-

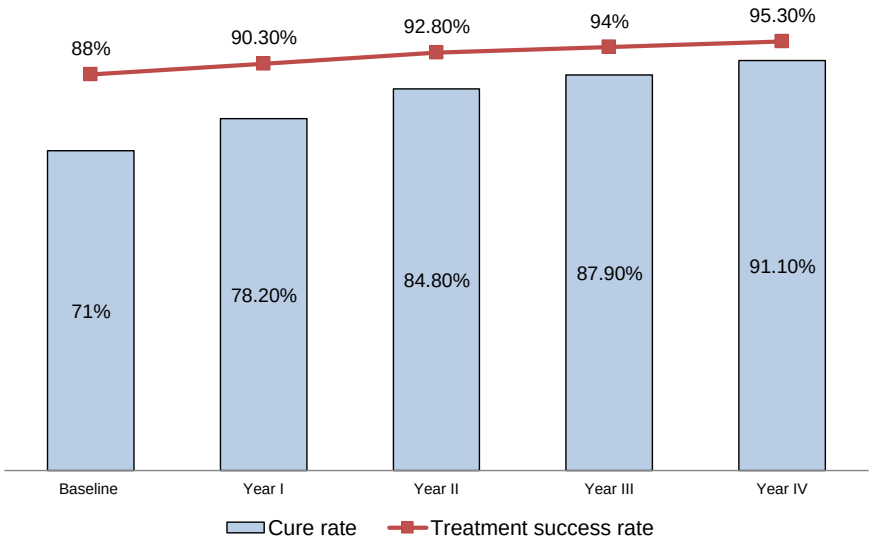

Fig. 5. Trend in treatment success and cure rates, 2011–2015.

related indicators reported in the health information system and counterchecking their data against what was reported by the health facilities. If there was any discrepancy, the supervisor and health facility manager discussed whether there was a recording problem or an issue with health workers' understanding of how to compute data on the indicators. The supervisor provided on-site feedback to improve the quality of recording and reporting.

The project has been covering the cost of quarterly supervision at the woreda level. On average, the woreda TB managers were in the field for one working day every quarter per health facility, at a cost of US $7.50 per facility. Although this project focused on TB, the TB focal persons supported other health areas during their visits, and integration of services is recommended to improve effectiveness and coordination with related programs. At the woreda and health facility levels, different health programs are coordinated by the same health worker as a focal person, so integrated mentorship could be easily implemented.

The results gained through use of the SOC tool have garnered acceptance locally, nationally, and even internationally. Adequate technical capacity has been created at the woreda and zonal levels. Moreover, the participatory approach followed since the inception of the tool fosters sustainability. Efforts have begun to make the SOC a nationwide tool and share it with other countries.

5. Conclusion

The use of SOC mentorship at the district level is a rational and effective approach to improve TB case finding, treatment outcomes, TB drug management, laboratory quality, infection control and comprehensive TB program monitoring. We also observed significant improvement in data quality after the SOC guided mentorship. The SOC is recommended for national application and could be replicated by other health programs for better monitoring and capacity building.

Ethical considerations

We received ethical approval from the ethics committees of the Amhara and Oromia Regional Health Bureaus to analyze the routine data and disseminate the findings. We used aggregate program-level reports for this analysis with the consent of the reporting institutions. No patient identifiers were included in the routine report.

Availability of data

There are no data other than those included in this article

Competing interests

The authors declare that they have no competing interests.

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Author contributions

MM conceived the idea and designed the tool together with BD and YK. MM, DH, YK, BG, SN, GN, YKH, DJ, NH, and ZG were involved in the implementation. PS and BKT critically reviewed the manuscript for intellectual content with all the research team and provided feedback on subsequent versions. All authors reviewed and approved the final version of the manuscript.

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Molecular tests expedite the diagnosis of multidrug-resistant tuberculosis in childhood

The diagnosis of paediatric tuberculosis (TB) is difficult, partly due to the low accuracy of traditional tests. Molecular TB tests can diagnose presumptive TB and drug-resistant TB (DR-TB) rapidly and may guide crucial clinical decision making, as illustrated below.

A 5-month-old male child hospitalised with cough, fever, poor appetite, weight loss and drenching night sweats for 2 months, with two known TB contacts, was empirically treated for drug-susceptible TB. Two weeks after starting TB treatment the child's clinical condition deteriorated further, prompting sputum testing by Xpert® MTB/RIF. *Mycobacterium tuberculosis* was detected with rifampicin resistance, warranting referral to the National DR-TB Treatment Centre. On examination the child was wasted, irritable, had lymphadenopathy and pallor of the conjuctiva. He weighed 7 kg and his mid-upper arm circumference (MUAC) was 11.5 cm, with a *Z*-score of <–3 standard deviation (SD). He had tachypnoea, with 89 breaths per minute, but chest auscultation findings were normal. Sputum acid-fast bacilli smear was negative, but culture on Löwenstein-Jensen media was positive and drug susceptibility testing (DST) revealed multidrug-resistant tuberculosis (MDR-TB) resistant to rifampicin, isoniazid and streptomycin.

The TB contacts, who were on treatment for drug-susceptible TB, had negative results on Xpert testing of sputum. The child was treated with a standardised MDR-TB treatment regimen consisting of amikacin, levofloxacin, cycloserine, ethionamide and pyrazinamide during the 6-month intensive phase, followed by a continuation phase of 14 months without amikacin. He received nutritional supplements and was vaccinated with bacille Calmette-Guérin (BCG) and diphtheria-pertussis-tetanus (DPT).

After one month of MDR-TB treatment, sputum culture had become negative, and by 6 months of treatment the clinical symptoms and radiological features had improved. His weight had increased to 12 kg and his MUAC to 16 cm, with a *Z*-score of <–1 SD. No treatment-related complications were observed.

This case illustrates two important observations: first, although childhood TB is usually attributed to exposure to contacts with TB in the home, this approach may not always be reliable and may not accurately identify the source of TB. Second, it is presumed that infants cannot expectorate quality sputum and they are often treated empirically based on the DST results of a known adult contact. In this case, testing the mucosalivary sputum samples obtained from the infant using Xpert was life-saving, enabling a timely diagnosis of MDR-TB.

Paediatric TB is underdiagnosed due to a low index of suspicion of TB by health workers and a lack of sensitive diagnostic tools.[1] Despite being associated with an increase in detection of TB cases, Xpert is not widely available. It requires a minimum volume of sputum[2] and multiple samples to achieve a high yield for TB.[3] Special skills and equipment are required to obtain appropriate body samples (induced sputum, gastric lavage, biopsy, etc.) for the diagnosis of TB in children. Without a correct diagnosis of TB and appropriate directed treatment, clinical outcomes in infants are poor.[4] This further reinforces the World Health Organization recommendations to use Xpert as an initial diagnostic test to ensure targeted TB treatment in children with presumptive TB.[5]

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Conflicts of interest: none declared.

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A case report of hot tub lung: identical strains of *Mycobacterium avium* from the patient and the bathroom air

In 1997, Kahana and colleagues reported a case of hot tub lung, a hypersensitivity-like pneumonia caused by *Mycobacterium avium* subsp. *hominissuis* (MAH).[1] Although the genetic relatedness between isolates from sputum and tub water has been reported,[2] homology with airborne isolates remained unproven. This is the first case of hot tub lung to prove the homology between a patient's sample and airborne isolates.

A 67-year-old man presented with a productive cough thought to be due to the winter season, as symptoms improved from spring to autumn without treatment, then worsened in winter. All vital signs were normal. Laboratory examinations were as follows: white blood cells 6500/μl, lactate dehydrogenase 261 IU/l, C-reactive protein 0.49 mg/dl and Krebs von den Lungen-6 1310 U/ml. High-resolution computed tomography (HRCT) of the chest revealed diffuse ground-glass centrilobular nodules across the entire lung. A transbronchial lung biopsy showed non-necrotising granulomas (Figure).

Three years later, MAH was identified from the patient's sputum, prompting us to suspect hot tub lung. We discovered that the patient used his bathroom heater only in winter, and that he saved the tub water overnight for cleaning his bathroom and laundry.

We collected the reserved tub water and swabs from the air outlet of the air-heater and showerhead. Growth of MAH in all samples was confirmed by polymerase chain reaction after culture for 18 days. The isolates were subcultured for *hsp65* sequence analysis, to identify the MAH subspecies and for variable number of tandem repeats (VNTR) analysis. For VNTR genotyping, 19 loci were examined, covering the two VNTR subsets in previous reports: 7 loci of representative mycobacterial interspersed repetitive units (MIRU) VNTR and 15 loci of *M. avium* tandem repeats (MATR) VNTR. The VNTR unit copy numbers for each of the 19 polymorphic loci were assigned based on their respective amplicon sizes, and compared with the copy number of the reference strain *M. avium* ATCC252913-4.

The patient followed his usual routine of filling the bathtub, then on the following day turning on the bathroom air-heater and running the shower. We collected bathroom aerosols in 100 l of ambient air using an air sampler (IDC-500C, BSMT Co., Ltd., Kanagawa, Japan) placed on the windowsill to avoid direct spray. Airborne particles were impacted onto an agar plate and then incubated at 35°C. Numerous MAH grew, accompanied by colour-pigmented pathogens. VNTR analysis showed that isolates from all five samples shared identical VNTR patterns (Table).

The patient's condition improved after he stopped leaving the tub water and using the air-heater.

To our knowledge, this is the first reported case of hot tub lung to identify MAH from bathroom aerosols and prove a genetic match with MAH from the patient's sputum.

The present study employed a commercially available air impactor for viable air sampling. The principle is the same as the Andersen six-stage cascade impactor used in the aerosol study of *M. tuberculosis*.[5] Air-containing particles are accelerated through an orifice toward an agar plate below the orifice; this causes the airstream to abruptly change direction. Particles that cannot follow the stream lines due to the law of inertia impact on the agar plate.

The bathroom air-heater may have significantly contributed to the patient's health problems by trapping and aerosolising MAH. Because the filter was behind heat-reflecting glass, its temperature did not rise significantly, allowing for growth of MAH. Transmission may have occurred from airborne MAH, from splashes of tub water or from the shower, being captured in the air-heater filter, then, following growth, dispersing when the air-heater was used.

In our patient, hot tub lung improved only after exposure to MAH had ceased, indicating that this condition is a type of hypersensitivity pneumonitis.

This report strongly supports the hypothesis that MAH inhalation causes hot tub lung. This insight will assist in fully understanding the nature of the disease and establishing appropriate treatment strategies.

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Childhood Tuberculosis in Nigeria: Disease Presentation and Treatment Outcomes

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ABSTRACT

OBJECTIVES: Understanding the factors that influence tuberculosis (TB) treatment outcomes in children is key to designing interventions to address them. This study aimed to determine the case category distribution of childhood TB in Nigeria and assess which clinical and demographic factors are associated with different treatment outcomes in childhood TB.

MATERIALS AND METHODS: This was a retrospective cohort study involving a review of medical records of children (0-14 years) with TB in 3 states in Nigeria in 2015.

RESULTS: Of 724 childhood TB cases registered during the review period, 220 (30.4%) were aged 0–4 years. A high proportion of patients had pulmonary TB 420/724 (58.0%), new TB infection 713/724 (98.5%), and human immunodeficiency virus (HIV) coinfection 108/724 (14.7%). About 28% (n = 201) were bacteriologically diagnosed. The proportion of TB treatment success was 601/724 (83.0%). Treatment success was significantly higher in children aged 5–14 years than those 0–4 years (85.3% vs 77.7%, $P = .01$). Factors associated with unsuccessful outcomes in patients aged 0–4 years are male sex (adjusted odds ratio [aOR]: 1.2), HIV-positive status (aOR: 1.2), and clinical method of diagnosis (aOR: 5.6).

CONCLUSIONS: Efforts should be made to improve TB treatment outcomes in children by ensuring early and accurate diagnosis, focused training of health workers on childhood TB-HIV care, and effective adherence counseling of caregivers.

KEYWORDS: Nigeria, children, tuberculosis, treatment outcomes, cohort review

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Background

Childhood tuberculosis (TB) and human immunodeficiency virus (HIV) syndrome are major public health concerns contributing to significant child morbidity and mortality. Globally, about 1 million incident childhood TB cases occur annually, only 359 000 were notified in 2014 indicating that two-thirds of the children who developed TB worldwide were not notified.[1,2] It is believed that these missing childhood TB cases were neither diagnosed nor initiated on TB treatment. The actual magnitude of childhood TB epidemic is difficult to assess, mainly due to diagnostic difficulties and noninclusion of children in most surveys.[1] Poor access and delay in diagnosing and initiating appropriate TB treatment in children have implications on child morbidity and mortality. In 2014, 136 000 children aged <15 years died of TB and about 40 000 of the deaths were in HIV-coinfected children.[1]

Childhood TB is a good indication of ongoing transmission of TB in the community. Tuberculosis in children has been shown to occur mostly among infant and young children aged <5 years.[3,4] These younger children are at higher risk of progressing to TB disease after infection as well as developing more severe forms of TB such as TB meningitis.[5,6] For those HIV positive, the situation is even worse.[6] However, childhood TB is not adequately recognized in some countries, based on the reported number of childhood TB cases. The World Health Organization (WHO) estimates that around 10% to 20% of total TB case notification is expected to occur in children and even higher in settings with high burden of TB.[1] Commonly, many national TB programs report numbers well below the estimated average. Reported treatment outcomes also vary, especially in children who are younger than 5 years of age. Studies from sub-Saharan Africa have reported outcomes for children ranging from 77.4% to 79.2%.[7,8] In Ethiopia and South Africa, children with some clinical features such as HIV coinfection have also been reported to have poorer outcomes.[9,10]

Nigeria has one of the highest burdens of TB and HIV-associated TB in the world. About 6000 children aged <15 years were notified to have TB in 2015, and this represented 6% of the estimated incident childhood TB cases.[1] The

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Nigerian National Tuberculosis Program (NTP) is well established. However, the NTP routine surveillance data do not disaggregate reported childhood TB cases in terms of type, site of disease, method of diagnosis, and previous treatment history, among others, which make programmatic interventions targeting specific childhood TB cases difficult. Among children, striking variations have been reported in the distribution of TB cases, and this has important implication for program interventions for childhood TB. Although important progress has been made in the overall treatment outcome with treatment success in the general population (all ages) exceeding 85% in recent time, poor outcomes have been reported among children, and even poorer outcomes are reported among younger children aged <5 years.[1,11] This suggests that there are underlying clinical and demographic factors associated with childhood TB that need to be explored.

Furthermore, little is known about the case distribution of childhood TB for different age groups. Treatment outcome measurement has historically focused on individuals with smear-positive TB, which is much less common in children—especially infants and young children who often have difficulty producing sputum. There are also few studies in Nigeria that evaluated treatment outcomes of childhood TB and risk factors. The few studies that undertake this task are limited to either a small cohort or geographical area and are not age specific.

Given this paucity of information on childhood TB in sub-Saharan Africa, this study focuses on providing information on childhood TB in Nigeria. The specific aims of this study are (1) to determine the case category distribution of childhood TB in Nigeria and (2) to assess which clinical and demographic factors are associated with different treatment outcomes in childhood TB.

Methods

Data

The research was conducted in Lagos, Ondo, and Osun states in Southwest Nigeria. Review of medical records of all childhood patients with TB undergoing treatment under the public and private health facilities between January and December 2015 was carried out. There are 726 designated TB treatment facilities across the 3 states, serving an estimated population of 21.7 million people, of which 7.5 million (35%) were children. These TB treatment facilities are located in 68 local government areas (LGAs) across the 3 states. Each LGA is supervised by a designated LGA TB supervisor. The study population consisted of all children aged <15 years who were diagnosed and treated of TB under the NTP. Information and data on demographic and clinical variables were extracted quarterly from the TB treatment cards and TB registers maintained in the TB treatment facilities by the LGA TB supervisors and entered into a designated LGA recording tool. These data were then extracted by 10 trained data entry clerks using a structured data extraction Microsoft Excel tool. The variables extracted include TB registration, type and category of TB, HIV status, sex, age (years), treatment category, and treatment outcome. Information on age-specific population was obtained from the National Population Commission Census Data 2006 and adjusted for annual population growth rate of 3.2%.[12]

This was a retrospective cohort study. States were selected based on convenience and to reflect a range of TB and HIV burdens and population coverage. Nigeria is one of the 30 countries with highest TB burden, with a TB incidence rate of 322 (189-488) per 100 000 population and HIV-associated TB incidence rate of 55 (31-85) per 100 000 population.[1] Tuberculosis incidence in children (0-14 years) was estimated at 586 (345-890) per 100 000. The NTP follows the WHO-recommended Directly Observed Therapy, Short Course (DOTS) strategy for TB treatment.[13] Samples were collected from symptomatic children for GeneXpert or acid-fast bacilli microscopy. For children who could produce sputum, sputum samples were collected for either GeneXpert or microscopy, whereas other samples (gastric lavage, cerebrospinal, and pleural biopsy) were collected for GeneXpert when a child could not produce sputum. The national program also approved clinical and radiologic diagnoses of childhood TB based on decision of a medical doctor to treat with full course of anti-TB treatment.

In 2015, the NTP intensified screening for TB among children attending health care facilities across the states and released guidelines endorsing GeneXpert MTB/RIF assay as the priority diagnostic tool for children with signs and symptoms of TB.[13] The national policy included recommendations for referral of samples (including gastric lavage) from health facilities where GeneXpert MTB/RIF services are not available to designated testing facilities with GeneXpert MTB/RIF services. Children diagnosed with TB received a standard treatment regimen consisting of Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E) for 2 months, followed by R and H for 4 months (2RHZ + E/4RH).

Measurement

Dependent Variables. Outcome variables were categorized as successful (cured and treatment completed) and unsuccessful (died, failure loss to follow-up, and not evaluated). Treatment outcomes categories (cured, treatment completed, died, treatment failure, loss to follow-up, and not evaluated) were assigned based on NTP/WHO guidelines.[13] Patients were followed up using laboratory or clinical evaluations at regular intervals, ie, second, fifth, and sixth months during chemotherapy.

Independent variables. Children were defined as those aged <15 years, with additional subcategories of younger (0-4 years) and older (5-14 years) children. Tuberculosis diagnosis was based on standard WHO/NTP methods, using any of sputum microscopy, clinical examination, chest X-ray, and GeneXpert for diagnosis.[13] Bacteriologically diagnosed cases included

Table 1. Demographic and clinical characteristics of childhood TB cases registered.

VARIABLES	CHILDREN 0-4Y, NO. (%)	CHILDREN 5-14Y, NO. (%)	TOTAL, NO. (%)	*P* VALUE[a]
Total	220 (30.4)	504 (69.6)	724	
Demographics				
Gender				
Female	107 (48.6)	293 (58.1)	400 (55.2)	
Male	113 (51.4)	211 (41.9)	324 (44.8)	.02
State				
Lagos	193 (87.7)	373 (74.0)	566 (78.2)	
Ondo	13 (5.9)	70 (13.9)	83 (11.5)	
Osun	14 (6.4)	61 (12.1)	75 (10.3)	<.01
Presentation and medical history				
Anatomic site of TB				
Pulmonary TB	137 (58.0)	283 (56.2)	420 (58.0)	
Extrapulmonary TB	83 (42.0)	221 (43.8)	304 (42.0)	.14
Method of diagnosis				
Bacteriologically diagnosed	14 (6.4)	187 (37.1)	201 (27.8)	<.01
Clinically diagnosed	206 (93.6)	317 (62.9)	523 (72.2)	
Category of patients with TB				
New TB cases	219 (99.5)	494 (98.0)	713 (98.5)	
Retreatment TB cases	1 (0.5)	10 (2.0)	11 (1.5)	.11
HIV status				
HIV positive	39 (17.7)	69 (13.7)	108 (14.9)	.17
HIV negative	181 (82.3)	435 (86.3)	616 (85.1)	

Abbreviations: HIV, human immunodeficiency virus; TB, tuberculosis.
[a]Fisher's exact test.

those who were diagnosed using either GeneXpert or sputum microscopy.

Analysis strategy

Data were double entered, checked, and analyzed using Epi Info 7 (Centers for Disease Control and Prevention, Atlanta, GA, USA). The analyses were based on intention to treat. Outcome variables were categorized as primary (rate of successful outcomes) and secondary (proportion of treatment failures at the end of chemotherapy). Descriptive statistics was used to determine the characteristics of the study population. Demographic and clinical characteristics and treatment outcome (successful and treatment failures) variables were compared using χ^2 test and Fisher exact or mid-*P* exact as appropriate, with a *P* value of .05 assumed to be statistically significant. Unadjusted odds ratios (ORs) and adjusted ORs (aORs) with their 95% confidence intervals were estimated using multivariable logistic regression analysis, with unsuccessful outcomes as the dependent variable and sex, age, site of disease, method of diagnosis, and HIV status as the predictor variables.

Protection of human subjects

Because the study was based on a retrospective review of existing records, did not include any patient interaction, and did not involve the collection of individual identifying information, the study involved no risk to participants. Clearance for exemption was granted by the Ethical Committee, State Ministry of Health. Institutional approval was obtained from the respective state and local government TBL Control program managers.

Results

Of the 724 childhood TB cases registered, 220 (30.4%) were aged 0–4 years and 504 (69.6%) were aged 5–14 years. The

Table 2. Treatment outcomes of childhood TB cases stratified by demographic and clinical characteristics.

CATEGORY	UNSUCCESSFUL OUTCOMES, NO. (%)*	SUCCESSFUL OUTCOMES, NO. (%)†	X^2	*P* VALUE
Total	123 (17.0)	601 (83.0)		
Sex				
Female	75 (18.7)	325 (81.3)		
Male	68 (21.0)	256 (79.0)	0.49	.45
Age				
0–4	49 (22.3)	171 (77.7)	6.23	.01
5–14	74 (14.7)	430 (85.3)		
Site of disease				
Pulmonary TB	49 (11.7)	371 (88.3)	1.84	.21
Extrapulmonary TB	26 (8.5)	278 (91.5)		
Method of diagnosis				
Bacteriological diagnosed	19 (9.5)	182 (90.5)		
Clinically diagnosed	104 (19.9)	419 (80.1)	11.19	<.001
Type of patient				
New TB cases	122 (17.1)	591 (82.9)	0.49	.70
Retreatment TB cases	1 (9.1)	10 (90.9)		
HIV status				
Positive	31 (28.7)	77 (71.3)	13.34	<.001
Negative	92 (14.9)	524 (85.1)		

Abbreviations: HIV, human immunodeficiency virus; TB, tuberculosis.
†Successful outcomes = cured and treatment completed; *Unsuccessful outcomes = died, failure, and not evaluated.

ratio of male to female was 1:1.2 (Table 1). Among these, 566 (78.2%) were registered in Lagos, 83 (11.5%) registered in Ondo and 75 (10.3%) in Osun states. About 58% (n = 420) were pulmonary TB cases, whereas 42% (n = 304) had extrapulmonary TB (EPTB). Most (98.5%; n = 713) were new TB cases and the remaining 11 (1.5%) cases had been treated for TB in the past. Nearly a third (27.8%; n = 201) were bacteriologically diagnosed, whereas 72.2% (n = 523) were diagnosed clinically. The TB/HIV coinfection rate was 14.9% (n = 108).

The treatment outcomes of patients are shown in Table 2. Of the 724 patients enrolled, the overall treatment success rate was 83% (n = 601). Children aged 5–14 years had higher treatment success rate than those aged 0–4 years ($P = .01$). Patients who were bacteriologically diagnosed and HIV negative had higher treatment success rates than those clinically diagnosed ($P < .001$) and HIV positive ($P < .001$), respectively. Treatment outcomes among male patients were worse compared with female patients but this difference was not statistically significant. There were no significant differences in treatment outcomes between patient type ($P = .07$) and site of disease ($P = .21$; Table 2).

Multivariable logistic regression analysis was used to identify significant predictors of unsuccessful treatment outcomes among childhood patients with TB as shown in Table 3. Clinically diagnosed, HIV-positive, and young children aged 0–4 years were significantly associated with unsuccessful treatment outcomes. After adjusting for confounders, aged 0–4 years (aOR: 1.4), clinically diagnosed (aOR: 2.1), and HIV-positive status (aOR: 1.9) remained independent predictors of unsuccessful outcomes (Table 3).

Further multivariable analysis showed that in children aged 0–4 years, male sex, HIV-positive status, and clinical method of diagnosis were significantly associated with treatment outcomes. After adjusting for confounders, male sex (aOR: 1.2), HIV-positive status (aOR: 1.2), and clinical method of diagnosis (aOR: 5.6) remained independent predictors of unsuccessful outcomes in patients aged 0–4 years (Table 4). No association was found between site, type of TB disease, and treatment outcomes. However, clinical method of diagnosis was associated with unsuccessful outcomes in patients aged 5–14 years (aOR: 0.6).

Table 3. Factors associated with unsuccessful treatment outcomes among childhood TB cases.

CATEGORY	OR (95% CI)	*P* VALUE	AOR (95% CI)	*P* VALUE
Sex				
Male	1.3 (0.7–1.6)	.22	1.1 (0.5–1.4)	.25
Female	1.0			
Age				
0–4	1.6 (1.1–2.4)	.009	1.4 (1.01–2.3)	.017
5–14	1.0			
Site of disease				
Pulmonary TB	1.4 (0.8–2.3)	.10	1.4 (0.7–2.3)	.21
Extrapulmonary TB	1.0			
Method of diagnosis				
Bacteriological diagnosed	1.0			
Clinically diagnosed	2.3 (1.4–3.9)	<.001	2.1 (1.3–4.0)	<.001
Type of patient				
New TB cases	2.0 (02–16.2)	.2	2.2 (0.3–45.5)	.41
Retreatment TB cases	1.0			
HIV status				
Positive	2.2 (1.4–3.6)	<.001	1.9 (1.1–3.4)	.001
Negative	1.0			

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; TB, tuberculosis.

Discussion

This study described the case distribution of childhood TB and treatment outcomes in Nigeria and assessed the relationship between demographic and clinical variables with treatment outcomes. We found that childhood TB treatment was characterized by relatively poor outcomes. Age, HIV status, and method of diagnosis were associated with unsuccessful treatment outcomes. Given that this study was designed to assess childhood TB distribution and care under program conditions, our study provides valuable insights into the underlying challenges of childhood TB management in high-burden, resource-limited settings. Although the proportion of children with previous history of TB treatment in our study is smaller (1.5%) compared with previous studies, our cohort had similar clinical features consistent with severe disease[5,6,14] such as smear positivity (30%-60%)[6] and abnormal radiography (40%-51%).[6,14,15] Compared with other studies, a higher proportion of children in our study were HIV positive (14.9% vs 11.3%)[16] and had EPTB disease (42% vs 34.6%)[17] suggesting differences in clinical presentation and complication in case management. The age-specific distribution of TB in our study showed that TB was most common among children aged 5–14 years, similar to findings from previous studies in Nigeria.[11] This is in contrast to the expected epidemiology of TB and findings of other studies which reported high proportions of childhood TB cases in the 0–4 years age group.[4,6,14] The reason for this difference is not clear; it may be due to under-notification of TB in the age group of 0–4 years as a result of diagnostic difficulties and the consequent passive health care sector in Nigeria.

We also found that the overall treatment success rate was 83.0%, which is consistent with the national average. However, the measure treatment success was lower than findings from Bhutan and India, which reported 93% to 96% treatment success rates.[15,17] The Nigerian NTP applies a standardized daily treatment regimen, and its policy guidelines rely on DOTS to be practiced throughout the duration of chemotherapy either by a DOTS provider or by a trained treatment supporter. Globally, studies have shown that early detection of TB and effective implementation of DOTS with good adherence counseling and patient education would result in high treatment success rate and reduce death.[3,4,6] The Roadmap for Childhood TB in this and similar settings should therefore focus on implementing key strategies to raise suspicion of TB among clinicians,[16] strengthen techniques for sputum collection for accurate bacteriological diagnosis, and improve overall

Table 4. Factors associated with unsuccessful treatment outcomes among childhood TB cases stratified by age group.

CATEGORY	AOR-1 (95% CI)[a] (N = 220)	AOR-2 (95% CI)[b] (N = 504)
Sex		
Male	1.2 (0.8-1.6)*	0.9 (0.7-1.1)
Female	1.0	1.0
Site of disease		
Pulmonary TB	1.1 (0.8-1.4)	0.9 (0.8-1.3)
Extrapulmonary TB	1.0	1.0
Method of diagnosis		
Bacteriological diagnosed	1.0	1.0
Clinically diagnosed	5.6 (3.3-10.3)*	0.6 (3.5-0.9)*
Type of patient		
New TB cases	0.6 (0.08-2.4)	1.1 (0.4-2.9)
Retreatment TB cases	1.0	1.0
HIV status		
Positive	1.2 (0.8-1.9)*	0.9 (0.7-1.3)
Negative	1.0	1.0

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; TB, tuberculosis.
[a]ORs adjusted for age group 0-4 years.
[b]ORs adjusted for age group 5-14 years.
*$P < .05$.

treatment outcomes via effective adherence counseling of caregivers.

Human immunodeficiency virus–positive status, age 0–4 years, and clinical method of diagnosis independently predicted unsuccessful treatment outcomes. The HIV-coinfected patients would require closer monitoring in an effective program. Poor treatment outcomes in childhood TB cases coinfected with HIV are consistent with findings of other studies.[10,18–20] This may be due to the predominant respiratory comorbidity which increases risk of delayed diagnosis and treatment, missed diagnosis, atypical presentation, and mortality in HIV-coinfected children, particularly those at the advanced stage of HIV disease.[3–21] Age-specific outcomes showed that treatment was less successful among children who are younger than 5 years of age, especially those HIV positive and male sex. Diagnosis and treatment for TB in children in resource-limited settings are associated with significant difficulties often due to presence of immature immune response, poorer cell-mediated immunity, unrestrained bacteria proliferation, parenchymal damage, and disseminated disease which are common in children, particularly in HIV-coinfected children.[22] A program that substantially reduces TB death and improves treatment success would considerably reduce the burden of TB.[23] An increasing prevalence of HIV infection in Nigeria provides the basis for greater collaboration, prioritization, and commitment by both TB and HIV programs to tackle childhood TB.

Limitations

Our study population was limited to childhood TB cases diagnosed and treated at health facilities under the NTP but did not include childhood TB cases managed outside the NTP system. Due to its retrospective nature, additional information such as antiretroviral therapy initiation, baseline and follow-up CD4 percent, and distance to health facility which could support deeper analysis were unavailable. Despite these, our study highlights the burden of TB in children in Nigeria particularly among younger children aged 0–4 years and provides insight that could form part of the roadmap to reducing treatment failures among childhood TB cases in Nigeria and in similar low-resource high-burden settings.

Conclusions

This study highlights the need for a renewed focus on strategies to reduce burden of TB in children, particularly among young children aged 0–4 years and HIV-coinfected children in this and other similar settings. The Nigerian TB control program should pay greater attention to early diagnosis and case management of childhood TB/HIV coinfection through investment on newer TB diagnostic technology and training of general health care workers on childhood TB/HIV

comanagement. Routine screening for TB and comorbidities such as HIV should also be intensified among children aged 0-4 years.

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Authors Contributions

CLO, VA, NC, MG and GE conceived and designed the study. EA, CE-U, VA, and CLO conducted data collection. VA, CLO, and EA analyzed and interpreted the data and wrote the first draft of the manuscript. All authors carefully reviewed and revised the manuscript for intellectual content. All authors read and approved the final manuscript.

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Delays to anti-tuberculosis treatment intiation among cases on directly observed treatment short course in districts of southwestern Ethiopia: a cross sectional study

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Abstract

Background: Delayed tuberculosis (TB) diagnosis and treatment increase morbidity, mortality, expenditure, and transmission in the community. This study assessed patient and provider related delays to diagnosis and treatment of TB.

Methods: A cross-sectional study was conducted among 735 new adult TB cases registered between January to December 2015 in 10 *woredas* equivalent to districts of southwestern Ethiopia. Data were collected through face-to-face interview of patients within the first 2 months of treatment initiation. Delay in days was tracked at three intervals: between onset of symptoms and self-presentation (Patient delay), Self-presentation to treatment initiation (Provider delay) and total delay. Days elapsed beyond median were used to define the delays. Bivariate and multiple logistic regression models were fit to identify predictors of delays and statistical significance was judged at $p < 0.05$.

Result: The median (inter-quartile range) of patient, provider and total delays were 25 (IQR;15–36), 22 (IQR:9–48) and 55 (IQR:32–100) days, respectively. More than half (54.6%) of the total delay was attributed to health system. Prior self-treatment [adjusted Odds Ratio (aOR)]: 1.72, 95% confidence interval [CI]:1.07–2.75), HIV co-infection (aOR:1.8, 95% CI: 1.05–3.10) and extra-pulmonary TB (aOR: 1.54,95% CI:1.03–2.29) were independently associated with increased odds of patient delay. On the other hand initial presentation to health posts or private clinics (aOR: 1.42, 95% CI: 1.01, 2.0) and patient delay (aOR: 1.81, 95% CI: 1.33–2.50) significantly predicted longer provider delay. Finally, having extra pulmonary TB (aOR: 1.6, 95% CI: 1.07–2.38), prior consultation of traditional healer (aOR: 3.72, 95% CI: 1.01–13.77) and use of holy water (aOR: 2.73, 95% CI: 1.11, 6.70) independently predicted longer total delay.

Conclusion: Tuberculosis patients waited too long time to initiate anti-TB treatment reflecting longer periods of morbidity and disease transmission. The delays are attributed to the patient, disease and health system related factors. Hence, improving community awareness, involving informal providers, health extension workers and TB treatment supporters can reduce the patient delay. Similarly, cough screening and improving diagnostic efficiencies of healthcare facilities should be in place to reduce the provider delays.

Keywords: Tuberculosis, Healthcare seeking, Patient delay, Provider delay, Total delay, Ethiopia

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Background

Tuberculosis (TB) has been recognized as a global public health problem since 1993 when an estimated 7–8 million cases and 1.3–1.6 million deaths occured [1] . Since then, different global strategies have been designed and implemented for the control of TB; consequently an estimated 54 million lives were saved between 2000 and 2017 [2]. Despite such achievement, TB remained to be among the major global public health problems. Globally, 10 million incident cases and 1.3milion deaths were estimated to occur in 2017. Of the estimated incident cases, only 6.4 million (64%) were notified to National TB programs (NTPs) [2].

Tuberculosis is among the major public health problems in Ethiopia accounted for third cause of hospital admission and second cause of death [3]. Ethiopia is among the 30 TB High Burden Countries (HBC) where about 172,000 new cases and 25,000 deaths were estimated to occur in 2017. Out of the estimated cases in 2017, only 117,705 (68%) were notified to NTP [2]. The first national prevalence survey in 2011 revealed smear positive pulmonary TB (PTB) prevalence of 108/100,000. The survey further reported 55% of the cases were first identified by the survey and were not on treatment until the survey [4].

Early detection and treatment of TB cases have been a priority in the prevention and control of TB [5]. The delay to TB treatment can be categorized into: 1) patient delay that constitute time elapsed between onset of TB symptoms and first self presentation to formal care, 2) provider delay as time elapsed between first presentation to formal care and anti-TB treatment initiation and 3) total delay as time elapsed between onsets of TB symptoms and anti-TB treatment initiation. When diagnosis of TB is delayed, patients go without treatment for long and transmit the disease. In high prevalence settings, each infectious case of TB can result in up to 20 secondary infections until detection [6] . Moreover, delays to diagnosis and treatment of TB result in more serious illness by the time of diagnosis, increased length of infectiousness and poor treatment outcomes [7–11] and represent a time span for additional costs [12]. Consequently, delays to diagnosis has been emphasized as a major obstacle to TB control [13].

Systematic reviews of studies across the world reported median patient delay of 30 days and provider delay of 7-28 days [13, 14]. On the other hand, diagnostic delays ranging from a median of 8-191 days at different levels of health care delivery systems [7, 8, 15–18] were reported. Studies from different parts of Ethiopia also reported longer delays to initiate treatment for TB with median patient delay of 20–90 days [16, 17, 19] and provider delay of 6-34 days [17, 19–21]. A prevalence survey in northern Ethiopia [22] reported two-thirds of active TB cases were not detected timely. The long patient, provider and total delays are attributed to female gender, older age, low awareness about TB, repeated visits to health facilities, visiting lower level health care facilities and traditional healer [23, 24].

The studies in Ethiopia are limited to smear positive PTB cases [21], focused on cases presenting to either health centers [20] or hospitals [25] but not both. Moreover, the studies were conducted when TB had been treated for 8 months. Studies have shown that shorter treatment regimens could dramatically accelerate the reductions in TB incidence and mortality that can motivate suspects to seek care early and treatment [26]. In Ethiopia, treatment regimen of 6 months was introduced in 2011. Thus, complete picture of the patterns of delay of different categories of TB at different health care setups and in the era of reduced treatment regimen is scanty in the country. As a result the national TB research advisory council has set identification of barriers for the different forms of delays to TB treatment as a national priority research agenda [27]. However, recent evidences are lacking in Ethiopia in general and the study area in particular. Therefore, this study investigated time delays to initiate formal care seeking, diagnosis and treatment along with factors associated with the delays among new TB cases on treatment at health centers and hospitals in districts of southwestern Ethiopia.

Methods

Study design and setting

A cross-sectional study was conducted among newTB cases on treatment from January through December 2015 in three *zones* of Southern Nation Nationalities and Peoples Region (SNNPR); one of the nine Regional States in Ethiopia. The three study *Zones* include Bench Maji, Kaffa and Sheka together comprised of 26 *woredas* and four town administrations where about 2,064,102 peoples reside [28]. During the study, there were three hospitals and 65 health centers providing TB diagnosis and treatment based on national guidelines adopted from WHO [29, 30].

Study population and sampling

The study population comprised of all new smear positive, smear negative and extra pulmonary TB cases older than 18 years and on anti-TB treatment at health centers and hospitals. Accordingly the sample size was computed using StatCalc program of EpiInfo using 95% significance level, 80% power, 38% expected proportion of illiteracy among those initiated formal healthcare seeking within 30 days of onset of illness and odds ratio (OR) 1.7 [31]. The calculation provided 486 cases, considering design effect of 1.5 and non-response of 10%, 802 new cases were required. Then ten woredas

from the three zones were selected and all healthcare facilities providing TB diagnosis and treatment in the selected woredas were included for the study. Thus a total of 11 health centers and three hospitals were included. The samples were proportionally allocated to the zones, woredas and health facilities based on the TB caseloads reported during the preceding fiscal year to the study period. Finally, consecutive consenting new smear positive, smear negative and extra pulmonary cases within the first 2 months of anti-TB treatment and older than 18 years were enrolled until the required sample was reached.

Data collection and analysis

Data were collected using structured questionnaire adapted from similar studies [4, 12, 32] and data abstraction checklist prepared from TB register and individual clinical chart. The questionnaire was translated into national language (*Amharic*) spoken by almost all residents in the study area. Ten diploma graduate nurse data collectors and three public health specialist (MPH) supervisors were recruited and trained for 3 days. Finally, new cases of TB were traced from the unit TB register and interviewed for their sociodemographic, health care seeking practices and knowledge towards TB.

Patient delay was assessed by asking the participants to recall or estimate the date or number of days elapsed between onset of TB constitutional symptoms (cough, fever, night sweats, chest pain, weight loss, loss of appetite) until they present to formal healthcare. Similarly, provider delay was estimated by asking date or number of days elapsed between first formal health care facility visit to final diagnosis and treatment initiation with anti-TB treatment. Finally, total delay was computed as a sum of patient and provider delay or number of days elapsed between onsets of illness to initiation of anti-TB treatment.

Knowledge about TB was assessed using eight items including cause of TB, TB is hereditary, TB is contagious, mode of TB transmission, (symptoms of TB, TB is curable, length of treatment and anti-TB drugs charge. Responses were recorded as 1 = yes as correct and 0 = no as wrong. The items internal consistency was checked (Cronbach's Alpha (α) = 0.75) before computing an index. Finally, a knowledge index was computed from the scores and dichotomized in to good for those scored above median or poor otherwise.

Data were entered into Epi data, and processed on SPSS version 21. The data were described using frequency, proportions, measures of location and dispersion. Distribution numeric variables were assessed using normality plots (Q-Q plots and/or histograms) or Kolmogorov-Smirnov test for normality. The distribution of number of days elapsed across different time points were not normal and median days were used as a cutoff point to define delays. Thus patient, provider and total delays were defined based on median days elapsed.

Comparisons of medians across different groups was made using Manwhitney U and Kruskual Walis tests. Finally, bivariate and multiple binary logistic regression models were fitted to identify independent predictors of delays. Selection of the variables for multiple regression were made based on p value <=0.25 on crude analysis. The logistic model fitness was checked using Hosmer and Lemeshow test. In all the statistical tests, statistical significance was judged at $p < 0.05$.

Definition of terms

- **Patient delay:**days elapsed between onsets of illness to first formal healthcare seeking
- **Health system /provider delay:** is days spent between first consultation to initiation of treatments
- **Total delay:** number of days elapsed since onset of illness to anti-TB treatment initiation
- **Healthcare facility:** health institutions including health post, clinics, health center, and hospital organized to provide formal healthcare.
- **Care seeking:** consulting formal healthcare from healthcare facilities following illness.
- **New case of TB:** is a patient who never had treatment for TB, or has been on anti-TB treatment for less than 4 weeks in the past.

Results

Sociodemographic characteristics of the patients

A total of 735 TB cases from three hospitals and 11 health centers in the three *zones* were studied. Accordingly, 469(63.8%) and 266(37.2%) of the cases were registered at health centers and hospitals, respectively. The median age of the cases was 27 (inter-quartile range (IQR:20–37) years. Among the cases, 389(52.9%) and 216(29.4%) had completed elementary school and farmer, respectively (Table 1).

Knowledge towards tuberculosis

Almost all 721(98.1%) of the cases mentioned their illness as TB. Only 539(73.3%) had ever heard about TB before they were diagnosed as TB case. Among those ever heard about TB, 253(48.3%), 200(38.1%), 191(36.4%) and 190(35.3%) had heard from mass media, health facilities, TB patients and relatives respectively. The aggregated knowledge score about TB revealed, 545(74.1%) had scored above a median of 4.5 out of the eight items and labeled as having good knowledge.

Delays to TB diagnosis and treatment

The median patient delay was 25 (IQR: 15–36) days. The median patient delay is significantly different across

Table 1 Sociodemographic characteristics of TB cases on directly observed short course treatment (DOTS) in districts of southwestern Ethiopia, January to December 2015 ($n = 735$)

Variable		Frequency	Percent
Gender	Male	446	60.7
Age(years)	18–34	503	68.4
	35–65	216	29.4
	>65	16	2.2
Marital status	Never married	275	37.4
	Currently married	404	55.0
	Widowed/divorced	56	7.6
Educational status	No formal education	212	28.8
	Completed elementary	389	53.0
	Secondary and above	134)	18.2
Occupation	Employed	172	23.4
	Farming	216	29.4
	Unskilled work [b]	51	6.9
	Dependants [c]	296	40.3
Religion	Orthodox	300	40.8
	Muslim	104	14.1
	Catholic	4	0.5
	Protestant	314	42.7
	Traditional	13	1.8
Residence	Urban	369)	50.2
	Rural	366	49.8
Household size	Mean/SD	4.3/2.1	

[a]Standard deviation [b]housemaid, daily laborer, [c] students, house wife, [d] father/mother /husband/ wife/brother/sister/employer

type of TB, educational status, marital status, and knowledge towards TB at $P < 0.05$(Additional file 1: Table S1). Three hundred seventeen (43.1%) cases perceived their first formal healthcare visit was delayed due to lack of money and waiting self limit was reported among 109 (26.1%) and 256 (80.8%), respectively. Clinically, cough, night sweating and fever were reported among 563(76.6%), 345(46.9%) and 300(40.8%) cases, respectively. While, 139(18.9%) of the cases took informal cares such as visiting traditional healer; only a third, 240(32.6%) consulted formal healthcare within 15 days of the onset of illness. The decision to ultimate visit to HCF was made upon referral and/or advice from relatives 280(38.6%), and TB patients on treatment 30(4.2%). Thus, 260 (35.4%) and 238(32.4%) of the cases first visited private clinics and public health centers respectively (Table 2).

Provider delay was at a median (IQR) of 22 (9–48) days. Among the included patients, 244(33.2%) and 112(15.2%) cases were diagnosed at the first visited HCF and during their first visit to HCF, respectively. Moreover, 623 (84.8%) cases were diagnosed after an average (SD) of 3.6 visits to

Table 2 Initial symptoms encountered and Health care seeking pathways among new TB cases on directly observed treatment short course (DOTS), Southwestern Ethiopia, January to December 2015 ($n = 735$)

Variable		Frequency	Percent
Initial symptoms encountered	Cough	563	76.6
	Night sweat	345	46.9
	Fever	300	40.8
	Loss of appetite	279	38.0
	Chest pain	267	36.3
	Weight loss	236	32.1
	Haemoptysis	144	19.6
	Others[a]	62	8.4
First action to illness	Visit HCF	596	81.1
	Self-treatment	98	13.3
	Visit holy water	26	3.5
	Consult traditional healer	15	2.0
Perceived reason for not visiting HCF first ($n = 149$)	Thought illness limit by itself	97	65.1
	Perceived long waiting time at HCF	37	24.8
	Perceived expensive service fee	37	24.8
	HCF too far	29	19.5
	Other [b]	22	14.8
First HCF visited	Private clinic	260	35.4
	Health center	238	32.4
	Hospital	221	30.1
	Health post	16	2.2
Source of advice/referral to visit first HCF	Self	472	64.2
	Parent/relative	280	38.1
	HEW [c]	32	4.4
	TB patient	30	4.1
	HIV care clinic	16	2.2
	Other[d]	31	4.2
Travel time to first HCF visited	<=1 h	582	79.2
	> 1 h	153	20.8
Patient delay (days)	Median(IQR)	25(15–36)	
	Median (95%CI)	25(21,28)	

[a]neck swelling, head ache, joint pain, back pain, wound,[b]HCF closed, mistrust health care provider, bad previous experience at HCF, fear of HIV test and fear of TB diagnosis, [c]HEW = Health Extension worker(trained females those provide household package of health care to household), [d]drug shop(13), holy water(14), traditional healer(4)

an average (±SD) of 2.2 (1.2) HCFs (Table 3). Following the diagnosis of TB, 613(83.4%) of the cases were put on anti-TB treatment immediately and the rest after a median 2(range:1–7) days. The median provider delay is significantly correlated with patient delay ($r = 0.2$, $P < 0.001$) and different with type of TB and type of first visited HCF at $P < 0.05$ (Additional file 1: Table S1). Taken together, the

Table 3 Clinical characteristics and Pathways to initiate anti-TB treatment among cases on treatment Southwest Ethiopia, January to December 2015

Variable		Frequency (%)	Percent
Place TB diagnosis made	Hospital	448	61.0
	Health center	188	25.6
	Private clinic	99	13.5
Type of TB	Smear positive Pulmonary	373	50.3
	Smear negative Pulmonary	213	29.0
	Extra pulmonary	149	20.3
Mode of diagnosis	Bacteriological	373	50.7
	Clinical	362	49.3
Weight at treatment initiation	Mean(SD)Kg	48.8	
HIV status	Positive	68	9.3
	Negative	667	90.7
Receiving ART[a] ($n = 68$)		27	39.7
Receiving CPT[b] ($n = 68$)		32	47.1
Number of HCF visited [c]	Median (IQR)	2(1–3)	
Number of visits made [d]	Median (IQR)	3(2–4)	
Provider delay (days)	Median (IQR)	22(8–48)	
	Median(95%CI)	22(19,25)	
Total delay (days)	Median (IQR)	55(32–100)	
	Median (95%CI)	55(49,61)	

[a]Antiretroviral therapy [b] Cotrimoxazole Prohylactic therapy [c] number of HCF visited until diagnosis of TB is made, [d] number of total visits made to different HCF until TB diagnosis

median total delay was 55(IQR: 32–100) days to initiate anti-TB treatment. More than half (54.6%) of the total delay was attributed to provider and the rest to patient.

Factors associated with delays to anti-TB treatment

HIV co infection, having extra pulmonary TB, taking self-treatment before HCF visit, and traveling more than an hour to the first visited HCF increase the likelihood of patient delay beyond 25 days. On contrary, having good knowledge about TB decrease the odds of patient delay beyond 25 days.Those cases travelled more than an hour to reach the first visited HCF are 37% more likely to have patient delay beyondn25days. Having extra pulmonary TB and HIV co infection are 54 and 80% more likely to have patient delay beyond 25 days (Table 4).

First presentation to non DOTS HCF, visiting more than one HCF until diagnoses, and having patient delay beyond 25 days more likely increase provider delay beyond 22 days. (Table 5). Those cases first visited non-DOTS center and having patient delay beyond 25 days are 42 and 81% more likely to have provider delay beyond 22 days (Table 5). Moreover, having extra pulmonary TB, first visitation to non DOTS HCF, consulting informal care before visiting formal care more likely to increase odds of total delay beyond 55 days (Additional file 1: Table S2).

Discussion

Prompt detection and treatment of cases has been a priority in the prevention and control of TB that can be realized upon timely care seeking by patients and diagnosis by the health system. Our study assessed the delay and associated factors with the care seeking, diagnosis and treatment of TB in rural districts of southwestern Ethiopia. We found long patient, provider, and total delays, among TB cases on treatment. TB patients had waited for a median of 25 and 55 days respectively to initiate formal care seeking and anti-TB treatment. Both patients and provider delays contribute nearly equally to the total delay which is consistent with other studies from Ethiopia [20] and elsewhere [14]. The longer time elapsed since onset of illness to treatment initiation implies increased risk of morbidity and mortality among the cases and diseases transmission in the community [10, 33–35]. All forms of the delays are attributed to patient, disease and health system related factors. This implies the delays are multifaceted that calls for intensified TB case finding through strengthening healthcare facilities and health promotion activities.

Patients had waited for a median of 25 days until seeking help at formal health care providers which is consistent with 30 days in northern part of Ethiopia [17, 31, 36], 28 days in Uganda [14] and 30 days in Angola [13]. The relatively lower delay could be due to better access to HCF where nearly 80% of the cases traveled less than an hour to reach the first HCF. However, only a third (32%) of the cases had made visits to formal health care within 15 days of recommended timeline for TB suspects to visit HCF [29].Besides, more than half (57%) of the cases did not perceive their care seeking was delayed which implies the symptoms are taken as common and less severe to urge consultation of healthcare provider.

Before visits to formal health care facility, patients had taken variety of actions those influence timing of care seeking. Consistent with other studies, patients who took prior self-treatment were more likely to delay seeking formal care compared to those first consulted health care providers [37, 38]. This could be due to use of some home remedies or over the counter antibiotics or analgesics those might lessen the manifestation of the illness for the time being [39]. Moreover, those patients first visited traditional healer and holy water are more likely to have higher total delay. This could be due to the beliefs attached to the traditional care and holy water those might inhibit timely presentation and diagnosis [24].

Table 4 Factors associated with patient delay among TB patients on DOTS, southwestern Ethiopia January to December 2015

Variable		Patient delay(days)		COR (95% CI)	AOR (95%CI)
		>25 *n*(%)	<=25 *n*(%)		
Age				1.01(0.99,1.02)	1.01(1.001,1.03)*
Educational status	Illiterate	89(42.0)	123(58.0)	1.00	1.00
	Completed primary	215(55.3)	174(44.7)	1.05(0.75,1.47)	1.23(0.85,1.78)
	Secondary and above	63(47.0)	71(53.0	0.92(0.59,1.42)	1.27(0.77,2.1)
Type of TB	Pulmonary positive	175(47.9)	190(52.1)	1.00	1.00
	Pulmonary negative	104(47.7)	114(52.3)	0.95(0.68,1.32)	0.93(0.65,1.33)
	EPTB	91(59.9)	61(40.1)	1.51(1.03,2.21)	1.54(1.03,2.29)*
HIV status	Positive	41(60.3)	27(39.7)	1.52(0.92,2.52)	1.80(1.05,3.1)
	Negative	329(50.7)	338(49.3)	1.00	1.00
First action to illness	Self treatment	60(61.2)	38(38.8)	1.84(1.19,2.85)	1.72(1.07,2.75)*
	Traditional care	11(73.3)	4(26.7)	3.21(1.01,10.2)	2.98(0.91,9.72)
	Holy water	18(69.2)	8(30.8)	2.2(0.96,5.03)	2.01(0.86,4.67)
	Consult HCP	281	315	1.00	1.00
First visited HCF	Health post	13(81.3)	3(18.8)	1.00	1.00
	Health center	130(54.6)	108(45.4)	0.26(0.07,0.95)	0.25(0.07,0.94)*
	Hospital	98(44.3)	123(55.7)	0.18(0.0,0.64)	0.17(0.05,0.64)*
	Private clinic	129(49.6)	131(50.4)	0.22(0.06,0.79)	0.22(0.06,0.81)*
Travel time to first HCF	<=1 h	205(46.9)	232(53.1)	1.00	1.00
	>1 h	165(55.4)	133(44.6)	1.37(1.02,1.84)	1.37(1.01,1.88)*
Knowledge towards TB	Good	264(48.4)	281(51.6)	0.77(0.55,1.07)	0.67(0.46,0.98)*
	Poor	106(55.8)	84(44.2)	1.00	1.00

*statistically significant at $p < 0.05$

Table 5 Factors associated with provider delay among TB patients on DOTS southwest Ethiopia, January to December 2015

Variable		Provider delay (days)		COR(95% CI)	AOR(95%CI)
		> 22 n(%)	<=22 n(%)		
Type of TB	Pulmonary positive	182(49.9)	183(50.1)	1.00	1.00
	Pulmonary negative	103(47.2)	115(52.8)	0.9(0.64,1.26)	0.87(0.60,1.25)
	Extra pulmonary	82(53.9)	70(46.1)	1.18(0.81,1.72)	1.08(0.72,1.62)
HIV status	Positive	39(57.4)	29(42.6)	1.38(0.84,2.30)	1.33(0.78,2.27)
	Negative	328(49.2)	339(50.8)	1.00	1.00
First action to illness	Self treatment	44 (44.9)	54(55.1)	0.81(0.53,1.25)	0.75(0.47,1.19)
	Traditional care	9(60.0)	6(40.0)	1.5(0.53,4.27)	1.19(0.47,3.51)
	Holy water	16(61.5)	10(38.5)	1.6(0.71,3.58)	1.28(0.55,2.99)
	Consult HCP	298(50.0)	298(50.0)	1.00	1.00
First visited HCF	DOTS center	203(44.2)	256(55.8)	1.00	1.00
	Non DOTS	164(59.4)	112(40.6)	1.85(1.36,2.50)	1.42(1.01,2.00)*
Number of visited HCF	1	233(62.0)	143(38.0)	2.77(2.05,3.73)	2.34(1.69,3.24)*
	> 1	133(37.2)	225(62.8)	1.00	1.00
Patient delay	Yes	213(57.6)	157(42.4)	1.80(1.36,2.50)	1.81(1.33,2.50)*
	No	154(42.2)	211(57.8)	1.00	1.00

HCP=Health Care Provider, *statistically significant at $p < 0.05$

Patients co infected with HIV are more likely to delay care seeking compared to those non- infected. This could be due to the alteration of classical clinical manifestations and signs of TB among HIV co infected patients [40]. On the other hand, patients suspected or tested HIV positive delay to present themselves to HCF due to fear of stigma attached to the co-occurrence of TB and HIV [9, 41, 42]. As a result, the high mortality among HIV co infected TB patients is partly explained by the delays to TB treatment [13, 43]. Those extra pulmonary cases patients are more likely to delay seeking care compared to the pulmonary cases. A similar finding was also reported form a study in northwest Ethiopia [25]. This could be due to the fact that extra pulmonary cases manifest with less severe and non-specific symptoms that urge patients to perceive the illness to be non-serious [44].

Patient's perception and knowledge towards the TB disease and control activities do have impact on the care seeking practices. The study revealed that patients with good knowledge towards the TB disease and program are less likely to delay seeking care. Similarly, other studies have reported lack of knowledge and mistrust of the TB program as a reason for delayed care seeking [23, 45, 46]. In contrast, awareness and belief about TB's curability is associated with longer patients delay [7, 14]. These imply need for awareness creation towards the TB illness and its control program to clear the paradox between the belief and longer delay.

The first consultation at HCF was made primarily (69.9%) at lower level public health care units (health posts and health centers) and private clinics. This is consistent with a study in Mediterranean countries that reported two thirds of patients first visited private sectors [46]. Nonetheless, diagnosis of TB was made primarily at hospital (61%) despite only few had made first visit to the hospitals. As a result, majority of the cases had made more than one visit to different HCFs until diagnosis. Similarly, studies from Uganda [14] and China [47] reported significant number of patients had visited more than one HCF until diagnosis. Subsequent to the missed opportunities during the repeated visits, diagnosis of TB had been made after a median of 22 days from the first visit to HCF. This is consistent with 21 days in a study from Amhara Region in Ethiopia [17] but higher than 6 in Addis Ababa [20] and 9 days in Tigray, northern Ethiopia [19]. The discrepancies could be due to the differences in accessibility to well equipped HCFs and skilled providers usually situated in cities like Addis Ababa. The longer provider delays due to the repeated visits portray high level of missed opportunities of early diagnosis that could have increased infectious period of the cases and costs incurred by the patients and households.

Longer provider delays had been reported among patients who first visited HCFs not providing DOTS services including health posts and private clinics. This is consistent with a study from Uzbekistan [38] and India [44].The higher provider delay at lower care units and private clinic could be due to lack of supplies, guidelines and skilled providers that enhance adherence to the national TB control program. In the current study, diagnosis of TB was mainly made at hospitals that depict unnecessary drugs and treatments provision at series of HCFs incurring extra cost. Besides the cost incurred, medications at the repeated visits themselves lead to delays to diagnosis and serious outcomes including drug resistance [48].On the other hand, the lower health care units and private clinics might lack proper logistics and skilled providers to timely diagnose the cases. Hence, expansions of the DOTS package to the lower and private clinic is required to curb the prevailing long delays.

Patients delayed to seek care are also more likely to have delayed diagnosis and treatment after they initiated care seeking. In contrast a study in Georgia [49] reported those patients with increased patient delay are less likely to have prolonged diagnostic delay. The discrepancy could be due to differences in measurement of the two delays. The higher odds of provider delay among those delayed to seek care can be explained by patients use of different forms of self-treatment and homemade remedies those might alter the manifestations of the TB illness that pose difficulties in timely diagnosis [39, 49]. Those patients delayed to seek care might have been ill for such long duration at which time productivity is compromised. Hence, the patients might be unable to cope with the costs required to have timely diagnosis even after initiating the care seeking. In addition, the long ill days are also associated with more severe disease at presentation [10] which hinders timely diagnosis [21].

Our study has few limitations. First, the study was carried out on those cases ultimately sought care and on treatment at the time of the study. Thus, measurement of delays relied on patient self-report that is liable to recall bias. We minimized this bias through interviewing patients soon after diagnosis and helping them to recall using local events. Second, the assessment of patients' knowledge towards the TB diseases and its control program might be influenced by the information provided during treatment initiation. Therefore, this could have brought egg and chicken dilemma as the knowledge or care seeking preceded one to other. Third, we studied only new and adult cases so that the findings cannot be generalized to all forms of TB cases among all age groups. Fourth, we were not able to interview patients died during the intensive phase of treatment those could underestimated the true total delay attributed to the severe illness.

Lastly our study lacked qualitative assessment of patients and health system those would have supplemented the quantitative data. On the other hand, consecutive enrollment of cases that minimized selection bias and triangulation of data sources from patient interview and chart reviews could be mentioned as strength of the study. Finally, our study is valid and generalizable to new adult cases in similar settings.

Conclusions

Tuberculosis patients in the study area had passed through too long journey to initiate anti-TB treatment. The long journey is attributed to patient and provider delays those are positively correlated and contributed nearly equally to the total delay. The long delays at different levels of healthcare facilities portray high level of missed opportunities of early diagnosis of TB. The patient, provider, and total delays are attributed to the patient, disease and health system related attributes reflecting need for multifaceted intervention at all levels. Therefore, improving community awareness, involving informal providers, health extension workers and TB treatment supporters can reduce the patient delay. Similarly, cough screening and improving diagnostic efficiencies of healthcare facilities should be in place to reduce the provider delays.

Additional file

Additional file 1: Table S1. Differences in median patient, provider and total delays among TB cases on DOTS, Southwestern Ethiopia, January to December 2015. **Table S2.** Factors associated with total delay among TB patients on DOTS, southwest Ethiopia January to December 2015 (DOCX 21 kb)

Abbreviations

ART: Antiretroviral Therapy; CI: Confidence Interval; CPT: Cotrimoxazole Prophylactic Therapy; DOTS: Directly Observed Treatment Short course; EPTB: Extra pulmonary Tuberculosis; HBC: High Burden Countries; HCF: Healthcare Facility; HIV: Human Immunodeficiency Virus; IQR: Inter-quartile Range; OR: Odds Ratio; PTB: Pulmonary Tuberculosis; TB: Tuberculosis; WHO: World Health Organization

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Availability of data and materials

The data generated and analyzed for this paper will be available from corresponding author upon reasonable request.

Authors' contributions

AA conceived and designed the study, collected and analyzed data, prepared manuscript: WD and DJ critically reviewed for intellectual content of the protocol and manuscript as primary and co-supervisors respectively. All authors approved the final version of the manuscript.

Ethics approval and consent to participate

The study was ethically approved by Institutional Review Board (IRB) of the College of Health Sciences at Addis Ababa University (protocol number: 045/14/sph). Written informed consent was sought from each study participant before the interview. Patient clinical profile from records and unit register was retrieved upon permission from respective health care facilities.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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RESEARCH ARTICLE

Knowledge, attitudes, and practices related to TB among the general population of Ethiopia: Findings from a national cross-sectional survey

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Data Availability Statement: Data are available upon request–it is required that official or reasonable request should come to the authors or their institutions to share, as the data has sensitive personal property related questions. The authors have uploaded many supporting documents including data collection tools and site selection procedures. The contact address for data requests is Challenge TB/MSH Ethiopia, Box 1157 code 1250, Addis Ababa, Ethiopia; Phone +251-116-630-145 or +251-116-630-164 or through the corresponding author -dgemechu@msh.org.

Abstract

Introduction

Ethiopia is among the high-burden countries for tuberculosis (TB), TB/HIV, and drug-resistant TB. The aim of this nationwide study was to better understand TB-related knowledge, attitudes, and practices (KAPs) and generate evidence for policy and decision-making.

Materials and methods

We conducted a cross-sectional TB KAP survey in seven regions and two city administrations of Ethiopia. Eighty *kebeles* (wards) and 40 health centers were randomly selected for the study. Using systematic sampling, 22 households and 11 TB patients were enrolled from each selected village and health center, respectively. Variables with a value of $p = < 0.25$ were included in the model for logistic regression analysis.

Results

Of 3,503 participants, 884 (24.4%), 836 (24.1%), and 1,783 (51.5%) were TB patients, families of TB patients, and the general population, respectively. The mean age was 34.3 years, and 50% were women. Forty-six percent were heads of households, 32.1% were illiterate, 20.3% were farmers, and 19.8% were from the lowest quintile. The majority (95.5%) had heard about TB, but only 25.8% knew that TB is caused by bacteria. Cough or sneezing was reported as the commonest means of TB transmission. The majority (85.3%) knew that TB could be cured. Men, better-educated people, and TB patients and their families have higher knowledge scores. Of 2,483 participants, 96% reported that they would go to public health facilities if they developed TB symptoms.

Discussion

Most Ethiopians have a high level of awareness about TB and seek care in public health facilities, and communities are generally supportive. Inadequate knowledge about TB

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transmission, limited engagement of community health workers, and low preference for using community health workers were the key challenges.

Conclusions

Given misconceptions about TB's causes, low preference for use of community health workers, and inadequate engagement, targeted health education interventions are required to improve TB services.

Introduction

Worldwide, tuberculosis (TB) is the leading cause of death from a single infectious agent. In 2017 about 10 million TB cases were estimated to occur, a third of them were missed, and about 1.6 million died in the same year [1]. TB is inequitably distributed and clustered among disadvantaged and socioeconomically deprived population groups [2–5]. TB is primarily a disease of the poor and its magnitude is high in socially disadvantaged populations or people residing in poor living condition, which are characterized by lack of education, poor housing, inadequate nutrition, overcrowding, and socioeconomic factors. Lack of awareness prevails in populations living in poor conditions, which leads to delay in health care-seeking due to lack of knowledge about the symptoms of TB and of prevention measures. Lack of awareness, in turn, leads to further transmission of the disease and poor treatment outcomes.

The decline of TB in developed countries with improved living conditions [6–8] indicates that poor living conditions, as reflected by lack of awareness, stigma, poor health care–seeking behavior, and deficient health systems, favor TB transmission and occurrence of disease [9–11]. In addition, distance, cost, and sociocultural barriers limit care seeking [12–14].

Studies have shown that awareness of or knowledge about TB and the availability of patient-centered services in settings with high burdens of human immunodeficiency virus (HIV) and TB is inadequate [15–17]. Generally, TB-related knowledge and attitudes vary across countries, ranging from an understanding of its infectious cause to the belief that its cause is the evil eye, and from supportive to highly stigmatized views toward the disease and patients. Adequate knowledge and positive attitudes about TB patients are expected to contribute to improved health care–seeking behavior. However, awareness about TB and the availability of services are often found to be suboptimal among underprivileged social groups, and illiterate, inaccessible, rural, and impoverished communities [18–22].

Ethiopia is among high-burden TB, TB-HIV, and drug-resistant countries. It has implemented TB programs for decades and rapidly decentralized TB services. However, the National TB Program (NTP) continues to miss about a third of estimated TB cases. This could be due to lack of awareness about TB, lack of access, poverty, and TB-associated stigma, as indicated by studies conducted in some parts of the country [23–25]. Therefore, understanding knowledge, attitudes, and practices (KAPs) related to TB and their underlying causes is important to design national responses to improve TB services in the communities of Ethiopia.

The NTP of Ethiopia has decentralized services to the community by deploying health extension workers (HEWs), who deliver preventive and promotive health services, including health education, to improve community awareness and enhance service delivery [26]. Although there is no direct measurement of the results of such efforts, evidence shows improvements in the level of awareness of or knowledge about TB [16, 23, 27–29]. However,

these lacked the depth of information required to understand KAPs, did not address sub-population groups, and were limited to smaller geographic areas. The aim of this study was to better understand national TB- related KAPs in Ethiopia and generate evidence for policy and decision-making.

Materials and methods

Study setting, population, and design

This TB KAP survey was conducted in seven regions and two city administrations of Ethiopia, covering 92% of the national population. Ethiopian Somali and Afar regions were excluded from the survey because they were not directly supported by the Challenge TB Project. Ethiopia is the third most populous country in Africa, with a population of more than 100 million people, of whom 85% live in rural areas. Currently, 256 hospitals and 3,390 health centers provide TB services, and over 16,000 health posts deliver community-based TB services in the country.

This was a cross-sectional population-based survey conducted from October to November 2017. A single population proportion formula was used to estimate sample size based on multiple indicators from the Ethiopia Demographic and Health Survey 2011 report [7]. For the other indicators where previous nationwide reports were unavailable, we used a percentage of 50% to obtain the maximum sample size. We used a design effect of 2 to adjust for the multistage cluster sampling and added 10% to adjust for non-response (S1 Table). The estimated sample was 3,463 in total and shown by regions (S8 Table).

Sixteen zones (provinces) and four sub-cities were selected from the regions and city administrations included in the study. From each zone or sub-city, two districts or *kebeles* (wards) were randomly selected. From each district, one rural and one urban kebele were identified for the study. The total number of kebeles included in the study was 80, which were divided into clusters as the final study unit. Households were identified by systematic sampling, and 22 participants were enrolled from the selected households in the clusters. Forty health centers were selected from districts of the regions, sub-cities, and kebeles of urban regions or cities (Fig 1) shows the description of the study site selection for the KAP survey in Ethiopia. Once we had selected the health centers and villages for study, we interviewed 11 TB patients from each health center and their families. The general population groups were selected from randomly selected blocks or clusters in urban and rural villages, respectively. Of these, 22 households were selected using a systematic sampling technique. From the households, a household member at least 18 years old who had lived in the house for at least 6 months was selected by lottery. We selected male and female participants alternately to ensure gender balance. If no one was home at the selected household during the day of data collection, it was replaced by the adjacent household.

Data collection tools, data analysis, and quality assurance

We collected KAP data from the sub-populations using data collection tool (S2 Table) but did not conduct any interviews of TB patients related to attitudes. Attitude-related interviews were conducted for the general population and families of TB patients, representing 2,619 participants. Under each category of the data collection tool, there were many variables for KAPs, which we categorized to measure the outcomes. Under educational status, those who attended but did not complete primary school were classified as "read and write only," while those who completed education until grade six were classified as having a primary school education.

We identified the total number of interview questions used to assess the knowledge of the study participants and the total number of expected correct answers. We calculated knowledge

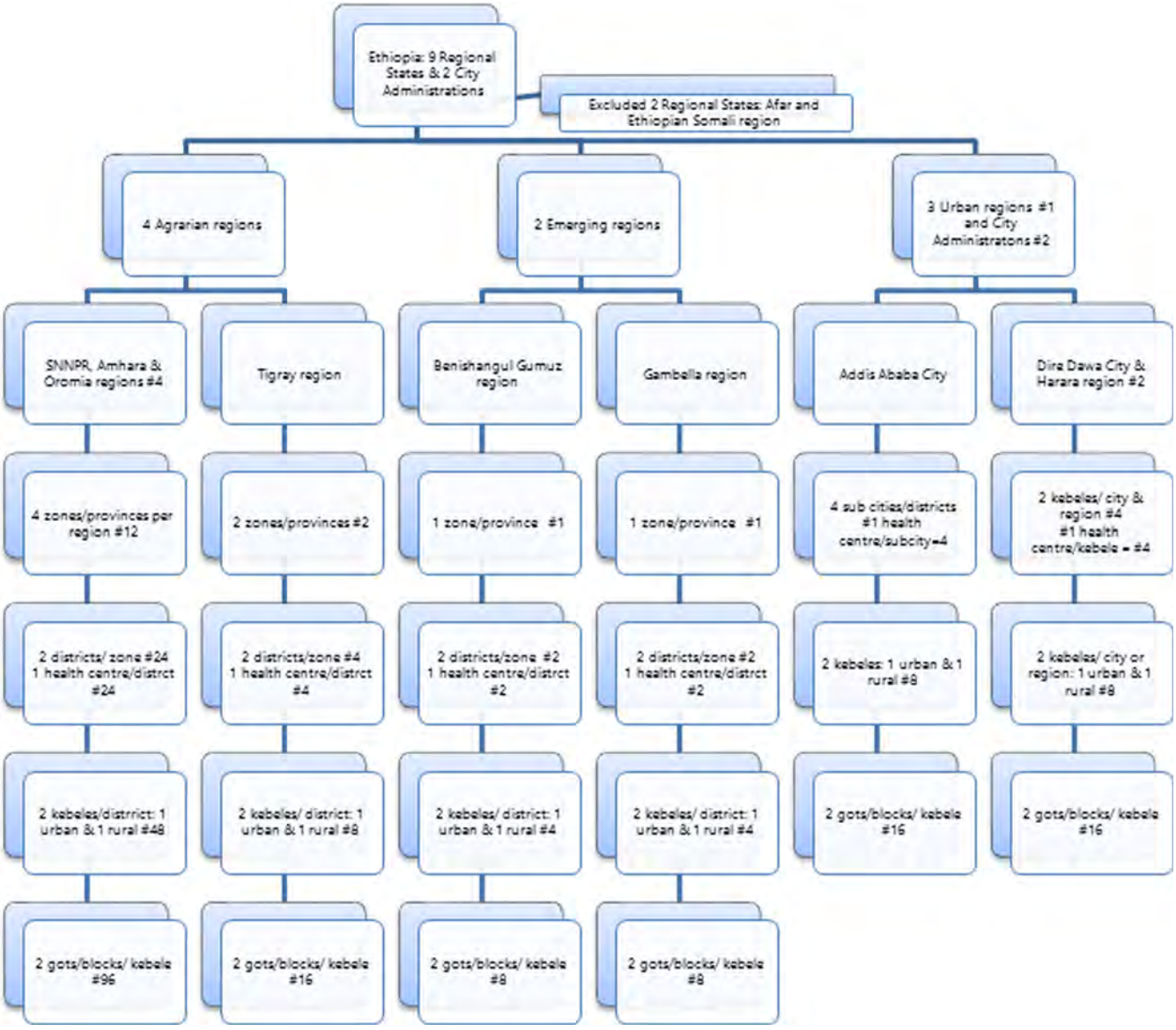

Fig 1. Study sites for the knowledge attitude and practice related to tuberculosis in Ethiopia.

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scores using the mean of the number of correct answers by the study participants as a cutoff point to categorize high or low knowledge scores. The study participants who answered above the mean score were classified as having a high score, while those who scored below the mean were classified as having a low knowledge score.

The national wealth index was constructed using the World Health Organization (WHO) tool for KAP surveys [30]. Wealth-related variables were initially constructed for rural and urban populations, and later we constructed a common wealth index using variables that were considered common for both rural and urban areas. Finally, both the rural and urban wealth index regression coefficients were mapped into the common wealth index, resulting in a composite "national" wealth index, which was categorized into quintiles.

We used pretested semi structured questionnaires, adopted from the WHO guide, to collect quantitative data (30). Tablets were used to collect data using the Web-based platform of Census and Survey Processing System (CSPro) software.

Data extracted from this platform were exported to SPSS version 25.0 (IBM SPSS Statistics, 2019) for analysis. We calculated composite knowledge scores using knowledge variables and used mean knowledge scores to dichotomize results into high and low scores. Variables associated with the outcome variable with a p value less than 0.25 were included in the multivariate regression model. A p value less than 0.05 was considered to be statistically significant.

We trained experienced data collectors and supervisors who speak local languages. The questionnaires were prepared in English, translated into regional languages, and back-translated to check for translation accuracy. Supervisors conducted household and random data checks. The data manager, a CSPro expert, centrally checked for data quality. A central research team supervised the data collection process.

Ethical considerations

The National Research Ethics Review Committee of the Ministry of Science and Technology approved the study. Oral informed consent was requested, as some of the study participants were illiterate and from rural communities, which makes obtaining written consent problematic. The Federal Ministry of Health provided a letter of support to conduct the study. Oral informed consent was obtained from the study participants and documented (S1 File).

Results

Sociodemographic characteristics of the study participants

We enrolled 3,503 study participants. Of these, 884 (24.4%), 836 (24.1%), and 1,783 (51.5%) were TB patients, families of TB patients and general population respectively. The mean age and standard deviation were 34.3 $\pm$ 12.9 years for both sexes, 34.9 $\pm$ 13.2 for men and 33.8 $\pm$ 12.5 for women. Fifty per cent of the study participants were in the age range of 18–30 years and 50% were women. Forty-six per cent (1,594) were heads of households, 62.2% were married, 32.1% were illiterate, 20.3% were farmers, and 19.8% were from lowest quintile (Table 1).

Knowledge about TB: Sources of information, cause, transmission, and prevention

Most of the population, 3,306 (95.5%) had heard about TB and 25.8% (986) knew that TB is caused by bacteria. However, 47% (1,626) of the participants did not know the cause of TB. Cough or sneezing was reported as a means of TB transmission by 70.4% (2,585) of the respondents. The commonest symptoms were cough in 85.5% (2,975), chest pain in 17.2% (596), fever in 17.1% (593), and other symptoms (weight loss, poor appetite, night sweats, blood in the sputum, shortness of breath, fatigue, or body swelling) in 67.6% (2,340) of participants.

Most of the study participants, 2,627 (75.9%), knew that anyone could get TB. Lung and bone were mentioned to be affected most by 80% (2,771) and 23.3% (807) of participants, respectively. Most of the study participants, 85.3% (2,953), knew that TB could be cured by taking medicine (Table 2).

TB patients and their families had better knowledge about TB related to the body parts it affects, whether TB is curable or not, and how TB can be cured compared to the general population. However, knowledge about the causes and means of transmission among the three groups was low (S3 Table).

Table 1. Sociodemographic characteristics of the study participants, 2017.

Variables	Variable Categories	Frequency	Percent
Population type	General population	1,783	51.5
	TB patients	844	24.4
	Families of TB patients	836	24.1
Sex	Male	1,730	49.96
	Female	1,733	50.04
Age in years	18–30	1,732	50.0
	31–60	1,587	45.8
	> 60	144	4.2
Relationship to head of household	Head	1,594	46.0
	Spouse	1,034	29.9
	Son/daughter	648	18.7
	Other relative	165	4.8
	Non-relative	22	0.6
Marital status	Married	2,153	62.2
	Never married/never lived together	829	23.9
	Divorced/separated	255	7.4
	Widowed	202	5.8
	Living together	24	0.7
Educational Status	Not able to read and write	1,113	32.1
	Read and write only[1]	219	6.3
	Primary[2]	1,007	29.1
	Secondary	734	21.2
	Above secondary	390	11.3
Occupation	Employed	438	12.7
	Housewife	685	19.8
	Farmer	703	20.3
	Daily laborer	362	10.4
	Trader	587	17.0
	Student	329	9.5
	No job/dependent	263	7.6
	Housemaid	75	2.2
	Others	21	0.6
Wealth quintile	Lowest	684	19.8
	Second	909	26.2
	Third	820	23.7
	Fourth	643	18.6
	Highest	407	11.8

1 Those who went to school but did not complete the primary level of education

2 Those who have completed education through grade six

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Most people, 668 (93.6%), of the population had heard about TB; 53.4% had heard from family, friends, neighbors, and colleagues. Television and radio contributed to 35.1% and 36.3%, respectively. Less than a third of the study population, 30.4% and 7.7%, had heard about TB from HEWs and Health Development Army (HDAs) respectively. The population that had heard from TV and radio varied by region ($p < 0.05$) but was smallest in Amhara

Table 2. Sociodemographic characteristics of the study participants, 2017.

Variables (n = 3,463)	Responses	N	%
Have you ever heard of TB?	Yes	3,306	95.5
	No	157	4.5
Cause of TB	Bacteria	986	28.5
	Superstitions[1]	739	21.3
	Don't know	1,626	47.0
How can a person get TB?	Coughing or sneezing	2,424	70.0
	Drinking raw milk	161	4.7
	Proximity[2]	2,141	61.8
	Don't know	472	13.6
Who can be infected with TB?	Anyone	2,627	75.9
	HIV-infected people only	210	6.1
	Poor people only	531	15.3
	Poor behavior[3]	671	19.4
Body parts affected by TB	Lung	2,771	80.0
	Intestine	290	8.4
	Bone	807	23.3
	Lymph nodes[4]	272	7.9
	Others	122	3.5
	Don't know	382	11.0
Symptoms of TB	Cough	2975	85.9
	Chest pain	596	17.2
	Fever	593	17.1
	Other constitutional symptoms[5]	2,340	67.6
	Don't know	163	4.7
Is TB a preventable disease?	Yes	2,638	76.2
	No	243	7
	Don't know	425	12.3
Prevention methods	Avoiding cough in front of people	1,873	54.1
	Safe disposal of sputum	852	24.60
	Ventilation of living room	608	17.6
	Avoiding close contact with TB patients	1,065	30.8
	Vaccination of children	170	4.9
	Others	285	8.2
	Don't know	206	6.0
Can TB be cured?	Yes	3,078	88.9
	No	63	1.8
	Don't know	165	4.8

[1]Evil eye, Satan, witchcraft, other causes

[2] Sharing utensils/bed; touching a person with TB; through food or water; sexual contact with a person who has TB; mosquito bites; exposure to cold; others

[3]Only homeless people; only alcoholics; only drug users; only those who have been in prison; others

[4] Refers to swelling around the neck, armpit, and inguinal areas that has lasted at least two weeks

[5] Weight loss; poor appetite; night sweating; blood in the sputum; shortness of breath; fatigue; swelling; others

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Region. Family, friends, neighbors, and colleagues contributed more as a source of information about TB in Oromia and Amhara regions ($p < 0.05$) (S4 Table).

About 20.9% (349) of the general population, 25.3% (238) of families of TB patients, and 28.9% (238) of TB patients have heard about DR-TB. Three-fourths of the sub-population knew that it was often caused by irregular intake of anti-TB drugs. Twenty-four percent of the study participants responded that they had heard about DR-TB, and the figure was higher among TB patients and their families compared to the general population. Of those who had heard about DR-TB, at least 75% indicated irregular drug intake as the main reason for its development. Less was known about its dangerousness, transmission, and possibility of cure (S4 Table).

Factors associated with knowledge

Men, better–educated people, and TB patients and their families had higher knowledge. Gambella and Oromia regions had higher knowledge than other regions, while Amhara Region had lower knowledge compared to other regions. Study participants from the lowest and second quintiles had lower knowledge. There was no significant difference whether the participants were from urban or rural kebeles (Table 3). Generally, knowledge scores were higher in families of TB patients and TB patients compared to the general population (S5–S7 Tables).

Attitude about tuberculosis

A total of 2,619 participants (families of TB patients and the general population) were interviewed. Half of the respondents, 51% (1,270), thought that they could get TB in their lifetime.

Table 3. Factors associated with knowledge about TB in Ethiopia, 2017.

Factors		COR	95% CI	AOR	95% CI
Sex	Female	1		1	
	Male	1.37	1.16–1.61	1.27	1.05–1.52
Education	Illiterate	1		1	
	Read and write only	1.66	1.19–2.33	1.62	1.13–2.31
	Primary	2.33	1.91–2.86	2.10	1.68–2.62
	Secondary	3.96	3.06–5.12	3.30	2.49–4.38
	Above secondary	7.91	5.14–12.17	5.88	3.70–9.34
Population type	General population	1		1	
	TB patients' families	1.61	1.30–1.99	1.72	1.37–2.16
	TB patients	1.31	1.07–1.60	1.46	1.17–1.83
Wealth quintile	Lowest	1		1	
	Second	1.44	1.16–1.78	1.27	0.99–1.61
	Third	2.12	1.67–2.69	1.92	1.44–2.56
	Fourth	3.09	2.35–4.07	2.76	1.93–3.95
	Highest	7.38	4.79–11.39	5.56	3.32–9.31
Residence	Rural	1		1	
	Urban	1.78	1.51–2.10	0.90	0.72–1.11
Region	Amhara	1		1	
	SNNP	1.83	1.44–2.31	2.78	2.14–3.61
	Tigrai	3.32	2.36–4.68	4.08	2.87–5.88
	Benshangul Gumuz	2.45	1.61–3.73	3.51	2.25–5.49
	Gambella	3.40	2.07–5.59	5.91	3.49–9.98
	Addis Ababa	6.28	4.12–9.59	4.08	2.58–6.45
	Dire Dawa	2.27	1.51–3.42	1.79	1.15–2.80
	Harari	1.77	1.20–2.60	1.64	1.08–2.48
	Oromia	2.47	1.93–3.17	4.56	3.45–6.01

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Sixty-six percent (1,634) reported that they would cope with TB, while 32% (786) reported that they would be afraid. About 5% reported that they would be surprised, ashamed, or embarrassed, or would feel sad or hopeless if they acquired TB (Table 4).

TB-related practices

Of 2,483 participants, 96% reported that they would go to public health facilities if they developed TB symptoms, while 13% preferred private facilities, 3% pharmacies, and 1% traditional healers. Of 2,463 respondents, 63% mentioned that they would go to health facilities immediately, while 30% would go in two weeks and 6% would go after two weeks.

We interviewed 1,668 study participants about practices. Of these, 197 (11.7%) had had TB symptoms during the study period. Of the 197, 67.5% visited public facilities, 10.7% visited pharmacies, and 17.3% did nothing. Among 210 respondents, those who had TB symptoms were advised by health care workers or community health extension workers to visit public and private facilities in 71.9% and 7.1% of cases, respectively. From the study participants who sought care, 5% contacted HEWs and HDAs for advice. Only 6 study participants (0.4%) informed HEWs and HDAs if they knew a person with TB symptoms. About a quarter (23.3%) of the population did nothing when they found presumptive TB cases in their community, while 3.2% (54) participated in presumptive TB case identification (Table 5).

Table 4. Attitudes of study participants about tuberculosis.

Questions	Variables	Responses	Number	Percent
Do you think you could get TB?		No	1,213	49%
		Yes	1,270	51%
What would be your reaction if you acquired TB?	Cope with it	Yes	1,634	66%
		No	849	34%
	Fear	Yes	786	32%
		No	1,697	68%
	Surprise	Yes	117	5%
		No	2,366	95%
	Shame	Yes	72	3%
		No	2,411	97%
	Embarrassment	Yes	48	2%
		No	2,435	98%
	Sadness/hopelessness	Yes	115	5%
		No	2,368	95%
Whom will you inform if you get TB?	Doctor/health worker	Yes	2,065	83%
		No	418	17%
	Spouse	Yes	532	21%
		No	1,951	79%
	Parent	Yes	690	28%
		No	1,793	72%
	Children	Yes	245	10%
		No	2,238	90%
	Other family member	Yes	632	25%
		No	1,851	75%
	Close friend	Yes	381	15%
		No	2,102	85%
	No one	Yes	22	1%
		No	2,461	99%

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Table 5. Practices related to TB among the general population in Ethiopia, 2017.

Variable		N	%
Action taken when experienced cough of at least 2 weeks		197	11.1
	Sought care from health institution	133	67.5
	Sought care from pharmacies	21	10.7
	Contacted HDA to get advice	5	2.5
	Contacted HEW to get advice	5	2.5
	Visited spiritual/traditional healer	7	3.6
	Did nothing	34	17.3
Action taken when encountered a person who had cough for at least 2 weeks		210	11.8
	Advised to seek care from public health institutions	151	8.5
	Advised to seek care from private health facilities	15	0.8
	Advised to seek care from pharmacies	10	0.6
	Informed the HDA to advise him/her	5	0.3
	Informed the HEW to advise him/her	1	0.1
	Advised to seek care from spiritual/traditional healer	4	0.2
	Did nothing	49	2.8
Involvement in TB prevention and control		54	3.0
	Referred family member to health facility	17	1.0
	Referred community member to health facility	26	1.5
	Involved in TB screening at community level	11	0.6
	Involved in tracing TB treatment defaulters	348	19.5
	Advised parents to get their infants vaccinated for TB	257	14.4
	Advised TB patients to take their drugs properly	141	7.9
	Served as TB treatment supporter	111	6.2
	Has family member with cough for 2 or more weeks	84	4.7
Action taken when family member had cough		111	6.7%
	Did nothing	27	1.5
	Took to public health facility	66	3.7
	Took to private health institution	12	0.7
	Took to pharmacy	3	0.2
	Took to spiritual/traditional healer	3	0.2

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Discussion

A high level of awareness about TB, supportive communities, and health care–seeking in public health facilities characterize the general population of Ethiopia. Most of the participants have heard about TB. However, inadequate knowledge about its transmission, limited engagement of community health workers, and low preference of the community for using community health workers were key challenges. To address them will require strengthening community-level interventions in Ethiopia. The findings also suggest the need for targeted health education interventions to close knowledge gaps and reach the most disadvantaged and affected communities.

A nationwide response to end TB requires adequate community knowledge about TB and its prevention and care [31]. We report higher knowledge about TB than other reports from Africa [17, 32–34] but lower knowledge than reports from Bangladesh, one of the high burden countries [35]. This could be due to difference in the study period, types of population groups studied, and existing health system [15]. The higher knowledge in Ethiopia could be explained by the increased access to primary health care created by the engagement of community health

workers. There are also regional knowledge variations, which could be explained by the extent of community engagement and the level of regional capacity. The lower level of knowledge in Amhara Region compared to other regions of Ethiopia could be a result of lower engagement of the HEWs in TB work or sociocultural factors despite more than a decade of intensive support. Improving the engagement of HEWs in providing continued TB-related health education requires consideration, as recommended in a previous study from the region [27].

Several studies have shown that TB awareness is higher in urban communities than in rural communities, due to the accessibility of health services and better socioeconomic conditions [21, 36–38]. However, unlike many studies, this study did not find knowledge differences between rural and urban communities of Ethiopia, which could be due to the community-based health extension program the conduct health education sessions in the community [25, 39]. However, we report that HEWs were contacted by only 5% of those sought care. This finding suggests a need to strengthen support for the community health program [40]. The results about the contribution of the HEWs may seem contradictory. Their effectiveness is affected by the level of support they receive, the strength of the health system, and commitment of the HEWs and other motivational factors, which vary across regions and limit the contributions of the HEWs. In the southern region of Ethiopia, where HEWs are actively engaged in TB prevention and control, however, they have significantly contributed to increased community knowledge about TB [41–43].

The main sources of information about TB were close relatives [8, 16] followed by mass media, radio, and television [44]. This indicates that the tradition of sharing health information within a society could be exploited as a means to reach the community and to design interventions to enhance community awareness. This could be an opportunity in countries where community health workers live and work in their communities.

Sub-population analysis showed that the general population has a lower level of knowledge about TB compared to TB patients and their families (S3 Table). This could be due to health education and counseling services provided by health workers and the presence of a TB patient in the household. Therefore, health education should be geared to raise the awareness of the general population using the health education media most accessible to the community (S4 Table).

Knowledge scores among TB patients were similar to those of their families and the general population. A patient-level study in Ethiopia showed that knowledge about TB among TB patients is just as low as in the general population [45]. However, knowledge varied by setting, socioeconomic condition, stigma, sex, and educational status [18, 28, 45, 46]. Men had better knowledge about TB compared to women. This could be due to access to better socioeconomic conditions, such as education and wealth, which in turn increased their access to health information and care. In addition, urban residence affected the level of knowledge about TB.

The level of community awareness about TB shapes the perceptions of the community about TB and affects health care–seeking behavior, the type of support the patient receives from the household or community, adherence to treatment, and future engagement in TB prevention and control efforts [23, 36]. In our study, the community was supportive of TB patients within the household and helped patients to adhere to treatment. This could be due to the low prevalence of HIV, sociocultural values of communal living, and lower awareness about TB transmission in rural settings. Among the study participants interviewed, 76% were heads of households or their spouses. This might have contributed to the creation of supportive communities. Studies from urban areas, however, indicate that there are negative perceptions about TB due to high HIV prevalence and its associations [47]. Attitudes about TB and health care–seeking are shaped by educational status, knowledge, and socioeconomic conditions, as found in other studies [19. 37. 48].

The generally low knowledge about DR-TB among the study population will remain a great challenge for the NTP in the fight against increasing drug resistance. However, most of those who had heard about DR-TB responded that it is caused by irregular drug intake, which is important information to communicate to patients and their families to encourage adherence to treatment. The NTP needs to ensure the inclusion of health education about DR-TB in health education sessions at health facilities and in communities if prevention and control of DR-TB are to be successful.

Most of the study participants mentioned that they could cope with TB if they acquired it. Compared to the report from Nigeria that reported depression as high as 45% among patients and 13.4% among family members [49], we found only about 5% of people with reactions that included surprise, shame, embarrassment, sadness, or hopelessness. This could be due to the lack of awareness about the risk of acquiring TB, as 49% of our respondents did not know that anyone can get TB. However, our findings could be an underestimate, since the study was not designed to assess people for depression. The self-perceptions of the patients and perceptions of the community toward them, and the impact of those perceptions on TB prevention and care, warrant further study.

Adequate knowledge about TB, availability of affordable services, and reassuring community support increase the capacity of patients to disclose their medical condition, seek care, and adhere to treatment [50]. Moreover, a study from Malawi reported that patients were interested in disclosing their status if they would not be stigmatized [51]. However, community reactions that TB patients are inferior, should feel ashamed, and should be avoided could affect their ability to disclose their illness [52]. In our study, only 28% of the study participants reported that they would disclose their TB status to their parents, as opposed to higher disclosure rates reported from Nigeria (86%) and Ghana (68% among women and 75% among men) [53, 54]. We report the level of misconceptions about the cause of TB to be about 21% lower than in similar studies in Ethiopia, which reported misconceptions of about 50% and higher stigma [16, 55]. This could be due to low awareness of stigma associated with TB that affects the capacity to disclose and warrants further study.

The strength of this study was that it is the first national-level survey in Ethiopia that explored different population groups. One of the limitations of the study is that it did not include two pastoralist regions, which could limit its generalizability. However, similar communities were included from other regions to compensate for the missing information. Second, we did not study the attitudes of TB patients about TB, which limits the possibility of comparing them with those of other sub-populations in the study. The results might have been affected by the capacity of the study participants to understand and respond to the questionnaire. The respondents might also have given socially desirable answers, which could lead to overestimation of positive responses. Using trained and experienced data collectors who speak local languages and could explain the aim of study is likely to have reduced information bias.

Conclusions

High community awareness, positive attitudes, and communities supportive of TB patients contribute to increased health care–seeking behavior. However, we found significant regional variations in the availability of adequate knowledge about the causative agent and means of transmission of TB, more so among underprivileged groups, the poor, those who are less educated, and women. These findings point to the need for targeted health education interventions to improve KAPs in the general population. The community generally has a positive attitude toward TB patients. However, people show limited interest in seeking care from community health workers. The NTP needs to address factors affecting the engagement of

community health workers in TB prevention and control. Further studies are required to understand the reasons for the regional variations, to understand the extent of stigma and delay related to health care–seeking, and to improve the performance of the NTP.

Supporting information

S1 Table. sample size estimation.
(PDF)

S2 Table. Data collection tools.
(PDF)

S3 Table. Knowledge cause and risk of TB.
(PDF)

S4 Table. Knowledge source of information.
(PDF)

S5 Table. Factors of TB knowledge in the general population.
(PDF)

S6 Table. Factors TB knowledge in families of TB patients.
(PDF)

S7 Table. Factors TB knowledge in TB patients.
(PDF)

S8 Table. The study population by regions in Ethiopia.
(PDF)

S1 File. Informed consent.
(PDF)

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A four-year trend in pulmonary bacteriologically confirmed tuberculosis case detection in Kampala-Uganda

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Abstract

Background: The management and control of pulmonary bacteriologically confirmed (PBC) tuberculosis (TB) also known as infectious TB is important not only to monitor for resistance but also to check for severity, treatment response and limit its spread.

Method: A retrospective analysis of diagnosis smear results of PBC TB patients in Kampala district registered between January 2012 and December 2015 at 65 TB diagnosis and treatment units (DTUs) was done.

Results: Of the 10,404 records; 6551 (63.0%) belonged to PBC TB patients, 3734 (57.0%) of whom were male. Sputum smear microscopy was the diagnostic test most commonly used 4905 (74.9%) followed by GeneXpert testing, 1023 (15.6%). Majority, 1951 (39.8%), of the PBC TB patients had a smear positivity grading of 3+ (> 10 acid-fast bacillus (AFB)/Fields). Public facilities diagnosed more PBC TB patients compared to private facilities, 3983 (60.8%) vs 2566 (39.2%). From 2012 through 2015, there was a statistically significant increase in PBC TB patients enrolled on anti-TB treatment from 1389 to 2194 ($p = 0.000$). The percentage of HIV positive co-infected PBC TB patients diagnosed decreased from 597(43%) to 890(40.6%) ($p = 0.000$) within same period. Linkage to HIV care improved from 229
(34.4%) in 2012 to 464 (52.1%) in 2015 ($p = 0.000$). The treatment success rate (TSR) for PBC TB patients improved from 69% in 2012 to 75.5% by end of 2015 ($p = 0.001$) with an improvement in cure rate from 52.3% to 62% ($p = 0.000$). There was an observed significant decrease in TB related mortality from 8.9 to 6.4% ($p = 0.013$).

Conclusion: The proportion of diagnosed PBC TB patients increased from 2012 to 2015. PBC TB patients diagnosed with 3+ smear positivity grading results consistently contributed to the highest proportion of diagnosed PBC TB patients from 2012 to 2015. This could be due to the delay in diagnosis of TB patients because of late presentation of patients to clinics. A prospective study of PBC TB patients diagnosed with 3+ smear positivity grading may elucidate the reasons for the delay to diagnosis. Further, we propose a study of wider scope to estimate how many people a single PBC TB patient is likely to infect with TB before being diagnosed and treated.

Background

Tuberculosis (TB) remains a global public health problem despite the presence of TB pharmacotherapy for more than 50 years and the use of vaccines for more than 90 years [1, 2]. According to the World Health Organization (WHO), TB remains one of the major global health threats of the twenty-first century [3] as well as a major cause of socio-economic distress [4, 5]. According to the 2016 Global Tuberculosis (TB) Report, in 2016 alone an estimated 10.4 million people developed TB and 1.4 million died from the disease with over 95% of these deaths occurring in low- and middle-income countries. An estimated 11% of the incident TB cases in 2015 were concurrently human immunodeficiency virus (HIV) positive [6].

TB has remained a public health challenge in low resource settings and, Uganda, ranked as one of the highest TB and TB/HIV burden countries in the world, remains disproportionately affected [6]. Uganda's TB

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prevalence is estimated at 253 per 100, 000 population [6]. Since 1998, the Uganda National Tuberculosis and Leprosy Program (NTLP) has implemented a series of WHO TB control strategies. The first of which was the Directly Observed Treatment Short Course (DOTS) strategy, which allows patients to take their daily drugs under the observation of health professionals, thereby improving treatment compliance and increasing the cure rate [7, 8]. This was replaced by the more comprehensive Stop TB Strategy implemented in 2006, followed by the End TB Strategy in 2015, to address the emerging challenges of drug-resistant TB, TB/HIV co-infection and the incorporation of new diagnostic tests, such as GeneXpert [9].

Reports have shown that PCB TB patients are more likely to transmit TB to susceptible hosts compared to those with a bacteriologically negative status [10]. A high proportion of PBC TB cases might imply more reliance on bacteriological examination to diagnose TB or a delay in diagnosis of both extrapulmonary (EP) and clinical pulmonary (PCD) TB which with time become easier to diagnose bacteriologically. On the other hand, low proportions may reflect several gaps in diagnosis such as lack of capacity by the program to accurately diagnose TB through bacteriological examination. Such programs majorly rely on clinical diagnosis basing on the presence of radiographic abnormalities on the radiograph or based on a high index of clinical suspicion which carries along with risks of falsely treating patients with other conditions for tuberculosis [11].

Although the proportion contributed by PBC TB patients to the total case notification is important in the monitoring of the quality of the national program, the trend of their notification has not been carefully studied to further inform the epidemiology of TB in this setting. We sought to determine the trend and outcomes of PBC TB over the four-year period of January 2012 –December 2015 in Kampala City.

Methods

Study design

This retrospective analysis examined TB patient-records in Kampala district for the calendar years January 2012 to December 2015. This audit was conducted at all of the six TB control divisions in Kampala district (Mulago, Central, Nakawa, Kawempe, Lubaga, and Makindye).

Study site

Data were collected from 65 TB diagnosis and treatment units (DTUs) in the six TB control divisions of Kampala district.

Kampala has a total population of approximately 1.5 million inhabitants by night; estimated to double during the day due to large numbers of people that come to work, conduct various business, or seek various services. Kampala district is surrounded by Wakiso district. A good proportion of TB patients come to seek medical services from Wakiso to Kampala [12]. National data shows that the burden of TB in Kampala is disproportionately high compared to the other districts in the country [13]. While the population of Kampala accounts for 4.3% of the national population, 17% of the total number of TB cases that are reported to the Ministry of Health derive from Kampala [13].

Study population

All TB patients registered between January 2012 and December 2015 among the 65 DTUs in Kampala were included and their bacteriological status was collected.

Data variables, collection, and source of data

Information on smear results and demographics such as age, sex, and place of residence were collected from the Unit TB patients register. Data on patient bacteriological status (PBC, PCD or EP) and HIV status were abstracted and matched from both the health unit and laboratory TB registers. For this study, a smear diagnosis of 1+ represents 9 Acid Fast Bacilli (AFB)/100 fields (scanty), 2+ represents 10–99 AFB/Fields (moderate) and 3+ represents > 10 AFB/Fields (numerous). For the purpose of the study, TB/HIV patients that were documented to have received Co-trimoxazole preventive therapy (CPT) or Antiretroviral therapy (ART) were considered as linked to HIV care. Treatment outcomes (cured, completed, died, lost to follow up, not evaluated and failure) of patients were also abstracted. Patients with a cure or completed outcome were categorized to have completed treatment successfully (treatment success rate) while other categories were classified as unfavorable patient outcomes.

Data entry and statistical analysis

A two-person independent data cleaning and verification was conducted in the health facilities. Errors and omissions in the data were corrected using primary data source documents at the DTUs. The data were coded and entered by trained data entry clerks under the supervision of the investigators into a pre-prepared computer Excel document. The Excel document was merged and exported to a Statistical Package for the Social Sciences (SPSS) version 16 software for subsequent analysis. Frequencies were tabulated to determine the trends of PBC TB by six TB control divisions, sex and age group. Mantel–Haenszel Chi Statistics and Odds ratios were calculated at 95% confidence intervals to test relevant relationships. The national average PBC TB notification rate over the four-year period was used to classify divisions as having a PBC TB notification rate

of either above or below the national average PBC TB notification rate.

Results

We assessed a total of 10,404 records of TB patients from the 65 active DTUs in the five divisions of Kampala during the period of January 2012 to December 2015. Of the 10,404 records of TB patients; 6551 (63.0%) were PBC, 2207 (21.2%) were pulmonary clinically diagnosed (PCD) and 1343 (12.9%) were extrapulmonary (EP) while 2.9% had no documentated classification of TB in the register.

The PBC TB patients had a mean age of 31.92 (SD ±11.24) years. The majority of PBC TB patients were male, 3734(57.0%). PBC TB patients contribution by division from highest to lowest was Kawempe, Lubaga, Makindye, Nakawa, and Central respectively, (see Table 1 for details). About 74.9% of all PBC TB patients were diagnosed by sputum smear microscopy test, 15.6% were diagnosed by GeneXpert testing, and only four patients (0.1%) were diagnosed by culture testing. The remaining records were undocumented and classified as unknown.

Trends of TB patient enrollment by disease classification

Throughout the period of January 2012 to the end of 2015, the number of PBC TB patients enrolled for treatment per year increased from 1389 (58.4%) to 2194 (66.8%) ($p = 0.000$). The number of PCD TB patients enrolled on anti-TB treatment was also observed to have attained a statistically significant increase per year from 418 (17.6%) to 745 (22.7%) patients between the years under review. While the number of EP TB patients and those with unknown disease classification had a statistically significant decrease per year from 437 (18.4%) and 136 (5.7%) to 342 (10.4%) and 5 (0.2%) respectively, (Table 2).

Diagnostic tests done for PBC cases

Diagnosis methods included; microscopy, GeneXpert, and culture. There was a decreasing trend in the use of microscopy and an increasing trend in the use of GeneXpert between 2012 and 2015. In 2012, all PBC TB patients diagnosed by microscopy were 1289 (92.8%) vs 1377 (62.8%) in 2015. The proportion of PBC patients diagnosed with GeneXpert increased from 66 (5.3%) in 2013 to 610 (27.8%) in 2015 (Table 3).

Sputum smear positivity grading

There was a percentage decline in PBC TB patients diagnosed with sputum smear positivity grade results of 3 + (> 10 AFB/Fields) and 2+ (10–99 AFB/Fields) per year from 42.1% in 2012 to 38.3% in 2015 ($p = 0.215$) and 31.7% in 2012 to 30.4% in 2015 ($p = 0.291$) respectively. Those with sputum smear positivity grade results of 1+ (9 AFB/100 fields) had a significant increase from 26.1% in 2012 to 31.3% in 2015 ($p = 0.003$), (See details in Table 4).

Table 1 Characteristics of all pulmonary bacteriologically confirmed TB patients who registered between January 2012 and December 2015

Background characteristics	*n* (%)
Total, *n*	6551
Residence of TB patients by division	
Kawempe	1807(27.6)
Lubaga	1206(18.4)
Makindye	1140(17.4)
Nakawa	649(9.9)
Central	401(6.1)
Others	1348(20.6)
Sex	
Female	2817(43.0)
Male	3734(57.0)
Age (years)	
< 5	20(0.3)
5–19	605(9.2)
20–34	3572(54.5)
35–49	1872(28.6)
50–64	358(5.5)
> 65	96(1.5)
Missing	28(0.4)
Mean Age	31.92 ± SD 11.24
HIV serostatus	
Positive	2843(43.4)
Negative	3593(54,6)
Unknown	115(1.76)
Diagnostic test	
Sputum smear microscopy	4905(74.9)
GeneXpert test	1023(15.6)
Culture test	4(0.1)
Unknown	619(9.4)
Type of facility	
Private	2566(39.2)
Public	3985(60.8)

Source: Primary Data. *TB*-Tuberculosis, *HIV*-Human Immunodeficiency Virus

Diagnosis of PBC TB by facility type

Findings showed more PBC TB patients diagnosed from public facilities compared to private facilities (See Table 1). Throughout the years 2012 to 2015, the percentage of PBC TB patients diagnosed from public facilities increased from 790 (56.9%) to 1465 (66.8%), ($p = 0.000$).

Table 2 Patient started on anti-TB treatment by TB diagnostic class

Characteristic	2012 *n* (%)	2013 *n* (%)	2014 *n* (%)	2015 *n* (%)	*P* value
PBC	1389 (58.4)	1244 (55.8)	1724 (68.7)	2194 (66.8)	0.000[a]
PCD	418 (17.6)	568 (25.5)	476 (19.0)	745 (22.7)	0.005[a]
EP	437 (18.4)	319 (14.3)	245 (9.8)	342 (10.4)	0.000[a]
Unknown	136 (5.7)	97 (4.4)	65 (2.6)	5 (0.2)	0.000[a]

Source: Primary Data, 95% Confidence Interval. *TB*-Tuberculosis, *PBC*-Pulmonary Bacteriologically Confirmed Tuberculosis, *PCD*-Pulmonary Clinically Diagnosed Tuberculosis, *EP*-Extrapulmonary Tuberculosis
[a]Statistically Significant Variable

Meanwhile, the percentage of PBC TB patients diagnosed from private facilities decreased from 599 (43.1%) to 729 (33.2%), ($p = 0.000$), (See details in Table 5).

HIV status for PBC TB patients and linkage to HIV care services

Although there was an increase in absolute numbers of PBC TB patients that tested HIV positive, a decline in the proportion that tested HIV positive was observed from 597 (43%) to 890 (40.6%) between 2012 and 2015 respectively ($p = 0.000$). The number of PBC TB/HIV co-infected patients linked to care improved from 229 (34.4%) in 2012 to 464 (52.1%) in 2015 ($p = 0.000$). The proportion of PBC TB/HIV co-infected patients on CPT improved from 225 (37.7%) in 2012 to 462 (51.9%) in 2015 ($p = 0.000$). Likewise, TB/HIV patients on ART improved from 212 (35.5%) to 431 (48.4%) for 2012–2015, See Table 6 for details.

Treatment outcomes

The treatment success rate (TSR) for PBC cases increased from 69% in 2012 to 75.5% by the end of 2015 ($p = 0.001$). The cure rate also improved from 52.3 to 62% ($p = 0.000$) during the same period. The percentage of PBC TB patients not evaluated by the time of establishing patient outcomes decreased from 12.4% in 2012 to 9.7% ($p = 0.069$) in 2015. Likewise, the number of PBC TB patients who died during treatment had a steady decrease from 8.9 to 6.4% ($p = 0.013$), see details in Table 7.

Discussion

This study analyzed TB patient records from January 2012 to December 2015 in all registered DTUs of the most highly burden district in Uganda. Our discussion of PBC TB patients gives detail that according to our knowledge has not been examined before in this country and district. As widely observed throughout the world and in the country, most of the PBC TB patients were male [14–16] in their young and productive years [15]. This is emphasized by the clear-cut gender differential that has been observed in many other studies [14, 16, 17] and the economic impact of TB due to its high incidence among people in the productive years [17].

Majority of the PBC patients were from Kawempe division, this could be due to the location of Mulago National Referral Hospital, the only national referral hopsital in the country, which also contributes to the highest number of TB cases notified each year in the district. About 2% of the PBC TB patients had an unknown/undocumented HIV status and it was noted that less than half of all PBC TB patients were HIV positive patients, a finding that was not surprising since it has been earlier noted by researchers that HIV positive TB patients are most likely to show up with EP TB [18].

The statistically significant increase in PBC TB patients diagnosed across the period for this study could be due to improvement in the quality of microscopy done leading to a better performance in the diagnosis of TB using smear microscopy. This could further be attributed to the NTLP's adoption of the use of GeneXpert machines to diagnose TB where 15.6% of all PBC patients were diagnosed by GeneXpert. The program and its partners have installed over 13 GeneXpert machines

Table 3 Number (proportion) of diagnostic tests done for pulmonary bacteriologically confirmed TB cases

Test	2012 *n* (%)	2013 *n* (%)	2014 *n* (%)	2015 *n* (%)	*P* value
Smear Microscopy	1289 (92.8)	1063 (85.5)	1176 (68.2)	1377 (62.8)	< 0.000[a]
GeneXpert	1 (0.1)	66 (5.3)	346 (20.1)	610 (27.8)	< 0.000[a]
Culture	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.2)	0.050
Unknown	99 (7.1)	115 (9.2)	202 (11.7)	203 (9.3)	0.000[a]

Source: Primary Data, 95% Confidence Interval
[a]Statistically Significant Variable

Table 4 Results of microscopy sputum examination grading by number of patients

Test	2012 *n* (%)	2013 *n* (%)	2014 *n* (%)	2015 *n* (%)	*P* value
3+	543 (42.1)	420 (39.5)	461 (39.2)	527 (38.3)	0.215
2+	409 (31.7)	310 (29.2)	334 (28.4)	419 (30.4)	0.291
1+	337 (26.1)	333 (31.3)	381 (32.4)	431 (31.3)	0.003[a]

Source: Primary Data, 95% Confidence Interval
[a]Statistically Significant Variable

within the district and released new guidelines in 2017 for the adoption of GeneXpert as the first diagnosis method for TB [19]. Given that GeneXpert has a higher sensitivity than microscopy [20], this could account for the registered increase in PBC TB pattients. It is to the knowledge of the authors of this paper that the NTLP moved forward to classify all patients that were GeneXpert positive as PBC patients [21] despite the fact that GeneXpert machines were in use before this decision was made. This may have affected the number of patients classified as PBC for a short period. It is worth noting that there was a significant increase in all classifications of TB within the study period.

We observed that through the study period, patients diagnosed with a 3+ (>10AFB) were persistently higher compared to those that were 2+ or 1+. The authors speculate that this could be caused by late diagnosis due to patient delay in seeking care, leading to an increase in the severity of infection, thus leading to more bacilli detection per length through microscopy. This possibility of total delay in seeking health care and diagnosis may contribute to unfavorable treatment outcomes [22]. In addition, a late diagnosis has implications on cross-transmission of TB to the rest of the population, health workers and other patients at the health centers [23]. However, the same results when expressed as proportions for each year revealed an increase in patients being diagnosed 1+ compared to 2+ and 3+ by the year 2013 that may be attributed to the initiation of active case finding/TB screening using community linkage facilitators (CLFs) leading to early case detection. The contribution of active case finding/TB screening may further be realized by the general decline in proportions of 3+ PBC TB cases diagnosed through the years. This may also be explained by the fact that there were less severely sick patients reporting to the facilities making it less likely diagnose patients as 3+ PBC TB compared to the baseline year 2012 where more severely sick patients would easily be diagnosed. Therefore, this observation could be attributed to both the use of active case finding and use of CLFs.

In Kampala, engagement of the private health provider is important in TB control. Most patients are commonly known to first seek care through private health care providers. There was a decline in PBC TB diagnoses by private facilities in 2015 that this study did not explore further. Researchers, however, speculate that this could be due to the commencement of referral of specimen from private facilities to public facilities for GeneXpert testing. Our research showed a statistically significant increase in GeneXpert testing through the years and this could have influenced the increasing trend of PBC TB patients observed during our study period. This also proved that smear microscopy alone could lead to underestimation of the burden of smear-positive pulmonary TB. More sensitive testing methods such as GeneXpert could provide a better estimate.

Over the years, there was a statistically significant increase in the number of TB/HIV co-infected PBC patients that were linked to HIV care. The proportion of PBC TB/HIV co-infected patients on CPT and ART improved from 37.7% to 51.9% and from 35.5% to 48.4% respectively. This observation could be accounted for by the emphasis on TB/HIV collaborative services by the NTLP and its partners. However, these results still reflected a low uptake of both CPT and ART. This may also be attributed to poor record keeping since many of the PBC TB/HIV co-infected patients did not have a documented status of their CPT and ART uptake.

There was an overall statistically significant improvement in cure rates and TSR throughout the study. This may be attributed to the URBAN DOTS approach that was implemented in Kampala starting 2012. There was

Table 5 Percentage of pulmonary bacteriologically confirmed TB patients by diagnostic facility

Test	2012 *n* (%)	2013 *n* (%)	2014 *n* (%)	2015 *n* (%)	*P* value
Private	599 (43.1)	525 (42.2)	713 (41.4)	729 (33.2)	0.000[a]
Public	790 (56.9)	719 (57.8)	1011 (58.6)	1465 (66.8)	

Source: Primary Data, 95% Confidence Interval
[a]Statistically Significant Variable

Table 6 Patients' HIV status and linkage to HIV care

Characteristic	2012 *n* (%)	2013 *n* (%)	2014 *n* (%)	2015 *n* (%)	*P* value
HIV Serostatus (n)	1389	1244	1724	2194	
Positive	597 (43.0)	608 (48.9)	782 (45.4)	890 (40.6)	0.000[a]
Negative	739 (53.2)	620 (49.8)	935 (54.2)	1299 (59.2)	0.000[a]
Unknown	53 (3.8)	16 (1.3)	7 (0.4)	5 (0.2)	0.000[a]
Linked to care	597	608	782	890	
Yes	229 (34.4)	320 (52.6)	381 (48.7)	464 (52.1)	0.000[a]
On CPT					
Yes	225 (37.7)	315 (51.8)	378 (48.3)	462 (51.9)	0.000[a]
On ART					
Yes	212 (35.5)	303 (49.8)	364 (46.5)	431 (48.4)	0.000[a]

Source: Primary Data, 95% Confidence Interval. HIV-Human Immunodeficiency Virus, CPT-Co-trimoxazole Preventive Therapy, ART-Antiretroviral Therapy
[a]Statistically Significant Variable

an overall decline in death rate of PBC TB patients that was below the 10% that is reported for all TB cases. This probably meant better chances of survival for PBC TB patients compared to all clases of TB patients combined. Public DTUs reported an overall better improvement in TSR compared to private facilities even though they handled more PBC patients thus highlighting the need to bridge the public private partnership gap in TB management.

The major limitation of our study was that over 26% of all the patients that were documented to be PBCs had unknown/undocumented diagnostic test type. This improper documentation may have misclassified patients to PBC that would have otherwise been classified as clinically diagnosed. The severity of PBC patients diagnosed by GeneXpert was not explored because it was documented by most facilities either Positive or Negative only, therefore, our study could not examine this trend, yet it would have clarified a more representative trend in the severity of PBC TB among patients diagnosed by GeneXpert.

Implication of findings

PBC TB patients are a reservoir for aerosol transmission of MTB infection and a primary emphasis on TB infection control in communities and crowded spaces. Late diagnosis of PBC TB is a likely influence on increased TB spread and the overall prevalence of TB in a population. Until this assessment, there had not been any effort made to document trends of positivity grading of PBC TB patients diagnosed in Uganda and very little of this kind of information has been shared from other findings elsewhere [24]. The NTLP's adoption of GeneXpert testing as the primary method of TB diagnosis for all presumptive TB patients will probably make the challenges of documentation of degree of smear positivity of PBC TB at a diagnosis more difficult due to the lack of emphasis made on the classification of GeneXpert positive results in some of the established recording tools. This may call for a revision of data collection tools and emphasis on proper recording for laboratory workers, TB clinic workers, and division supervisors.

Table 7 Treatment outcomes for pulmonary bacteriologically confirmed TB patients from 2012 to 2015

Outcome	2012 *n* (%)	2013 *n* (%)	2014 *n* (%)	2015 *n* (%)	*p*-value
Total	1389	1244	1724	2194	
Cured	726 (52.3)	743 (59.7)	985 (57.1)	1360 (62.0)	0.000[a]
Completed Treatment	233 (16.8)	185 (14.9)	233 (13.5)	296 (13.5)	0.004[a]
TSR	959 (69.0)	928 (74.6)	1218 (70.6)	1656 (75.5)	0.001[a]
Unfavorable	430 (31.0)	316 (25.4)	506 (29.4)	538 (24.5)	0.001[a]
Died	123 (8.9)	80 (6.4)	120 (7.0)	140 (6.4)	0.013[a]
Failure	31 (2.2)	20 (1.6)	36 (2.1)	40 (1.8)	0.568
Lost to follow up	106 (7.6)	83 (6.7)	126 (7.3)	145 (6.6)	0.363
Not evaluated	170 (12.4)	133 (10.7)	224 (13.0)	213 (9.7)	0.069

Source: Primary Data, 95% Confidence Interval. TSR – Treatment Success Rate
[a]Statistically Significant Variable

Establishment of the severity of PBC TB at diagnosis or treatment may also help guide the priority for contact tracing in limited resource settings.

Conclusions

The study sought to analyze and profile PBC TB trends in Kampala over the study period. The proportion of PBC patients increased throughout the years under review. PBC TB patients diagnosed with smear microscopy positivity grading as 3+ consistently contributed to a higher population of those diagnosed as PBC throughout the years compared. This called to attention the consistency in the delayed seeking of care among PBC TB patients and is a stumbling block for effective TB control. We recommend a study of wider scope to estimate how many people a single PBC TB patient is likely to infect with TB per year before s/he is diagnosed and treated. This is crucial in estimating risk and developing strict policies on early detection of PBC TB in this population. GeneXpert testing was a possible contributor to the increase in PBC cases and a challenge to the relevance of microscopy in TB diagnosis [25]. Albeit, we recommend adoption/emphasis of better results reporting options such as MTB detected low, MTB detected intermediate or MTB detected high into the national reporting tools and guidelines used by health workers. This will help capture the severity of the disease at diagnosis in the patient as well as be a marker to late diagnosis/seeking of care.

Abbreviations

AFB: Acid-Fast Bacillus; ART: Anti-Retroviral Therapy; CPT: Cotrimoxazole Preventive Therapy; DOTS: Directly Observed Treatment Short Course; DTU: Diagnostic and Treatment Unit; EPTB: Extrapulmonary Tuberculosis; HIV: Human Immune-deficiency Virus; MDG: Millennium Development Goal; MTB: *Mycobacterium tuberculosis*; MoH: Ministry of Health; NTLP: National Tuberculosis and Leprosy Program; PBC: Pulmonary Bacteriologically Confirmed Tuberculosis; PCD: Pulmonary Clinically Diagnosed Tuberculosis; TB: Tuberculosis; TSR: Treatment success rate; WHO: World Health Organisation

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Availability of data and materials

The dataset used and/or analyzed during the current study is available from the corresponding author on reasonable request.

Authors' contributions

CN and NKS conceived the research idea. NKS and DK development the proposal and wrote the manuscript. NKS, DK and DL finalized the data analysis, conducted final revisions of the draft. CN, DS, DAO, SN, RB, and SK assisted in proposal development, interpretation of results and contributed to the overall manuscript. SK provided guidance on design and provided revisions of the manuscript. All authors read and approved the manuscript.

Ethics approval and consent to participate

The assessment was conducted under the guidance and approval of the Kampala Capital City Authority. Since the study was based on records review, re-verification and re-analysis of routinely collected information and reports by Kampala Capital City Authorities [26, 27], ethical approval was not necessary. In addition, since no patient identifying information was used, the investigators did not consider patient consent as a requirement for this study. There was no anticipated risk or benefit to the patients in the analysis of this information.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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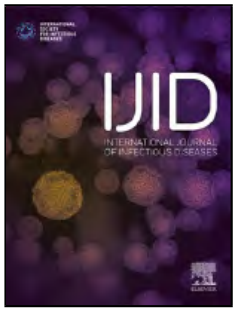

Prevalence of tuberculosis among mentally ill patients in conflict-stricken Afghanistan: a cross-sectional study

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Prevalence of tuberculosis among mentally ill patients in conflict-stricken Afghanistan: a cross-sectional study

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Highlights

- TB and mental illness share causes such as poverty, malnutrition, and stress.
- Out of 8,598 patients, 275 (17%) were diagnosed with TB, of whom 91% were women.
- The TB rate was 10 times higher among the mentally ill than in other people.

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- TB services should be integrated into mental health care and vice versa

ABSTRACT

Objectives: Tuberculosis (TB) and mental illness share underlying factors such as poverty, malnutrition, and stress. This study's objective was to determine the prevalence of TB among mentally ill patients in Afghanistan.

Methods: A cross-sectional study was conducted in five public one private health facility. All patients in those centers were screened for TB, and the diagnosis of TB was made with GeneXpert or made clinically by a physician.

Results: Out of 8,598 patients registered, 8,324 (96.8%) were reached and 8,073 (93.9%) were screened for TB, of whom 1,703 (21.1%) were found to be presumptive TB patients. A total of 275 (16.7%) were diagnosed with all forms of TB, of whom 90.5% were women. Eighty-eight (32%) of them were bacteriologically confirmed and 187 (68%) were clinically diagnosed. The number needed to screen(NNS) was 29.3 and the number needed to test(NNT)was 6.1. The overall prevalence of TB among mentally ill patients was 3,567/100,000—20 times higher than the national incidence rate. TB was independently associated with married and widowed adults, young adults, females, and oral sleep drug users.

Conclusions: TB among mentally ill patients is very high, and we recommend that TB care and prevention services be integrated into mental health centers.

Keywords: Afghanistan; TB services; mental disorders; disease susceptibility; delivery of health care; women

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INTRODUCTION

Mental illness contributes to approximately 10% of the global disease burden, according to Marquez and Saxena (2016). The prevalence of mental disorders and substance abuse in the WHO Eastern Mediterranean Region is estimated to be 11%, and more than 50% of the world's refugees exist in this region and are also highly vulnerable to mental illness (Shakoor and Hasan, 2016). In a population-based study led by the Centers for Disease Control and Prevention in Afghanistan, the prevalence of depression was found to be 73% and 59%; of anxiety, 84% and 59%; and of post-traumatic stress disorder, 48% and 32%, for females and males, respectively (Cardozo et al., 2005). In a separate study done among Afghanistan refugees living in Iran, anxiety and depression rates were lower than in the previous study, at 39.3% and 22.1%, respectively (Hosseini Divkolaye and Burkle, 2017). Afghanistan is also a high-TB-burden country, with an incidence of 189 100,000 population(WHO, 2018). In 2017 Afghanistan notified 47,406 TB cases (WHO, 2018).

Research has shown that people with mental disorders are also susceptible to TB (Singh et al., 2015). In Korea the risk of TB among patients with depression was more than twice as high as it was among individuals with no mental health problems, and TB incidence was higher for patients with severe depression (Hosseini Divkolaye and Burkle, 2017). In Taiwan, prevalence of TB was 1.6 times higher in patients with mental health disorders, and another study found that the incidence of risk of TB in schizophrenic patients was 1.52 times higher than in those without mental illness (Kuo et al., 2013).

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The reverse is also true, according to studies that have shown that TB patients have a high risk of developing mental illnesses. In an Ethiopian study, 57% of TB patients had probable depression (Ambaw et al., 2017), and another study in Ethiopia reported depression in 43.4% of TB patients and anxiety in 41.5% (Duko et al., 2015). Duko et al. (2015) also found out that among TB/HIV patients, the odds of having common mental disorders were 1.7 times higher than among non-TB/HIV patients. In Zambia the rate of any anxiety disorder among TB and TB/HIV patients was 30.8%; major depressive disorder, 11.3%; suicidality, 34.8%; and panic disorder, 4.1% (van den Heuvel et al., 2013). Post-traumatic disorder among TB patients was 29.6% in South Africa (Peltzer et al., 2013). Mental illnesses are also a cause of poor quality of life, TB treatment interruption, and poor treatment outcomes (Ambaw et al., 2018; Pachi et al., 2013; Sikjær et al., 2018; Theron et al., 2015).

In Afghanistan rates of mental illness are high because of decades of conflict, stress, and poverty, post-traumatic syndromes, and illicit drug abuse (Cardozo et al., 2005; Trani et al., 2016; Cardozo et al., 2004; Miller et al., 2008). Considering the high prevalence of mental disorders and TB in Afghanistan, we designed this study to identify the prevalence of TB among mentally ill patients. We believe that the prevalence of TB among mentally ill patients observed in this study will reorient TB and mental health policy and strategies in Afghanistan.

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METHODOLOGY

Study Setting

Afghanistan, with a population of 35 million, is one of the high-TB-burden countries, with a TB incidence of 189/100,000, based on which we can extrapolate that 65,000 TB patients existed in 2016 (WHO, 2017). The country has been engulfed in conflicts for more than four decades, which have seriously affected the health care system and the health of the citizens (Cardozo et al., 2004). We conducted this study in Kabul, Jalalabad, Kandahar, Herat, and Mazar-e-Sharif provinces, where most of the mental health facilities are located.

Study Participants and Procedures

This cross-sectional study was conducted between May and December 2017 in the five public and one private mental health centers in the five provinces. The study included all patients diagnosed with mental health conditions and treated as either outpatients or inpatients and who are receiving follow-up care in the health facilities.

We recruited and trained nurses working in these mental health centers as data collectors. The trained nurses invited all mental health patients registered in the health facilities' for TB screening during a regular follow-up visit, via a telephone interview, or through a home visit. Patients who gave verbal consent to participate in the study were invited to come to health facilities, asked for sociodemographic data, and screened for TB using the WHO screening criteria of two or more weeks of cough and two or more of constitutional symptoms such as night sweating and weight loss (WHO, 2012). Patients with those symptoms were considered presumptive TB cases, and further diagnostic investigation was pursued. Presumptive TB cases gave sputum for GeneXpert (Xpert® MTB/RIF assay, Cepheid, Sunnyvale, USA) if they could

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produce sputum. Two of hospitals had a GeneXpert machine, and four hospitals transported the sputum to another hospital for testing. The laboratory professionals who did the GeneXpert tests were trained following the national guidelines, and they received regular on-site mentoring by national laboratory experts. Patients with presumptive TB were instructed to rinse their mouths before collecting the sample to remove any food particles and to cough deeply and forcefully to obtain sputum from the alveoli and bronchial areas. Then the laboratory professional checked the quality of sputum and the quantity of sputum, which should be 2–4 ml, although a smaller quantity may be acceptable if it is mucoid with a minimum of 1 ml (Afghanistan GeneXpert training manual-draft).

Those with other symptoms or who were found to be negative after GeneXpert testing were referred to a hospital physician trained on TB for further examination and diagnosis. The physician ordered chest X-rays for those with presumptive pulmonary TB with nonproductive cough; if there was a lung lesion, the physician might decide to diagnose TB or proceed with other investigations. Chest X-rays were read by two independent radiologists, and if there was a difference in interpretation, a third senior radiologist was used as a tie-breaker. Extra pulmonary TB cases were diagnosed clinically and in a few cases with the support of histology or cytology. Patients who were bacteriologically confirmed to have TB, clinically diagnosed with the support of chest X-ray, or empirically diagnosed were considered TB patients. All mentally ill patients diagnosed with TB then enrolled in treatment in a nearby DOTS center.

Data Collection and Analysis

The nurses who had been trained as data collectors collected information on mental illness diagnosis and its category from the cards and registers of the mental health patients. The data

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collectors also collected data on sociodemographic variables by interviewing the study participants. Then the data collectors interviewed the study participants about signs and symptom of TB and recorded the investigation results in the TB register. The data were entered into SPSS version 23, and the principal investigator checked their consistency. The yield of TB was then calculated using the number needed to screen (NNS) and number needed to test (NNT). NNS is the number of people who have to be screened to detect a single case of active TB; NNT is the number of people with presumptive TB who have to be evaluated to detect a single case of active TB. To address the missed variables, we calculated multiple imputations using R, mean inter-item-correlation, for type of mental disorder and TB. The logistic regression was calculated using the variation inflation factors function of the *R Companion to Applied Regression* (Fox and Weisberg, 2018). We calculated the association between TB and mental illness, and $p = < 0.05$ was considered to be statistically significant. In this article, mental health condition, mental illness, and mental health disorder are used interchangeably to indicate psychiatric illnesses.

Ethical Considerations

We received written informed consent for each study participant. Their information was kept confidential and not shared with anyone outside of the study team. Those patients who did not consent were excluded from the study. For patients with mental illness who were unable to give consent per the interviewer's assessment or who were under the age of 18, we sought permission from their next of kin, parent, or guardian, and the screening was done with the assistance the next of kin.

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RESULTS

In total, 8,598 patients with mental illnesses were registered in the six centers that provided mental health services, 8,324 (96.8%) of them were reached; of those, 8,073 (93.9%) gave consent to participate in the study (Figure 1). The majority of the patients with mental health conditions (5,680 or 70.4%) were women, and the mean age of the study participants was 33.6 years, with a median of 30.0 years. The majority of the study participants (5,546 or 68.7%) were married, while 2,109 (26.1%) were single; 314 (3.9%) widowed; 12 (0.1%) divorced; and 22 (0.3%) separated. The most common mental health condition diagnosed was general anxiety disorder, which affected more than half of the patients (4,411 or 54.6%). Depression affected 1,141 patients (14.1%), while 559 (6.9%) expressed headache alone, 348 (4.3%) had epilepsy, 321 (4.0%) suffered from schizophrenia, 218 (2.7%) experienced panic attacks, 95 (1.2%) had post-traumatic stress disorder, and 32 (0.4%) had psychosis. Four hundred and fourteen study participants (5.1%) had other types of mental disorders, and for 534 (6.6%) the diagnosis was not registered or missing. About 21.7% of the patients with mental illness used one or more substances (Table 1).

Out of the 8,073 patients with mental illness screened for TB, 1,703 (21.1%) were found to have presumptive TB and 275 (16.1%) were diagnosed with TB. One hundred and eighty-seven (68%) of them were clinically diagnosed, and the remaining 88 (32%) were bacteriologically confirmed (Figure 1). Four (4.5%) of the bacteriologically confirmed TB cases were rifampin-resistant TB.

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The NNS to detect a single case of TB was 29.3. The NNTs were 6.1 and 19.3 for all forms of TB and bacteriologically confirmed TB, respectively. Overall the prevalence of TB among patients with mental health conditions was 3,411/100,000 population. If we add the 13 TB patients who were on treatment at the start of the study, the prevalence would be 3,567/100,000 population. The prevalence for bacteriologically confirmed cases was 1,091/100,000 population.

Among the 275 mentally ill patients diagnosed with TB, their mental illness diagnoses were general anxiety (115 or 41.8%) and depression (72 or 26.2%), respectively. In the multivariate analysis, people aged between 16-24, 25-34, and > 45 years (AOR 2.96: 95% CI 1.62-10.01, AOR 1.89: 95% CI 1.08-10.06, and AOR 2.81: 95% CI 1.03-9.9) respectively; married and widowed patients (AOR 1.57: 95% CI 1.02-2.48 and 2.05: 1.03-4:00) respectively; females (AOR 3.1: 95% CI 2.05-4.86) ; and users of oral tablets for sleep/sedation (AOR 3.1: 95% CI 3-4.72)were all independently associated with TB. Depressed patients (AOR 0.26: 95% CI 0.17-0.40) had a 74% lower chance of TB (Table 2).

DISCUSSION

The prevalence of mental disorders in Afghanistan is as high as 50% (Alemi et al., 2014). Our study found that the prevalence of TB among patients with common mental health disorders was 3,567/100,000 population, which is almost 20 times higher than the incidence rate in the general population (WHO, 2018). As it is described in the literatures, various factors could explain the high TB prevalence among mentally ill people. The complex interplay among poverty, undernutrition, immunosuppression, behavioral factors, and substance abuse might have contributed to the TB epidemic in Afghanistan (Theron et al., 2016). Poverty is a common driver

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of TB (WHO, 2013; Figueroa-Munoz et al., 2008; Lund et al., 2011) and mental illnesses (Lund et al., 2011). Mental illness can result from having TB disease because of stigma, social vulnerabilities such as malnutrition, and the side effects of TB drugs (Sweetland et al., 2017). The poor lack adequate housing and food; experience more stress than people who are better off; and lack access to health care. The situation of people with mental illness is worse because of neglect, poverty, or lack of understanding about the need for care (Peltzer et al., 2013; Figueroa-Munoz et al., 2008). The relationship of malnutrition to mental illness has been established, because malnutrition lowers immunity and people with mental illness, especially those who are depressed, can be vulnerable to malnutrition (WHO, 2013; Gupta et al., 2009).

In the case of Afghanistan, because of decades of war, mental illness is very common. In one study that compared the rates of mental illness among disabled and non-disabled people aged 15 years and above in Afghanistan, the rates of depression were 67.7% and 71.7%, and the rates of anxiety were 72.2% and 84.6% for non-disabled and disabled people, respectively. In the same study, the rate of post-traumatic stress disorder for both groups was 42.1%, and with respect to both depression and post-traumatic stress disorder, women had poorer mental health than men (Cardozo et al., 2004). Another study also reported higher rates of mental illness in Afghan women as compared to men (Cardozo et al., 2002). In our study, more women (249 or 90.5%) were diagnosed with TB than men ($p < 0.001$), and 70.4% of the study subjects were women. In developing countries, a high risk of mental illness in women has been reported, mainly due to high poverty among women (Lund et al., 2011; Patel et al., 1999). These factors could explain the high number of TB cases we found among mentally ill patients in our study.

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Conflict, mental illness, and poverty, all of which feed the TB epidemic, are also associated (Singh et al., 2015; Pachi et al. 2013; Theron et al., 2015). After decades of civil war and several natural disasters, close to 5 million Afghan citizens have migrated to other countries for security and better living conditions. Within Afghanistan, 5.8 million Afghans have returned since 2002; there is also an unknown number of internal migrants; the exact locations of returned refugees and migrants are not known (UNHCR update 2015-2016). Refugees and migrants are at higher risk of developing TB and MDR-TB than the rest of the native population (Lönnroth et al., 2017). In a meta-analysis study among Afghan refugees, there was moderate to high depression and post-traumatic stress disorder, factors associated with distress, conflict, and loss of family and friends (Alemi et al., 2014). The interplays among migration, poverty, mental illness, and TB should be considered in Afghanistan because these risk factors are common in this setting.

The NNS of 29.3 is lower than what is reported for contact screenings in Uganda, 131 (Sekandi et al., 2014), and 40 in Ethiopia (Jerene et al., 2015) but higher than the reported NNS of 19 in India (Nair et al., 2016). In another contact investigation study in Afghanistan, we found out that the NNS to diagnose a single case of all forms of TB was 59.2 and the NNT was 11.1(unpublished data of the authors). The contacts of people with TB have a higher risk of developing TB disease than persons having no contacts, and these countries (Uganda and Ethiopia) have a high HIV prevalence, while HIV prevalence in Afghanistan is very low, but the low NNS in our study shows that the risk of TB among the mentally ill is even higher than the risk reported for contacts in Uganda, Ethiopia, and Afghanistan. The NNT was also high, 6.1, which is close to the NNT reported in Ghana, 8 for contact screening (Ohene et al., 2018). The NNS and NNT also depend on the TB incidence of the country, and Afghanistan has a high TB incidence, at 189/100,000 population (WHO, 2018).

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We found out that, among mentally ill patients who were married women or widowed, their marital status was independently associated with TB. In a study in Ethiopia, 54% of TB patients were reported to have depression, and it was higher for women, married people, and divorced people (Ambaw et al., 2017), a study in South Korea reported that males with depression had a higher risk of TB than women (Oh et al., 2017). South Korea is a low–TB-incidence country (WHO, 2018), and the difference in TB incidence vis-a-vis sex with Afghanistan could be explained by the difference in incidence, in which Ethiopia is similar to Afghanistan. Women in Afghanistan have a higher rate of mental illness than men (73% vs. 59% for depression, 84% vs. 59% for anxiety, 48% vs. 32% for post-traumatic disorders), respectively (Cardozo et al., 2005). The high burden of TB among Afghan women, therefore, can be also explained by this difference in the rate of mental illness between the two sexes.

Age was significantly associated with TB for mentally ill patients aged 16-34 and > 45. It is reported that the burden of mental illness is more common in early young adults and in the middle age of 25 and 50 years, and drug use is also more common in these age bracket. According to a global study, Afghanistan has one of the highest rates of mental illness among young adults, mainly related to ongoing conflict, and probably illicit drug use (Whiteford et al., 2013). This could be one reason for the high association of TB with mental illness in this age group seen in our study.

Although we did not study the effects of medicines used to treat mental illness or the effects of TB drugs, the literature shows that clozapine was the only antipsychotic agent associated with a 63% increased risk of TB (AOR = 1.63, p = 0.014) (Liu et al., 2018). TB drugs such as

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cycloserine have also been associated with depression (Doherty et al., 2013). Health workers should consider these interactions during the management of mentally ill and TB patients.

Limitations

One limitation of this study is that we did not substantiate the accuracy of diagnoses of mental illness. We also did not test people for HIV because the national guidelines do not recommend that all TB patients be tested for HIV, since HIV prevalence is very low in Afghanistan. We do not know if it is also low among mentally ill patients. .

CONCLUSION AND RECOMMENDATIONS

The burden of TB is very high among mentally ill people. Because the two disease are synergistic and Afghanistan has high burdens of both TB and mental illness, integration of TB services into mental health facilities is important. Mental health experts need to be trained on TB screening and diagnosis and the interplay of the two diseases.

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AUTHORS' CONTRIBUTIONS

Designed the study and led the research: G. Qader, M. Melese, K.M. Rashidi, and P. G. Suarez. All others participated in the data analysis and writing. All authors have approved the manuscript for submission.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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Figure 1. Procedures followed for TB screening of patients with mental health conditions

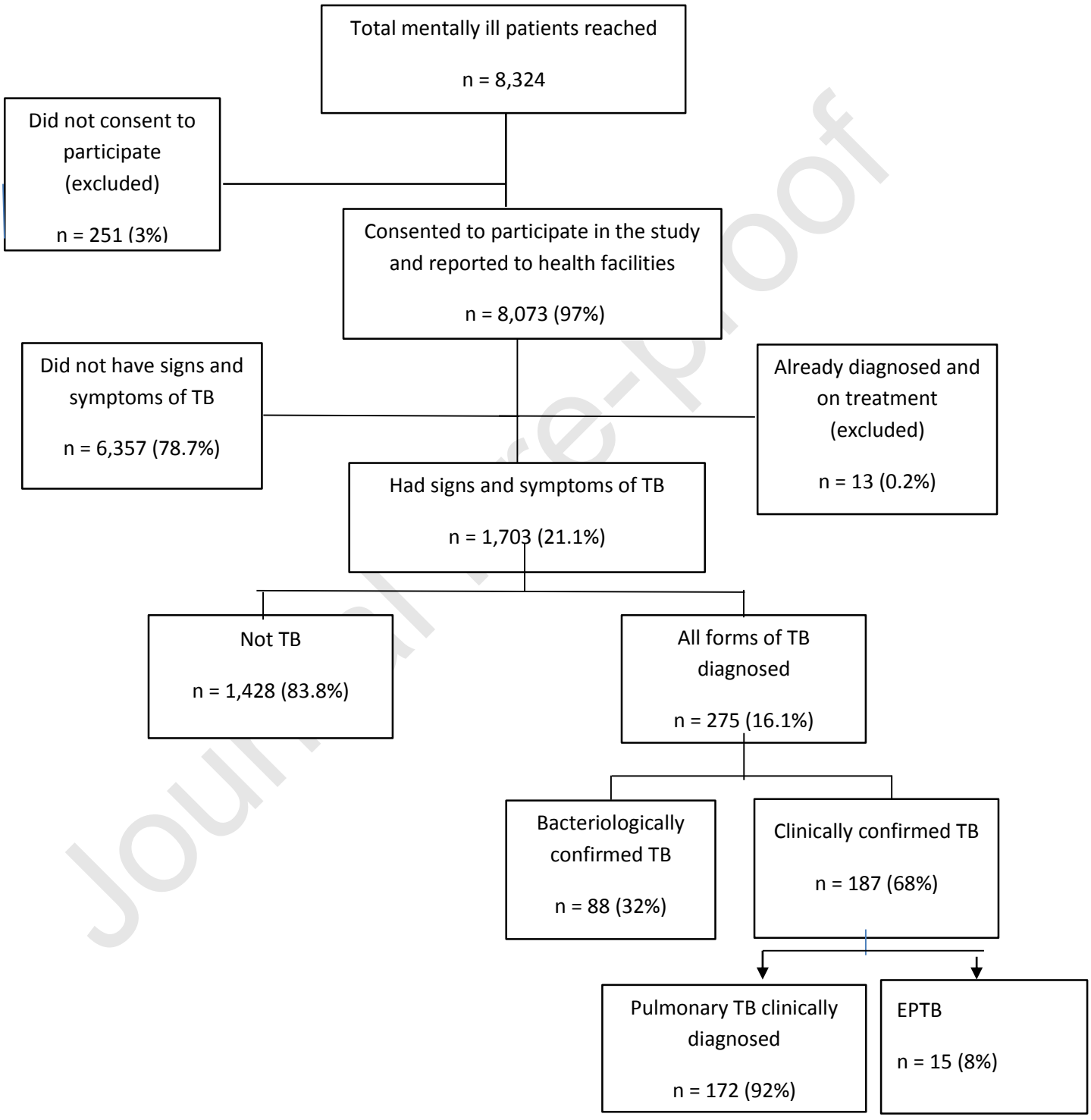

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Table 1. Sociodemographic characteristics of psychiatric patients screened for TB

Characteristics		**Number (%)**
Age	< 15	467 (5.8%)
	16-24	1,977 (24.5%)
	25-34	2,057 (25.5%)
	35-44	1,592 (19.7%)
	45+	1,918 (23.8%)
	Missing data	62 (0.8%)
Sex	Male	2,392 (29.6%)
	Female	5,680 (70.4%)
	Missing data	1 (0.01%)
Marital status	Married	5,546 (68.7%)
	Divorced	12 (0.1%)
	Separated	22 (0.3%)
	Widowed	314 (3.9%)
	Single	2,109 (26.1%)
	Missing data	70 (0.9%)
Drug use	Opiates	1,060 (13.1%)
	Oral tablets for sleep/sedation	209 (2.6%)
	Mouth snuff	484 (6.0%)
	I do not take any drug	5,982 (74.1%)

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	Others	30 (0.4%)
	Missing data	308 (3.8%)
Smoking status	Yes	446 (5.5%)
	No	6,158 (76.3%)
	Not disclosed	1,469 (18.2%)
Type of mental illness	General anxiety	1,141 (14.1%)
	Depression	4,411 (54.6%)
	Headache	559 (6.9%)
	Epilepsy	348 (4.3%)
	Schizophrenia	321 (4.0%)
	Panic attack	218 (2.7%)
	Post-traumatic stress disorder	95 (1.2%)
	More than one diagnosis	414 (5.1%)
	Psychosis	32 (0.4%)
	Missing data	534 (6.6%)
HIV status (patient report)	Positive	8 (0.1%)
	Negative	6,212 (76.9%)
	Unknown/not disclosed	1,853 (23.0%)

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Table 2. Associations among TB, type of mental illness, and duration of mental illness

Variables		TB Cases (%)	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Type of mental disorder	Headache	33/559 (5.9)	1	
	Depression	72 /4,411 (1.6)	**0.24 (0.16-0.37)**	**0.26 (0.17-0.40)**
	General anxiety	115/1,141 (10.7)	**1.66 (1.14-2.48)**	1.39 (0.94-2.09)
	Panic attack	4 /218 (1.8)	**0.28 (0.08-0.7)-**	0.42(0.12-1.08)
	Post-traumatic stress disorder	3/95 (3.1)	0.65 (0.19-1.66)	
	Schizophrenia	5/321 (1.5)	**0.22 (0.08-0.52)**	0.42 (0.12-1.08)
	Other (more than one diagnosis)	27/414 (6.5)	1 (0.59-1.67)	
	Epilepsy	6/348 (1.7)	**0.26 (0.1-0.57)**	0.46 (0.17-1.06)
	Psychosis	1/32 (3.1)	0.47 (0.03-2.28)	
Duration of mental illness (years)	< 1	79/,1846 (4.2)	1	
	1-5	125/4,164 (45.5)	**0.66 (0.51-0.87)**	0.92 (0.69-1.22)
	6-9	18/663 (2.7)	**0.60 (0.36-0.96)**	0.87 (0.51-1.43)
	≥ 10	20/302 (6.6)	**0.59 (0.35-0.93)**	0.89 (0.52-1.45)
Marital status	Single	37/2109 (0.1)	**1**	
	Married	251/5,582 (4.4)	**2.28 (1.62-3.29)**	**1.57 (1.02-2.48)**
	Divorced	0/12 (0)		

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	Separated	2/22 (9.0)	5.39 (0.84-19.32)	
	Widowed	20/314 (6.3)	**3.79 (2.13-6.54)**	**2.05 (1.03-4.00)**
Age	< 15	4/467 (0.8)	**1**	
	16-24	65/1,977 (3.3)	**3.93 (1.62-12.99)**	**2.96 (1.16-10.01)**
	25-34	75/2,057 (3.6)	**4.51 (1.86-14.83)**	**2.89 (1.08-10.06)**
	35-44	55/1,592 (3.4)	**4.14 (1.69-13.73)**	2.38 (0.87-8.4)
	45+	74/1,918 (3.8)	**4.65 (1.92-15.32)**	**2.81 (1.03-9.9)**
Sex	Male	26/2,392	1	
	Female	249/5,680(4.3)	**4.17 (2.83-6.41)**	**3.10 (2.05-4.86)**
Drug use	I do not take any drug	224/5,982 (3.7)	1	
	Opiates	0/1,060		
	Oral tablets for sleep/sedation	31/209 (33.9)	**4.41 (2.9-6.51)**	**3.13 (2.02-4.72)**
	Mouth snuff	16/468 (3.2)	0.87 (0.5-1.41)	
	Others	2/30 (6.7)	1.76 (0.28-5.89)	

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DRUG DELIVERY

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A gastric resident drug delivery system for prolonged gram-level dosing of tuberculosis treatment

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Multigram drug depot systems for extended drug release could transform our capacity to effectively treat patients across a myriad of diseases. For example, tuberculosis (TB) requires multimonth courses of daily multigram doses for treatment. To address the challenge of prolonged dosing for regimens requiring multigram drug dosing, we developed a gastric resident system delivered through the nasogastric route that was capable of safely encapsulating and releasing grams of antibiotics over a period of weeks. Initial preclinical safety and drug release were demonstrated in a swine model with a panel of TB antibiotics. We anticipate multiple applications in the field of infectious diseases, as well as for other indications where multigram depots could impart meaningful benefits to patients, helping maximize adherence to their medication.

INTRODUCTION

Lack of medication adherence is a worldwide problem. As many as 50% of patients experience difficulty following treatment recommendations (*1*). Whereas adherence is driven by many factors including the socioeconomic status of a patient and the quality of the health care team, drug regimen complexity also affects treatment outcomes (*1*). For example, adherence decreases as the number of pills per dose and the number of doses per day increases (*1*). For diseases where potent medications are available, depot formulations provide sustained drug release to simplify dosing. For diseases lacking potent compounds for treatment, there remains an unmet need for depot systems that could transform medication adherence (*2*).

Tuberculosis (TB) is one such disease with a high pill burden, where poor patient adherence to the treatment regimen is a major cause of treatment failure and contributes to the emergence of drug-resistant TB strains (*1*). For example, an average 60-kg patient with TB needs to take 3.3 g of antibiotics per day, which is a dose that exceeds the largest swallowable capsule and current depot systems (*3*–*6*). According to the World Health Organization (WHO), 10 million people developed TB in 2017 with a global economic burden amounting to $12 billion annually (*7*, *8*). Furthermore, TB is the most serious pathogen in the global antimicrobial resistance crisis (*9*). Unless radical action is taken, drug-resistant strains of TB will account for 25% of antimicrobial resistance–related deaths and will cost the global economy $16.7 trillion by the year 2050 (*9*, *10*).

There are multiple factors that influence adherence among people living with TB (*11*). These include a provider-focused system of care delivery, high pill burden, transport difficulties, and other competing

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daily priorities. In 1994, the WHO endorsed the directly observed treatment short course (DOTS) strategy, which is now accepted worldwide (*12*). DOTS involves administration of oral fixed-dose combination formulations of TB drugs at a designated clinic in the presence of a health care provider either daily or three times per week (*3*, *13*). Although some studies have shown DOTS to be effective, it requires substantial infrastructure with adequately staffed health care personnel to achieve desired results (*11*, *14*–*20*). Furthermore, a recent study found that patients who fully adhered to a dosing regimen 7 of 7 days per week had more favorable outcomes compared to patients who were fully adherent to a dosing regimen 6 of 7 days per week (*21*). Full adherence may not be easily achieved in resource-constrained environments, where DOTS is costly to provide and time consuming for both patients and caregivers (*22*, *23*).

The WHO End TB strategy has patient-centered care as a central pillar, and achieving such care requires innovative methods of treatment support and drug delivery (*24*–*26*). Shorter and simplified regimens, electronic reminder systems, and incentive programs are being implemented to improve adherence (*27*–*29*). Yet, additional interventions will be necessary to eliminate TB. Technologies that enable extended drug release of medication have the potential to help patients adhere to long and frequent dosing regimens. For example, ingestible gastric resident devices for controlled release drug delivery of antimalarials and antiretrovirals have been demonstrated in large animal models (*30*, *31*). Although easy to administer and capable of tunable drug release profiles, these systems have capacities limited to approximately <500 mg of drug, which is a fraction of the daily dose of treatment for a patient with TB (*3*).

The challenge with designing drug depot systems for diseases such as TB is to balance the ease and safety of administration with the accommodation of multigram-level quantities of drugs. During the intensive phase of treatment, a 60-kg patient with TB swallows almost 100 g of antibiotics in 1 month (*3*). Inspired by the recognized capacity of the stomach to hold large objects including bariatric balloons and bezoars, we reasoned that a gastric resident system (GRS) capable of prolonged gram-level dosing could help patients adhere to TB treatment (*32*, *33*). Drug delivery via the gastrointestinal (GI) tract offers multiple advantages, including ease of administration, immunotolerance to a broad range of materials, and the ability to accommodate gram-level dosing in line with current regimens for TB. Here, we describe a proof-of-concept study demonstrating the capacity of a device to be administered through the nasogastric (NG) route, to safely reside in the gastric cavity of a large mammal, to hold a multigram drug load, to provide controlled release of the drug over several weeks, and to be retrieved via an NG tube. We investigated the potential for patient and practitioner acceptability using a field questionnaire distributed in TB clinics in India and demonstrated the potential economic advantages associated with the implementation of a GRS intervention.

RESULTS

Design of a GRS for multigram dosing

A large-dose GRS for long-term treatment should (i) have a size and shape that can fit through the esophagus of a patient to non-surgically access the stomach, (ii) have the ability to adopt an alternative conformation in the stomach that prevents passage through the pylorus, (iii) achieve high concentrations of drug loading, (iv) be composed of biocompatible materials that are stable for an extended duration in the acidic gastric environment, (v) have no potential for gastrointestinal obstruction or perforation, and (vi) either be able to degrade into forms that can safely pass or be retrieved after the drug has been released from the device (*30*). Inspired by the rapid deployment of a gastric balloon through similar means, we set out to design a GRS that could be administered through an NG tube, which is inserted via the nose to access the stomach (*34*). After reaching the stomach, the GRS forms a cylindrical coil and continually releases grams of drug over the course of weeks, whereupon the device is retrieved back through an NG tube (Fig. 1A). The assembled GRS consists of a superelastic nitinol wire as the retention frame upon which drug pills are strung with a retainer and tubing at the ends of the device (Fig. 1B) (*35*). To tailor the drug loading and duration of therapy, the length of the GRS and formulation of drug pills can be modified (fig. S1).

We deployed a coiled nitinol wire inside tubing to the gastric cavity of 30- to 75-kg Yorkshire pigs to demonstrate transesophageal administration and safe gastric retention in vivo. Yorkshire pigs have similar gastric anatomy to humans and have been previously used to evaluate long-acting drug delivery platforms (*30*, *36*). Representative serial abdominal radiographs during device deployment and month-long residence revealed the feasibility of the GRS to pass through the esophagus and form a coil in the stomach within 50 s (Fig. 1C). The GRS was able to curl back into its original coil shape in the gastric cavity after passing through the esophagus because of the superelasticity of nitinol (*37*). Safe long-term gastric residence was evaluated by serial radiographs obtained over the course of 1 month and through endoscopic evaluation (Fig. 1C and fig. S2). Even after prolonged gastric residence of these large devices, mucosal surfaces of the animals' stomachs did not show injury, erosions, or ulcerations; in addition, the animals did not show any weight loss, evidence of GI obstruction, or limitation in the passage of food or liquid (fig. S3).

We designed the GRS to be retrieved through an NG tube after the release of the drug payload in the gastric cavity. The retrieval device consists of a Hall effect sensor to determine the distance between a magnet on the end of the GRS and a magnet at the end of retrieval device (Fig. 1D) (*38*). To ensure the stability of the Hall effect sensor in a low pH environment, we placed it in simulated gastric fluid (SGF) for 90 min; the measured voltage was comparable to the voltage measured in air before immersion in SGF (fig. S4A). A three-dimensional (3D) printed in vitro human stomach model was constructed to test the feasibility of the retrieval procedure (fig. S4B and data file S1). A magnet was placed on each end of the GRS to maximize likelihood of retrieval. In vivo demonstration of GRS retrieval was successful, as demonstrated by representative serial radiographs (Fig. 1D). Thus, we demonstrated the potential of the GRS to be safely administered, to reside safely in the gastric cavity for 1 month, and to be retrieved through the esophagus.

Controlled drug release with coated drug-matrix pills

We fabricated pills of a single drug mixed inside a silicone matrix and encapsulated each pill in a polymer coating to enable tailored dosing of each drug (Fig. 2A). Vinylpolysiloxane (VPS) was selected as a drug release matrix because of its flexibility, rapid curing time, and low-temperature mixing process with drug. Because of their mechanical and chemical properties, polysiloxanes have been extensively used for controlled drug delivery applications (*39*–*42*). We spray-coated a 300-μm-thick Eudragit RS 100 polymer coating to prevent

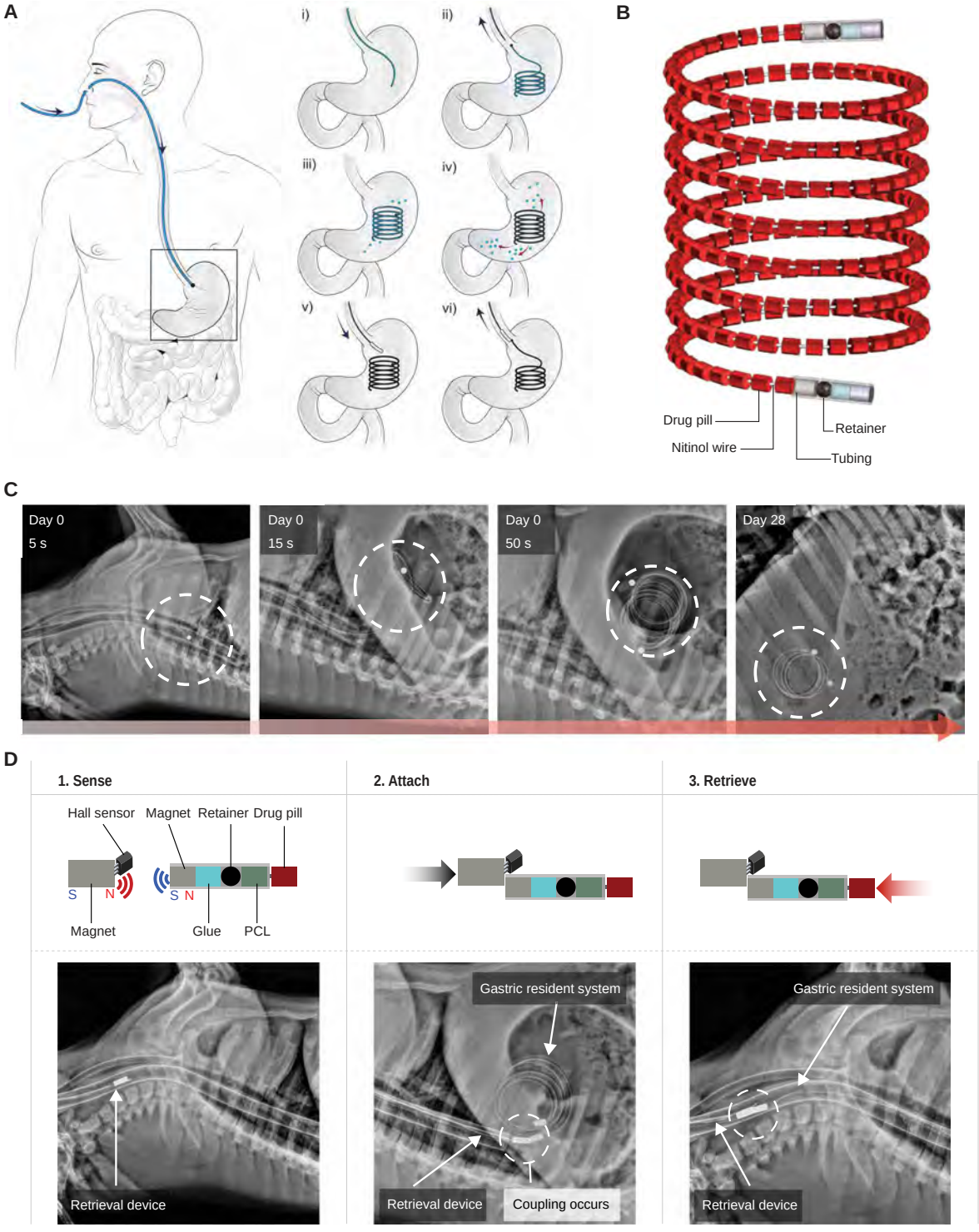


Fig. 1. Design and in vivo evaluation of a large-dose GRS for drug delivery. (**A**) (i-ii) An NG tube is first placed as a conduit for the large-dose GRS to be non-surgically administered, and then the NG tube is removed from the patient. (iii-iv) The GRS resides in the gastric cavity while releasing drugs. (v-vi) An NG tube is again placed in the patient for deployment of a retrieval device to attach and remove the GRS from the gastric cavity. Black arrows indicate direction of movement of the NG tube and retrieval device, and red arrows indicate drug release. (**B**) The GRS consists of a series of drug pills on a coiled superelastic nitinol wire; the ends are protected with a retainer and tubing. (**C**) Representative radiographs of the GRS immediately after deployment and on day 28 in a swine model. Dashed circles indicate GRS location. (**D**) The retrieval device consists of a Hall effect sensor and a magnet that can detect and attach to the magnets on either end of the GRS. Representative stepwise radiographs of the retrieval process executed in a swine model are shown below. Dashed circles indicate coupling of retrieval device with GRS. The components of both ends of the GRS [glue, a retainer, and a poly(Ɛ-caprolactone) (PCL) plug] are also shown.

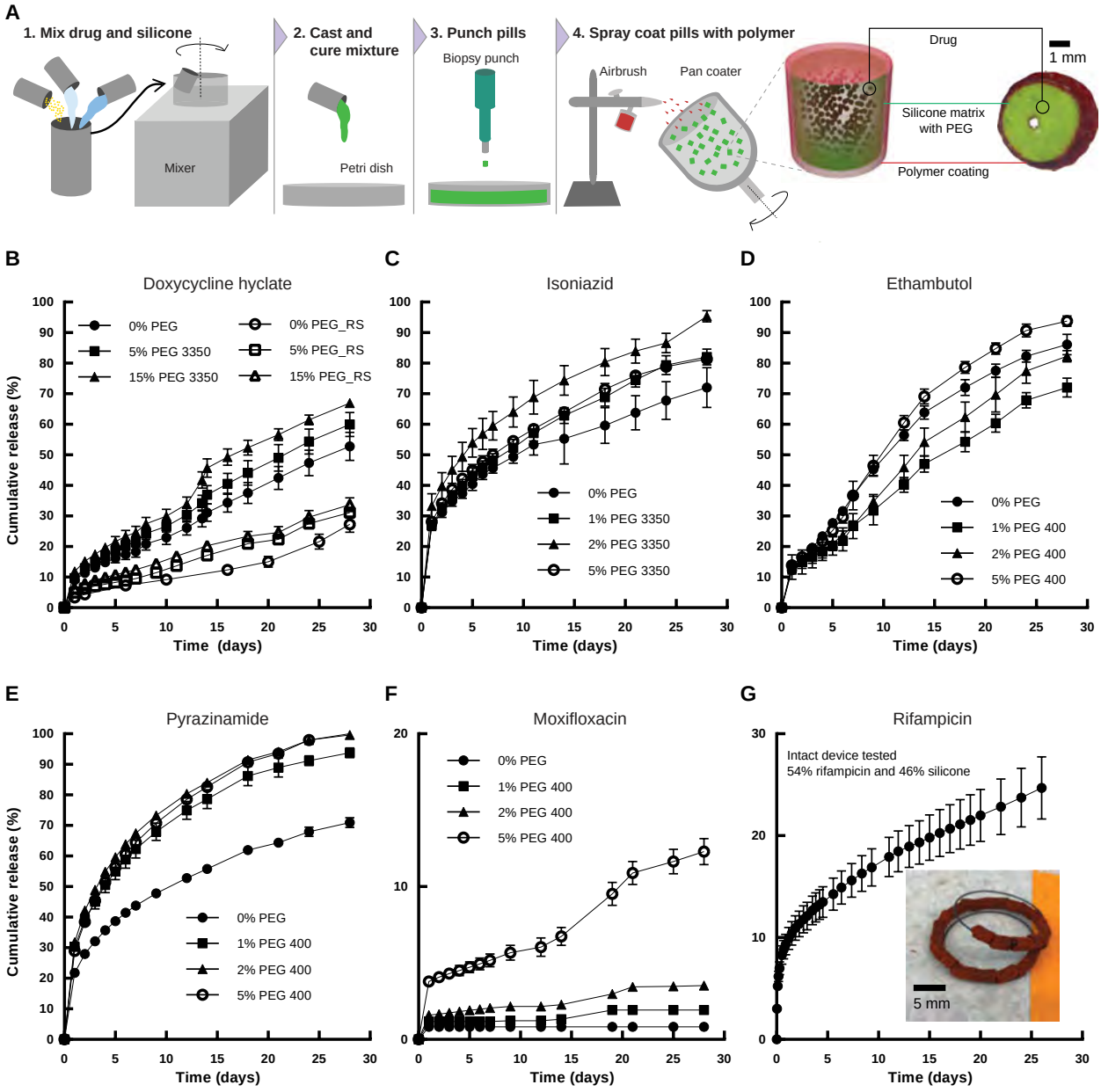


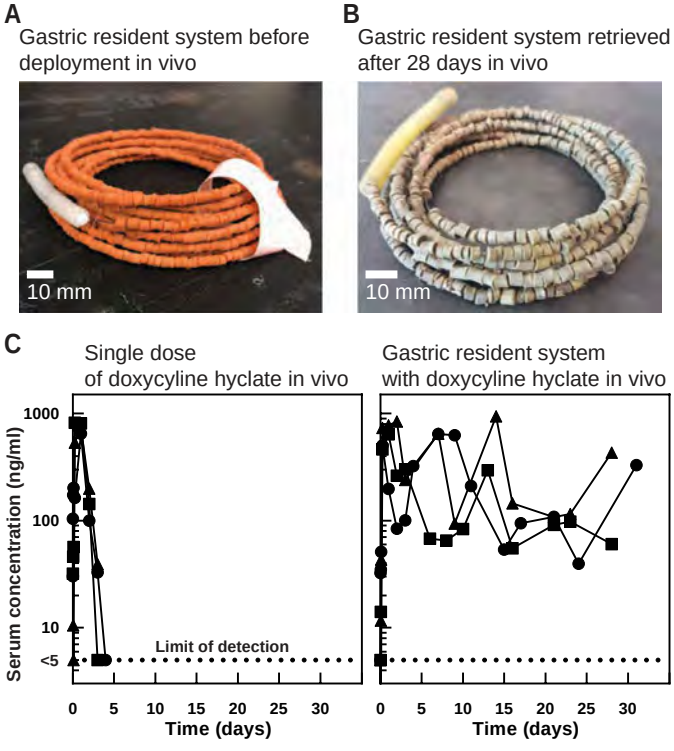
Fig. 2. Fabrication and in vitro release of TB antibiotics from individual drug pills. (**A**) Coated drug pills are made by mixing drug with silicones and extracting individual pills from the homogeneous matrix using a biopsy punch before spray-coating pills in a pan coater. A schematic visualization and a cross-sectional image of the Eudragit RS 100–coated doxycycline hyclate pill are shown. (**B**) In vitro release of doxycycline hyclate from a drug pill in SGF with formulations including different concentrations of PEG and Eudragit RS 100 coatings. (**C**) In vitro release of isoniazid from a drug pill in water. (**D**) In vitro release of ethambutol from a drug pill in SGF. (**E**) In vitro release of pyrazinamide from a drug pill in SGF. (**F**) In vitro release of moxifloxacin from a drug pill in SGF. (**G**) In vitro release of rifampicin in water from devices with 2 g of drug and 0% PEG. Inset: Image of the rifampicin-loaded device. Error bars represent SD for $n = 3$ samples in each group.

the burst release of drug from the surface of the matrix (*43*–*46*). Each pill had a height and diameter of 4 mm with a 0.5-mm hole in the center through which to pass the nitinol wire and contribute to the assembled GRS (Fig. 2A).

We assembled drug-VPS pills for multiple antibiotics used for TB treatment including doxycycline hyclate, isoniazid, ethambutol, pyrazinamide, moxifloxacin, and rifampicin (*3*, *47*, *48*). As demonstrated with doxycycline hyclate, the drug release rate from the VPS matrix in SGF can be tuned by varying the amount of a hydrophilic polymer, poly(ethylene glycol) (PEG), mixed within the VPS (Fig. 2B). The PEG domains act as channels inside the hydrophobic VPS matrix that can dissolve and form pores for the doxycycline hyclate to release. Furthermore, formulations that were coated with Eudragit RS 100 showed a linear kinetic profile with limited burst release of doxycycline hyclate (Fig. 2B). The drug-VPS pills were also able to release isoniazid, ethambutol, pyrazinamide, moxifloxacin, and rifampicin in vitro, indicating that the VPS matrix is compatible with a wide variety of TB drugs (Fig. 2, C to G).

In vivo sustained delivery of antibiotic for 4 weeks

Having demonstrated controlled release with coated drug-matrix pills in vitro for 1 month, we prepared the GRSs loaded with 10 g of doxycycline hyclate as a model drug (Fig. 3A) and administered them in swine. The GRS was assembled to contain 600 pills using four different formulations—two each with Eudragit RS 100 or PCL coatings—which released drug simultaneously (fig. S5) (*49*–*51*). After 28 days of gastric residence in vivo, the GRS was safely retrieved (Fig. 3B). The serum concentration profile of a 100-mg single dose is shown in Fig. 3C. The drug was absorbed rapidly, and detectable concentrations were observed within 15 min. No drug was detectable after 3 days with the single-dose formulation. In contrast, drug was detectable for at least 28 days when doxycycline hyclate was dosed in the GRS. We also incorporated rifampicin into the GRS and achieved detectable serum concentrations for a week in vivo (fig. S6).



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Formulation	Total drug incorporated (g)	AUC (ng/ml × day)	Duration of release (days)
Single dose	0.1	1019 ± 203	3
GRS	10	7118 ± 3170	>28

Fig. 3. In vivo release of doxycycline hyclate from the GRS in a swine model. (**A**) Representative photograph of a GRS after assembly of drug pills along a nitinol wire before deployment in vivo. (**B**) Representative photo of a retrieved GRS after 28 days in vivo in a swine model. (**C**) Left: Concentration-time profiles of doxycycline hyclate in serum after administering a single dose of 100 mg (n = 3). Right: Concentration-time profiles of doxycycline hyclate in serum after administering the GRS, which had 10 g of drug across four formulations (n = 3; fig. S5). (**D**) Area under the curve (AUC) and the duration of drug release for a single dose compared to the formulations of the GRS administered in vivo, with the mean value and SD reported for n = 3 samples in each group.

Preliminary end-user assessment and economic impact of the GRS

We surveyed 111 TB health care providers and 300 patients with TB at DOTS clinics in India and learned that a long-term drug delivery device administered through an NG tube was acceptable and feasible in the field (figs. S7 and S8, tables S1 and S2, and data file S2). An established model was used to evaluate the potential impact of a GRS on patients with TB, with savings estimated at more than $8000 per patient in New Delhi, India (table S3 and data file S3) (*52*, *53*).

DISCUSSION

Here, we report the development of a GRS capable of multigram-level dosing of a TB antibiotic over the course of 4 weeks. The GRS drug pills are compatible with all first-line TB antibiotics, and we anticipate that further formulation development and large-scale manufacturing with an array of polymer matrices and coatings will optimize a linear drug release profile in the gastric cavity to reduce variability in serum concentrations and match drug release kinetics across drugs. These macrodevices showed no evidence of GI obstruction or injury during gastric residence and retrieval, as supported by radiographic, endoscopic, and histopathologic evaluation in a swine model.

Adherence to TB treatment is challenging because of the long and frequent dosing regimen, and additional patient-centered interventions are necessary to supplement DOTS in resource-constrained environments (*1*, *20*, *22*). Technologies such as the GRS described here can improve the effectiveness of DOTS by ensuring that patients receive their medication over the course of extended periods of time, thereby reducing the frequency of clinic visits. Less frequent dosing visits would reduce the potential impact on daily life, specifically on productivity of individuals receiving treatment for TB (*11*). The ability of the GRS to contain and serve as a multigram drug depot in the gastric cavity supports further development of prolonged drug depots on the order of weeks and even months, which could mitigate the effects of poor adherence (*54*).

To establish a route for translation, we anticipate that the full development of these devices will include preclinical evaluation in an additional animal model such as the dog, which has gastric compressive forces and transit times similar to humans (*55*). Optimizing drug release kinetics is a critical next step, such that serum concentrations of the drug remain within the therapeutic window and do not increase the likelihood of drug resistance. Different diet conditions will also need to be tested to understand the effect on pharmacokinetic parameters across a broad spectrum of drugs. Ultimately, safety and efficacy of the GRS will need to be confirmed in humans.

In addition, we recognize the importance of amplifying training of health care workers to deploy NG tubes safely, so that the GRS can be implemented alongside DOTS interventions in the field where trained personnel are generally present (*56*, *57*). Because patients will be conscious during the NG tube procedure, they will be able to speak to a health care worker to ensure correct placement of the tube (*58*). The cost of this additional intervention as part of DOTS will need to be assessed in further fieldwork.

To begin addressing the acceptability and feasibility of the NG tube approach, we conducted a preliminary field questionnaire of 300 patients with TB and 111 TB health care workers in TB clinics in India. Our survey results indicated that more than 90% of health

care personnel have experience deploying NG tubes, and patients prefer the use of an NG tube for deployment of a month-long TB treatment as opposed to swallowing many capsules or drinking liters of water-drug mixture as potential alternative modes of generating large drug depots. We further demonstrated the potential impact of the implementation of our GRS to improve adherence in terms of lives saved and economic savings for patients suffering from TB.

One limitation of the field study is the incorporation of an NG tube description versus physical NG tube insertion into the questionnaire subjects. Although this questionnaire was administered to patients and health care providers with a comprehensive understanding of TB, ultimately, the physical discomfort of NG tube placement along with GRS retrieval requires further evaluation.

We believe that macrodevices consisting of multigram drug depots could have an impact across a range of diseases in addition to TB and could be coupled to other procedures such as endoscopy. For broad implementation, a range of chemical therapeutics will need to be studied and incorporated into the modular pill design of the GRS. Formulations will need to be optimized to ensure high drug loading efficiencies and controlled release profiles for efficacious treatment and controlled drug release. The GRS has potential as a platform technology for improving medication adherence and thereby also improve outcomes for patients suffering from a myriad of diseases.

MATERIALS AND METHODS

Study design

We designed, fabricated, and tested devices for month-long drug delivery in the gastric cavity. This GRS contains a series of drug pills loaded onto a nitinol shape memory alloy wire. The device forms a coil shape after reaching the stomach. A retrieval device compatible with nasogastric administration uses a sensor and magnet to attach to a magnet on the GRS. Approvals were obtained from the Committee on Animal Care at the Massachusetts Institute of Technology to assess the safety and long-term drug release of the GRS, as well as the feasibility of the retrieval device in a swine model. Radiographic, endoscopic, and histopathologic evaluation were conducted.

We assessed the end-user acceptability and feasibility of NG tube placement through a questionnaire of 111 TB health care providers and 300 patients with TB at DOTS clinics in New Delhi, India. The field questionnaire study was approved by the Massachusetts Institute of Technology Committee on the Use of Humans as Experimental Subjects and all required ethical committees of the hospitals in India. Sample sizes were determined on the basis of a conservative method with a 90% confidence interval and 8% margin of error for the health care providers and 90% confidence interval and 5% margin of error for the patients (*59*). All health care providers who filled out more than 90% of the questionnaire were included in the analysis. All 300 patients who provided consent for the study were included in the analysis. We also applied an economic model to quantify the impact of the GRS on the Indian government and patients with TB. The data, assumptions, and economic calculations were derived from a previous model, and we conducted sensitivity analysis on several of our assumptions.

Statistical analysis

For all experimentation shown, the mean is plotted with error bars representing the SD of $n = 3$. Individual subject-level data for Figs. 2 (B to G) and 3 (C and D) and figs. S3A, S4A, S5B, S6, S7 (B, C, E, and F), and S8 are shown in table S4.

SUPPLEMENTARY MATERIALS

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Materials and Methods
Fig. S1. Physical parameters of the GRS as the drug weight increases.
Fig. S2. Serial radiographs of the GRS over 1 month in a swine model.
Fig. S3. Effect of the GRS on the weight and stomach tissue of swine.
Fig. S4. Hall effect sensor acid stability and retrieval using an in vitro stomach model.
Fig. S5. In vivo formulations and their corresponding 4-week in vitro drug release profiles of doxycycline hyclate–silicone pills of the 10 g GRS.
Fig. S6. In vivo release of rifampicin from the GRS in a swine model.
Fig. S7. Field questionnaire results at TB clinics in New Delhi, India.
Fig. S8. Field questionnaire results on NG tube deployment at TB clinics in New Delhi, India.
Table S1. Demographics of 111 TB health care providers who responded to the questionnaire study across TB clinics in New Delhi, India.
Table S2. Demographics of 300 patients with TB who responded to the questionnaire study across TB clinics in New Delhi, India.
Table S3. Modeled impact of TB treatment interruptions on health and economic costs in New Delhi, India annually.
Table S4. Individual subject-level data for Figs. 2 (B to G) and 3 (C and D) and figs. S3A, S4A, S5B, S6, S7 (B and C), S7 (E and F), and S8 (Excel format).
Data file S1. In vitro design of 3D stomach model.
Data file S2. Field questionnaire study to inform mode of administration.
Data file S3. Sensitivity analysis of health and economic model.
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Population-based screening for pulmonary tuberculosis utilizing community health workers in Ethiopia★

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ABSTRACT

Objective: To evaluate the utility of a volunteer health development army in conducting population screening for active tuberculosis (TB) in a rural community in southern Ethiopia.
Methods: A population-based cross-sectional survey was conducted in six *kebeles* (the lowest administrative units). Volunteer women community workers led a symptom screening programme to identify adults ≥15 years of age with TB in the community. Individuals with a cough for ≥2 weeks had spot and morning sputum samples taken, which were examined using acid-fast bacillus (AFB) smear microscopy, culture, and Xpert MTB/RIF.
Results: All 24 517 adults in the study area had a symptom screen performed; 544 (2.2%) had had a cough for ≥2 weeks. Among those with a positive symptom screen, 13 (2.4%) were positive on sputum AFB smear microscopy, 13 (2.4%) had a positive culture, and 32 (5.8%) had a positive Xpert MTB/RIF test. Overall, 34 TB cases (6%) were identified by culture and/or Xpert, corresponding to a prevalence of 139 per 100 000 persons.
Conclusions: This study demonstrated the capability of community health workers (volunteer and paid) to rapidly conduct a large-scale population TB screening evaluation and highlight the high yield of such a programme in detecting previously undiagnosed cases when combined with Xpert MTB/RIF testing. This could be a model to implement in other similar settings.
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Introduction

The fight against tuberculosis (TB) has been bolstered by the development of new molecular diagnostics, drugs, and a recent high-level United Nations meeting addressing the epidemic; however, many challenges to TB control remain. One of the most pressing challenges to eliminate TB is the high number of undetected cases. Only 6.4 of an estimated >10 million cases (64%) were officially notified in 2017, leaving a gap of >3.5 million cases unreported and potentially undetected. Most of these missed cases occur in low- and middle-income countries (LMICs) and among vulnerable populations (WHO, 2018). Rural settings are particularly challenging areas to detect and diagnose TB due to limited healthcare services, poor healthcare-seeking behaviour, and limited awareness and knowledge about TB (Cambanis et al., 2005; Sudha et al., 2003). Understanding the burden of TB in poor rural areas has large implications for TB control and is needed to design optimal case finding strategies (Cambanis et al., 2005; Sudha et al., 2003). This study was performed to evaluate the utility of a volunteer health development army (HDA) in conducting population screening for active TB in a rural setting in southern Ethiopia.

Active case-finding (ACF) for TB is influenced by individual (care-seeking behaviour), social (access to healthcare), and biomedical (diagnostic capability) factors (Shargie et al., 2006a). In rural communities, ACF can help reach persons with no transport or limited mobility, scarce resources, and persons who rarely seek healthcare (Yassin et al., 2013; Datiko et al., 2015). The Ethiopian national TB programme (NTP) relies on passive case

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finding, as do most control programmes and NTPs globally; however, there is a recognized need to strengthen community screening given variations in disease epidemiology across diverse geographic and cultural settings (Kebede et al., 2014).

Ethiopia is one of 14 countries to be included on all three World Health Organization (WHO) high burden country lists for TB, TB/HIV, and multidrug-resistant TB (MDR-TB). The TB incidence in Ethiopia in 2017 was estimated to be 164 per 100 000 population (WHO, 2018). The prevalence of smear-positive pulmonary TB was 108 per 100 000 per population according to a national population-based TB survey conducted from October 2010 to June 2011, in which the vast majority of those identified were newly diagnosed cases that had not been captured by the control programme and most (55%) were among the younger age groups (15–34 years) (Kebede et al., 2014). Additional studies across various rural settings in Ethiopia have found a range of smear-positive pulmonary TB prevalence rates (from 30 to 174 per 100 000 population) suggesting that disease epidemiology varies across different geographical locations of the country (Berhe et al., 2013; Hamusse et al., 2017; Shargie et al., 2006b; Deribew et al., 2012; Yimer et al., 2009; Tadesse et al., 2011).

This study was performed to evaluate the efficacy of a population screening programme for active pulmonary TB using volunteer and paid community health workers in a rural area in southern Ethiopia. As a brief background, Ethiopia launched a health extension programme (HEP) in 2003 with the objective of increasing population access to basic health services including TB. The HEP consists of female health extension workers (HEWs) who receive 1 year of training and then become salaried healthcare workers equipped to provide basic health services to the same community from which they were recruited (Yassin et al., 2013; Datiko et al., 2015; Datiko and Lindtjorn, 2009; Datiko et al., 2017). The HEWs are based at local health posts and provide health promotion to the community at the household level. In 2013, to further expand healthcare services and to ease the burden on HEWs, the Ethiopian government rolled out a programme called the health development army (HDA) (Tulloch et al., 2015), which consists of female community-level volunteers who receive basic training on health by the HEWs. They are recruited based on their leadership qualities and their interest in being involved in the health of their community. They live within the communities and aid the HEWs at the household level. They have regular meetings among themselves and with the HEWs to deal with health issues in the community. The main goal of this study was to assess the feasibility and utility of a population screening programme for active TB led by HDAs.

Methods

Study setting and design

A cross-sectional study was performed in the Hawassa Zuria Woreda (a rural district), in the Sidama zone of southern Ethiopia. Hawassa Zuria Woreda has 23 *kebeles* (the lowest administrative units within Ethiopia, each with an average population of approximately 5000 persons or 1000 households), and a total population of 153 190 persons, 79 858 of whom were ≥15 years (52%). The Woreda has one hospital, four health centres, and 23 health posts serving the population. Each health centre is associated with five satellite health posts and combined they form a primary healthcare unit (PHCU). The health service coverage of the Woreda is 80% (accessible health service is defined as having a health facility within two hours walking distance). For this study, three health centres were selected in the district with a functional PHUC. Two *kebeles* were randomly selected from each of the three health centres, and thus the study area included six of the 23 *kebeles*. All households in the study *kebeles* were surveyed. Inclusion criteria were community members without known TB and who had had a cough for ≥2 weeks, age ≥15 years, and voluntary study participation with signed written consent. Exclusion criteria were patients currently on anti-TB treatment, those who were disabled or immobilized, patients with a severe illness, unable to provide a sputum sample, and community members who were not available for screening at the time of screening due to travel or hospitalization. The study was conducted from May 8, 2016 through June 9, 2016.

Data collection

Prior to the study, meetings were convened with *kebele* leaders, HEWs, and members of the HDA to inform them of the study objectives and procedures and to receive input and feedback. Subsequently, training was conducted with the field supervisors and HEWs at the health posts.

The identification of presumptive TB cases (i.e., those with a positive cough screen) was conducted by members of the HDA. There were 30 to 58 HDAs in each *kebele* depending on the population size and approximately 350 HDAs were involved in active TB case finding. Prior to the survey, community mobilization (creating awareness about the study) was done through religious institutions and schools in the community. Afterwards, the HDA conducted house-to-house visits to identify people who had had a cough for at least 2 weeks. Individuals with a cough for ≥2 weeks were considered as presumptive TB cases and brought to the health post. At the health post, they were evaluated by field supervisors (health professionals who have experience in TB and community work) and HEWs. Those who met the eligibility criteria were interviewed and asked to submit two sputum samples (spot and morning). For all study participants, a pretested (validated) structured questionnaire was used to collect data on patient demographics, clinical presentation, and associated risk factors for the transmission of TB. Two field supervisors and the study principal investigator (YM) monitored the daily data collection process. The duration of patient screening and data collection was 5 days for each of the six *kebeles* between May 8, 2016 and June 9, 2016.

Laboratory testing

AFB smear preparation was performed at the health posts by laboratory technicians assigned for the study. Slides were prepared on the same day as the sputum collection and along with the remaining portions of the sputum samples were transported daily to a health centre approximately 25 kilometres away. Here the slides were stained using the Ziehl–Neelsen (ZN) hot staining technique and examined for acid-fast bacilli (AFB) using regular light microscopy (Federal Democratic Republic Ethiopia Ministry of Health, 2014). The remaining portions of the two sputum samples were pooled and stored at −20 °C until transported to Armauer Hansen Research Institute (AHRI) in Addis Ababa where culture was performed using Löwenstein–Jensen (LJ) medium according to standard procedures (WHO, 1998).

HIV counselling and screening was offered to all participants diagnosed with TB, and HIV serology was performed based on the national testing algorithm. Finger stick blood was tested for HIV (1/2) with the Antibody Colloidal Gold (KHB) test and positive results were confirmed with Stat-Pak, while discordant results were resolved by HIV-1/2 Unigold Recombinant assay.

Definitions

A confirmed pulmonary TB case was defined as one in whom a sputum specimen was Xpert MTB/RIF test and/or culture positive.

Clinical treatment outcomes were defined as per national guidelines (Federal Democratic Republic Ethiopia Ministry of Health, 2016).

Data management

All data were double-entered into an online REDCap database (Harris et al., 2009) and analysed using Stata software. Differences in categorical variables were tested using the Chi-square test. A multivariable logistic regression model was used to evaluate the independent association of potential risk factors for TB. Model building and selection was based on the purposeful selection of covariates strategy, as described previously, based on findings in the univariate analysis and biological plausibility (Hosmer and Lemeshow, 2000). A p-value of <0.05 was considered significant.

Ethical considerations

The study was approved by the institutional review boards of Addis Ababa University and AHRI, as well as the Ethiopian National Ethics Review Committee. Study permission was also obtained from the Southern Regional Health Bureau, Zonal Health Department and the Woreda health office. Patients diagnosed with active TB were referred to their catchment health centre and hospital for treatment.

Results

All 24 517 adults in the six *kebeles* had a cough symptom screen for TB performed during the 1-month study period and 544 (2.2%) were found to have had a cough for ≥2 weeks. All patients with a prolonged cough submitted two sputum samples. Among the 544 adults with a positive cough screen, the median age was 36 years (interquartile range (IQR) 29–48 years) and the majority were female ($n = 354$, 65%) (Table 1). There were 152 participants (28%) with a history of contact with a TB patient, 160 (29%) who reported previous anti-TB treatment, and 12 (2%) with a history of incarceration (Table 3). There were high rates of reported symptoms including fever (80%), night sweats (87%), weight loss (85%), and chest pain (81%).

Prevalence of pulmonary tuberculosis

A total of 34 (6%) persons with a positive cough screen were found to have pulmonary TB (Table 2). All 34 cases were confirmed by Xpert MTB/RIF ($n = 32$) and/or a positive culture result ($n = 12$). Only 13 of the 34 cases (38%) had a positive AFB sputum smear microscopy result (Table 2). Two culture-positive cases had a negative Xpert MTB/RIF test and negative sputum smear microscopy results. Two cases were rifampicin-resistant according to Xpert MTB/RIF testing, with one of the cases having a prior history of anti-TB treatment. During the study period, only one case of a patient on anti-TB treatment was identified, who was not included in the calculated TB prevalence. The overall point prevalence of confirmed pulmonary TB cases was 139 per 100 000 population (95% confidence interval (CI) 96–194) (Table 2).

Almost three fourths (25/34, 74%) of the confirmed TB cases were newly diagnosed, while 9/34 were previously treated cases. There was a similar distribution among females (53%) and males (47%) (Table 3). None of the 31 TB cases who had HIV testing performed had a positive result. A treatment outcome was available for 29 patients, 28 of whom were cured; one had completed treatment. Five persons with TB moved out of their *kebeles* and outcomes were not available.

Risk factors for tuberculosis

In the univariate analysis, longer duration of cough, older age, and close contact with a known TB case were associated with an increased risk of having confirmed TB among persons with a positive cough screen (Table 3). In the multivariate analysis, a cough of >4 weeks (adjusted odds ratio (aOR) 4.23, 95% CI 1.94–9.23) was associated with the risk of having bacteriologically confirmed TB, while older age (aOR 0.047, 95% CI 0.005–0.43) was associated with a reduced risk of bacteriologically confirmed TB among those with a positive symptom screen (Table 4).

Discussion

Utilizing a large volunteer healthcare workforce in rural southern Ethiopia, it was possible to conduct a massive population-based screening programme for active TB among more than 24 000 adults over a short time-period (approximately 1 month) and 34 previously undiagnosed active TB cases were detected, primarily through the use of Xpert MTB/RIF. This study demonstrates the feasibility of a large TB screening programme using community health volunteers doing the initial symptom screen and referrals and paid community health workers for further testing and confirmation. The high prevalence of previously undiagnosed TB identified in the current study highlights the hidden burden of TB in rural settings and the need for additional active screening programmes. In our setting, it was found that an approach using community health workers made it possible to conduct an impressive large-scale screening programme and this may be a useful approach to consider for other similar rural LMIC settings.

Innovative approaches using community health workers to increase the case detection rate are growing in number (Yimer et al., 2009), and in this regard practical changes were observed in southern Ethiopia by applying a community-based TB intervention. Community-based interventions at the village level using female community health workers (HEWs) have made TB diagnosis and treatment services more accessible to the community and have significantly improved TB diagnosis and treatment in

Table 1
Distribution of the population and confirmed tuberculosis cases by *kebeles* of Hawassa Zuria Woreda, Ethiopia.

Kebeles	Number of households	Total population			≥15 years			Positive cough screen			Confirmed TB		
		Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
1	1272	6231	3103	3128	3248	1618	1630	77	27	50	3	2	1
2	1508	7390	3680	3710	3852	1918	1934	91	28	63	7	5	2
3	1976	9681	4821	4860	5047	2513	2534	131	35	96	10	3	7
4	1127	5534	2756	2778	2885	1437	1448	46	13	33	3	2	1
5	2436	11 447	5701	5746	5967	2972	2995	113	48	65	6	2	4
6	1373	6749	3361	3387	3518	1752	1766	86	39	47	5	3	2
Total	9692	47 032	23 422	23 609	24 517	12 210	12 307	544	190	354	34	16	18

TB, tuberculosis.

Table 2
Distribution of confirmed tuberculosis cases by *kebeles*, Hawassa Zuria Woreda, Ethiopia.

Kebeles	≥15 years	AFB positive	Culture positive	Xpert positive	Confirmed TB	Rate	95% CI
1	3248	1	1	3	3	92	19.05–269.69
2	3852	3	3	7	7	182	73.09–374.06
3	5047	4	4	9	10	198	95.05–364.08
4	2885	1	1	3	3	104	21.45–303.59
5	5967	2	2	5	6	101	36.91–218.73
6	3518	2	2	5	5	142	46.16–331.36
Total	24 517	13	13	32	34	139	96.06–193.74

AFB, acid-fast bacilli; TB, tuberculosis; CI, confidence interval.

Table 3
Predictors of pulmonary TB among persons with a positive cough screen, Hawassa Zuria Woreda, Ethiopia.

Characteristic	Total (n = 544), n (%)	No TB (n = 510), n (%)	TB (n = 34), n (%)	Univariate analysis	
				OR (95% CI)	p-Value
Female sex	354 (65)	336(66)	18 (53)	0.58 (0.28–1.17)	0.12
Mean age (years)	38	38	31		
Age category (years)					
15–24	68 (12)	61 (12)	7 (22)		
25–34	143 (27)	132 (26)	11 (34)	0.72 (0.26–1.94)	0.52
35–44	159 (29)	150 (29)	9 (28)	0.52 (0.18–1.46)	0.21
45–54	94 (17)	90 (18)	4 (13)	0.38 (0.10–1.38)	0.14
≥55	80 (15)	79 (15)	1 (3)	0.11 (0.01–0.92)	0.04
Illiterate	401 (74)	383 (75)	18 (53)	0.37 (0.18–0.75)	0.006
Unemployed	533 (98)	501 (98)	32 (94)	0.28 (0.05–1.38)	0.12
Married	470 (86)	440 (94)	30 (88)	0.83 (0.28–2.45)	0.74
Duration of cough in weeks					
2–4	333 (61)	321 (63)	12 (35)		
>4	211 (39)	189 (37)	22 (65)	3.11 (1.50–6.43)	0.002
Symptoms					
Fever	437 (80)	409 (80)	28 (82)	1.15 (0.46–2.85)	0.76
Night sweats	472 (87)	443 (87)	29 (85)	0.87 (0.32–2.34)	0.79
Loss of appetite	288 (53)	268 (53)	20 (59)	1.28 (0.63–2.61)	0.47
Weight loss	464 (85)	433 (85)	31 (91)	1.83 (0.54–6.15)	0.34
Chest pain	439 (81)	411 (81)	28 (82)	1.12 (0.45–2.78)	0.80
Shortness of breath	315 (56)	294 (58)	21 (62)	1.18 (0.58–2.42)	0.63
Previous anti-TB treatment	160 (29)	151 (30)	9 (26)	0.85 (0.39–1.87)	0.69
Contact with TB case	152 (28)	137 (28)	15 (44)	2.02 (1.00–4.10)	0.049
Presence of TB patient in the family	89 (16)	80 (16)	9 (26)	1.99 (0.85–4.21)	0.11
Absence of window in the home	490 (90)	457 (90)	33 (97)	3.82 (0.51–28.5)	0.19
Alcohol use	13 (2)	11 (2)	2 (6)	2.83 (0.60–13.3)	0.18

TB, tuberculosis; OR, odds ratio; CI, confidence interval.

Table 4
Multivariate analysis of risk factors for pulmonary tuberculosis among persons with a positive cough screen, Hawassa Zuria Woreda, Ethiopia (n = 544).

Characteristics	Multivariate analysis	
	aOR (95% CI)	p-Value
Age category in year		
15–24	1.00	
25–34	0.70 (0.24–2.07)	0.528
35–44	0.29 (0.09–0.96)	0.043
45–44	0.22 (0.05–0.86)	0.031
≥55	0.047 (0.005–0.43)	0.007
Duration of cough in weeks		
2–4	1.00	
≥4	4.23 (1.94–9.23)	<0.001
Close contact with known TB patient		
No	1.00	
Yes	1.99 (0.93–4.26)	0.073

aOR, adjusted odds ratio; CI, confidence interval; TB, tuberculosis.

the rural settings of southern Ethiopia (Yassin et al., 2013; Datiko and Lindtjorn, 2009; Datiko et al., 2017). In contrast to these previous studies in Ethiopia, and as part of an innovative approach, our study used HDAs to identify symptomatic TB individuals in the community. Using HDAs, a very high number of TB cases were identified in a short period of time. Involving HDAs helped us reach the entire community and trace the symptomatic cases easily. HDAs live in the community and come across symptomatic neighbours in their daily routines. They also participate in community meetings and work closely with the HEWs on health-related issues. They are not paid, but contribute voluntarily to improve the health of the community. A similar approach has been reported among others in Uganda where voluntary Village Health Teams (VHT) are involved in improving and promoting health at the community level (O'Donovan et al., 2018).

Improved screening is inadequate without appropriate diagnosis and treatment. Linking the HDAs with a rapid molecular diagnostic tool such as Xpert MTB/RIF has proved to be a successful approach in detecting presumptive TB cases early for rapid diagnosis and treatment, thus reducing the burden as well as the adverse social and economic consequences of TB. The HEP in Ethiopia employs salaried staff and has continued to be productive for over a decade and a half. The HDA extension is on the other hand relatively new and relies heavily on volunteer women, raising issues of sustainability. The driving force for their active involvement needs to be investigated in terms of motivation. It was observed in Uganda, for example, that volunteer community health workers (CHWs) were actually participating with an

expectation of future rewards (Kasteng et al., 2016). In contrast, a qualitative study from this region of Ethiopia suggested the current dominance of intrinsic motivators (such as community recognition and appreciation) among the HEWs and their supporters (Tulloch et al., 2015).

We detected 544 individuals with a positive cough screen among more than 24 000 screened. The overall prevalence of laboratory-confirmed TB was 139 per 100 000 population, much lower than the national prevalence of 277 per 100 000 population (95% CI 208–347) (Kebede et al., 2014). The prevalence of smear-positive pulmonary TB was also lower than in several previous studies in Ethiopia, including the national prevalence survey (Kebede et al., 2014; Berhe et al., 2013; Hamusse et al., 2017; Shargie et al., 2006b; Yimer et al., 2009; Tadesse et al., 2011), but higher than a report from southwest Ethiopia (Deribew et al., 2012). Direct comparison is difficult because of differences in study methodology, population, and time. More than 50% of all confirmed TB cases in the national survey had no cough but were identified through chest X-ray (CXR) screening (Kebede et al., 2014), a method not included in this study; chest radiography is not available at most health centres in Ethiopia and CXR is not routinely employed in the diagnosis of pulmonary TB. Ethiopia has overall shown a declining trend in TB in the last years (WHO, 2018).

We diagnosed 34 previously undetected cases of active pulmonary TB in just 4 weeks using a community-based ACF strategy. In contrast, only one pulmonary TB patient was identified by the routine passive case finding procedure in the same period in the study population. ACF has the added benefit of reaching those with limited access, the economically disadvantaged, elderly people, and those with poor health seeking behaviour (Yassin et al., 2013; Datiko et al., 2015). The routine TB diagnostic method in the health facilities, including at our study site, is smear microscopy, which is known for its poor sensitivity (Merid et al., 2009). Xpert MTB/RIF is being rolled out at many health centres in Ethiopia. This study used a combination of smear microscopy, Xpert MTB/RIF, and culture. Xpert MTB/RIF detected 94% of the TB cases, whereas smear microscopy detected only 38%. In the present study, the culture yield was much lower than expected (38%). This may be due at least in part to the loss of viability of *Mycobacterium tuberculosis* following repeated freeze and thaw of sputum samples due to power failures in the field during specimen storage and transportation to AHRI for culture.

TB prevalence rates are higher in men than in women globally (WHO, 2001) and this is true for Ethiopia as well (WHO, 2018). However, unlike in health facility-based passive case finding, the proportion of women with TB has increased consistently when community-based screening has been conducted in southern Ethiopia (Yassin et al., 2013; Datiko and Lindtjorn, 2009; Datiko et al., 2017), probably due to improved access by women who would otherwise have remained undetected. In a case–control study in communities where HEWs were employed in active case finding, the male to female ratio of TB cases changed from 1.3:1 to 1:1 following the intervention (Yassin et al., 2013; Datiko and Lindtjorn, 2009). The male to female ratio of 1:1.1 among newly diagnosed cases in the present study seems to further confirm the value of community-based health interventions in accessing the hard to reach pockets among the rural population.

In the multivariate analysis, a cough of $\geq$4 weeks was an independent risk factor associated with a TB diagnosis among persons with a positive symptom screen, while TB was less likely to be present among older persons ($\geq$35 years of age) with a positive symptom screen. TB–HIV co-infection was not reported in our study and this could be related to the overall low prevalence of HIV infection in rural communities of southern Ethiopia (EPHI, 2015).

The low case detection rate remains a global challenge, with 36% of prevalent cases missing (WHO, 2018). Community-based TB activities are increasingly reported from several high burden countries. Ethiopia is strengthening surveillance and improving the diagnostic capacity (WHO, 2012) of the TB control programme with a rollout of Xpert MTB/RIF testing (Federal Democratic Republic Ethiopia Ministry of Health, 2016). In the experience reported here, the reach of the HEWs was extended deep into their communities through the engagement of HDAs. Symptomatic screening at the community level coupled with rapid diagnosis using Xpert MTB/RIF allows health system access to underserved rural community pockets more effectively. HEWs in Ethiopia are paid female professionals who bridge care and are extensively engaged in community service packages that link health with integrated development; they satisfy the three main principles recently proposed by Palazuelos et al., which are essential values for trust in the health system and a path to equitable outcomes of health coverage (Palazuelos et al., 2018).

In conclusion, this study identified a very high proportion of undiagnosed TB cases using volunteer women community workers in the rural community of Hawassa Zuria Woreda and allowed us to screen large communities (>24 000 persons) in a relatively short period of time with minimal costs. The use of volunteer community workers together with Xpert MTB/RIF has the potential to increase TB case detection, reducing the pool of undetected cases and curbing the transmission of TB in the rural settings of Ethiopia. Implementation and scale-up of this strategy could help LMICs increase case detection in rural settings.

Conflict of interest

None declared.

Financial disclosure statement

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Ethical approval

The study was approved by the institutional review boards of Addis Ababa University and the Armauer Hansen Research Institute (AHRI), as well as the Ethiopian National Ethics Review Committee. Study permission was also obtained from the Southern Regional Health Bureau, Zonal Health Department and the Woreda Health Office. Patients diagnosed with active TB were referred to their catchment health centre and hospital for treatment.

Author contributions

YM contributed to the conception and design of the study, acquisition of data and interpretation, and drafting and writing of the manuscript. YW, MA, and DD contributed to the design of the study and supervision and revision of the manuscript. TH contributed to data management and analysis. MH contributed to data analysis and revision of the manuscript. GH contributed to laboratory work. AA contributed to the design of the study and supervision, interpretation of data and revising the manuscript. All authors approved the final version of the manuscript.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2019.10.012.

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RESEARCH ARTICLE Open Access

Stigma matters in ending tuberculosis: Nationwide survey of stigma in Ethiopia

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Abstract

Background: Tuberculosis (TB) affects, and claims the lives of, millions every year. Despite efforts to find and treat TB, about four million cases were missed globally in 2017. Barriers to accessing health care, inadequate health-seeking behavior of the community, poor socioeconomic conditions, and stigma are major determinants of this gap. Unfortunately, TB-related stigma remains unexplored in Ethiopia.

Methods: This mixed methods survey was conducted using multistage cluster sampling to identify 32 districts and 8 sub-cities, from which 40 health centers were randomly selected. Twenty-one TB patients and 21 family members were enrolled from each health center, and 11 household members from each community in the catchment population.

Results: A total of 3463 participants (844 TB patients, 836 from their families, and 1783 from the general population) were enrolled for the study. The mean age and standard deviation were 34.3 ± 12.9 years for both sexes (34.9 ± 13.2 for men and 33.8 ± 12.5 for women). Fifty percent of the study participants were women; 32.1% were illiterate; and 19.8% came from the lowest wealth quintile. The mean stigma score was 18.6 for the general population, 20.5 for families, and 21.3 for TB patients. The general population of Addis Ababa (AOR: 0.1 [95% CI: 0.06–0.17]), those educated above secondary school (AOR: 0.58 [95% CI: 0.39–0.87]), and those with a high score for knowledge about TB (AOR: 0.62 [95% CI: 0.49–0.78]) had low stigma scores. Families of TB patients who attended above secondary school (AOR: 0.37 [95% CI: 0.23–0.61]) had low stigma scores. TB patients educated above secondary school (AOR: 0.61 [95% CI: 0.38–0.97]) had lower stigma scores, while those in the first (AOR: 1.93: 95% CI 1.05–3.57) and third quintiles (AOR: 1.81: 95% CI: 1.08–3.05) had stigma scores twice as high as those in the highest quintile. Fear of job loss (32.5%), isolation (15.3%), and feeling avoided (9.3%) affected disclosure about TB.

Conclusions: More than a third of Ethiopians have high scores for TB-related stigma, which were associated with educational status, poverty, and lack of awareness about TB. Stigma matters in TB prevention, care, and treatment and warrants stigma reduction interventions.

Keywords: Tuberculosis, Stigma, Ethiopia

Background

Tuberculosis (TB) is a worldwide public health crisis. A third of the world's population is infected, and 10 million people developed TB disease, while 1.6 million died of TB, in 2017. National TB Programs (NTPs) have diagnosed and treated millions of TB cases over the years. However, about 4 million TB cases were missed globally in 2017 alone [1]. This gap could be due to problems related to health service delivery and poor health-seeking behavior of the community, which are affected by factors that include awareness about TB, gender, stigma, and constrained socioeconomic conditions [2–4].

Community health-seeking behavior is also affected by the accessibility of services, the availability and quality of services, and cultural factors. These vary by the type of health condition and the views and perceptions of the clients and communities, which are expressed in a range of behaviors, including stigma [4]. Stigma is described as social determinant of health because it is shaped by community norms, interpersonal relations, and health institutions' culture [5, 6]. Unfortunately, people with

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living some diseases, including TB, HIV, and leprosy, face deep-rooted and longstanding stigma within the community [7, 8].

Understanding of stigma toward TB, unlike HIV, is limited [9]. TB is primarily a disease of the poor and is associated with high stigma in the community. In addition to the stigmatizing community response [10, 11], self-stigmatization by TB patients affects the will of TB patients to seek care and adhere to their treatment [12], which is also affected by the association of TB with HIV and negative cultural beliefs or norms [13]. Moreover, victim blaming by health workers and the community, such as associating TB with bad behavior on the part of patients, reinforces the grip of stigma in communities and the health system [14].

Studies have shown higher stigma among the poor, the less educated, women, and socially disadvantaged communities. However, the magnitude of stigma varies across settings and is worst when a person is discriminated against by society and household members, with negative consequences on marital life, quality of life, and future opportunities [15, 16].

Understanding perceptions about TB and community misconceptions is an entry to designing patient-centered services. Qualitative studies have reported that patients prefer to be treated well and receive adequate counseling at appropriate times, and want supportive mechanisms during their illness [17, 18]. But negative perceptions about TB affect patients' capacity to disclose their disease status to relatives and family members. This has demoralized patients and resulted in selective disclosure of their status only to trusted community members [19]. However, in communities with better awareness about TB, where health care workers are supportive and adequate patient support mechanisms are available, the magnitude of stigma was reported to be low [10].

Ethiopia has a high burden of TB, TB/HIV, and multidrug-resistant TB, with comorbidities and high stigma [8, 9, 20]. Nearly 30% of estimated TB cases are still missed by the NTP. High stigma among the poor, women, and rural communities could be one of the factors contributing to the case detection gap [21–23]. However, there has been no large-scale study of TB-related stigma. Therefore, we aim to describe the magnitude of stigma related to TB in communities: TB patients, their families, and the general population of Ethiopia.

Methods

Study setting and population

This is the first national stigma survey conducted in seven regions and two city administrations of Ethiopia. The Challenge TB project operates in nine regions, covering 92% of the national population. The NTP started implementing the WHO-recommended DOTS strategy in 1995. Currently, 256 hospitals and 3390 health centers provide TB services, and over 16,000 health posts deliver community-based TB care. The community health services mainly focus on conducting regular health education sessions, identifying and referring presumptive TB cases, and providing adherence support. Despite these efforts, the NTP continues to miss a third of estimated cases [1].

Study design and sampling

This is a mixed methods study conducted from October to November 2017 in the nine Challenge TB–supported regions of Ethiopia.

Sample size for the quantitative study

A single population proportion formula was used to estimate sample size [24]. A design effect of 2 and 10% was added to compensate for the non-response rate. A total of 3463 participants were enrolled for the study: 1783 from the general population, 836 from families of TB patients, and 844 TB patients.

Study area

Ethiopia is administratively divided into nine regional states and two city administrations. This survey was conducted in seven regions and two city administrations. From these, 16 zones (provinces) and four sub-cities were selected. From each zone or sub-city, two districts were randomly selected. From each district, one rural and one urban *kebele* (lowest administrative unit with an average population of five thousands) were identified for the study. Finally, from the total of 40 districts selected, 80 kebeles were included in the study. The kebeles were divided into *gots* or clusters as the final study unit. Households were identified by systematic sampling, and 22 household participants were enrolled from each *got* or cluster.

Forty health centers were identified to enroll TB patients and their families. From each health center, we interviewed 11 TB patients and their families after obtaining informed consent. We recruited TB patients who were at least 18 years old who had been on treatment for at least 1 month. From their households, a household member who was at least 18 years old who had lived in the house for at least 6 months was selected by lottery.

Qualitative studies

We conducted 18 focus group discussions (FGDs) and 76 in-depth interviews (IDIs). The kebele administrators assisted the research team in the identification of participants. The participants in the IDIs were selected from program managers (10 regional, 8 provincial, and 10 district TB focal persons), 12 health care workers, 12 TB patients, 12 family members of TB patients, and 12

health extension workers (HEWs), who are community health workers. TB patients and families of TB patients were approached in the health centers, while participants of FGD from the community were identified by kebele administrators.

Data collection

To collect quantitative data, we pre-tested and used semistructured questionnaires from the WHO guide, which contains a generic questionnaire for data collection about stigma and wealth index [(2)]. The questionnaire has variables related to perception of TB patients toward themselves, anticipated stigma from their households and the community, and enacted stigma that the patients had experienced.

Trained data collectors were employed for the study. Tablets for data collection used web-based CSPro software Version 7.2 (Census and Survey Processing System, US Census Bureau and ICF Macro; 2019).

FGDs and IDIs were conducted in the local languages by trained, experienced data collectors using pretested, semistructured, and open-ended topic guides. The FGDS and IDIs were audiotaped. Supervisors were assigned to conduct random data checks and household visits. Built-in validation checks (character, data type, range, limit, required fields, skip, etc.) were designed in the questionnaire, and a regular check was done by a central CSPro expert, the data manager.

Data analysis

Quantitative data were extracted from the web-based system and exported to IBM SPSS Statistics Version 25 (Armonk, NY, USA: IBM; 2019) for analysis. Descriptive analysis was done using SPSS. Binary logistic and multivariate logistic regression, for variables with $p < 0.25$, were used.

Knowledge scores were constructed using the total number of interview questions employed to assess the knowledge of the study participants and the total number of expected correct answers. We calculated knowledge scores using the mean of the number of correct answers given by the study participants as a cut-off point to categorize the knowledge scores into high or low. The study participants who answered above the mean score were classified as having a high knowledge score, while those who answered below the mean score were classified as having a low knowledge score.

Wealth-related variables were initially constructed for rural and urban populations, and later a common wealth index was constructed using variables that were considered common both rural and urban areas. Finally, both the rural and urban wealth index regression coefficients were mapped into the common wealth index, resulting in a composite "national" wealth index, which was categorized into quintiles.

Qualitative data were imported to OpenCode software (version 3.6) and analyzed using thematic content analysis. Direct verbatim quotations and results from the coding and categorization were used to develop the narrative.

Ethics approval and consent to participate

Ethical clearance was obtained from the Ethics Review Board of the Ministry of Science and Technology. We obtained support letters from the Federal Ministry of Health. We also sought and received informed verbal consent from the study participants. The Ethics Review Board approved informed verbal consent for the study.

Results

Sociodemographic and economic characteristics

General population

Among the 1783 study participants interviewed, the mean age (SD) was 34.6 years (SD ± 12.9). Of the total number of participants, 828 (46.8%) were men, 48.7% of whom were heads of household, and 33.5% of whom were married. Among the study participants from general population, 66% were married, 22% were housewives, and 30.1% of the study participants could not read and write (Table 1).

Families of TB patients

Of the 836 family members of TB patients interviewed, the mean (SD) age was 33.8 (11.6). In this group, 48.7% were males, 39.4% were head of households, 65% were married, 33.9% were illiterate, and 21.3% were farmers (Table 1).

TB patients

Of the 844 TB patients interviewed, the mean (SD) age was 34 (13.8) years, and 29.7% were in the age range 18–30 years. More than half (57.8%) were males, 46.9% were heads of household, 51.4% were married, 24.1% were farmers, and 34.7% could not read and write (Table 1). The mean family size and number of people sleeping per room were 4.5 and 3.6, respectively. Among the TB patients, more than a third (37.4%) had at least one child under the age of five.

Attitudes about and stigma toward tuberculosis

General population

Almost two-thirds (64.5%) of the study participants reported that they could cope with TB, but 31.9% expressed fear. When asked who they would tell, 82.7% of participants reported that they would inform a doctor, while 21.5% would tell a spouse, 16.5% close friends, and 25.7% family members. The majority (95.8%) of the participants reported that they would go to public facilities,

Table 1 Sociodemographic characteristics of the study population in Ethiopia

		General population		Families of TB patients		TB patients	
Variables	Categories	Number	%	Number	%	Number	%
Gender	Male	835	46.8	407	48.7	488	57.8
	Female	948	53.2	429	51.3	356	42.2
Age in years	18–30	872	48.9	405	48.4	251	29.7
	31–60	828	46.4	414	49.5	246	29.1
	>60	83	4.7	17	2.0	164	19.4
Relationship	Head	869	48.7	329	39.4	93	11.0
	Spouse	597	33.5	248	29.7	52	6.2
	Son/Daughter	266	14.9	160	19.1	38	4.5
	Other relative	44	2.5	88	10.5	396	46.9
	Non-relative	7	0.4	11	1.3	189	22.4
Marital Status	Married	1176	66	543	65.0	186	22.0
	Never married	343	19.2	203	24.3	7	0.8
	Divorced	143	8	46	5.5	4	0.5
	Widowed	107	6	38	4.5	434	51.4
	Living together	14	0.8	6	0.7	283	33.5
Educational Status	Illiterate	537	30.1	283	33.9	66	7.8
	Read and write only	128	7.2	51	6.1	57	6.8
	Primary	517	29	227	27.2	4	0.5
	Secondary	398	22.3	173	20.7	292	34.7
	Above secondary	203	11.4	102	12.2	40	4.7
Occupation	Employed	210	11.8	126	15.1	263	31.2
	House wife	393	22	178	21.3	163	19.3
	Farmer	322	18.1	178	21.3	85	10.1
	Daily laborer	179	10	80	9.6	102	12.1
	Trader	381	21.4	121	14.5	114	13.5
	Student	136	7.6	84	10.0	203	24.1
	No job/dependent	114	6.4	47	5.6	103	12.2
	House maid	38	2.1	19	2.3	85	10.1
	Other	10	0.6	3	0.4	109	12.9
Wealth Quintile	Lowest	355	19.9	166	19.9	102	12.1
	Second	350	19.6	169	20.2	18	2.1
	Third	365	20.5	162	19.4	8	0.9
	Fourth	352	19.7	173	20.7	168	19.9
	Highest	361	20.2	166	19.9	169	20.0

while 14% reported that they would go to private facilities. More than two-thirds (68.5%) of the community felt compassion for TB patients, but 20.5% stated that TB patients are rejected by the community (Table 2).

Some participants (11.9%) would keep TB disease secret, but 84.5% would disclose their status, and if they did so, 84.6% would tell family members. Of the participants, 18.1% reported that the community would think less of them, 24.2% said the community would avoid them, 15.1% said they would be asked to stay away, and 14.9% would be ashamed. Of the general population, 9.8% responded that they would not disclose TB disease to a confidant; 16.4% would think less of themselves, and 6.5% expected that family would think less of them (Table 3).

Families of TB patients

Among family members of TB patients, 514 (63.1%) reported that they could get TB, and 558 (68.5%) responded that they would cope with it if they did. Of the respondents,

Table 2 Attitude and stigma towards tuberculosis among the general population

Variables		#	%
Do you think you can get TB ($n = 1668$)		756	45.3
Reaction if you were found out that you have TB ($N = 1668$)	Cope with it	1076	64.5
	Fear	532	31.9
	Surprise	80	4.8
	Shame	55	3.3
	Embarrassment	33	2
	Sadness or hopelessness	78	4.7
	Other	9	0.5
Who would you talk to about your illness if you had TB? ($N = 1668$)	Doctor/other medical worker	1380	82.7
	Spouse	358	21.5
	Parent	450	27
	Children	169	10.1
	Other family member	428	25.7
	Close friend	276	16.5
	No one	18	1.1
	Others	5	0.03
What would you do if you thought you had symptoms of TB?	Go to public health facility	1598	95.8
	Go to private health facility	233	14
	Go to pharmacy	46	2.8
	Go to spiritual/traditional healer	25	1.5
	Pursue other self-treatment options	4	0.2
	Others	2	0.1
	Don't know	11	0.7
If you would not go to health facility, what is the reason? ($N = 24$)	Not sure where to go	7	29.2
	Cost	11	45.8
	Transportation related	2	8.3
	Don't trust health workers	4	16.7
	Would be cured by religion	1	0.1
If you had symptoms of TB, at what point would you go to the health facility?	Immediately	1080	64.7
	In few days	305	18.3
	One to 2 weeks	172	10.3
	After 2 weeks	93	5.6
	I will not go to health facility	14	0.8
	Other	4	0.2
How expensive do you think TB diagnosis and treatment in this country?	It is free of charge	782	46.9
	It is reasonably priced	187	11.2
	It is moderately expensive	139	8.3
	It is very expensive	142	8.5
	Don't know	418	25.1
Know people who have/had TB		815	48.9
Statement closest to your feeling about people with TB	I feel compassion and desire to help	1142	68.5
	I feel compassion but tend to stay away from these people	208	12.5
	It is their problem and I don't want to get TB by trying to help them	74	4.4

Table 2 Attitude and stigma towards tuberculosis among the general population *(Continued)*

Variables		#	%
	I fear them because they may infect me	98	5.9
	I have no particular feeling	145	8.7
	Other	1	0.1
How TB patient usually regarded/treated In your community?	Most people reject him/her	342	20.5
	Most people are friendly, but they generally try to avoid	295	17.7
	The community mostly supports and helps him/her	683	40.9
	I don't have the experience	345	20.7
	Others	3	0.2

685 (84.0%) reported that they would like to talk to medical personnel if they had TB. Some family members (8.9%, or 73) reported that they would not disclose their status even to a confidant (Additional file 1: Table S2).

Among family members, 637 (78.2%) mentioned that they knew people who had TB, and 637 (78.2%) reported that they would feel compassion and want to help them. Slightly more than half (432, or 53%) of the respondents mentioned that the community supported and helped TB patients. Some of the respondents - 205 (25.2%) and 176 (21.6%) -indicated that the community avoided and rejected them, respectively (Additional file 1: Table S1). One hundred and fifty-two (18.6%) and 134 (16%) respondents reported that others would avoid them and think less of them if they had TB, respectively.

TB patients

Most TB patients, 82.5% (679) reported that they would not disclose having TB to a confidant, while 107 (13%) would not disclose. Two hundred and forty-seven (30%) and 234 (28.5%) reported that they would not find a job or would lose their job, respectively (Additional file 1: Table S3). Of 380 who had no partner, 15.8% reported that they would have a problem in finding a spouse even after their cure. Of 443 who had a partner, 46.5% reported that their partner would refuse to have sex with them. Of 361 participants who had children, 80.1% of them reported that being a TB patient is a problem for their children (Additional file 1: Table S3).

Stigma score and factors associated with stigma

General population

The mean stigma score was 18.6 (range: 9–45). Of the respondents, 645 (38.7%) had high stigma scores. A high stigma score was inversely correlated with educational status, region, and a high knowledge score. Addis Ababa had the lowest stigma score. Oromia had 10 times higher stigma compared to Addis Ababa (AOR: 0.1 [95% CI: 0.06–0.17]). Compared to those who could not read and write, those who were educated above secondary school had a 42% lower mean stigma score (AOR: 0.58 [95%CI: 0.39–0.87]). Respondents who had high knowledge scores had a

Table 3 Response of the general population to TB stigma related questions

Stigma related questions ($N = 1668$)	Agree		Indifferent		Disagree	
	#	%	#	%	#	%
If yourself got TB, you would want it to remain secret.	198	11.9	61	3.7	1409	84.5
If a member of your family got TB, you would want it to remain secret.	194	11.6	63	3.8	1411	84.6
If you had TB, others would think less of you.	302	18.1	164	9.8	1202	72.1
If you had TB, you would be ashamed or embarrassed.	250	14.9	79	4.7	1339	80.3
If you had TB, others would avoid you.	403	24.2	205	12.3	1060	63.6
If you had TB, you would be asked to stay away from a social group.	251	15.1	191	11.5	1226	73.5
If you had TB, you would not disclose even to a confidant	164	9.8	91	5.5	1413	84.7
If you had TB, you would think less of yourself.	273	16.4	108	6.5	1287	77.2
If you had TB, others would think less of your family.	109	6.5	43	2.6	1516	90.9

A total of nine items were used to assess stigma and they had high internal consistency (Cronbach's alpha = 0.98)

lower 38% odds of having a high stigma score (AOR: 0.62 [95% CI: 0.49–0.78]) (Table 4).

Families of TB patients

The mean stigma score was 20.46 (range: 10–46). Of the family members, 310 (38.0%) had high stigma scores. A high stigma score was associated with educational status and region. Respondents who had completed primary school (AOR: 0.6: 95% CI: 0.39–0.93), secondary school (AOR: 0.52; 95% CI: 0.32–0.84), and above secondary school education (AOR: 0.37: 95% CI: 0.23–0.61) were less likely to have high stigma scores compared to those who could not read and write. High stigma scores were observed in Oromia Region compared to other regions of Ethiopia (Additional file 1: Table S4).

TB patients

The mean stigma score was 21.31 (range: 9–45). Of the 844 TB patients, 356 (43.3%) had high stigma scores. A high stigma score was associated with educational status, wealth status, and region. Oromia Region had the highest and Addis Ababa had the least mean stigma scores. Compared to those who could not read and write, those with secondary school education had a 39% lower odds of having high stigma scores. TB patients in the first (AOR: 1.93: 95%CI 1.05–3.57) and third quintiles (AOR: 1.81: 95%CI: 1.08–3.05) had stigma scores twice as high as those in the highest wealth quintile (Additional file 1: Table S5).

Of the TB patients, 75.5% felt that family members were supportive. Most of the patients (75.3%) perceived that their utensils were separated. Close to half of TB patients (45.9%) feared reduced family income due to their condition, while 37% felt increased sadness, 32.5% felt the threat of losing their jobs, 25.4% mentioned that people behaved differently toward them, and 15.3% felt isolated within the family. Some (9.3%) felt avoided by family members (Table 5). Three-quarters (75.7%) of TB patients reported that they felt compassion for and a desire to help other TB patients, 7% reported no particular feeling, and

Table 4 Factors associated with stigma towards tuberculosis in the general population

Variables		Stigma High # (%)	Stigma Low # (%)	COR (95% CI)	AOR (95%CI)
Gender	Male	293 (37.4)	490 (62.6)	0.91 (0.74–1.1)	NA
	Female	352 (39.8)	533 (60.2)	1	
Education	Not able to read and write	220 (46.5)	253 (53.5)	1	1
	Read and write only	48 (40.7)	70 (59.3)	0.79(0.52–1.19)	0.9(.57–1.38)
	Primary	180 (37.0)	306 (63.0)	0.68 (0.52–0.88)	0.84(.63–1.11)
	Secondary	143 (36.8)	246 (63.2)	0.67 (0.51–0.88)	0.92 (0.68–1.25)
	Above secondary	54 (26.7)	148 (73.3)	0.42 (0.29–0.6)	0.58 (0.39–0.87)[a]
Wealth	Lowest	122 (39.9)	184 (60.1)	1.53 (1.11–2.11)	0.83 (0.55–1.25)
	Second	146 (45.3)	176 (54.7)	1.91 (1.4–2.62)	0.97 (0.65–1.43)
	Third	137 (40.7)	200 (59.3)	1.58 (1.15–2.16)	0.88 (0.61–1.28)
	Fourth	132 (38.2)	214 (61.8)	1.42 (1.04–1.95)	0.85 (0.6–1.2)
	Highest	108 (30.3)	249 (69.7)	1	1
Setting	Rural	314 (42.5)	425 (57.5)	1.33 (1.1–1.63)	0.95 (0.75–1.21)
	Urban	331 (35.6)	598 (64.4)	1	1
Knowledge score	High	280 (33.5)	555 (66.5)	0.65 (0.53–0.79)	0.62 (0.49–0.78)[a]
	Low	365 (43.8)	468 (56.2)	1	1
Region	Oromia	192 (58.4)	137 (41.6)	1	1
	Amhara	121 (36.1)	214 (63.9)	0.4 (0.3–0.55)	0.35 (0.25–0.49)[a]
	SNNP	81 (25.5)	237 (74.5)	0.24 (0.18–0.34)	0.23 (0.16–0.32)[a]
	Tigray	95 (53.7)	82 (46.3)	0.83 (0.57–1.19)	0.8 (0.55–1.17)
	Benshangul Gumuz	43 (48.3)	46 (51.7)	0.67 (0.42–1.07)	0.61 (0.37–0.98)[a]
	Gambella	19 (23.2)	63 (76.8)	0.22 (0.12–0.38)	0.22 (0.12–0.38)[a]
	Addis Ababa	22 (12.7)	151 (87.3)	0.1 (0.06–0.17)	0.1 (0.06–0.17)[a]
	Dire Dawa	35 (43.2)	46 (56.8)	0.54 (0.33–0.89)	0.54 (0.33–0.91)[a]
	Harari	37 (44.0)	47 (56.0)	0.56 (0.35–0.91)	0.54 (0.32–0.88)[a]

[a]Statistically significant. The study participants were grouped as having high and low stigma score using the mean stigma score as a cut-off point

Table 5 Perception of TB patients regarding their relationships and livelihood

Variables N = 823	Agree		Indifferent		Disagree	
	#	%	#	%	#	%
Family members are cooperative towards me	621	75.5	33	4.0	169	20.6
Utensils are separated for me	620	75.3	27	3.3	176	21.4
I have fear of reduction of family income	378	45.9	75	9.1	370	44.9
Threat of loss of job/wages	267	32.5	84	10.2	472	57.4
Most people behave differently	209	25.4	67	8.1	547	66.5
Feel isolated within the family	126	15.3	49	6.0	648	78.8
Family members avoid me	76	9.3	36	4.4	711	86.4
I have increased sadness	305	37.1	79	9.6	439	53.4

17.2% reported that they would stay away because of fear of re-infection (Additional file 1: Table S3).

Socioeconomic consequences of TB on the patients

Of the 844 TB patients, 64.9% reported that nothing had happened after they developed TB. However, 8.9% TB patients lost their jobs, 21% encountered a reduction in income, 1.5% divorced, and 3.4% interrupted school.

Qualitative findings

The community felt that TB is a serious disease and treatment takes a long time, and they feared acquiring TB. People were afraid to share utensils with TB patients and sit near a TB patient who has a cough. Participants mentioned that TB patients are isolated or discriminated as against because TB is infectious and a communicable disease.

> *"…TB patients have difficulty of getting houses to rent because of the fear of transmission of TB to people who live in the same compound…" (Addis Ababa, Female, FGD).*

> *"My husband's family stigmatized me a lot. Since they knew that I am a TB patient, they didn't sleep in our house. They sleep outdoors. They are not also willing to eat with me. ...Before I was infected with TB, our social life with other people was great. The social life of DD community is well known. But after they knew that I am a TB patient, only one of my neighbors sometimes comes to visit me. In order not to come to my house frequently, she used to say I am tired and I have a lot of work to do at home" (Dire Dawa, Female TB patient).*

> *"…acquiring TB may be considered as a curse…" (Addis Ababa, Female, FGD).*

Some participants reported that the extent of stigmatization and isolation of TB patients has significantly decreased these days because people know that it is curable. TB patients are not prohibited from obtaining services in the community due to their illness.

> *"We should not discriminate [against] TB patients, rather we should help them with diets, proper care and anything else they require…" (Southern Nations, Nationalities, and Peoples' Region, Male, FGD).*

Family members reported that they supported TB patients by providing nutritious food, arranging a separate bedroom, accompanying them when they go to collect drugs from the health centers/health posts, and allowing them to have adequate rest.

Discussion

We report high fear of TB and stigma in the general population of Ethiopia, which are reflected by the community's perception of TB patients and self-stigmatization by patients. Stigma is associated with educational status, level of awareness about TB, and wealth status, and its levels varied across regions.

Stigma related to TB is a perceived and/or internalized attitude of a community or families toward TB patients due to social norms. The poor, women, ethnic minorities, migrants, and refugees were reported to be highly affected by TB-related stigma and its consequences, including isolation, lack of support, and loss of employment, depending on the cultural context and level of awareness in the community [18, 19, 25, 26].

Community perceptions about TB can positively or negatively affect the capacity of the community to offer support to TB patients and the effectiveness of TB programs [18]. In settings where understanding and caring exist, the capacity of TB patients to seek care, adhere to treatment, and receive support [27]. Perceptions are shaped by knowledge about the disease, capacity to seek care, and factors affecting this capacity. Unfortunately, despite the existence of free and decentralized TB services, the attitudes, perceptions, and reactions of the

community toward TB patients have affected service delivery and could result in delayed care seeking and affect treatment outcomes [5, 28]. TB remains a highly stigmatized disease, mainly because of its association with HIV and misconceptions about its transmission. This is confirmed by qualitative findings that TB patients were denied housing and sometimes the disease was considered a curse. In such communities, the capacity to access care is compromised and patients tend to remain at home rather than seek care when they develop symptoms.

As in our study, high self-disclosure to family members was reported from Nigeria. However, they believed that TB is an embarrassment to the family and did not share utensils or beds [29]. This could be due to TB-associated stigma within the community and associated consequences.

Perceptions about the disease also affect patients' capacity to cope with it. In our study, 60% reported that they could cope with TB. The patients think less of themselves, however, and experience problems related to social engagement, employment, marriage, feelings of sadness, depression. and self-stigmatization [19, 30]. A study from Zambia found that stigma results in low self-esteem, affects disclosure capacity, and has social consequences for patients and their children, [15] findings that merit implementation of stigma reduction interventions.

Urban areas have higher knowledge about TB, which is reflected by lower stigma. However, in areas with high HIV prevalence, the opposite scenario existed, due to HIV-related stigma [8]. In other contexts, high knowledge scores were not paralleled by low stigma, which requires further study.

Stigma shapes the disclosure of TB status within a community. From the qualitative part of the study, we learned TB is sometimes considered a curse, which makes it more difficult for patients and households to disclose it to the community. Therefore, TB patients mainly disclosed their TB status to family members [31]. However, disclosure was affected by patients' perception that they would not be stigmatized. Patients' trust in the family and the community played a crucial role in supporting disclosure. In our study, the majority of study participants reported that they would seek public health facilities and disclose their symptoms to doctors. This could be due to low HIV-associated TB in rural communities, where patients dare to seek care and share information with health workers.

Patients affected by TB expressed stigma within the household, as reported from the FGDs in the qualitative part of the study. They indicated that the family members were not willing to share utensils or eat with them. More than the stigma from the community and families, internalized stigma by TB patients (self-stigmatization) plays an important role in care seeking and social engagement [10]. The fact that TB patients expect rejection by the community if they are known to have TB requires intervention to ensure that patients are accepted and supported when seeking care. This could be done through the decentralization of services, better health education about TB, and community support to patients. Engaging community HEWs and Ethiopia's Health Development Army that reaches households is crucial to enhance the level of community support for patients. This is reflected in the qualitative part of the study, which underscores the importance of supporting TB patients in the community.

Ethiopia's high TB burden may be due in part to TB-related stigma and perceptions about TB and sociocultural factors, as another study from Ethiopia has found [18]. The NTP needs to develop a stigma reduction strategy to reduce this barrier to seeking care. Stigma is associated with wealth, educational status, setting (rural/urban), and knowledge that TB is a preventable and curable disease, so tailored interventions are needed to the reach cases in the community missed as a result of stigma [19].

Limitations of the study

This is the first national study about TB-related stigma in Ethiopia. However, cultural and socioeconomic conditions might have affected the understanding and expression of stigma in the communities. The interviewers speak the local language, created conducive environment and encouraged better communication by giving opportunities to compensate for this.

Conclusions

TB-related stigma remains a challenge to TB prevention and control in Ethiopia. Therefore, tailored stigma reduction interventions are needed to increase community awareness about TB, improve health-seeking behavior, and promote support for TB patients in their households and the community.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12889-019-7915-6.

Additional file 1: Table S1. Attitude and stigma related to TB among families of TB patients. **Table S2.** Responses of families of TB patients to TB stigma related questions. **Table S3.** Responses of TB patients to TB stigma related questions. **Table S4.** Factors associated with stigma towards tuberculosis in the families of TB patients. **Table S5.** Factors associated with stigma towards tuberculosis among TB patients.

Abbreviations

DOTS: Directly observed treatment, short course; FGD: Focus group discussion; HEW: Health extension worker; HIV: Human immunodeficiency virus; IDI: In-depth interview; NTP: National Tuberculosis Programme; TB: Tuberculosis; WHO: World Health Organization

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Authors' contributions
DJ and PS designed the study. DGD supervised the data collection. DGD wrote the manuscript. All authors reviewed and approved the final version.

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Availability of data and materials
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Ethics approval and consent to participate
This study was approved by the Ethiopian Science and Technology Commission, Ethics Review Board. We also obtained letters of support from the National TB Programme of the Federal Ministry of Health and Regional State Health Bureaus to conduct the study in the respective provinces, districts, health facilities, and communities. The study participants were recruited after obtaining informed consent, approved by review board.

Consent for publication
Not applicable.

Competing interests
The authors declare no conflict of interest.

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Reduction of diagnostic and treatment delays reduces rifampicin-resistant tuberculosis mortality in Rwanda

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SUMMARY

SETTING: In 2005, in response to the increasing prevalence of rifampicin-resistant tuberculosis (RR-TB) and poor treatment outcomes, Rwanda initiated the programmatic management of RR-TB, including expanded access to systematic rifampicin drug susceptibility testing (DST) and standardised treatment.

OBJECTIVE: To describe trends in diagnostic and treatment delays and estimate their effect on RR-TB mortality.

DESIGN: Retrospective analysis of individual-level data including 748 (85.4%) of 876 patients diagnosed with RR-TB notified to the World Health Organization between 1 July 2005 and 31 December 2016 in Rwanda. Logistic regression was used to estimate the effect of diagnostic and therapeutic delays on RR-TB mortality.

RESULTS: Between 2006 and 2016, the median diagnostic delay significantly decreased from 88 days to 1 day, and the therapeutic delay from 76 days to 3 days. Simultaneously, RR-TB mortality significantly decreased from 30.8% in 2006 to 6.9% in 2016. Total delay in starting multidrug-resistant TB (MDR-TB) treatment of more than 100 days was associated with more than two-fold higher odds for dying. When delays were long, empirical RR-TB treatment initiation was associated with a lower mortality.

CONCLUSION: The reduction of diagnostic and treatment delays reduced RR-TB mortality. We anticipate that universal testing for RR-TB, short diagnostic and therapeutic delays and effective standardised MDR-TB treatment will further decrease RR-TB mortality in Rwanda.

KEY WORDS: TB; Rwanda; MDR-TB programmatic management; MDR-TB diagnosis; MDR-TB treatment

RIFAMPICIN (RMP) is the most powerful anti-tuberculosis drug, and resistance to RMP is a reliable surrogate marker for multidrug-resistant tuberculosis (MDR-TB), a major challenge for TB management and control.[1] Rapid diagnostic tools, such as Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA), have greatly increased access to RMP drug susceptibility testing (DST) and reduced diagnostic delay.[2]

Globally, the vast majority (75%) of new RMP-resistant TB (RR-TB) patients remained undiagnosed in 2017,[3] fuelling RR-TB transmission.[4] Logistical challenges related to sample transport and result reporting can cause diagnostic delays.[5] Other challenges, such as the lack of decentralised RR-TB treatment or access to RR-TB drugs, can cause therapeutic delays in those already diagnosed. In 2017, the global RR-TB treatment success rate was a mere 55%,[3] with diagnostic and/or therapeutic delays associated with poorer treatment outcome and pre-treatment loss to follow-up (LTFU).[2,6–13]

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Table 1 Timeline showing changes to the programmatic management of MDR-TB in Rwanda

Period/year	Intervention	Implementation context
Before 2005	Passive surveillance of drug-resistant TB	Selected patients' samples (mostly those failing and relapsing from the WHO Category 2 regimen) were shipped to collaborating laboratory for DST, but no standard treatment for MDR/RR-TB
2005	Programmatic management of RR-TB and systematic surveillance of drug-resistant TB among retreated patients	The programmatic management of RR-TB (PMDT) was launched as a core component of the NTP.[15] PMDT comprised countrywide surveillance of drug-resistant TB among previously treated TB patients and the standardised long-duration MDR-TB regimen. As the NRL's capacity to perform DST was insufficient, patient samples were shipped to external collaborating laboratories such as the Institute of Tropical Medicine (Antwerp, Belgium), resulting in long diagnostic delays[26]
2007	Strengthening RR-TB diagnostic capacity of the NRL	The NRL introduced phenotypic DST using the proportion method on Löwenstein-Jensen medium (phenotypic)
2009	Strengthening RR-TB diagnostic capacity of the NRL	The NRL introduced GenoType® MTBDR*plus* LPA (Hain Lifescience, Nehren, Germany) for the rapid detection of MDR-TB
2012	Strengthening RR-TB diagnostic capacity at referral laboratories	Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) was piloted in six referral hospitals
2013	Strengthening RR-TB diagnostic capacity at the countrywide laboratory network	The logistics of sputum sample transportation (≥2/week motorbike visits from each health centre to an Xpert site, and weekly sample transportation from intermediate health facilities to connect with LPA facilities) and timely reporting of results (phone call to a dedicated NTP number in case of RR-TB results) strengthened this diagnostic network.[35] Moreover, reducing the diagnostic delay and a high number of Xpert tests was rewarded through a performance-based financing policy[29]
2014	Expending access to RR-TB rapid diagnostic	Xpert testing was decentralised to the district hospital level and became easily accessible to all 515 peripheral health facilities as first-line diagnostics for all those aged ≥55 years and presumptive TB patients with HIV coinfection, as well as all smear-positive TB patients.[15] The shorter MDR-TB treatment regimen was introduced.[36] All patients diagnosed with RR-TB were considered eligible for the shorter MDR-TB regimen (previously only those patients diagnosed with rifampicin and isoniazid resistance, i.e., MDR-TB, were eligible for the long regimen). Effective coordination between diagnostic centres and the Rwandan health facilities where TB care is provided was essential

MDR-TB = multidrug-resistant TB; TB = tuberculosis; WHO = World Health Organization; RR-TB = rifampicin-resistant TB; PMDT = programmatic management of drug resistant TB; NTP = National Tuberculosis Control Programme; DST = drug susceptibility testing; NRL = national reference laboratory; LPA = line-probe assay; HIV = human immunodeficiency virus.

However, evidence on the effect of shortened delays on RR-TB mortality is lacking.[14]

In Rwanda, the first patients with RR-TB were documented in 1989 at the Kigali University Hospital, Kigali, Rwanda. No standardised treatment regimen was available and little could be offered to these patients.[15] In 2005, the programmatic management of RR-TB (PMDT) was launched as a core component of the National TB Control Programme (NTP).[15] Countrywide access to RR-TB testing and MDR-TB treatment increased (Table 1). However, the effect of increased access and shortened delays on RR-TB mortality has never been investigated in Rwanda. We therefore studied data from all RR-TB patients since the start of PMDT in Rwanda—a study period of more than 10 years in order 1) to describe trends in RR-TB diagnosis and enrolment into MDR-TB treatment, 2) to compare diagnostic and therapeutic delays between different RMP DST methods and 3) to estimate the association between shortened delays and RR-TB mortality. To the best of our knowledge, this is the first such nationwide population-based study.

METHODS

Design and study population

In this longitudinal retrospective analysis, we included consecutive patients diagnosed with pulmonary RR-TB who were registered between July 2005, when the PMDT started, and December 2016.

Data collection

Patients were assigned a unique ID on treatment initiation, or laboratory ID for those who did not start treatment. Patient files were retrieved from their respective health facilities. The National MDR-TB register and the National Reference Laboratory (NRL) registers were reviewed to extract relevant data.

A standardised data collection tool (see Supplementary Data) was used to capture demographics, baseline clinical characteristics, type of RMP DST used for diagnosis, dates of sample collection for RMP DST, dates that RMP DST results were available at the RR-TB testing laboratory, date of MDR-TB treatment initiation, the programmatic

outcome (death before treatment initiation, death during treatment, treatment success—cure or treatment completion, treatment failure, treatment discontinuation and LTFU) and the outcome date.

Two trained MDR-TB experienced nurses collected the data. They were supervised by the investigators. Data were double-entered in a dedicated EpiData database (EpiData Association, Odense, Denmark) by two encoders. Discordances were resolved by referring to the source.

Definition of variables

RR-TB diagnostic delay was defined as the number of days between the date of collection of the first sputum sample that led to RR-TB diagnosis and the date that RMP DST results became available at the laboratory. RR-TB therapeutic delay was defined as the number of days between the date that RMP DST results became available at the laboratory and the date that MDR-TB treatment was started. Total RR-TB delay was defined as the sum of RR-TB diagnostic delay and RR-TB therapeutic delay.

A binary outcome "mortality" was constructed. Patients were categorised as "dead" if they died before or during MDR-TB treatment or as "survived throughout treatment", after excluding those with treatment failure or LTFU. In a sensitivity analysis, patients with treatment failure or LTFU were considered as dead (worst case scenario). It is plausible that the majority of these patients with MDR-/RR-TB and without (sufficient) treatment died.

Data analysis

RR-TB incidence was calculated as an average of cases registered in three recent years (2014, 2015 and 2016) divided by the estimated population size (2012 Demographic and Health Survey), and was expressed per 100 000 population. The equality-of-medians test was used to compare the median delays within groups. RR-TB diagnostic delay and RR-TB therapeutic delay were categorised to facilitate logistic regression. Univariate analysis was conducted for each independent variable with mortality as the outcome variable. To assess the effect of both types of delay on mortality, adjusted for potential confounders, variables with $P < 0.2$ on univariate analysis were included, together with both delay variables in the multivariable logistic regression analysis. Statistical significance was set at 0.05. Kaplan–Meier techniques were used to estimate survival. Follow-up time started on the date of the first sputum sample collection that led to RR-TB diagnosis, the outcome event was death. Patients who survived throughout treatment were censored on the date of treatment outcome. STATA v14.2 (Stata Corp, College Station, TX, USA) was used for data analysis.

Table 2 RR-TB national notification vs. proportion sampled

Year	RR-TB notification *n*	Sampled for the study *n* (%)
2005 and 2006	90	67 (74.4)
2007	102	94 (92.2)
2008	74	73 (98.6)
2009	80	80 (100)
2010	91	86 (94.5)
2011	82	66 (80.5)
2012	57	53 (93.0)
2013	43	41 (95.3)
2014	82	73 (89.0)
2015	94	77 (81.9)
2016	81	77 (95.1)
Total	876	787 (89.8)

RR-TB = rifampicin-resistant tuberculosis.

Ethics

The study protocol was approved by the Rwanda National Ethical committee (RNEC), Kigali, Rwanda (IRB 00001497 of IORG0001100; Ref No.0069/RNEC/2017); the Institutional Review Board of the Institute of Tropical Medicine, Antwerp, Belgium (IRB/AB/AC/062; Ref No. 1208/17; 19/03/2018); and the Ethics Committee of the Antwerp University Hospital (UZA, *Universitair Ziekenhuis Antwerpen Ethische Commissie*), Antwerp, Belgium (REG No. B300201836458; 14/05/2018).

RESULTS

From 1 July 2005 to 31 December 2016, the Rwanda NTP notified 876 patients with RR-TB. Of these, 787 (89.8%) had available records available (Table 2, Figure 1), 730 (92.7%) of whom were included in the primary RR-TB mortality analysis, while 39 (5.0%) were excluded from any analysis and 18 were only included in the sensitivity analysis.

Of the 730 eligible RR-TB patients, more were male (57.5%) and the median age was 34 years (interquartile range [IQR] 27–43). The human immunodeficiency virus (HIV) co-infection status was documented for 698 (95.6%), 291 (39.9%) of whom were HIV co-infected (Table 2); this remained stable over the study period ($P = 0.28$, data not shown). The majority of the patients ($n = 390$, 53.7%) came from Kigali City, with an estimated RR-TB incidence of 2.38 per 100 000 population per year, with the lowest incidence in Northern Province (0.21/100 000).

Of the 730 RR-TB patients, 49 (6.7%) died before starting treatment (Table 3). In 611/681 (89.7%) patients, treatment initiation was based on the RMP DST result, while in 70 (10.3%), MDR-TB treatment initiation was based on a presumptive RR-TB diagnosis, most of whom (70/74, 94.6%) were confirmed later. The majority ($n = 510$, 74.9%) of the patients were treated with the World Health Organization (WHO) long regimen, and 171 (25.1%)

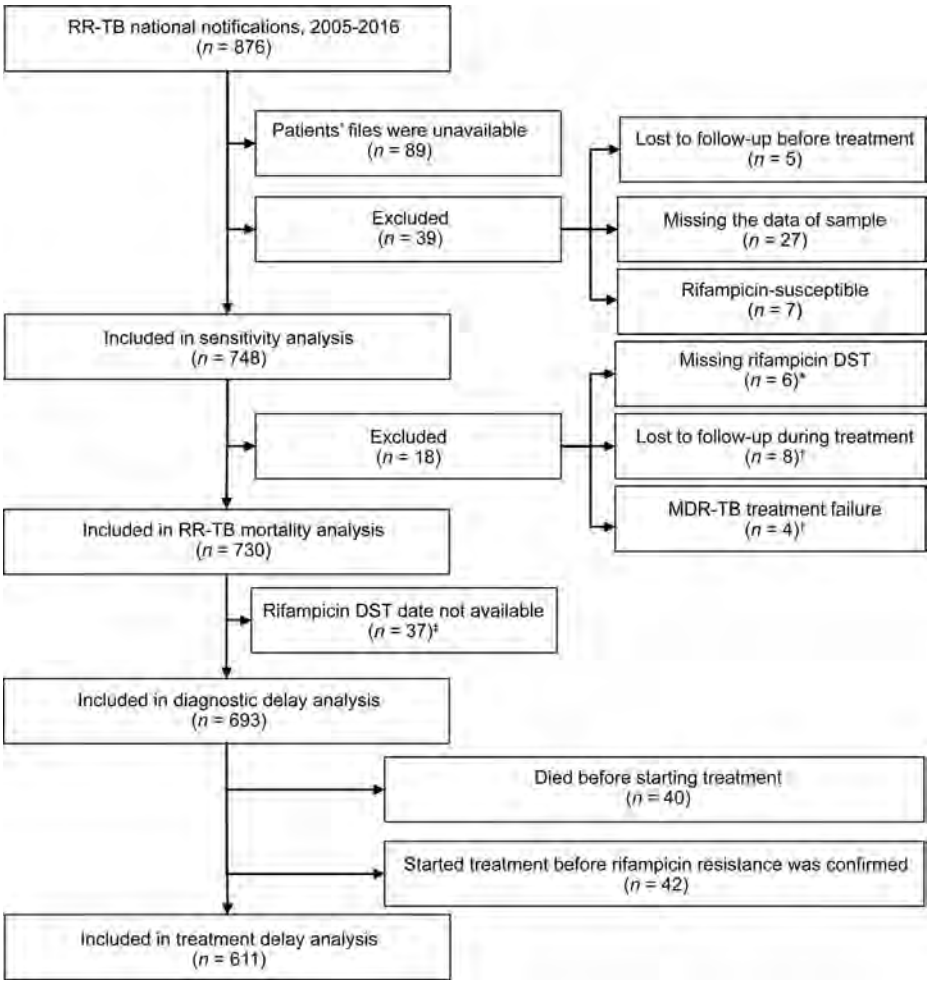

Figure 1 Flowchart showing inclusion and exclusion criteria for study participants. * Programmatic outcome used in sensitivity analysis. † In sensitivity analysis, we assumed the worst outcome (death) in these patients diagnosed with RR-TB, but without treatment or treatment failed. ‡ Includes patients who died before starting treatment ($n = 9$) and 28 patients who started treatment before RR-TB confirmation. RR-TB = rifampicin-resistant tuberculosis; DST = drug susceptibility test; MDR-TB = multidrug-resistant TB.

were treated with the shorter regimen,[16,17] which was introduced in mid-2014.

The history of TB treatment was known for 697 (95.5%) patients: 511 (73.3%) were previously treated for TB and 186 (26.7%) were new TB patients, 149 (80.1%) of whom had been diagnosed since 2013. The ratio of new to previously treated TB was 1.5:1 since 2013, a sharp increase from 0.09:1 before 2013. Among previously treated TB patients, the majority ($n = 215$, 79.6%) had failed the WHO Category 2 treatment regimen before 2010, while over half of patients (124, 51.5%) had failed Category 1 (Figure 2) since 2010.

Among the 611 patients initiated on treatment based on confirmed RR-TB, 228 (100%) were initiated based on phenotypic DST before 2009, which decreased to 3 (1.2%) after the implementation of line-probe assays (LPAs) and Xpert (Figure 3). After the countrywide scale-up of Xpert testing in 2014, 170 (81.3%) patients were initiated based on Xpert results and 39 (18.7%) based on LPA results, and none based on phenotypic DST (Figure 3).

RR-TB diagnostic and treatment delays

The date of RR-TB diagnosis was available for 693/730 patients, (Figure 1): the overall median diagnostic delay was 58 days (IQR 6–85). Of these 693 patients, 82 were excluded from the therapeutic delay analysis, as they died before starting treatment ($n = 40$) or started treatment before RR-TB confirmation ($n = 42$) (Figure 1); the remaining 611 patients had an overall median therapeutic delay of 8 days (IQR 4–20).

The median diagnostic delay was significantly longer for patients diagnosed using phenotypic DST (median 87 days, IQR 78–98) compared to LPA (median 40 days, IQR 25–55) or Xpert (median 1 day, IQR 0–3) ($P < 0.01$). The median therapeutic delay was 2.6 times longer for patients who initiated treatment based on phenotypic DST (median 21 days,

Table 3 Characteristics of RR-TB patients diagnosed between 2005 and 2016 in Rwanda, who were included in the analysis ($n = 730$)

	n (%)
Sex	
Male	420 (57.5)
Female	310 (42.5)
Age, years	
<30	252 (34.5)
30–44	307 (42.1)
45–54	96 (13.2)
>54	71 (9.7)
Unknown	4 (0.6)
Median [IQR]	34 [27–43]
Province	
East	85 (11.6)
Kigali	390 (53.7)
North	36 (4.9)
South	144 (19.7)
West	72 (9.9)
Other country (Uganda)	3 (0.4)
HIV status	
Negative	407 (55.7)
Positive	291 (39.9)
Unknown	32 (4.4)
TB treatment history	
New	186 (25.5)
Previously treated*	511 (70.0)
Unknown	33 (4.5)
First RMP testing method	
Phenotypic	347 (47.5)
LPA	199 (27.3)
Xpert	184 (25.2)
Treatment centre	
Kabutare	563 (82.7)
Kibagabaga	71 (10.4)
Kibungo	47 (6.9)
MDR-TB treatment regimen	
Long duration	510 (69.9)
Short course	171 (23.4)
Not treated†	49 (6.7)
Treatment outcome	
Cured	457 (62.6)
Completed	161 (22.1)
Death during treatment	63 (8.6)
Death before treatment	49 (6.7)

* Previously treated patients includes WHO Category 1 failure ($n = 158$, 30.9%), Category 2 failure ($n = 262$, 51.3%), Category 1 clinical relapse ($n = 51$, 10%), Category 2 clinical relapse ($n = 21$, 4.1%), Category 1 defaulter ($n = 2$, 0.4%), Category 2 defaulter ($n = 6$, 1.2%), MDR-TB treatment relapse ($n = 5$, 1%), MDR-TB treatment failure ($n = 1$, 0.2%) and others ($n = 5$, 1%).
† Patients died before initiating treatment.
RR-TB = rifampicin-resistant TB; IQR = interquartile range; HIV = human immunodeficiency virus; RMP = rifampicin; LPA = line-probe assay; MDR-TB = multidrug-resistant TB; WHO = World Health Organization.

IQR 9–53) compared to LPA (median 8 days, IQR 5–13) and five times longer compared to Xpert (median 4 days, IQR 2–5) ($P < 0.01$) (Table 4).

The median diagnostic delay was significantly longer ($P < 0.01$) in patients who died (median 80 days, IQR 34–96) than in patients who survived throughout MDR-TB treatment (median 50 days, IQR 5–84); however, the difference between the two groups was not statistically significant ($P = 0.96$) (Table 4).

Female patients had slightly longer diagnostic (median 67 days, IQR 11–86) and therapeutic (median 9 days, IQR 5–23) delays than males (median diagnostic delay 50 days, IQR 3–85 days; median therapeutic delay 7 days, IQR 4–18), although this was not statistically significant ($P = 0.09$ for diagnostic, and $P = 0.07$ for therapeutic delay) (Table 4).

Diagnostic and therapeutic delays were significantly shorter among patients aged >54 years: respectively 3 and 2 times shorter among those aged <30 years. Diagnostic delay was shorter ($P = 0.01$) in HIV co-infected patients (median 44 days, IQR 4–83) than in HIV-negative patients (median 66 days, IQR 8–86), although the difference was not statistically significant ($P = 0.33$) (Table 4).

Patient treatment outcome and factors associated with death

Of the 730 patients included in the overall mortality analysis, 49 (6.7%) died before starting MDR-TB treatment, while 63 (8.6%) died during treatment (Table 3). Treatment was successful in 618 patients (84.7%, 95% confidence interval [CI] 81.8–87.2), 457 (62.6%) of whom were declared cured and 161 (22.1%) completed MDR-TB treatment.

Before 2009 when a long RR-TB diagnostic delay was the norm, mortality was significantly higher ($P < 0.01$) in patients for whom MDR-TB treatment initiation had been based on available RMP DST results (28.3%, 95%CI 21.9–35.4) than in those who had been started on MDR-TB treatment before RR-TB was confirmed (8.9%, 95%CI 2.3–21.2).

RR-TB-related mortality decreased significantly from 30.8% (95%CI 19.9–43.4) in 2006 to 6.9% (95%CI 2.3–15.5) in 2016 (Figure 4). In a multivariable analysis, total delay of at least 100 days was independently associated with mortality (adjusted odds ratio [aOR] 2.45, 95%CI 1.35–4.46) (Table 5). After including patients who failed treatment and those lost to follow-up as dead, and those with unknown status of HIV under the HIV-coinfected category, and excluding all RR-TB diagnosed with very low bacillary load (*Mycobacterium tuberculosis*, $n = 31$) using Xpert in sensitivity analyses, a total delay of at least 100 days was still significantly associated with mortality (respectively aOR 2.82, 95%CI 1.60–4.97), aOR 3.71 (95%CI 2.09–6.58) and aOR 2.38 (95%CI 1.31–4.34) (Table 6).

HIV co-infection (aOR 2.27, 95%CI 1.35–3.82) and age (>54 years; aOR 4.83, 95%CI 2.10–11.10) remained associated with increased mortality (Table 5). Other variables such as sex, MDR-TB treatment clinic and MDR-TB treatment regimen were not significantly associated with mortality (Table 5). Figure 5 shows that patients with a shorter diagnostic delay and those who were HIV-negative were more likely to survive ($P < 0.001$ and $P = 0.01$, respectively).

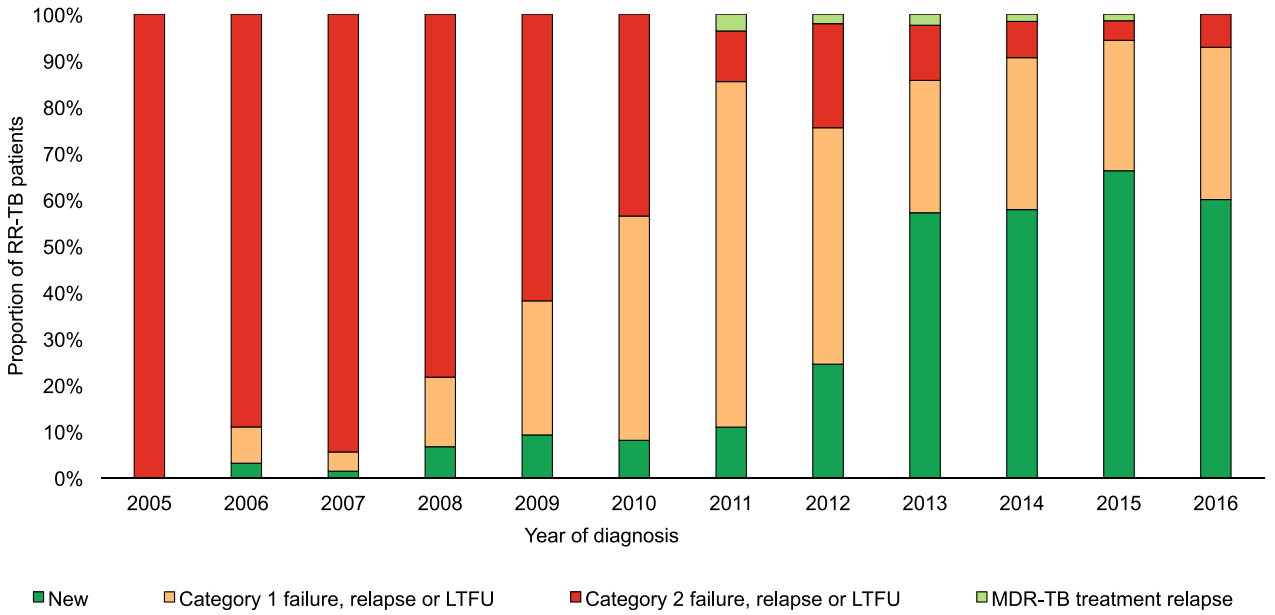

Figure 2 Proportion of patients with RR-TB based on their history of TB treatment by year of diagnosis. RR-TB = rifampicin-resistant tuberculosis; MDR-TB = multidrug-resistant TB.

DISCUSSION

To the best of our knowledge, this is the first nationwide RR-TB population-based study to show that a shortened diagnostic delay is associated with a decline in mortality. In Rwanda, RR-TB mortality dropped from 30.8% in 2006 to 6.9% in 2016. Mortality was more than two-fold higher in patients with a total delay of ≥100 days than in those with a delay of <35 days. Delays in diagnosing and treating RR-TB have been reduced through the nationwide scale-up of rapid molecular RMP DST since 2014 (Table 1), when 100% of RR-TB patients were diagnosed using molecular diagnostics, either Xpert (81.3%) or LPA (18.7%).

Our study showed that MDR/RR-TB mortality decreased as delays were reduced, mainly due to the implementation of Xpert. This findings contrasts with some previous studies which did not show an effect of the use of Xpert on TB mortality.[18,19] On the other hand, our findings complement those from a Peruvian study conducted in patients already started

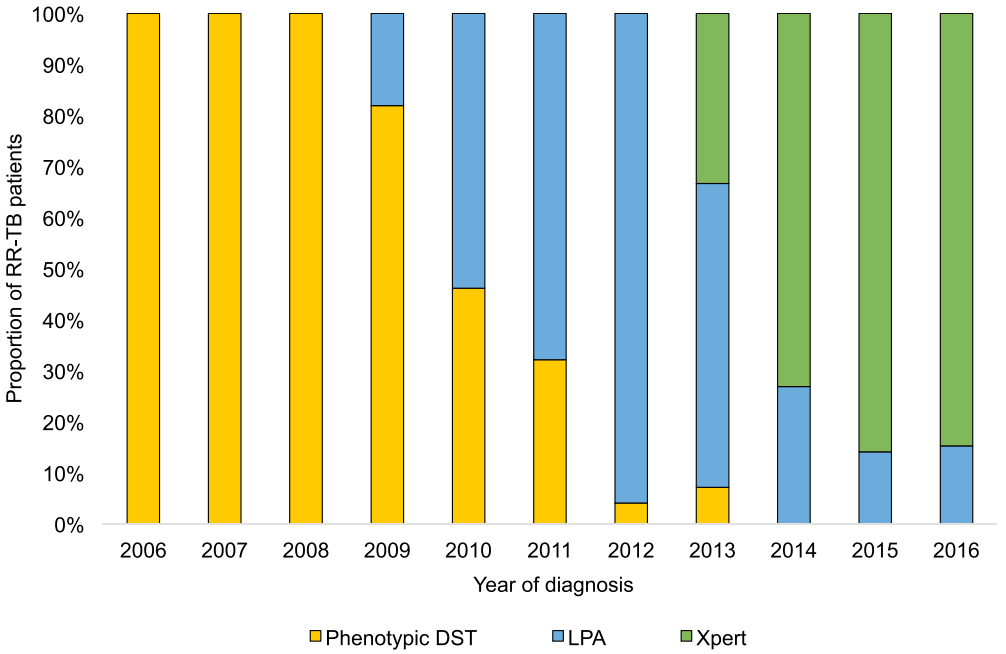

Figure 3 Diagnosis of RR-TB by type of RR-TB DST and year of diagnosis among patients with confirmed RR-TB ($n = 611$) before MDR-TB initiation. RR-TB = rifampicin-resistant tuberculosis; DST = drug susceptibility test; LPA = line-probe assay.

Table 4 RR-TB diagnostic and treatment delay

		RR-TB diagnostic delay (n = 693)* (days)				RR-TB treatment delay (n = 611)† (days)			
		Patients n	Median	IQR	P value	Patients n	Median	IQR	P value
Sex	Male	406	50	3–85	0.09	356	7	4–18	0.07
	Female	287	67	11–86		255	9	5–23	
Age, years‡	<30	236	74	16–91	Reference	211	11	6–30	Reference
	30–44	290	53	5–83	0.07	255	8	4–17	0.02
	45–54	94	61	4–80	0.27	83	7	3–15	0.03
	>54	70	24	1–78	0.02	62	5	2–9	<0.01
Province§	Kigali	245	26	2–74	Reference	224	7	4–13	Reference
	East	70	13	1–63	0.81	67	4	2–9	0.03
	North	23	39	1–57	0.27	23	5	2–11	0.46
	South	104	34	2–62	0.33	101	7	3–9	0.90
	West	52	31	3–77	0.70	52	7	3–12	0.94
HIV¶	Negative	392	66	8–86	0.01	364	8	4–22	0.33
	Positive	277	44	4–83		246	7	4–17	
DST confirming RR-TB	Phenotypic	313	87	78–98	Reference	241	21	9–53	Reference
	LPA	197	40	25–55	<0.01	187	8	5–13	<0.01
	Xpert	183	1	0–3	<0.01	183	4	2–5	<0.01
Survival	Survived#	591	50	5–84	<0.01	556	8	4–19	0.96
	Died	102	80	34–96		55	8	3–26	

* Days between sample collection and rifampicin DST result available at RR-TB testing laboratory.
† Days between rifampicin resistance diagnosis available at RR-TB testing laboratory and start of RR-TB appropriate treatment.
‡ Patients without age information were not categorised.
§ Patients diagnosed and initiated on MDR-TB treatment since 2009 onward.
¶ Patients with unknown HIV coinfection status were not included.
# Patients who were reported as cured and those completed treatment.
RR-TB = rifampicin-resistant TB; IQR = interquartile range; HIV = human immunodeficiency virus; DST = drug susceptibility testing; LPA = line-probe assay; MDR-TB = multidrug-resistant TB.

on MDR-TB treatment, which showed a decreased odds (0.5) of death and increased odds (1.4) of treatment success associated with the implementation of rapid phenotypic (microscopic-observation drug susceptibility) and genotypic (LPA) DST.[13]

Consistent with findings from other studies,[13] HIV coinfection and older age were associated with mortality, although HIV-coinfected and older patients were diagnosed more rapidly than HIV-negative and younger patients.

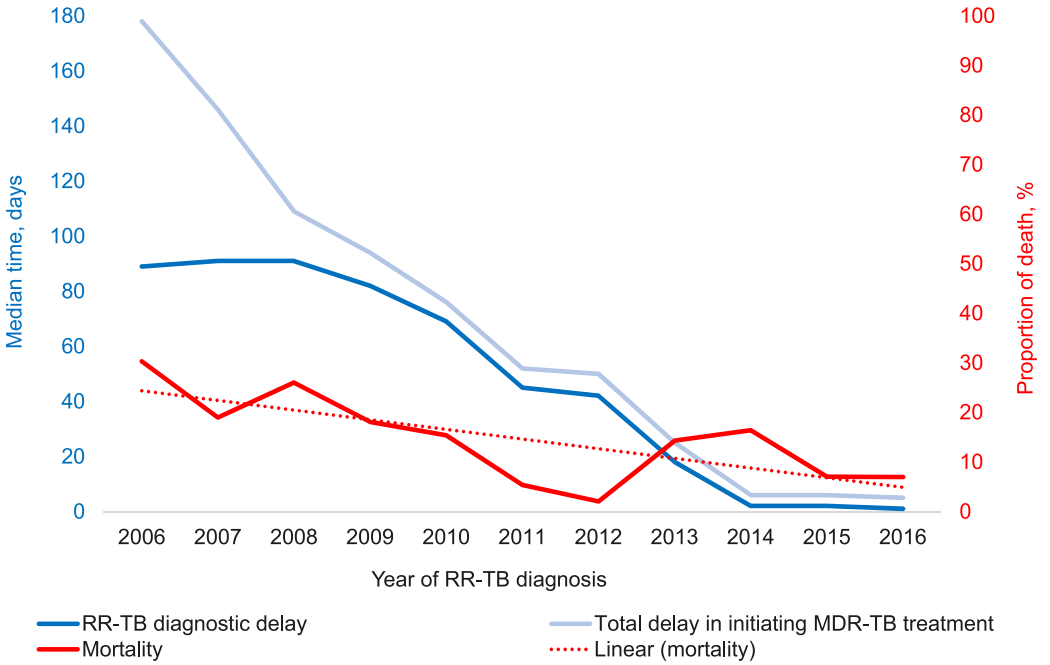

Figure 4 RR-TB diagnostic delay and total delay in initiating MDR-TB (time in days between the date of sample collection that led to diagnosis of rifampicin resistance and date of MDR-TB treatment initiation) and mortality recorded by year of diagnosis. RR-TB = rifampicin-resistant tuberculosis; MDR-TB = multidrug-resistant TB.

Table 5 Factors associated with RR-TB mortality

	Total *n*	Death* *n* (%)	Univariate analyses OR (95% CI)	Multivariable analyses aOR (95% CI)†
Total	730	112 (15.3)		
Sex				
Female	310	41 (13.2)	Reference	Reference
Male	420	71 (16.9)	1.33 (0.88–2.02)	1.57 (0.93–2.62)
Age, years				
<30	252	22 (8.7)	Reference	Reference
30–44	311	59 (19.0)	2.45 (1.45–4.12)	2.11 (1.08–4.12)
45–54	96	15 (15.6)	1.94 (0.96–3.91)	2.20 (0.95–5.08)
>54	71	16 (22.5)	3.04 (1.50–6.17)	4.83 (2.10–11.10)
HIV				
Negative	407	34 (8.4)	Reference	Reference
Positive	291	47 (16.2)	2.11 (1.32–3.38)	2.27 (1.35–3.82)
Unknown	32	31 (96.9)		
RR-TB total delay, days‡				
1–34	232	23 (9.9)	Reference	Reference
35–99	235	29 (12.3)	1.28 (0.72–2.28)	1.28 (0.68–2.44)
At least 100	226	50 (22.1)	2.58 (1.51–4.40)	2.45 (1.35–4.46)
Unknown	37	10 (27.0)		
MDR-TB treatment clinics				
Kibagabaga	71	5 (7.0)	Reference	
Kibungo	47	4 (8.5)	1.23 (0.31–4.83)	
Kabutare	563	54 (9.6)	1.40 (0.31–4.83)	
Not treated	49	49 (100)		
MDR-TB treatment regimen				
Short course	510	14 (8.2)	Reference	
Long duration	171	49 (9.6)	1.19 (0.64–2.22)	
Not treated	49	49 (100)		

* A total number of 112 persons died. Data were missing for some explanatory variables: total delay was missing for 37 patients, age was missing for 4 patients (imputed median age was used), HIV status was not known for 31 patients and for 49 no MDR-TB treatment regimen and clinic was assigned, as they died before starting treatment. For patients missing therapeutic delay, imputed values based on patients' age, sex, HIV coinfection and diagnostic delay were used.
† Adjusted for age, sex and HIV co-infection.
‡ Sum of time (in days) between sample collection and rifampicin susceptibility test result availability at testing laboratory and time (in days) between rifampicin resistance diagnosis availability at testing laboratory and start of appropriate RR-TB treatment.
RR-TB = rifampicin-resistant tuberculosis; OR = odd ratio; CI = confidence interval; aOR = adjusted OR; HIV = human immunodeficiency virus; MDR-TB = multidrug-resistant TB.

Although the clinical decision to start MDR-TB treatment before laboratory confirmation is challenging, it resulted in a lower mortality during the period that rapid molecular DST was not available and when diagnostic delays were very long.[7] This should not be surprising. In patients with multiple risk factors, a susceptible RMP DST result is unlikely to lower the post-test probability below the treatment threshold, the minimal level of probability of having RR-TB that is required to start MDR-TB treatment.[20] Hence, empirical RR-TB treatment seems justified in such situations, especially when an effective treatment is available and when delay is associated with mortality.[21]

In our study, the treatment success rate was relatively high (84.7%).[13] The high rate of treatment success is in line with low rates of resistance to second-line drugs such as fluoroquinolones[22,23] and second-line injectables. None of the over 400 RR-TB

Table 6 Sensitivity analysis for factors associated with RR-TB mortality

Total RR-TB delay, days§	aOR (95% CI)*	aOR (95% CI)†	aOR (95% CI)‡
1–34	Reference	Reference	Reference
35–99	1.31 (0.71–2.40)	1.73 (0.93–3.18)	1.13 (0.58–2.18)
At least 100	2.82 (1.60–4.97)	3.71 (2.09–6.58)	2.38 (1.31–4.34)

§ Sum of days between sample collection and RR-TB DST result available at testing laboratory and days between rifampicin resistance diagnosis available at testing laboratory and start of RR-TB appropriate treatment.
* Considering patients who failed treatment and those lost to follow-up as dead, adjusted for age, sex and HIV co-infection when lost to follow-up and failure on MDR-TB treatment were considered dead.
† Considering those with unknown status of HIV as HIV-coinfected, adjusted for age, sex and HIV co-infection when patients with unknown HIV coinfection status are considered as HIV-positive.
‡ Excluding all RR-TB identified diagnosed on Xpert with very low bacillary load (very low *M. tuberculosis*, $n = 31$), adjusted for age, sex and HIV co-infection excluding patients diagnosed on Xpert with TB very low (high likelihood of being false RR-TB).
RR-TB = rifampicin-resistant TB; aOR = adjusted odd ratio; CI = confidence interval; HIV = human immunodeficiency virus; MDR-TB = multidrug-resistant TB.

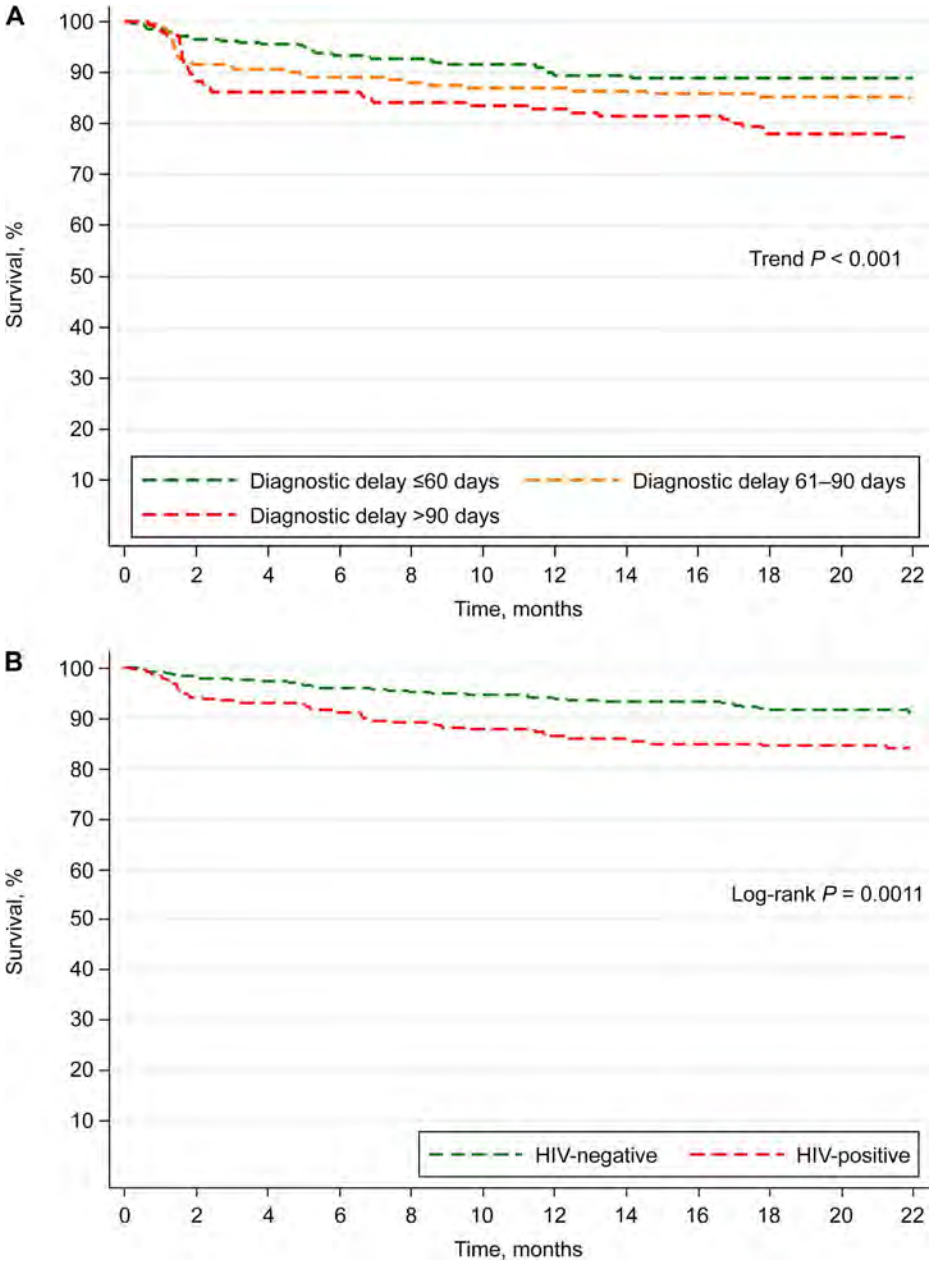

Figure 5 Kaplan-Meier survival estimates in patients with rifampicin-resistant tuberculosis by **A)** diagnostic delay, and **B)** HIV coinfection. HIV = human immunodeficiency virus.

patients routinely tested since 2010 displayed resistance to these drugs (NRL Rwanda, unpublished findings), confirming that the standardised MDR-TB treatment used was effective in curing RR-TB and halting its spread. In fact, before the implementation of PMDT in Rwanda, the estimated prevalence of RR-TB among new TB patients rose from 1.3% (95%CI 0.7–2.1) in 1993 to 3.9% (95%CI 2.5–5.7) in 2005,[24,25] likely fuelled by ongoing transmission.[26] Before RR-TB testing became easily accessible, the majority of the RR-TB patients diagnosed before 2013 had a primary RR-TB strain, but received multiple rounds of ineffective RMP-based treatment, while spreading RR-TB in their communities. This probably explains the increase of RR-TB prevalence among new TB patients, as shown in 2005.[25] Since the implementation of PMDT, drug resistance surveys revealed a statistically significant decline in RR-TB prevalence among new TB patients, from 3.9% (95%CI 2.5–5.7) in 2005 to 1.4% (95%CI 0.7–2.1) in 2015.[25,27] Thus, the combination of early RR-TB diagnosis with effective MDR-TB treatment likely reduced transmission and probably explains the decrease in RR-TB prevalence, as observed in the 2015 survey.[27]

Nonetheless, the programme should be cautious of sole dependence on rapid molecular testing because 1) a shortage of reagents (e.g., cartridges) could

completely paralyse the diagnostic system,[28,29] 2) the increased sensitivity of the newly developed Xpert® MTB/RIF Ultra (Cepheid) may complicate its use in detecting true treatment failures or relapses, as persistent DNA may not reflect active disease,[30] 3) commercial rapid molecular diagnostics miss RMP resistance-conferring mutations outside the 81 base pair RMP resistance-determining region (RRDR), such as Val170Phe and Ile491Phe,[31,32] and 4) false-positive RR-TB results on Xpert may be associated with low bacillary load in the sample.[33] However, a sensitivity analysis which excluded all RR-TB identified using Xpert with very low bacillary load did not affect the interpretation of the final model.

Our study had several important strengths. First, 85.4% of all patients diagnosed with RR-TB in Rwanda over a period of more than 10 years were included in the study. Our findings thus represent the current reality of the MDR/RR-TB programme in Rwanda. Second, in contrast with most studies on RR-TB outcomes, data from patients who died before starting treatment were included. Survival bias was therefore limited. Third, we validated data by comparing data collected from different sources (patient files, the national MDR-TB register and NRL registers). When discrepancies were identified, sources were consulted a second time. Finally, a sensitivity analysis including those who failed treatment or were lost to follow-up, was used to confirm the findings of the primary analysis.

Our study also had some important limitations. We did not collect data on the delay between the day a patient became at risk for MDR-/RR-TB and the date RMP DST was requested. In addition, we did not collect data on the severity of TB disease, such as extensiveness of TB on X-ray, the bacterial load in diagnostics or patient body mass index. Moreover, second-line drug susceptibility was not tested systematically and could not be taken into account. However, it should be noted that resistance to second-line drugs is extremely rare in Rwanda. Another important limitation was the lack of systematic data on timing of antiretroviral therapy initiation. The strong association between HIV-coinfection and RR-TB mortality could thus not be explored further. Finally, as this was a retrospective study, we could only adjust for those variables that were routinely collected.

In conclusion, diagnostic and treatment delays were strongly associated with RR-TB mortality in Rwanda. As the NTP were able to control delays, mortality declined from 30.8% in 2006 to 6.9% in 2016. Other factors that likely contributed to improved MDR-/RR-TB outcomes were universal RMP resistance surveillance enhanced by performance-based financing and the implementation of effective standardised MDR-TB treatment. We anticipate that universal testing of all TB patients for RR-TB, short diagnostic and therapeutic delays, and effective MDR-TB treatment will further reduce RR-TB prevalence in Rwanda.

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RÉSUMÉ

CONTEXTE : En 2005, en réponse à une prévalence croissante de la tuberculose résistante à la rifampicine (RR-TB) et aux résultats médiocres du traitement, le Rwanda a initié la gestion programmatique de la RR-TB, notamment l'expansion de l'accès systématique au test de pharmacosensibilité de la rifampicine et au traitement standardisé.

OBJECTIF : Décrire les tendances du retard au diagnostic et au traitement et estimer leur impact sur la mortalité de la RR-TB.

SCHÉMA : Une analyse rétrospective de données individuelles de 748 (85,4%) patients sur 876 ayant eu un diagnostic de RR-TB déclarée à l'Organisation mondiale de la Santé entre le 1er juillet 2005 et le 31 décembre 2016 au Rwanda. La régression logistique a été utilisée pour estimer l'impact du retard au diagnostic et au traitement sur la mortalité de la RR-TB.

RÉSULTATS : Entre 2006 et 2016, le délai médian du diagnostic a significativement diminué de 88 jours à 1 jour et le délai de traitement, de 76 jours à 3 jours. Parallèlement, la mortalité liée à la RR-TB a significativement diminué de 30,8% en 2006 à 6,9% en 2016. Un retard de traitement de la TB multirésistante (MDR-TB) de plus de 100 jours a été associé à un risque plus de deux fois supérieur de décès. Quand les délais ont été longs, la mise en œuvre d'un traitement empirique de la RR-TB a été associée à une diminution de la mortalité.

CONCLUSION : La diminution du retard au diagnostic et au traitement a réduit la mortalité de la RR-TB. Nous nous attendons à ce que le test systématique de RR-TB, un délai court de diagnostic et de traitement et un traitement standardisé efficace de la MDR-TB diminue encore la mortalité de la RR-TB.

RESUMEN

MARCO DE REFERENCIA: En el 2005, en respuesta a un aumento en la prevalencia de la tuberculosis resistente a rifampicina (RR-TB) y los desenlaces terapéuticos desfavorables, se inició en Rwanda el manejo programático de la RR-TB, que incluía la expansión del acceso a las pruebas sistemáticas de sensibilidad a rifampicina y al tratamiento normalizado.

OBJETIVO: Describir las tendencias del retraso en el diagnóstico y el tratamiento y analizar su efecto sobre la mortalidad por RR-TB.

MÉTODO: Se realizó un análisis retrospectivo de los datos individuales de 748 de los 876 pacientes (85,4%) con diagnóstico de RR-TB notificados a la Organización Mundial de la Salud entre el 1° de enero del 2005 y el 31 de diciembre del 2016 en Rwanda. Mediante regresión logística se calculó el efecto del retraso en el diagnóstico y el tratamiento sobre la mortalidad por RR-TB.

RESULTADOS: Del 2006 al 2016, la mediana del retraso diagnóstico disminuyó de manera considerable de 88 días a un día y la mediana del retraso terapéutico pasó de 76 a 3 días. De manera simultánea, se observó una importante disminución de la mortalidad por RR-TB, de 30,8% en el 2006 a 6,9% en el 2016. Un retraso total del comienzo del tratamiento de la tuberculosis multirresistente (MDR-TB) superior a 100 días se asoció con una posibilidad de mortalidad superior al doble. Donde los retrasos eran prolongados, el comienzo empírico del tratamiento contra la RR-TB se asoció con una menor mortalidad.

CONCLUSIÓN: La disminución de los retrasos en el diagnóstico y el tratamiento disminuyó la mortalidad por RR-TB. Se propone que la realización de la prueba de resistencia a rifampicina a todos los pacientes, un corto lapso hasta el diagnóstico y el comienzo del tratamiento y un tratamiento eficaz normalizado de la MDR-TB disminuirán aún más la mortalidad por RR-TB en Rwanda.

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RESEARCH ARTICLE Open Access

High urban tuberculosis case notification rates can be misleading: evidence from an urban setting in Ethiopia

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Abstract

Background: Tuberculosis (TB) is a major public health problem. Its magnitude the required interventions are affected by changes in socioeconomic condition and urbanization. Ethiopia is among the thirty high burden countries with increasing effort to end TB. We aimed to describe the case notification rate (CNR) for urban tuberculosis (TB) and estimate the percentage of TB patients who are not from the catchment population.

Methods: This cross-sectional study used data from TB registers from 2014/15 to 2017/18. We calculated the CNR and treatment success rate for the study area.

Results: Of 2892 TB cases registered, 2432 (84%) were from Adama City, while 460 (16%) were from other sites. The total TB CNR (including TB cases from Adama and other sites) was between 153 and 218 per 100,000 population. However, the adjusted TB CNR (excluding cases outside Adama City) was lower, between 135 and 179 per 100,000. Of 1737 TB cases registered, 1652 (95%) were successfully treated. About 16% of TB cases notified contributing to CNR of 32 per 100,000 population is contributed by TB cases coming from outside of Adama city.
The CNR of 32 per 100,000 population (ranging from 18 to 46 per 100,000) for Adama City was from the patients that came from the surrounding rural areas who sought care in the town.

Conclusion: Although the TB CNR in Adama City was higher than the national CNR, about one-fifth of TB cases came from other sites-which led to overestimating the urban CNR and underestimating the CNR of neighboring areas. TB programs should disaggregate urban TB case notification data by place of residence to accurately identify the proportion of missed cases.

Keywords: Urban, Cities, Case notification, Ethiopia

Background

Tuberculosis (TB) is a disease deeply rooted in social fabrics that requires both a biomedical and social response. It has been long recognized as a disease whose transmission is favored by the density of urban populations [1–4]. TB is a disease of the poor, and its burden often serves as a marker of social inequality [5]. Although the effect of urbanization on TB burden is mixed [6], compared to rural areas, TB case notification rates (CNRs) in urban and peri-urban areas reflect high TB burden in urban areas [7]. This is due to underlying social and economic determinants of health that include not only poverty but also overcrowding, urban in-migration, deficient social protection, stigma and discrimination, HIV infection, and limited access to health services [8–10].

Given these socioeconomic problems, it is not a surprise that urban areas carry the highest burden of TB and notify more cases. Furthermore, the size of urban populations and socioeconomic problems are rapidly increasing in developing and high-TB-burden countries [3], which will increase the number of people exposed to high-risk environments for communicable diseases, including TB. Consequently, higher CNRs from urban areas are often taken as markers of higher disease burden, which has resulted in a tendency and commitment to direct more resources and target efforts to urban

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areas through ambitious major global Zero TB initiatives [6, 11]. However, other factors that contribute to higher TB case notification in cities or draw cases to cities are rarely considered. The "pull" factors that lead to seeking care in urban areas might influence the CNR. These factors might include the need for better health care, inadequacies in rural TB services, inaccessibility of services, patient preference, stigma and discrimination, limited case-finding interventions, shortage of diagnostic facilities, or inadequate technical capacity of health care workers. Despite these factors, in rural areas there has been limited effort to disaggregate TB patients to their place of residence and calculate the actual CNR by the source community for the notified TB cases. TB patients in peri-urban areas travel to seek care in urban facilities which compromises patient follow up. Outcomes for patients are, therefore, undermined; these include increased loss to follow-up, poor treatment adherence (due to inadequacies in referral linkage to treatment sites and the need for frequent travel to distant sites by patients), and unaffordable cost of seeking care. Because these patients come from other catchment areas, they are subject to more out-of-pocket expenditures and opportunity costs, which extend from the patient to their households or relatives [12, 13]. These factors contribute to making TB services prohibitively expensive and demand attention from National TB Programs (NTPs) [14–17].

On one hand, urban areas consistently have higher CNRs, more than the estimated TB burden in some cities [18]. The higher CNRs in urban areas, on the other hand, may lead to an inaccurate impression of higher success in terms of achieving targets for case finding and lead to reluctance, and reduction in efforts, to intensify case finding within the community. The NTP assumes equal incidence for urban and rural TB and reports cases by reporting site, not the address where patients live. To our knowledge, there has been no national review to see if urban areas have actually achieved targets or missed cases within their populations.

Objective

The aim of this study was to describe urban CNR and estimate the percentage of TB patients who came from other catchment areas in the study area.

Methods

Study area and design

This was a cross-sectional study involving the analysis of secondary data from the unit TB registers in urban areas.

Ethiopia is among the 30 high-TB-burden countries [7]. TB diagnostic and treatment services are provided in health centers and hospitals. The End TB strategy has been adopted and the country is committed to reaching missed TB cases in the vulnerable population.

Adama is one of the urban areas in Oromia region, located about 100 km away from Addis Ababa, the capital of Ethiopia. It has a population of about 386,237 people living in the areas. The health service coverage has reached to 95% of the population. Adama city is surrounded by rural district and rural communities who dwell on farming. A total of 26 health facilities, one public hospital, two non-governmental organization (NGO) clinics, 8 public health centers, and 15 private facilities provide health services to the population in the area. All public and private health facilities provide TB screening services for their clients. Ninety-two percent of the health facilities provide diagnostic and treatment services while 77% provide diagnostic services. TB case finding and treatment outcome data were obtained from the TB registers of facilities in Adama City from 2014/15 to 2017/18. All TB patients that were registered and received treatment in the selected health facilities were included in the study.

Data management

Data sources and variables

The variables used for the study include age, sex, place of residence, age, TB classification, TB category, and the treatment outcome. The data were obtained from unit TB registers in the health facilities. The outcome variables are case notification rate and treatment success rates.

Data collection and quality assurance

Health facilities providing TB diagnosis and treatment services record and report their quarterly case notification data and treatment outcomes from their unit TB registers. The data for this study were extracted from those registers. A senior data expert worked with the Oromia Zonal Cluster Coordinator and Adama City TB Program Coordinator, and TB focal persons collected the data. In discussion with the TB focal person in the health facilities, we have identified all TB registers that were used and currently in use for patient registration and follow up for the study period. All the data from the registers were entered into using trained data clerk loosely working with our senior data analyst. We used an electronic data capturing method. All TB unit registers containing lists of TB patients' records for the study period were scanned. The data were transcribed by a senior data clerk. The senior data expert worked with the senior data clerk to conduct the data entry, cleaning, and analysis.

Data analysis

The data were analyzed by age, sex, TB classification, TB category, treatment outcome, and place of residence.

Patients were classified into two groups based on their place of residence: those from Adama City and those from outside the city. The CNR was calculated by the number of TB cases notified per 100,000 population. The treatment success rate was calculated by dividing the number of TB cases cured or who completed treatment by the total number of TB cases registered for treatment. Case finding and treatment outcomes were calculated based on the standard definition in the national guidelines. No report was generated based on place of residence, however.

Ethical considerations

Because this study was a retrospective review of data gathered under routine program implementation as a public health practice, ethical approval was not required as no personally identifiable data were collected, so the privacy and confidentiality of patients were assured.

Results

Tuberculosis case finding

A total of 2892 TB cases were registered at health facilities providing TB services in Adama City. Of these, 2432 (84%) TB cases were from Adama City, while 460 (16%) were from other catchment areas (Table 1). Of 2432 TB cases, 46% of the TB cases were females and 60% were in the age range of 25–64 years. The mean age was 31 years (SD ± 14.5). Of the total number of cases, 34% (981) were bacteriologically confirmed (PPOS), 29% (822) were pulmonary negative (PNEG), and 37% (1072) were extrapulmonary (EPTB) cases. Of the TB cases, 95% of the TB cases were newly diagnosed, and 7% were children under the age of 15 years.

The total or unadjusted TB CNR (including TB cases registered from the Adama catchment population and nearby catchment population) varied between 153 and 218 per 100,000 population over the 1 years of the study. However, the adjusted TB CNR (excluding TB cases outside of Adama City) fell between 135 and 179 per 100,000 population. On average, about 16% of the TB cases notified by the Adama City TB program were not from the Adama catchment population (Table 2).

The CNR of 32 per 100,000 population (ranging from 18 to 46 per 100,000) for Adama City was from the patients that came from the surrounding rural areas who sought care in the town (Fig. 1).

Table 1 TB cases notified in Adama City, 2014/15–2017/18

TB Case Finding[a]	PPOS[b]	PNEG[c]	EPTB[d]	Total
Within Adama	801	691	928	2420
	82%	84%	87%	84%
Outside Adama	180	131	144	455
	18%	16%	13%	16%
Total	981	822	1072	2875[1]
	100%	100%	100%	100%

[a]17 TB cases were not included because the patients' addresses were missing
[b]PPOS: pulmonary smear positive TB cases [c]PNEG: clinically diagnosed smear negative pulmonary TB cases [d]EPTB: extra pulmonary TB cases

Tuberculosis treatment outcomes

Of 1782 TB cases registered, data about treatment outcome were available for 1737 (97%) cases. The treatment success rate was 95% both from outside and within Adama City; i.e., 65% completed treatment (65% from Adama City and 61% from outside) and 30% were cured (28% from Adama City and 34% from outside). There is no statistically significant difference in treatment outcome among patients, whether they reside within Adama City or not ($P = 0.45$) (Tables 3 and 4).

Discussion

In this study, we report high TB CNRs in Adama City. However, about one-fifth of the TB cases notified were contributed by patients from outside the catchment population. This overstates the urban CNR and underestimates the CNR of the neighboring catchment areas. However, disaggregating the data about TB cases by place of residence offset the high CNR in urban and low CNR in adjacent communities, which could give the real picture of TB case notification in the areas. Like other studies in urban populations [19–21], studies from Ethiopia show that the urban population, representing only 8% of the country's population, contributed 11% of the total TB cases notified [22]. This phenomenon could be due to patients coming from neighboring catchment areas for access to better diagnostics and availability of technical expertise, thereby increasing urban poverty,

Table 2 Trends in TB case notification in Adama City, 2014/15–2017/18

Year	2014/15	2015/16	2016/17	2017/18
Total population	323,999	338,940	355,475	372,817
TB cases treated in Adama City	707	760	762	569
TB cases living in Adama City	581	604	667	502
% TB cases living in Adama city	82.2%	79.5%	87.5%	88.2%
CNR (*per 100,000 population*)*				
TB cases enrolled in Adama City	218	224	214	153
TB cases living in Adama City	179	178	188	135
TB cases living outside Adama City	39	46	26	18

* $X^2 = 12$, P-value = 0.213

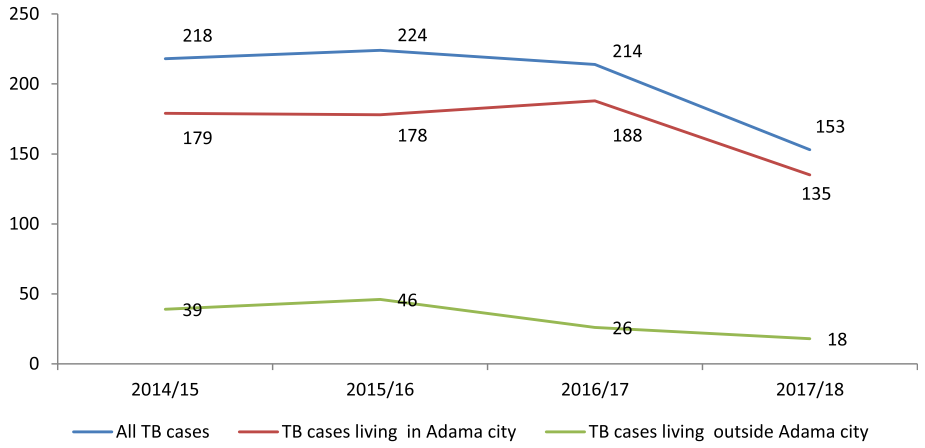

Fig. 1 Trends of TB case notification rate in Adama City, 2014/15–2017/18

overcrowding, urban migration, HIV infection, and disease transmission [9]. This pattern of care seeking might have contributed to the increasing focus on urban TB programs.

The Zero TB Cities Initiative is one of the major efforts to combat TB and its transmission [6]. Such efforts, however, should consider detailed analysis of case finding in urban areas by place of residence, which is not commonly done [22]. Without specific analysis with regard to place of residence, the CNR of adjacent rural districts may be underestimated and the urban CNR may be inflated. Thus, high CNRs may give the impression that targets are being met in urban areas and may lead to reluctance to target TB in surrounding areas by urban TB programs. Inadequate data can, in turn, affect resource allocation. An increase in resources for urban TB programs could undermine efforts to reach surrounding catchment areas, which could contribute to continued disease transmission in peri-urban areas.

Evidence has shown that disaggregation of data about notified TB cases by urban or rural place of residence has reduced the CNRs of areas that were known for

Table 3 Treatment outcomes of TB cases in Adama City, 2014/15–2017/18

Treatment outcome	PPOS[a]	PNEG[b]	EPTB[c]	Total
Cured*	515			515
	88%			30%
Treatment completed*	52	507	612	1137
	9%	95%	94%	65%
Treatment failure	2	3	8	13
	0%	1%	1%	1%
Died	9	20	23	52
	2%	4%	4%	3%
Lost to follow-up	3	6	5	14
	1%	1%	1%	1%
Moved to MDR-TB register	4	0	2	6
	1%	0%	0%	0%
Total	585	536	650	1737
	100%	100%	100%	100%

[a]*PPOS* Pulmonary smear positive TB cases [b]*PNEG* Clinically diagnosed sear negative pulmonary TB cases [c]*EPTB* Extra pulmonary TB cases
*The mean treatment success rate (cure rate d + treatment competed rate) of PPOS cases was 97% (SE = 0.007) and PNEG was 95% (SE = 0.009), Z = 1.72 *p*-vale = 0.086 with no statistical significance. In comparison with EPTB compare to EPTB with treatment success rate of 94% 9SE = 0.009), Z = 2.52, *p*-value = 0.012 which is statistically significant

Table 4 Treatment outcomes of TB cases treated in Adama City, 2014/15–2017/18

Treatment Outcome[a]		Outside Adama	Inside Adama	Total
Cured	No.	98	417	515
	%	34%	28%	30%
Treatment completed	No.	175	962	1137
	%	61%	65%	65%
Treatment failure	No.	2	11	13
	%	1%	1%	1%
Died	No.	8	44	52
	%	3%	3%	3%
Lost to follow-up	No.	4	10	14
	%	1%	1%	1%
Moved to MDR-TB[b] register	No.	2	4	6
	%	1%	0%	0%
Total	No.	289	1484	1737
	%	100%	98%	100%

Treatment success rate was 95% (34% cured and 61% treatemen comlplted) for those from outside Adama and 93% (28% cured and 65% treatemen comlplted) for those from inside Adama city, with no statistical significance, $p = 0.45$
[a]Comparison of treatment outcome was not statistically signficant, $X^2 = 35$, *p*-value = 0.243
[b]*MDR-TB* Multi drug resistant tuberculosis

higher CNRs and increased the CNRs of areas that did not report many cases. A ten-year review of TB cases notified by districts in southern Ethiopia showed that about 23% of the TB cases notified came from other catchment areas or districts. The disaggregation of TB cases by their residence reduces the high CNRs of urban areas and increases the lower CNRs in adjacent rural areas [23].

Higher CNRs could be driven by patient preference, better service quality, increased geographic accessibility, better community awareness, and access to better diagnostics and treatment [23]. Analysis of CNR by place of residence offsets both under- or over-reporting in urban and rural communities. Failure to consider this reality may contribute to urban bias, with the possible resource implications mentioned above, and may affect the type and magnitude of interventions designed by NTPs. Therefore, interventions in urban settings should analyze cases by place of residence, consider factors underlying higher CNRs, and design appropriate interventions to reach TB cases missed in the urban population.

While there are clear justifications for prioritizing TB in urban areas, other factors should be considered to ensure efficient use of scarce resources. In most resource-limited settings, a significant portion of urban health-service seekers come from rural areas, sometimes travelling long distances, due to lack of quality health services in remote areas. In addition, frequent bidirectional movements of people between urban and rural areas [24] for various purposes may increase disease transmission. Since most project-driven TB case-finding efforts use accessibility, feasibility, and yield as criteria for selection of intervention sites, there is a high probability that remote, rural, and low-case-notifying areas will be left behind. This issue suggests the need for review of the deceptively high CNRs in urban areas, so that efforts to reach remote areas or areas with low CNRs are not undermined. Urban areas, with their higher populations and compromised socioeconomic conditions, require interventions to strengthen the networking of urban-rural programs to reach their actual catchment populations in order to improve case finding. Ending TB will only be possible if the urban rural disaggregation of data leads designing interventions and reaching missed cases whether they are not diagnosed which will remain to be source of continued transmission or diagnosed and not notified by the health system.

In the absence of subnational TB prevalence reports, TB investment and the performance of TB programs should be evaluated in the light of actual CNRs, using data about patients' place of residence as well as their place of treatment. This analysis will ensure the use of accurate data for decision-making and action. Further analysis of program limitations related to referral linkages, treatment success, and program capacity to reach target populations is needed.

Failure to account for patients from Adama City who might have sought care in surrounding rural areas could have led to underestimating the CNR in urban areas, and inability to verify the address registered, whether it is place of residence or temporary address, might have affect the results. Our study is limited to Adama city and did not measure the case notification and treatment success of the surrounding population which could give better estimate of the contribution of rural communities and identify TB cases from urban who received treatment in the rural. Further study is required to understand the patient flow between urban and rural areas to estimate CNRs in such settings.

This study could be generalized to urban sites were TB patients receive services within the catchment population and receive patents from surrounding areas that could increase the reported case notification of urban sites. In areas where patients are not strictly receiving treatment within their place of residence such underestimation of the real picture of the surrounding sites could be noticed while the urban areas could have higher notification rate which could be misleading. The results of the study should be cautiously interpreted as the sample size across the two groups was small to pick statistical difference among the two groups.

Conclusion

Urban TB program managers need to understand that the number of TB cases notified from urban areas includes cases from surrounding sites. Therefore, NTPs should analyze urban TB data by disaggregating the data by place of residence to identify gaps in case finding and strengthen urban case finding to reach missed or unreached cases in urban communities. Larger studies are warranted to address the needs of key populations in urban areas.

Abbreviations

CNR: Case Notification rate; EPTB: Extra pulmonary Tuberculosis; HIV: Human Immunodeficiency Virus; NTP: National Tuberculosis Program; PNEG: Pulmonary Smear Negative Tuberculosis; PPOS: Pulmonary Smear Positive Tuberculosis; TB: Tuberculosis

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Authors' contributions
DGD designed the study and coordinated the field work. AH was the senior expert in charge of data collection.AH and DD did the analysis. DD drafted the manuscript. DJ and PS reviewed the manuscript. All authors reviewed the final manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed in this study is available from the corresponding author on reasonable request.

Ethics approval and consent to participate
Support letter was obtained from the Adama City TB program to proceed with the programme review with health facility managers, and TB focal persons in the health facilities. Ethical clearance was not required as it was done under routine programme condition to understand how urban TB programme performs.

Consent for publication
Not applicable (NA).

Competing interests
The authors declare that they have no competing interests.

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ORIGINAL RESEARCH

Use of Xpert Contributes to Accurate Diagnosis, Timely Initiation, and Rational Use of Anti-TB Treatment Among Childhood Tuberculosis Cases in South Central Ethiopia

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Background: Childhood tuberculosis (TB) was under-prioritized, and only 15% of childhood TB cases are microbiologically confirmed. Hence, most childhood TB diagnoses are made on a clinical basis and prone to over- or under-treatment. Xpert is a rapid method for the diagnosis of childhood TB with high sensitivity.

Objective: To assess the use of Xpert for accurate diagnosis, timely initiation, and rational use of anti-TB treatment among childhood TB.

Methods: In 2016, the hospital facilitated the installation of the Xpert machine. We reviewed data trends over four consecutive years; two years before the arrival of the machine and two years following the implementation of Xpert. Data were extracted retrospectively from electronically stored databases and medical records and entered to SPSS 21 for analysis.

Results: In the pre-intervention period (2014–2015), 404 cases of children presenting with symptoms or signs suggestive of TB ("presumptive TB") were evaluated using AFB microscopy. A total of 254 (62.8%) TB diagnoses were made, of which 54 (21.3%) were confirmed by smear AFB while 200 (78.7%) were treated as smear-negative TB cases. The mean waiting time to start anti-TB treatment was 6.95 days [95% CI (3.71–10.90)]. During the intervention period (2016–-2017), 371 children with presumptive TB were evaluated using Xpert. A total of 199 (53.6%) childhood TB cases were notified, of which 88 (44.2%) were Xpert positive and 111 (55.8%) were treated as Xpert-negative probable TB cases. The tendency to initiate anti-TB treatment for unconfirmed TB cases was reduced by a third. Compared with smear AFB, Xpert improved accuracy of diagnosing pediatric TB cases two-fold. The average waiting time to start anti-TB treatment was 1.33 days [95% CI (0.95–1.71)]. There was a significant reduction in the waiting time to start anti-TB treatment, with a mean time difference before and during intervention of 5.62 days [95% CI (1.68–9.56)].

Conclusion: Xpert use was associated with a significant increase in the accuracy of identifying confirmed TB cases, reduced unnecessary anti-TB prescription, and shortened the time taken to start TB treatment.

Keywords: Xpert, AFB smear, childhood TB, confirmed TB, presumptive TB

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Background

Childhood TB remains among the most prevalent infectious diseases resulting in significant morbidity and mortality in children. In settings where TB has a high burden, childhood TB accounts for 15–20% of total TB incidence.[3] TB is one of the

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most contagious infectious human diseases with a high infection rate particularly in children aged less than five years.[1–3]

TB is a poverty-related disease, disproportionately affecting the poorest, most vulnerable, and marginalized population groups wherever it occurs. Children with the disease frequently live in poor communities with few health services.[2–4]

Ethiopia has been identified as one of the 30 High Burden Countries (HBC) for TB, TB and human immunodeficiency virus coinfection (TB/HIV), and multidrug-resistant TB (MDR-TB). In 2016, Ethiopia had an annual estimated TB incidence of 177 people per 100,000 population and a death rate of 25 per 100,000 population. Among the notified TB cases in 2016, 2.7% of new TB cases and 14% of previously treated TB cases were also estimated to harbor drug-resistant TB.[4]

Microscopy was the mainstay modality of TB diagnosis for years despite exhibiting low diagnostic sensitivity, particularly among children. Under optimal conditions, the sensitivity of smear microscopy for the diagnosis of childhood TB remains less than 15%. Microbiological confirmation of mycobacterium TB by culture detected only 15–50% of pediatric cases and the procedure takes a longer time so it is not usually used for routine clinical care. Therefore, one of the 10 priority indicators for monitoring the implementation of the WHO End TB Strategy is the percentage of new and relapsing TB cases that have been tested with a WHO-recommended rapid diagnostic measure at the time of diagnosis.[5–12]

The Xpert system was introduced in 2004. It provides user-friendly molecular testing by fully integrating and automating the three processes required for real-time polymerase chain reaction (PCR)-based molecular testing (namely specimen preparation, amplification, and detection) and additionally detects both live and dead bacteria.[8] Xpert represents a paradigm shift in the diagnosis of TB and simultaneously detecting multidrug resistance. It amplifies sputum samples in a closed system suitable for use outside conventional laboratory settings. The turnaround of Xpert is less than 2 hours.[9,10]

The sensitivity of the test is much better than smear microscopy and similar to that of solid culture. The limit of detection is 5 genome copies of purified DNA per reaction or 131 colony-forming units/mL in mycobacterium TB whereas identification of TB bacilli by microscopic examination requires at least 10,000 bacilli per milliliter of sputum.[9–11] Upfront access to Xpert testing in pediatric presumptive pulmonary TB cases was associated with a two-fold increase in bacteriologically confirmed pulmonary TB.[4]

In the current analysis, we examined childhood presumptive TB data collected before and after the implementation of Xpert. Our goal was to assess the significance of the improvement afforded by Xpert for TB diagnosis, use of anti-TB treatment for unconfirmed cases, and waiting time to initiate anti-TB treatment among positive cases.

Materials and Methods

Study Setting, Design, and Selection of Study Units

We conducted a retrospective medical document review study which was approved by the Arsi University institutional review board. The study was conducted in 2018 at Asella Teaching and Referral Hospital (ATRH), located about 175 km from the capital, Addis Ababa. The hospital is the only teaching and referral center in the region of South-Central Ethiopia delivering service to a population of approximately four million.

Acid-Fast Bacillus (AFB) smear microscopy has been used for the clinical diagnosis of TB at ATRH for decades. In the beginning of 2016, the Xpert machine was installed by the minister of health in collaboration with Challenge TB Ethiopia. The hospital was selected as a pilot site and the Xpert service was indicated to childhood TB and TB-HIV co-infection. All relevant health professionals attended on-site training on the operation of the machine and samples were processed using a standard operating procedure. We enrolled all cases of childhood presumptive TB (<15 years) from January 1, 2014, to December 31, 2017, who met the criteria for childhood presumptive TB; based on two or more typical symptoms of TB (cough, fever, poor weight gain) for more than 2 weeks or contact with a patient diagnosed with TB.

Data Collection and Management

All childhood presumptive TB cases during the consecutive four years (2014–2017) were included. Data were sourced from patient medical records, hospital electronic medical records, and the TB clinic registry book. Laboratory results were retrieved from the laboratory center data storage unit. Consistency, completeness, and accessibility of the data were assessed using a random subset of the data. For each variable reported in this study, approximately 20 medical records and digitally stored database entries were randomly reviewed to ensure that the objectives of the study were met.

Data collectors were blinded to the results of each case. Data collectors were nurses qualified in chart review and underwent a two-day training course on the use of the data collection tool. The data collectors independently reviewed clinical notes and completed a standardized data-entry format for presenting symptoms, time taken to receive laboratory result, final diagnosis, and date of starting anti-TB treatment for positive cases. Data collectors were supervised and could ask advice concerning any ambiguities or other problems. All data were reviewed by a third person for consistency and completeness. The primary outcome was the proportion of patients to receive a positive TB diagnosis.

Data Analysis

Descriptive statistics and cross-tabulation were used to quantitatively analyze the relationship between data acquired for patients before and after the implementation of the new diagnostic technology. A paired *T*-test was used to estimate the difference in waiting time before the commencement of anti-TB treatment in the two time periods. Adjusted odds ratios were calculated for factors associated with the effect of Xpert and smear AFB using a multiple logistic regression.

Operational Definitions[2,3,7,9,18,21]

Presumptive TB: child presented with a cough lasting two or more weeks AND/OR any of the following clinical symptoms: contact with a TB patient, fever, weight loss, or failure to gain weight.

Confirmed TB: child with at least 1 defined sign or symptom suggestive of TB AND microbiologically confirmed TB, defined as at least one positive smear or positive Xpert.

Probable TB: child meets two or more of the following criteria: history of TB contact, a clinical feature suggestive of TB, reactive tuberculin, skin test >10 mm, or radiographic findings compatible with TB (miliary TB, cavitary lesions, hilar lymphadenopathy, or primary complex), no response to trial of broad-spectrum antibiotics.

Compatible Chest-X-ray: Hilar lymphadenopathy, cavitary lesion (common with older children), and miliary TB.

Trial of broad-spectrum antibiotics: antibiotic treatment prescribed for a patient with presumptive TB who has been evaluated clinically, radiologically, and microbiologically, in which the findings were inconsistent with TB and therefore the patient was given broad-spectrum antibiotics for a possible alternative diagnosis of pneumonia.

Ethical Considerations

Ethical clearance was obtained from Arsi University, College of Health Sciences research ethical review board. As per the Arsi University college of health science ethical review board, consent of patient/guardian is not needed for secondary data research as it is not feasible to access them. Hence, the requirement for obtaining consent was waived and the research was conducted in accordance with the Declaration of Helsinki. However, confidentiality of information retrieved from patients' medical records was upheld and data were not disclosed to any third parties.

Results

A total of 775 presumptive TB cases with complete medical records were enrolled; 404 of these formed the pre-intervention group (January 2014–December 2015), and the remaining 371 subsequent to the installation of the Xpert system (January2016-December2017). Over the four-year period, a total of 453 (58.5%) patients were diagnosed with TB. From the total TB cases, 142 (31.3%) were confirmed microbiologically either using AFB microscopy or Xpert, and 311 (68.7%) were microbiological negative and treated as "probable" TB cases (see Table 1).

Subgroup Analysis

Pre-Intervention (2014–2015)

A total of 404 (n = 204 male; 50.1%) childhood presumptive TB cases were evaluated using smear AFB. Cough, fever, and weight loss were the leading clinical presentations (see Table 1). The mainstay of TB diagnosis was conventional AFB microscopy. A total of 54 (13.4%) were found to be smear AFB positive. During this period, a total of 254 childhood TB diagnoses were made, of which 54 (21.3%) were confirmed by AFB microscopy and 200 (78.7%) were treated as smear-negative "probable" TB cases. A total of 244 (60.4%) cases were prescribed a trial of broad-spectrum antibiotics for a possible alternative diagnosis other than that of a bacterial respiratory infection. Of these, 105 (43.0%) made a clinical improvement, and the remaining 139 (57.0%) were re-enrolled for TB work up. There was no association between antibiotic use and the rate of positive smear AFB, AOR 2.69 (95% CI, 082–8.30). The smear-positive rate was comparable in children under five years of age and those between 5 and 15 years (see Table 2).

Table 1 Patients Clinical Feature and Some Laboratory Characteristics, ATRH, 2018

Demographic			Pre-Intervention, n= 404	During Intervention, n=371	p-value
	Age, median (IQR), year		10 (7–12)	8(4–12)	0.121
	Sex	Male Female	204(50.1) 200(49.9)	199(53.6) 172(46.4)	0.065
Presenting clinical feature					
Cough, n(%)			375(91.9)	352(94.9)	0.056
Fever, n(%)			315(77.2)	277(74.7)	0.072
Weight loss, n(%)			250(61.3)	242(65.2)	0.062
Severe acute malnutrition, n(%)			51(12.5)	49(13.2)	0.323
BCG Vaccination, n(%)			41(10.0)	62(16.7)	0.051
Contact with chronic cougher, n(%)			106(26.0)	135(36.4)	0.032
Contact with TB patients, n(%)			75(18.4))	116(31.3)	0.012
Trial of antibiotic use, n(%)			244(60.0)	247(66.6)	0.071
Improved for trial of antibiotic, n(%)			105(25.7)	165(45.0)	0.013
Highly elevated ESR(>50mm/hr)			210(51.5)	181(48.8)	0.081
Anemia(hemoglobin<11g/dl)			122(29.9)	101(27.2)	0.187
Waiting time to start anti-TB, median (IQR), days			3(2–5.75)	2(0–4)	0.015

Abbreviations: ATRH, Asella Teaching and Referral Hospital; BCG, Bacille Calmette–Guérin; ESR, erythrocyte sedimentation rate; IQR, interquartile range; TB, tuberculosis.

Table 2 Multivariate Logistic Regression: Factors Associated with Tuberculosis Case Notification at ATRH, 2018

		"Probable" TB Cases, N=311	Smear AFB Positive N=54	XPert Positive N=88
		AOR, 95% CI	AOR, 95% CI	AOR, 95% CI
BCG vaccine	No	0.81(0.55–1.21)	2.06(0.96–2.38)	1.06(0.57–2.03)
SAM	Yes	3.29(1.91–5.71)	1.97(0.87–4.44)	2.00(1.07–3.70)
Contact with chronic cougher	Yes	1.56(1.14–2.15)	1.28(0.66–2.47)	1.55(0.96–2.53)
Contact with TB patient	Yes	1.67(1.24–2.24)	1.03(0.56–1.88	1.44(0.89–2.31)
Weight loss	Yes	1.21(0.92–1.61)	2.03(1.11–3.72)	1.33(0.77–2.30)
Age category	≥5 years	1.73(1.25–2.40)	1.01(0.45–2.55)	1.02(0.59–1.75)
Anemia	Yes	1.81(1.38–2.38)	2.08(1.21–3.58)	1.22(0.76–1.95)
ESR level (mm/hr)	50–99	2.06(1.46–2.91)	1.95(0.83–4.61)	2.42(1.24–4.73)
	≥100	5.9(2.6–13.3)	5.26(1.8–15.7)	4.55(1.51–13.7)
Chest X-ray compatible with TB	Yes	11.3(7.4–17.4)	5.7(3.2–10.2)	7.5(4.5–12.6)
Xpert implementation	Before	1.89(1.44–2.78)		

Abbreviations: AFB, acid-fast bacilli; AOR, adjusted odds ratio; ATRH, Asella Teaching and Referral Hospital; BCG, Bacille Calmette–Guérin; CI, confidence interval; ESR, erythrocyte sedimentation rate; SAM, severe acute malnutrition; TB, tuberculosis.

During Xpert Use (2016–2017)

Xpert was introduced as a primary diagnostic modality of TB for under 15 years of age. During this period, a total of 371 childhood presumptive TB cases were evaluated (n = 199 male; 53.6%). Cough, fever, and weight loss were the leading clinical presentations (see Table 1). Of these cases, 88 (23.7%) were positive for mycobacterium TB (MTB), and no cases of rifampicin resistance were reported. During this period, a total of 199 TB cases were diagnosed of which 88 (44.2%) were confirmed by Xpert, and 111

(55.8%) were treated as "probable" TB cases. This represents a 77% (almost twofold) increase proportionately in the number of presumptive TB cases to be microbiologically confirmed from the first period to the second period.

A total of 247 (66.4%) patients were prescribed a trial of broad-spectrum antibiotics for a possible alternative diagnosis of non-TB bacterial respiratory tract infection, of which 165 (45.0) showed a clinical response to antibiotic treatment. The proportion of patients prescribed with broad-spectrum antibiotic treatment is not significantly different between the two periods but the number of patients showing a clinical response to the antibiotics significantly increased following implementation of Xpert (Table 1 and Figure 1).

The waiting time for TB-positive patients to start anti-TB treatment was compared between the two periods. The implementation of Xpert significantly shortened the waiting time to an average of 2.6 days (95% CI 1.5–3.5 p 0.014) compared to 5.5 days (95% CI 3.7–7.4) beforehand. Moreover, one-quarter of TB patients diagnosed using Xpert started anti-TB treatment on the day of evaluation compared to only 7.5% of TB patients in the first period (Figure 2).

Factors Affecting the Rate of Positive Smear AFB vs Xpert

Patients who had contact with a patient with TB or chronic cough were likely to have their TB diagnosis confirmed by either AFB microscopy or Xpert (odds ratio 1.57, 95% CI 1.09–2.25, p-0.014).

Bacille Calmette–Guérin (BCG) vaccination status did not show any association with any form of TB diagnosis. Patients with chest x-ray findings consistent with pulmonary TB, elevated erythrocyte sedimentation rate (ESR), and presence of malnutrition were highly likely to have a positive smear AFB or Xpert result (Table 2).

The trends of confirmed TB cases increased after the introduction of Xpert while "probable" TB cases decreased in line with the overall trend in decreasing TB case presentation.

Prescription of broad-spectrum antibiotic treatment for respiratory complaints has significantly reduced after the introduction of Xpert compared the preceding two years (odds ratio 0.134, 95% CI 0.08–0.23, p<0.001). This may indicate improved rationale in the use of antibiotics (Figure 1). There was no association between antibiotic use and positive Xpert results (odds ratio 2.33, 95% CI, 0.49–11.10).

Similarly, the initiation of anti-TB treatment for cases of unconfirmed TB decreased significantly during intervention.

Discussion

There is a critical need for improved diagnosis of TB in children, particularly in young children as this deficit represents the most neglected sectors of population and those posing the greatest diagnostic challenges. There is also

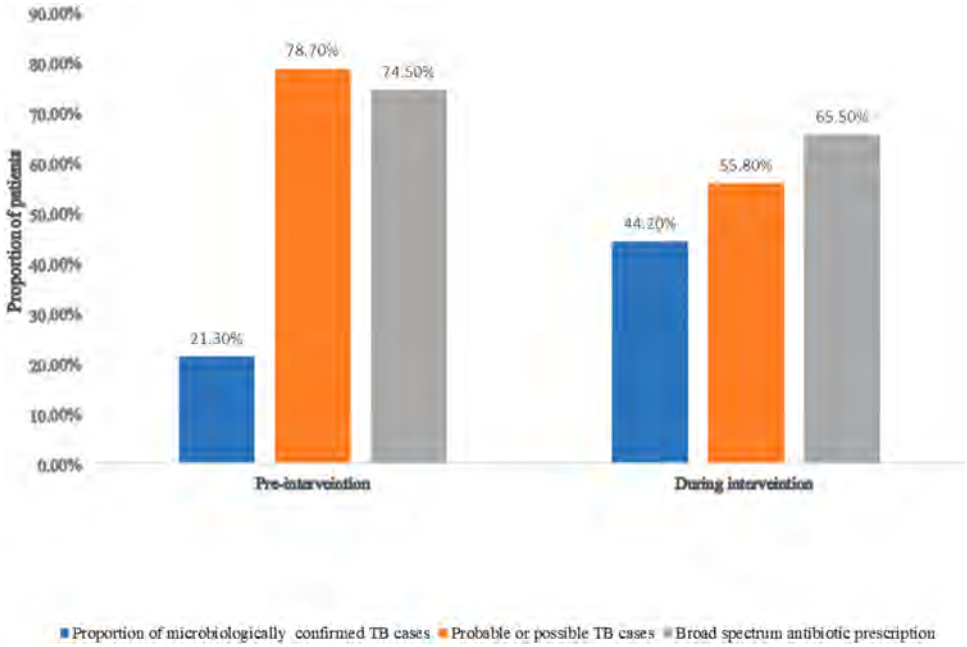

Figure 1 Bar chart comparison of trends of microbiologically confirmed TB cases, probable or possible TB cases, and utilization of antibiotics at Asella Teaching and Referral Hospital in 2018.

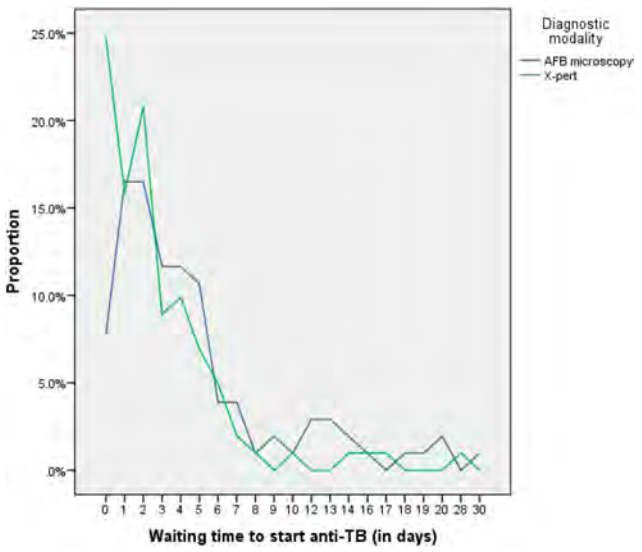

Figure 2 Statistical summary of trends of waiting time to start anti-TB before and during intervention at Asella Teaching and Referral Hospital in 2018.

a need for standardization of clinical definitions for the evaluation of diagnostic methods in prospective clinical research studies, including those involving children in whom TB is suspected but not confirmed microbiologically.[2,6] The present study found that prior to the implementation of Xpert, the rate of positive smear AFB results amongst presumptive TB cases was 54/404 (13.4%). Of cases to receive a positive diagnosis, 54/254 (21.3%) were microbiologically confirmed, making the remaining 200 cases (78.7%) were treated as smear-negative "probable" TB diagnoses. This finding is consistent with the findings of a national survey, which reported the proportion of smear-positive TB cases to be 23.1% with three-quarters of patients being treated for unconfirmed TB diagnoses.[2,4,10] This diagnostic disparity motivated the recent introduction of the new diagnostic modality known as Xpert.

In our study, the proportion of total presumptive TB cases to receive a positive diagnosis of MTB using Xpert was found to be 88/371 (23.7%), an almost two-fold increase compared to using smear AFB. This finding is higher than a recent study from France which reported smear microscopy and gene Xpert detection rates to be 4.8% and 10.4%, respectively. This difference could be explained by the difference in the epidemiological distribution of the disease between the two countries, as well as differences in the definitions of suspected TB and the skill and experience levels of individuals performing AFB microscopy.[4]

In this study, the diagnostic efficacy of Xpert MTB was assessed in comparison to conventional AFB smear microscopy. Taking the clinical definition of TB diagnosis as the gold standard, Xpert showed improved diagnostic capacity compared to AFB smear microscopy, demonstrated through a two-fold increase in the number of confirmed TB diagnoses using Xpert compared to AFB smear microscopy. This is in agreement with reports from South Africa and Brazil showing increases in confirmed TB diagnoses of 30–37%.[1,2,5-7] In our study, unconfirmed TB diagnoses decreased significantly after the introduction of Xpert. The decline in "probable" TB cases' after the introduction of Xpert reduced the margin of error on the decision to commence anti-TB treatment. As such, this mitigates the negative impact of unnecessary anti-TB treatment on a significant number of patients and their families.[3,4,8-10] Most patients who were initially presumed to have TB and who received a negative Xpert diagnosis were given an alternative diagnosis and improved with the prescription of broad-spectrum antibiotics. Broad-spectrum antibiotic use was not statistically different before and after implementation of Xpert; however, the number of patients showing a positive response to prescribed antibiotics was significantly higher in the latter period. This is likely due to the higher sensitivity and specificity of Xpert compared to AFB microscopy. A study by Lucian Davis et al and others reported that continued Xpert use could conceivably have significant clinical and public health consequences by decreasing unnecessary use of anti-TB treatment through contact screening. Pulmonary TB was the most commonly diagnosed form of TB in the present study, which is in agreement with 2019 WHO survey report among other reports where the majority of cases were diagnosed in children older than 5 years of age.[12–17,25]

The waiting time between first hospital visit and commencement of anti-TB treatment is one of the critical priorities for interrupting disease transmission and halting the circulation of the bacilli in the community. It is also equally important to start the patient on treatment rapidly so as to decrease patient suffering and improve clinical outcome.[26,30] In line with this, our study assessed the impact of Xpert in shortening waiting times. We reported that the implementation of Xpert significantly reduced the average waiting time to start anti-TB treatment, indicating reducing patient suffering, improved treatment outcomes, reduced risk of transmission, and improved TB control overall. A recent multicenter study showed that the median time to positive TB diagnosis for the gene Xpert test was zero (0) days (IQR 0–1), compared with 1 day (0–1) for microscopy, 30 days (23–43) for solid culture, and 16 days (13–21) for liquid culture. Use of Xpert reduced the

median time to treatment for smear-negative TB from 56 days (39–81) to 5 days.[6,7,9,11,14]

Children who received BCG vaccination were at lower risk of having smear-positive TB while its overall TB preventive efficacy is not significantly different from the unvaccinated population. BCG vaccination reduces severe forms of mycobacterium TB infection (eg, central nervous system TB) in children; however, it has only minimal effects on secondary TB and TB of the lung. BCG, therefore, plays an insignificant role in strategies to control TB.[2,3,17]

Our study demonstrated that the implementation of Xpert considerably decreased the frequency and impact of unnecessary broad-spectrum antibiotic prescription for presumptive TB cases which is in agreement with the findings of other studies. Similarly, even though the present study did not entirely characterize the impact of Xpert in contact case tracing, there are a number of reports indicating that its use can also improve contact screening.[1-3,4,19–24,27–30]

Limitations

The research findings were generated by using retrospective data analysis through reviewing patient medical records. Data retrieval was subject to some issues of inconsistency and incompleteness. However, the output of the research carries a significant scientific impact and provides a fertile ground for future prospective studies.

Conclusion and Recommendation

The implementation of Xpert was associated with a significant increase in the proportion of confirmed childhood TB cases and a significant reduction in prescription of anti-TB treatment for unconfirmed TB cases and improved response to the use of antibiotics for patients receiving a TB-negative diagnosis. Further, Xpert use was associated with a significant decrease in the time taken to start anti-TB treatment among children presenting as presumptive TB. Xpert use provides significant improvement in the TB diagnosis and treatment of children. With wider-scale use, it will have a profound impact on the success of the WHO End TB Strategy.

Abbreviations

AFB, Acid-Fast Bacilli; AIDS, Acquired Immune Deficiency Syndrome; ATRH, Asella Teaching and Referral Hospital; BCG, Bacille Calmette–Guérin; EPHI, Ethiopian Public Health Institute; ESR, Erythrocyte Sedimentation Rate; FMOH, Federal Ministry of Health; HIV, Human Immunodeficiency Virus; MDR-TB, Multi-Drug Resistance Tuberculosis; TB, Tuberculosis; MTB/RIF, Macrobacterium Tuberculosis/Rifampicin; PCR, Polymerase Chain Reaction.

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Disclosure

The authors report no conflicts of interest in this work.

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RESEARCH ARTICLE

The yield of community-based tuberculosis and HIV among key populations in hotspot settings of Ethiopia: A cross-sectional implementation study

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Abstract

Objective

To determine the yield of tuberculosis (TB) and the prevalence of Human Immuno-deficiency virus (HIV) among key populations in the selected hotspot towns of Ethiopia.

Methods

We undertook a cross-sectional implementation research during August 2017-January 2018. Trained TB focal persons and health extension workers (HEWs) identified female sex workers (FSWs), health care workers (HCWs), prison inmates, homeless, internally displaced people (IDPs), internal migratory workers (IMWs) and residents in missionary charities as key and vulnerable popuaiton. They carried out health education on the importance of TB screening and HIV testing prior to recruitment of the study participants. Symptomatic TB screening and HIV testing was done. The yield of TB was computed per 100,000 background key population.

Results

A total of 1878 vulnerable people were screened, out of which 726 (38.7%) presumptive TB cases and 87 (4.6%) TB cases were identified. The yield of TB was 1519 (95% CI: 1218.1–1869.9). The highest proportion (19.5%) and yield of TB case (6,286 (95% CI: 3980.8–9362.3)) was among HCWs. The prevalence of HIV infection was 6%, 67 out of 1,111 tested. IMWs and FSWs represented 49.3% (33) and 28.4% (13) of the HIV infections, respectively. There was a statistically significant association of active TB cases with previous history of TB (Adjusted Odds Ratio (AOR): 11 95% CI, 4.06–29.81), HIV infection (AOR: 7.7 95% CI, 2.24–26.40), and being a HCW (AOR: 2.42 95% CI, 1.09–5.34).

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Competing interests: The authors have declared that no competing interests exist.

Conclusions

The prevalence of TB in key populations was nine times higher than 164/100,000 national estimated prevalence rate. The prevalence of HIV was five times higher than 1.15% of the national survey. The highest yield of TB was among the HCWs and the high HIV burden was detected among the FSWs and IMWs. These suggest a community and health facility based integrated and enhanced case finding approaches for TB and HIV in hotspot settings.

Introduction

The incidence of TB has dropped in most regions of the world, including in Ethiopia [1]. However, the disease is largely concentrated in vulnerable or socially excluded populations and high-risk settings [2]. If vulnerable populations are not put at the forefront of any intervention, they will continue to be among the missed TB cases [1,2].

Ethiopia was estimated to miss 58,893 (34%) of expected TB cases in 2018 [3]. According to 2010 unpublished Ethiopian TB report, about 59% of the missed TB cases could be due to failure to detect TB in the community and among vulnerable populations. In order to identify the missed TB cases, the country has adopted the global target to identify at least 90% of TB cases among key populations by 2025 [4]. Hence, the national TB program prepared an operational guide and implementation plan on key affected populations for TB in 2017 [5].

Key and vulnerable populations for TB are defined and identified based on increased risk of TB disease due to biological and socioeconomic factors, lack of access to health services for diagnosis and treatment, and the experience of human rights violations [5]. Country-specific situations can be useful in defining key and vulnerable groups for TB [6]. Accordingly, Ethiopia has identified people living with HIV, people with diabetes, children, elders, prisoners, university residents, contacts of TB patients, miners or internal migratory workers (IMWs), cross-border refugees, internally displaced people (IDPs), homeless, female sex workers (FSWs), HCWs as key and vulnerable populations for TB [5].

On the other hand, there has been slowing or stabilizing general HIV epidemic over the last decade in Ethiopia[7]. The prevalence of HIV was 1.5% in 2011 [8] and decreased to 1.15% in 2018 [9]. The estimated number of deaths declined from 11,000 in 2015 to 5,000 in 2018 [9]. Also, the rate of TB/HIV co-infection significantly decreased from 18% in 2012 to 7% in 2017 [8,9]. Nevertheless, the burden of HIV in Ethiopia remained to be congregated in the hotspot settings such as urban areas and big cities [7,10]. Besides, the HIV epidemic is slowly rising among the high-risk population groups such as FSW and their partners [11]. Hence, it is paramount to assess HIV among the key populations in the hotspot settings of Ethiopia to deal with HIV and HIV related TB. This could contribute to the achievement of the three 90's of the global targets for both TB [4] and HIV [12].

Less evidence exists, however, about the prevalence of TB and HIV among the key and vulnerable population groups in Ethiopia. Moreover, it is essential to identify vulnerable populations based on their context [6] i.e in the hotspot setting for HIV and TB. Therefore, this study tried to determine the yield of enhanced TB case finding and the prevalence of HIV among the vulnerable population at the selected hotspot settings of Ethiopia.

Materials and methods

Settings

Ethiopia is the second-most populous nation in Africa, with a population of about 110 million [13]. It ranks 10th among the 30 high-TB-burden countries, with TB incidence of 164/100,000

in 2018 [3]. Harar, Dire Dawa, Woldiya, Shakiso, and Adola were the five towns in Ethiopia with a TB/HIV co-infection rate higher than 10% [14–16] (S1 Fig). These towns contribute to 2.7% of the national population. Geographic clustering of high-risk sub populations exists in these towns due to gold mining, factories, poverty, and cash crops, paving the way for high TB and HIV transmission—hence the term hotspot setting.

Study design and interventions

We undertook a cross-sectional implementation research during August 2017-January 2018 with funding from the US Agency for International Development under the Challenge TB project. In Ethiopia, Challenge TB provided support to the national TB program in nine of the 11 administrative regions. We initiated the study after consultation with regional, zonal, and district TB focal persons. The project built the capacity of the program managers, HCWs, and HEWs on TB and TB/HIV screening, diagnosis and treatment. The project also technically and financially assisted supportive supervisions and program reviews on TB and TB/HIV. Improving sputum specimen and patient referral system, and strengthening data quality and reporting system through the district health information system (DHIS) were another support issued to the national TB program by Challenge TB project.

Identification of hotspot settings and key populations

We selected the five study towns as the hotspot for TB and HIV because of their higher TB/HIV co-infection rate [14–16] as compared to other towns in the country. All the missionary residents, hotels, mining or construction offices, correctional facilities, health facilities, street tukuls of the homeless and refugee centers in the five towns were selected as sites of the data collection.

TB focal persons, HCWs that coordinate comprehensive TB and TB/HIV activities, and HEWs—the female community workers employed to execute the health extension program—were trained on the procedures of defining [5,6 &13], identifying and sampling the key populations in the data collection areas. They were also trained on the information they need to deliver during health education to the key population before recruitment; such as TB transmission, purpose of the study and the advantages of being screened for TB and HIV. Hence, they carried out 15–20 minutes of health education before recruitment and data collection among the key population to enhance the TB screening and HIV testing.

They recruited FSWs at the hotels after obtaining permission from the owner of the hotel. The HEWs and TB focal persons deployed homeless individuals in the street. IDP, HCWs, prison inmates and IMW were recruited after the heads of the offices of road construction and mining (for IMW), health care facility (for HCWs), correctional facility (prisoners) and refugee centers (IDPs) were approached. The HCWs were clinicians, such as registered nurses, interns, medical doctors and public health officers that were involved in managing patients in public health facilities found in the study towns. IDPs were those individuals that were displaced from Somalia region of the country to Harari region due to ethnic conflict during the study period. The IDPs arrived at refugee center near Harar town 4–6 weeks prior to data collection.

The key population that understood the objective of the study and willing to participate after the health education, and in a relative good health status were involved in the study. Those who understood the aim of the study but refused to be part of the study and/or were sick during the data collection were excluded (Fig 1).

Sampling the key population

There were a total of 3,400 prison inmates, 250 residents of facilities operated by charities and 350 HCWs reported from the five towns' health office. These numbers were taken as a

sampling frame. One-third of the sampling frame from each of these key population was randomly selected to be a study population in the five towns. Excel sheet was used to undertake the simple random selection of the study population from the sampling frame for the prison inmates, missionary residents and HCWs.

However, the number for FSWs, IMWs, IDPs and homeless could not be obtained. Hence, the sampling frame was established during the data collection. That is, when the HEWs and TB focal persons visited the FSWs in the hotels, IMWs at the workplace, IDPs in the refugee centers and homeless in the street, they registered these key populaiton on excel sheet (sampling frame). Then one-third of the sampling frame was randomly selected to be the study participants. Accordingly, there were 639 FSWs, 730 IMWs, 315 IDPs, and 55 homeless individuals that were registered as sampling frame from where random sampling was carried out during the study period.

All in all, 5729 key populations were taken as sampling frame or background key population in the five study towns. A total of 1929 vulnerable population were selected randomly and approached for TB screening; 1125 prison inmates, 87 residents of facilities operated by charities, 123 HCWs, 225 FSWs, 245 IMWs, 105 IDPs and 19 homeless individuals. About 1878 (97%) of them accepted the screened for TB; 221 FSWs, 237 IMWs, 1112 prison inmates, 79 residents of facilities operated by charities, 113 HCWs, 102 IDPs, and 14 homeless (Fig 1).

Screening and diagnosis of TB, and HIV testing among the key population

The HEWs and TB focal persons carried out symptom-based screening for TB. At the same time, they did confidential HIV testing and counseling. An individual having cough, fever, and night sweating of more than two weeks or weight loss were taken as a presumptive TB case or positive screening test [17]. Nationally approved rapid HIV test kits were used for HIV testing. The identified presumed TB cases and HIV positive key populations were referred to the health facilities in study towns having TB DOTS and chronic HIV care services. These were the facilities with external quality control for diagnostic tests. At the health facilities, depending on their complaint, the presumed TB cases underwent clinical evaluation (history and physical examination), acid-fast bacilli (AFB) test, Gene X-pert test, fine needle aspiration (FNA) or chest X-ray. For a single key population, the time spent for recruitment, TB screening, HIV testing and counseling, and recording all the outcomes of TB screening and evaluation ranged from 15–20 minutes.

TB cases were categorized as bacteriologically confirmed pulmonary TB (PTB) cases where the diagnosis is made using AFB or Gene X-pert, clinically diagnosed smear-negative PTB if the diagnosed is based on clinical findings, and clinically diagnosed extra-PTB (EPTB) if the diagnosis is based on clinical evidence and the disease is out of the lung. The classification of TB was also made as drug-susceptible TB if the disease is responding to first-line anti-TB drug and Multi-drug resistance or rifampicin resistance TB (MDR-TB/RR-TB) if the TB disease is resistance at least to rifampicin and isoniazid [17]. The key populations that had already known their HIV status were also recorded.

Data source

The study coordinators prepared a register of key and vulnerable populations which the TB focal persons and HEWs used to record the number of people approached for TB screening, their sociodemographic characteristics, presumed TB cases, TB cases, and HIV status. The register of key and vulnerable population captured the information obtained from the individual key population and the outcomes of the clinical evaluation and laboratory investigations.

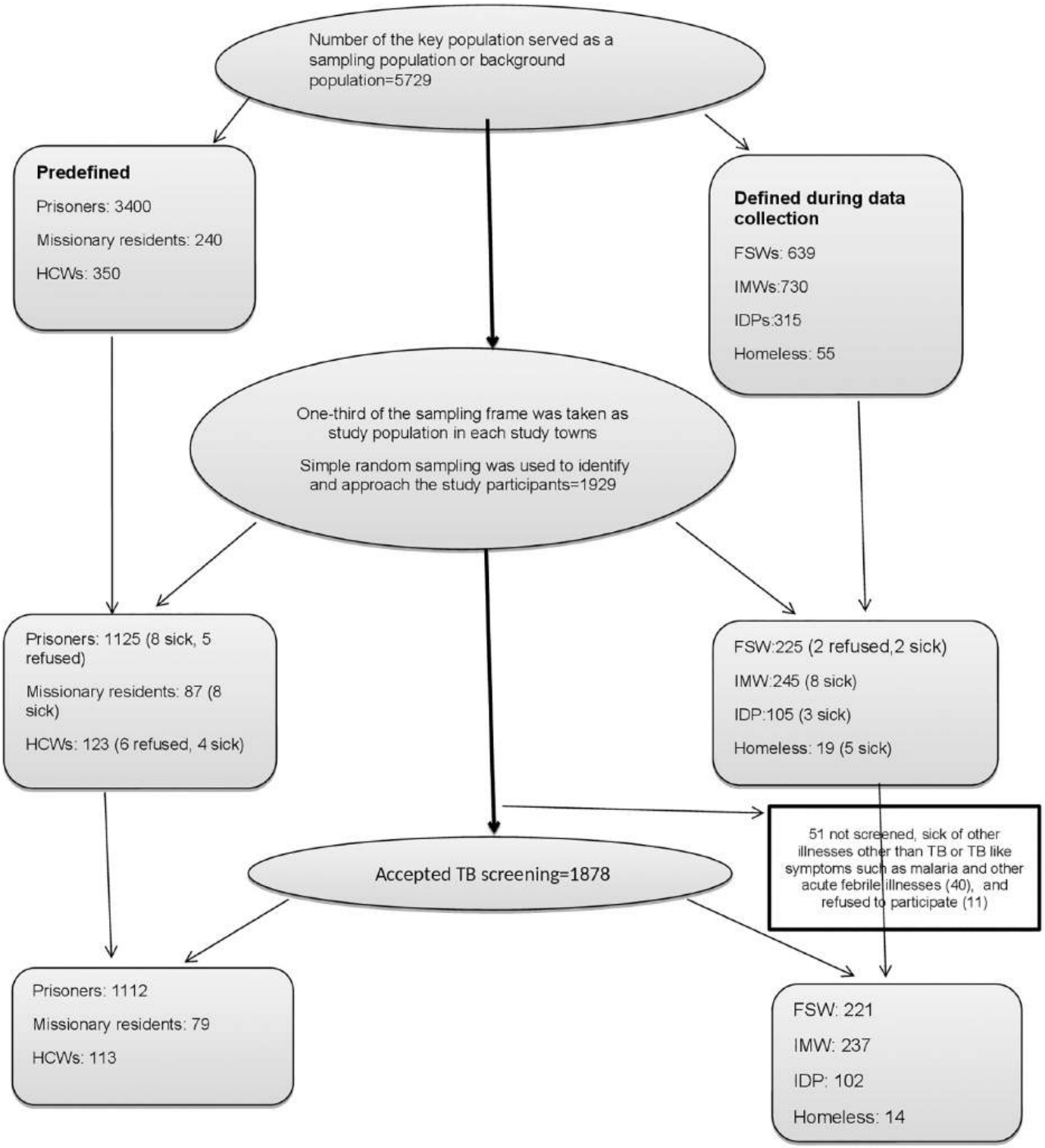

Fig 1. The flow chart shows sampling and selection of the key population. Predefined key population are those whose number had already been documented and reported by the study towns' health offices. The **"defined during data collection"** key population were those whose number were not known by the study towns' health office and their background population was determined during the data collection period. The sampling frame was taken as the total key population in the study towns, and thus the background population to compute the yield or prevalence of TB. Bold arrow is to show the crude procedure one after the other; listing the sampling frame, random selection of one-third of the sampling frame, approaching for TB screening. Light arrow is to show the same procedure in each key population; FSW (female sex workers), IMW (internal migratory workers), IDP (internally displaced people), HCW (health care workers), missionary

residents are the one supported by the charity organization. Most of the refusals were from HCW and FSW for they were busy, and from prison inmates. The malaria illness and other acute febrile illness made the other key population difficult to participate in the study.

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Data quality

We deployed two trained data entry clerks. The first carried out primary data entry and the second checked for discrepancies in the data. The study coordinators also supervised data collection and data entry for consistency and completeness.

Data analysis

The Epi Info statistical package (Version 7.2.2.16; Atlanta, Georgia: Centers for Disease Control and Prevention; 2018) was used for data entry and cleaning. We imported the data to Stata (College Station, Texas: StataCorp; 2013) for data analysis. Frequency, percentage, mean, and other descriptive statistics were used. The notified TB cases per 100,000 background key population and proportions were used to compute the prevalence of TB in the key population. Adjusting for sociodemographic characteristics in the key population, bivariate and multivariable (forward conditional) logistic regression—applying the odds ratio and 95% confidence interval (95% CI)—were used to determine factors associated with active TB in the key population. The independent variable was the presence of TB case. The dependent variables were sex (male and female), age (categorized based on the median, below and above 28 years), educational status (below high school, high school and above), marriage (married/with partner and non-married or without partner), HIV status (HIV positive and HIV negative), previous history of TB (having at least one episode of TB before and never had TB case), and type of key population (FSW, IWM, IDPs, HCWs).

Ethical considerations

The ethical review committee (ERC) of the respective regions of the study towns approved the study protocol. These were ERC of Oromia regional health bureau, Institutional Review Board (IRB) of the Amhara public health institute, the ERC of the research wing of Dire Dawa health bureau and ERC of Harari regional health bureau. We obtained support letters from the ERC and IRB of these regions and towns to communicate with the relevant local organizations and town health offices where the key population were found. We also sought and received informed written consent from the study participants before data collection. Permission was requested from the guardian and parents in case of children. Even though a separate consent requested for TB screening and HIV screening, it was asked one after the other; first for TB screening and then for HIV testing. All the key and vulnerable population were informed that it is their full right to exit from the study if they are not willing. However, all were getting a TB screening, evaluation and treatment services irrespective of their willingness or refusal to participate in the study. That is, the respective TB case and HIV positive key population were linked to and managed at the TB DOTS and chronic HIV care of the health facilities in the study towns.

Results

Sociodemographic characteristics

Of the 1,878 participants approached and screened for TB, 1326 (70.6%) were men. The mean and the median age were 30.5 years and 28 years (Range: 5–80 years), respectively. About half

Table 1. Sociodemographic characteristics of the vulnerable population in the selected five towns of Ethiopia, August 2017- January 2018.

Variables	Frequency	Percent
Types of vulnerable populations		
FSWs	221	11.77
IMWs	237	12.62
Prisoners	1,112	59.21
Residents of missionary charity facilities	79	4.21
Homeless people	14	0.75
IDPs	102	5.43
HCWs	113	6.02
Total	1,878	100
Sex		
Female	552	29.39
Male	1,326	70.61
Total	1,878	100
Age in years		
< 15	19	1.0
15–24	594	31.9
25–34	721	38.7
35–44	334	17.9
> 44	195	10.5
Total with age determined	1,863	100
Marital status		
Married	911	50.36
Divorced/separated	245	13.54
Single/never married	636	35.16
Widowed	17	0.94
Total with marital status determined	1,809	100
Educational status		
Primary school (1st-6th grade)	855	47.77
7th-8th grade	628	35.08
9th-12th grade	184	10.28
12th grade or above	123	6.87
Total with educational status determined	1,790	100

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of the study participants were married and had attended at least primary school (Table 1). The detail of sociodemographic characteristic of each key population is described in S1 Table.

Screening and evaluation

One hundred and one (5.4%) of the screened vulnerable population had a history of previous TB treatment, and five of them (0.3%) were on treatment during data collection. Of the 1,878 screened, 726 (38.7%) were presumptive TB cases, of whom 210 (28.9%) were clinically evaluated, 126 (17.4%) were investigated using acid-fast bacilli (AFB) testing and 612 (84.3%) were tested by GeneX-pert. A total of 959 key population underwent at least a clinical evaluation or TB laboratory test. A total of 87 (4.6%) TB cases were identified and 65 (74.7%) were bacteriologically confirmed; 62 (95.4%) were drug susceptible TB and 3 (4.6%) were MDR-TB cases (Table 2). Note that five of the vulnerable (IMW) were already on treatment and had clinical EPTB (1) and PTB (4).

Table 2. Tuberculosis screening, evaluation, and final status of the vulnerable population in the five towns of Ethiopia, August 2017–January 2018.

Variables	Frequency	Percent
Previous TB episode		
Had TB once	92	4.9
Had TB twice	9	0.5
On treatment now	5	0.3
Never	1,772	94.4
Total	1,878	100.0
Outcome of TB screening		
Positive	726	38.7
Negative	1,152*	61.3
Total	1,878	100.0
Means of TB investigation		
AFB	126	13.1
GeneXpert	612	63.8
Clinical only	210	21.9
Chest x-ray	9	0.9
FNA	2	0.2
Total evaluation done using at least one of the above criteria	959	100.0
Outcome of the investigation		
No TB	1,748	93.3
TB diagnosed during the study period	87	4.6
Result could not be found	38	2.1
Total	1,873	100.0
Type and site of TB		
Drug-susceptible TB		
Bacteriologically confirmed PTB	62	71.3
Clinical extrapulmonary TB (EPTB)	11	10.3
Clinical pulmonary TB (PTB)	16	14.9
MDR-TB (all new and bacteriologically confirned PTB)	3	3.4
Total	92	100.0

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The prevalence of TB, HIV, and TB/HIV co-infection among the vulnerable population

Of the 87 TB cases, 27 (31%) were prisoner inmates and 22 (25.3%) were HCWs. The highest proportion of TB cases was found among HCWs (19.5%) and the lowest was among IDPs (1%). Overall, the yield of TB cases per the 100k background vulnerable population was 1,519 (95% CI:1218.1–1869.9), nine times the estimated prevalence rate of 164/100k in the general population during the study period. The prevalence of TB among HCWs was the highest of all (6,286 (95% CI:3980.8–9362.3)), the least being among the IDPs (317.5 (95% CI: 80.4–1756.0)). No TB case was detected among the homeless individuals (Table 3).

About 1293 (69%) of the identified key population were approached for HIV testing and counseling; 1111 (59.2%) were tested and 183 (14.2%) refused testing. The overall prevalence of HIV infection, new plus already on treatment, was 67 out of the tested 1111 (6%), five times the 1.15% prevalence estimate in the general population. IMWs and FSWs represented 49.3% (33) and 28.4% (13) of the HIV infections, respectively (Table 4). Note that HIV positives reported here include those who had already known their status and were on HIV care.

Table 3. Tuberculosis case finding among the vulnerable populations in the five towns of Ethiopia, August 2017–January 2018.

Type of Vulnerable Population	Result of TB screening and evaluation		Total key population selected and screened	Number of background key population/ sampling frame	Proportion of TB among the screened and evaluated	Notified TB cases per 100,000 background vulnerable population (95% CI)	Comparison with the estimated TB prevalence for the general population (164/100,000)
	No TB	TB					
FSWs	203	18	221	639	8.1	2,817 (1677.8–4415.5)	17.2
IMWs	214	18	237	730	7.6	2,466 (1467.8–3869.0)	15.0
Prison inmates	1,061	27	1,112	3,400	2.4	794 (524.0–1153.3)	4.8
Residents of missionary charity	64	1	79	240	1.3	417 (105.5–2299.5)	2.5
IDPs	101	1	102	315	1	317.5 (80.4–1756.0)	1.9
HCWs	91	22	113	350	19.5	6,286 (3980.8–9362.3)	38.3
Homeless	14	0	14	55	NA	NA	NA
Total	1,748	87	1,878	5,729	4.6	1,519 (1218.1–1869.9)	9.3

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Forty-nine (4.4%) of the key population with the documented HIV status had already aware that they were HIV infected and were on HIV care. Eighteen (26.9%) were new HIV-positive patients detected during the study. There were 21 (31.3%) TB cases among the HIV infected key population. HIV testing was carried out in 41 (47%) of the newly identified TB cases where 21 (51.2%) were HIV positive (S2 Table).

Factors associated with TB cases among the vulnerable population

In the bivariate analysis, having not married, being health care work, attending the lower educational level with the previous history of TB and infection with HIV have a statistically significant association with the diagnosis of TB case among the vulnerable population. In the multivariable analysis, previous history of TB disease (AOR: 11 95%; CI, 4.06–29.81), HIV infection (AOR: 7.7 95%; CI, 2.24–26.40) and being HCW (AOR: 2.42; 95% CI, 1.09–5.34) remained statistically related to active TB (Table 5).

Discussion

This study defined and identified FSWs, IMWs, missionary facility residents, prison inmates, IDPs, HCWs, and the homeless as key and vulnerable populations in the selected hotspot

Table 4. The status of HIV screening, testing, and results among the vulnerable population in five towns of Ethiopia, August 2017–January 2018.

Type of Vulnerable Population	HIV test result [a]			Total key population	Total tested (%)	HIV positive (%)	Comparison with the estimated prevalence in the general population (1.15%)
	Positive	Negative	Refused				
FSWs	19	102	22	221	121(54.8)	15.7	13.7x
IMW s	33	127	51	237	160 (67.5)	20.6	17.9x
Prison inmates	13	671	84	1112	684 (61.5)	1.9	1.7x
Missionary facility residents	2	34	25	79	36 (45.6)	5.6	4.8x
Homeless	0	8	0	14	8 (57.1)	0.0	0x
HCWs	0	102	0	113	102 (90.3)	0.0	0x
IDP	NA (note applicable)	NA	NA	102	NA	NA	NA
Total	67	1,044	182	1878	1,111 (59.2)	6.0	5.2x

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Table 5. Bivariate and multivariable analysis of factors associated with active TB among key and vulnerable populations in the five towns of Ethiopia, August 2017–January 2018.

Variables	Category (% TB case)	Bivariate analysis		Multivariable analysis	
		Crude odds ratio (COR)	95% CI	AOR	95% CI
Sex (N = 87)	1. Male (70.1)	0.97	0.61–1.56	0.65	0.37–1.16
	2. Female (29.9)	1			
Age in years (N = 86)	1. >28 years (52.3)	1			
	2. >= 28 years (47.7)	0.83	0.54–1.28	0.8	0.08–7.78
Marital status (N = 80)	1. Not married (73.8)	2.98	1.80–4.95	2.09	0.86–5.06
	2. Married (26.2)	1			
History of TB (N = 87)	1. Yes (34.5)	11.54	6.93–1921	11	4.06–29.81
	2. No (65.5)	1			
Educational status(N = 80)	1. Below high school (78.8)	2.16	1.32–3.54	0.41	0.11–1.47
	2. High school and above (21.3)	1			
HIV status (N = 41)	1. HIV+ (51.2)	23.37	11.84–46.13	7.7	2.24–26.40
	2. HIV- (48.9)	1			
Type of vulnerable population (N = 85)	1. HCWs (25.9)	2.73	1.39–5.33	2.42	1.09–5.34
	2. IMWs (21.2)	0.93	0.46–1.83	1.18	0.51–2.72
	3. Prisoners (31.8)	0.28	0.15–0.52	0.51	0.24–1.06
	4. FSWs (21.2)	1			

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settings. Through the enhanced community-based TB/HIV intervention in the selected hotspot settings, we reported an overall nine times more TB cases and five times more HIV infections among the key and vulnerable population as compared to the general population. Also, the study indicated that being HCW, having HIV infection and previous episode of TB disease seem statistically associated with the development of active TB. Hence, ending the TB epidemic in Ethiopia cannot be successful without collaboration to find and treat TB and HIV at the community level among the disproportionately affected vulnerable and key populations in hotspot settings. The implementation of comprehensive, tailored and enhanced TB case finding should be prioritized in these congregate settings.

Other studies support the finding that HCWs have a high incidence and prevalence of TB [18–20]. The yield of TB among the HCWs in this study is even higher than the studies in China [18,19]. This might be due to poor TB infection control at health facilities in Ethiopia [20]. Similarly, a systematic review in low- and middle-income countries indicated that the incidence rate of TB among HCWs is 2.94 times higher (95% CI, 1.67–5.19) than in the general population [21]. Although HCWs have the highest rate of TB, there was no detected HIV infection among them. The stigma associated with HIV disclosure [22] might make it difficult to find HIV-infected HCWs [23]. This could also indicate that it is worth looking for other determinants of the high TB incidence among HCWs though HIV remains a key risk factor for TB among HCWs in high-HIV-burden settings [24]. For instance, poor TB infection control in health facilities [25] and repeated exposure to TB infection and thus nosocomial TB infection [21] could explain the high TB prevalence rate among HCWs. This could partly due to greater attention to the TB symptoms and higher awareness of the disease among the HCWs. TB infections at health facilities could be due to unidentified and unsuspected TB cases [26] and the prolonged period prior to diagnosing TB cases [27]. Therefore, reducing delay in the diagnosis of TB in health facilities could be one of the approaches to lower the high TB burden among HCWs [27]. Practising comprehensive TB infection control could also reduce the high TB transmission in health facilities [25]. In addition, periodic clinical

evaluation and tuberculin skin tests, and provision of preventive therapy could be considered to avert the occurrence of active TB among HCWs in Ethiopia.

As compared to other vulnerable and key populations, FSWs and IMWs were found to have a high TB case notification rate in the background of higher HIV prevalence. Both are sexually active, young and usually migrate to cash crop areas. IMWs are often the clients of FSWs at mega projects and mining areas [28]. Due to their low socioeconomic and educational status, IMWs and FSWs live in congregate and overcrowded homes and practice risky sexual behavior [28]. Hence, they are at risk of contracting and transmitting both HIV and TB infections. In addition, IMWs and FSWs play a key role in the epidemics of TB and HIV. In high-burden settings, the two diseases reinforce each other and share common risk factors [29]. So, a single service provided to people with multiple related risks represents a missed opportunity to diagnose, treat, and prevent TB or HIV. The shortcomings of this approach are evident in communities that are considered vulnerable populations [30]. Establishing and strengthening the integration of TB and HIV interventions at primary health care facilities and at the community level in hotspot settings among these vulnerable and key populations is therefore critical.

As we would expect, the yield of TB among prison inmates was five times higher than in the general population. The prevalence rate of TB among inmates in this study is higher than the rate in a recent systematic review in Ethiopia [31]. This could be because the prisoners in our study came from a hotspot area where HIV could have also contributed. However, the yield of TB case is lower than the prevalence rate reported in Côte D'Ivoire where it is 10–44 times higher than the rate in the general population [32]. This difference may be due to the variation in the diagnostic facilities and TB epidemiology between the two settings. In our study, the prison inmates represented the highest number of vulnerable and key populations screened, and they contributed to the highest proportion of overall TB case notification. So, they remain the vulnerable population most in need of tailored interventions to address TB transmission in correctional and detention centers. Like IMWs and FSWs, prisoners may also serve as a reservoir of TB and could shift the TB epidemic from correctional facilities to the community [33]. Therefore, entry and exit screenings and scheduled mass screenings are worth carrying out in correctional and detention centers in Ethiopia. Nevertheless, the prevalence of HIV infection among the prisoners was slightly higher than in the general population (1.7 vs 1.2%). Yet 11% of them refused HIV testing. The risk of TB among prisoners might not be explained only by HIV infection [34,35] but could also be due to weak implementation of TB infection control [20].

The homeless were identified as one of the vulnerable and key populations, although they were few, with no TB and HIV cases identified. Evidence shows that they have a higher burden of TB [36] due to malnutrition and addiction of various kinds, such as smoking [37]. Women who live on the street are also at high risk of sexual assault and concurrent risk for HIV infection [38] and thus for TB. The study also identified a few individuals living in missionary facilities, with low TB case identification. Some of these were children, in whom TB diagnosis is usually difficult [39]. Nevertheless, the homeless and residents of charities are at risk for TB and HIV infections. Future studies involving higher numbers of these populations could complement the investigation of the prevalence of TB and HIV infection in Ethiopia.

During the study period, Ethiopia experienced unrest that displaced several people, specifically in the eastern part of the country, where two of the study towns are located. The outreach activity to IDPs detected fewer TB cases. Evidences have reported that IDPs and other refugees are at risk for TB disease [40,41]. The longer IDPs stay in refugee centers, the higher the likelihood that they will develop TB [41]. Hence, follow-on TB and HIV screening and evaluation might detect additional TB and HIV cases. This is because overcrowding, stressful living

conditions, malnutrition, and lack of access to health services could put these vulnerable people at high risk for TB [42].

The findings in this study should be interpreted cautiously, for there were limitations. Although the study included a high number of key and vulnerable populations at the community level, it should have included more homeless, refugee, cross-border refugees, children and diabetic mellitus in the other areas of the country other than the five towns. The data is skewed towards male for there were a lot of male HCWs, prison-in-mates and IDP, possibly challenging the generalization to similar settings. Only a few independent variables were considered for risk factor analysis. Thus, future studies need to investigate other risk factors for TB infection and disease in key and vulnerable populations. Besides, the shortage of the HIV testing kits made HIV testing difficult for some key population. The living situation of the homeless and the working environment of the FSW challenged the sampling and data gathering. Eventually, the crude comparison of the prevalence or notification of TB case between the national figure and the key population should consider the mixed TB case finding—of active and passive—in the general population and the enhanced active TB case finding in this study.

Conclusions

The enhanced community-based TB/HIV activity detected more HIV and TB cases among vulnerable and key populations in hotspot settings as compared to the general population. The yield of TB among HCWs and HIV prevalence among FSWs and IMWs were significant. Therefore, mapping hotspot settings and prioritizing key and vulnerable populations at high risk for TB and HIV are essential to slow the transmission of both diseases. This suggests that ending the TB epidemic and also of HIV in Ethiopia will not be successful without community-based collaboration of TB and HIV programs among the disproportionately affected vulnerable and key populations in hotspot settings.

Supporting information

S1 Fig. The map of Ethiopia with the major cities and study towns: The irregular line on the map of Ethiopia shows the administrative boundary between regions. The cities in red colors are bigger cities in Ethiopia and are also the capital cities of the regions; they had less than 10% TB/HIV co-infection. The area with green-yellow color spot are the study towns assigned as hotspot settings for the TB and HIV, with TB/HIV co-infection of at least 10%.
(DOCX)

S1 Table. Table showing the sociodemographic details of each key population. Age is categorized based on the median of the overall population. In the marital status, divorced and widowed were merged to show a key population without a partner. The educational category was based on grading of the Ethiopian education system. Numbers in the bracket are to show the percentage.
(DOCX)

S2 Table. This table demonstrates HIV, TB/HIV, and linkage to ART services. HIV counseling and request for test was offered for 1293 key populations. Testing was offered for 1111 of them. 182 refused testing, and the other 585 HIV counselling and testing was not undertaken due to the shortage of HIV testing kits. Therefore, the respective TB screened 182 and 582 key populations were not tested for HIV due to refusal and shortage of HIV screening test kits.
(DOCX)

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Adherence to the MDR-TB intensive phase treatment protocol amongst individuals followed up at central and peripheral health care facilities in Uganda - a descriptive study

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Abstract

Background: Following initiation of MDR-TB treatment, patients have a choice to receive follow up DOT supervision at either the central initiating facility or at a peripheral facility.

Objectives: We describe the adherence patterns of MDR-TB patients undergoing DOT supervision at the two health facility categories during intensive phase of treatment.

Methods: We used a retrospective cohort of patients initiated on MDR TB treatment at Mulago National Referral Hospital between 2014 and 2016. We extracted data from the National Tuberculosis and Leprosy Program records and analysed these using STATA V14.

Results: Majority (84.01%) of the patients received their DOT supervision from the peripheral facilities. Males made up 62.1% of patients, and 91.2% had had their household contacts screened for MDR-TB. 26.5% of the patients on peripheral DOT supervision had good adherence to treatment protocol compared to 0% among patients on central initiating health facility DOT supervision. Among the patients with good adherence, 24.1% had contacts screened for MDR-TB as compared to 3.6% with poor adherence.

Conclusion: More patients preferred MDR-TB DOT supervision at peripheral facilities, which had better adherence to the treatment protocol compared to the central initiating facility. Younger people and those with household contacts screened had better adherence to the treatment protocol, highlighting areas for targeted interventional programs for MDR-TB in resource limited settings.

Keywords: MDR-TB; adherence; central initiating; peripheral health facility; DOTS; SORT IT.

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Background

Multi-Drug Resistant Tuberculosis (MDR-TB) remains a public health threat worldwide with an estimated 558,000 MDR -TB cases registered globally in 2017[1]. Poor adherence to TB treatment has been cited as a major con-tributor to the development of MDR-TB[2-5]. In addition to the spread of MDR-TB, poor adherence while on treatment can lead to poor treatment outcomes for the sick individual[6].

The major mile stone in the management of MDR-TB is sputum conversion, mostly expected to occur while still in the intensive phase of treatment[7]. Adherence to

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treatment is cited among the factors associated with sputum conversion[8]. In order to enhance adherence, WHO recommends the use of Directly Observed Therapy (DOT) in managing TB especially MDR-TB[9,10].

DOT is part of the support package offered to all TB patients who include the MDR-TB patients[11]. This package is sensitive and supportive to the patient's needs, with a treatment supporter observing intake of every dose, and paying due attention to the dosing and dosage of the right drugs[11]. DOT among MDR-TB patients is at a health facility by a health worker[10] and in the past patients have been hospitalized and managed till they achieved sputum conversion[12]. However, as a result of resource limitations, this aspect in TB management has changed over the years.

In Uganda, patients are diagnosed and initiated on MDR-TB treatment at central facilities, typically referral hospitals. These patients are then counselled and given one of two options for follow up of facility DOT supervision – either at the central initiating health facility or at a peripheral health facility; except when patients are very sick and need to be hospitalized till improvement when the two options are then presented to them. Despite the option chosen, the patients are expected to return to the central initiating facility monthly for a routine clinical check-up, evaluation of on-going care, and assessment for treatment side effects.

This strategy is not used in Uganda alone; other countries such as South Africa, Kenya, Peru and regions like Tomsk in Russia, among others[13-16], are using a similar system in an effort to address resource limitations at the central initiating facilities while enabling patients to receive treatment from a convenient location[17].

DOT was designed to address poor drug adherence; however, several others factors play a role in poor adherence to MDR-TB treatment. For example, long duration of treatment, coupled with drug toxicities, and unfavorable dosage formulations have been cited[13]. Poor adherence among MDR-TB patients increases the risk of disease transmission in the community as well as having a poor prognosis in the affected patient[18].

While acknowledging that all factors that lead to poor adherence need to be addressed, the authors of this paper find that there is a need to evaluate the impact that choice of facility for DOT follow-up has on adherence to MDR-TB treatment, a factor on which there is a paucity of information. Previous comparison studies showed better treatment outcomes among individuals receiving treatment at peripheral rather than central health facilities, and poorer adherence in patients receiving DOT follow-up at central facilities as compared to peripheral facilities[13-16].

We therefore aimed to describe the adherence patterns of MDR-TB patients undergoing DOT supervision following initiation at Mulago National Referral Hospital in central Uganda in 2014-2016. Furthermore, we aimed to describe characteristics associated with the adherence patterns seen at both the central initiating facility and the peripheral facilities.

Methods

This was a retrospective cohort study among MDR TB patients initiated on treatment between 1st January 2014 and 31st December 2016 at Mulago National Referral Hospital (MNRH). MNRH serves as a specialist treatment and diagnostic centre for MDR TB with a 39-bed in-patient capacity. There were 1,384 MDR-TB patients registered by NTLP country wide with 494 at the hospital between January 2014 and December 2016.

We included all patients diagnosed with pulmonary MDR-TB and initiated on treatment at MNRH between 1st January 2014 and 31st December 2016. We excluded those patients that were below the age of 15 because of the difficulties in detecting bacteria in their sputum even when actually present.

Upon confirmation of MDR-TB, patients are counselled and given the option of either receiving treatment from the central initiating facility (MNRH) or a peripheral facility (health centres that patients might feel are conveniently located near them). Although they would receive their daily treatment at these facilities, they would be expected to report back to the central facility at the end of every month, during which time, they would undergo clinical evaluation, including a check for sputum conversion.

Data collection

We extracted data from the electronic MDR-TB register which is maintained by the National Tuberculosis and Leprosy Program (NTLP). We extracted data on the following: date of initiation of MDR-TB treatment, site of DOT supervision, submitted sputum samples collected on a monthly basis, age, sex, baseline smears, HIV sero-status, di- agnostic category, treatment regimen one is started on, and type of patient (retreatment or new patient).

The availability of results from the monthly submitted sputum samples during the intensive phase of treatment was used as a proxy for adherence to the treatment protocol during the intensive phase of treatment.

Adherence is defined as one having submitted ALL six sputum samples at the monthly visits during the intensive phase of treatment among ambulatory patients. All patients included in this study were ambulatory and all of them were counselled and offered a choice of follow up at either the central initiating facility or peripheral health facility, with the instruction to return every month to the central initiating facility to submit sputum samples.

Data management

The extracted data was checked for accuracy and was later double-entered into Epi Data.

Data analysis

Categorical variables were summarised using proportions and percentages. The continuous variables were summarised using means and standard deviations or medians and interquartile ranges depending on their distribution. To determine the statistical significance of the observed differences, a p-value of 0.05 or less was used. Pearson's Chi square ($\chi 2$) test for two independent proportions was used to test for significance.

Power of 98% was calculated for Pearson $\chi 2$ test at $P<0.05$ when we took sample size of 268 at peripheral health facilities and 51 at central initiating facility and effect size of 30%.

Ethical considerations

Approval to conduct the study was obtained from Makerere University, School of Medicine Review Ethics Committee (SOMREC).

Results

Of 319 MDR-TB patients initiated on treatment at Mulago National Referral Hospital between 1st January and 31st December 2016, 268 opted for a DOT supervision programme at a peripheral health facility. The patients were evenly distributed in the different categories of age used in the study. Majority of them were male (62.5%) and had standard treatment for MDR-TB (90.5%). 54.1% of the study participants were HIV positive and 91.8% had had their household contacts screened for TB (table 1).

Table 1: Baseline characteristics of the study population

	Peripheral-DOTs/ n (%)	Central-DOTs/ n (%)	Total/ n (%)
AGE			
15-25	93 (91.20)	9 (8.80)	102 (31.9)
26-35	85 (77.30)	25 (22.70)	110 (34.6)
>=36	90 (84.10)	17 (15.90)	107 (33.5)
Total	268 (84.01)	51 (15.99)	319 (100)
SEX			
Female	103 (85.10)	18 (14.90)	121 (37.9)
Male	165 (83.30)	33 (16.70)	198 (62.1)
TYPE OF PATIENT			
New	134 (82.70)	28 (17.30)	162(50.8)
Retreatment	134 (85.40)	23 (14.60)	157 (49.2)
CONTACTS SCREENED?			
No	7 (25.00)	21 (75.00)	28 (8.8)
Yes	261 (89.70)	30 (10.30)	291 (91.2)
REGIMEN TYPE			
Empirical	7 (100.00)	0 (0.00)	7 (2.2)
Standard	240 (83.60)	47 (16.40)	287 (90.5)
Individualized	21 (91.30)	2 (8.70)	23 (7.3)
DIAGNOSTIC CATEGORY			
INH Mono resistant	3 (60.00)	2 (40.00)	5 (1.6)
MDR Confirmed	153 (91.60)	14 (8.40)	167 (52.3)
Pan Sensitive	7 (70.00)	3 (30.00)	10 (3.1)
RIF-Mono resistant	105 (76.64)	32 (23.36)	137 (43.0)
HIV STATUS			
Positive	133 (77.30)	39 (22.70)	172 (54.1)
Negative	135 (92.50)	11 (7.50)	146 (45.9)

Adherence to the intensive phase of the MDR-TB treatment protocol

There was poor adherence to the intensive phase of the MDR-TB treatment protocol with only 26.5% of the individuals at the peripheral sites adhering and 0% of those at the central initiating facility.

Within the overall poor adherence, individuals aged 15 to 25 years reported the highest adherence to the protocol (30.4% at peripheral facilities). Furthermore, only 3.6% of individuals who had not had their household contacts screened had good adherence in comparison to 24.1% of the individuals who had had their household contacts screened (See table 2).

Table 2: Factors affecting adherence to intensive phase of MDR-TB treatment

	Adherence to policy during intensive phase		
	Good adherence/ (%) **n**	**Poor adherence/ n (%)**	**p.value**
Facility DOT supervision			
Peripheral-DOTs	71 (26.50)	197 (73.50)	
Central-DOTs	0 (0.00)	51 (100.00)	<0.001*
RECODE of AGE (AGE)			
15-25	31 (30.40)	71 (69.60)	
26-35	18 (16.40)	92 (83.60)	
>=36	22 (20.60)	85 (79.40)	0.043*
SEX			
Female	28 (23.10)	93 (76.90)	
Male	43 (21.70)	155 (78.30)	0.767
TYPE OF PATIENT			
New	39 (24.10)	123 (75.90)	
Retreatment	32 (20.40)	125 (79.60)	0.428
CONTACTS SCREENED?			
No	1 (3.60)	27 (96.40)	
Yes	70 (24.10)	221 (75.90)	0.013*
REGIMEN TYPE			
Empirical	2 (28.60)	5 (71.40)	
Standard	67 (23.30)	220 (76.70)	
Individualized	2 (8.70)	21 (91.30)	0.248
HIV STATUS			
Positive	34 (19.80)	138 (80.20)	
Negative	37 (25.30)	109 (74.70)	0.234

**Variable is significant using a p-value of ≤ 0.05 for statistical significance*

Smear results recorded at the monthly visits during the intensive phase of MDR-TB treatment

Fig 1 shows the percentages of patients who submitted their monthly sputum samples after the baseline visit.

The trend for the patients who received DOT supervision at the central initiating facilities shows over 70% of patients did not submit any monthly sputum samples after initiation on treatment. The remaining approximately 30% of patients submitted at least one sputum sample, with none submitting more than 4, that is, 5 or 6 monthly sputum samples after initiating treatment.

Among the patients who received DOT supervision at the peripheral facilities, 26.1% of them submitted all the 6 monthly sputum samples after initiation of treatment during the intensive phase, 20.9% and 22.4% submitted 4 and 5 samples respectively while 4.9% did not submit any samples.

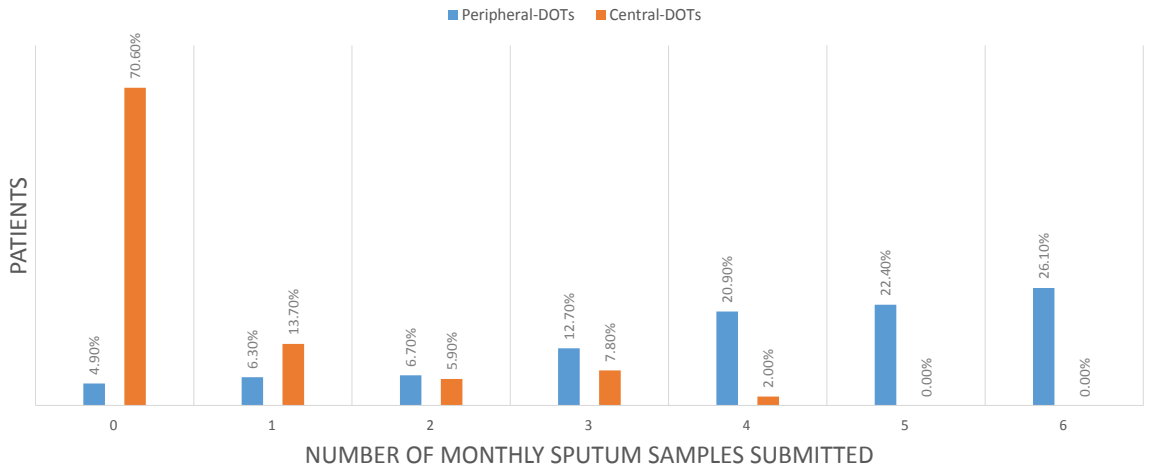

Fig 1: A bar graph of recorded monthly smear results at the peripheral and central DOT supervising facilities

Discussion

In this study we aimed to describe the adherence patterns of MDR-TB patients undergoing DOT supervision in central or peripheral health facilities, following treatment initiation at a central one, in Uganda, in 2014-2016. Furthermore, we aimed to describe characteristics associated with the adherence patterns seen at both types of facilities. We found that of 319 MDR-TB patients initiated on treatment at Mulago National Referral Hospital between 1st January and 31st December 2016, 268 (84.01%) opted for a DOT supervision programme at a peripheral health facility. We also found that although adherence to the treatment protocol was generally poor, it was significantly better in those aged 15-25, those who had their household contacts screened and those using a peripheral facility for DOT supervision.

Furthermore, this study found that majority (84.01%) of patients preferred DOT supervision at peripheral health facilities. This might be explained by the fact that these peripheral facilities that are allowed to offer DOT supervision being spread out amongst different regions are closer to the patients than the central facility would be. This makes their access more convenient in comparison, unless the patient lives within reasonable distance of the central facility. This finding is different from what was observed in South Africa where less than half (47.5%) of patients chose to receive treatment from the peripheral health facilities13. This observed difference might be due to a difference in availability of resources at the different health facilities. For example, Mulago National Referral Hospital has a bed capacity of only 39 at the MDR-TB section of the TB clinic, which automatically limits the number of MDR-TB patients that can be hospitalised and be fully monitored at the central health facility. Coupling the two reasons could explain the observed higher percentages of individuals choosing to receive DOT supervision from the peripheral health facilities in Uganda.

The overall adherence to the intensive phase of the treatment protocol was poor. Only 26.5% of individuals who had DOT supervision at the peripheral health facilities had good adherence to the protocol while at the central facility, this proportion was actually 0%, representing an overall adherence percentage of 24.76%. The overall adherence to the protocol could have been affected by the long duration of MDR-TB treatment, the side effects of the drugs and the route of administration of some MDR-TB drugs[13]. However, the difference between the central and peripheral health facilities could be explained by the long distances to the central facility and possibly higher and more intimate support given to patients who receive DOT supervision at the peripheral sites. This group had more house hold members having been screened and thus more people were aware of their illness and the need for daily dosing and submission of sputum samples on a monthly basis. These possibly supported them more to adhere to the treatment protocol as compared to those who had DOT supervision at the central health facility. The study from South Africa refrred to earlier found a much higher overall adherence of 78.28% which may be because the study assessed adherence to treatment defining it as not missing treatment for more than two months[13]. This is different from the outcome used in our study of adherence to treatment protocol which defined adherence as

submission and having results of the monthly sputum samples throughout the intensive phase of treatment.

Of the 291 patients who had had their household members screened for TB, 89.7% were from patients who were having DOT supervision at the peripheral health facilities. This may be because of a more intimate relationship with staff at the peripheral facility, as they most likely would be living in the same area. It may also be because of proximity to the health facility whereby it is easier to invite household folks to it than if they had to travel to the central facility in the city. This results in more aware and counselled family members, which in turn leads to a higher degree of support that is given to individuals receiving DOT supervision from the peripheral facilities from these family and friends. An individual having to go to the health facility for dosing daily or regularly would most likely raise a lot of questions amongst his peers and household members, which would be uncomfortable and even eventually lead to defaulting on the visits, if they had not been involved and/or did not have a good understanding of the process. Once the household members are in the know, they may be more supportive and encouraging for patients to adhere to treatment, and thus the observed higher percentages among individuals choosing peripheral facilities for their follow-up treatment.

Individuals aged 15-25 years of age had better adherence to the protocol (30.4%) as compared to 16.4% and 20.6% from 26-35 and above 35 years age groups. In Uganda, individuals below 25 years typically are still under care of their parents or guardians. The adults are in control of the health of this age group, and determine their health seeking behaviour. Individuals in this age group go to hospital for screening for TB in the company of an adult, and upon confirmation of TB, the parent or guardian is counselled into encouraging the patient to adhere to the treatment protocol. As a result of this

continuous support from the adult, patients 15 to 25 years might have better adherence as compared to other age groups where there is no external influence on adherence. However, we note that our results are different from those observed in Southern Ethiopia where age had no bearing on adherence[19]. This difference might be a result of the study in Ethiopia being among TB drug sensitive patients with shorter duration of treatment. In addition, there might be a differing social structure where individuals leave their parents' or guardians' care much earlier in Ethiopia as compared to Uganda.

The percentages of individuals who submitted monthly sputum samples during the intensive phase of treatment increased with time among individuals receiving DOT supervision from the peripheral facilities, while reducing with time among those at the central initiating facility. 4.9% of the individuals receiving DOT supervision from the peripheral facilities did not return any sputum samples after initiating on treatment, while this proportion was 70.6% among those at the central initiating facility. This high attrition rate at the central initiating facility could be attributed to the long distances the patients might have needed to travel to the central facility, the failure to build personal relationships with health workers at the central facility and less family and community involvement and support for patients to adhere to the treatment protocol. Taking DOT supervision to the peripheral facilities is more convenient to the patients, and the patients can build bonds with the health workers at the facilities in addition to the community and family support which accounted for the 26.1%, 22.4% and 20.9% of the patients submitting 6, 5 and 4 sputum samples respectively during the intensive phase of treatment in our study.

Strengths of this study

This is the first study that we know of looking at adherence to treatment protocols at the different facilities offering DOTS for MDR-TB in Uganda. In a bid to find lasting solutions to a problem like Drug Resistant TB, the findings are a critical step in improving the context of the disease and its solutions in the country.

The study capitalised on routine NTLP records which reflect the actual settings in the program. Being retrospective, they also provide information independent of potential behavioural modifications by patients which is likely to arise if they were recruited for a prospective cohort study. In addition, this study also uses routine data to identify a local problem which would call for a tailored solution, away from 'one-size-fits-all' solutions that are not contextualised.

Limitations of the study

The study used routine data that is collected at the MDR-TB DOT supervision health facilities. This data is often prone to being incomplete and may thus affect the study results.

We made an assumption that the records of results equates directly to the fact that a sputum sample was submitted for examination. This might be an underestimation if there are persons who submitted a sample but for some reason did not get the sample examined or the results recorded.

Implications for policy

In this study, it is clear that peripheral health facilities are doing better with MDR-TB patients adhering to the treatment protocol during the intensive stage of treatment. This raises the confidence in using these for follow up of patients for DOTS and similar interventions. It should also be motivation for equipping these centres more, to enable them manage more numbers of these kinds of patients.

The study showed a generally low adherence overall, but especially in the central initiating facility. This calls for health managers to devise means to improve adherence overall but also target the central facilities and the particular groups like older individuals. It also calls for interventions that increase screening in household contacts. This would not only help identify those affected but also increase awareness that seems to be important for adherence of those already diagnosed.

Implications for research

It is not completely clear why there is poor adherence at the central facility to a very high level. This might not be entirely explained by distance from the facility. Therefore, there is need to carry out a better designed study probing the factors driving adherence at both central and peripheral facilities. This would provide a better understanding of the factors and other issues that can be addressed by particular interventions.

Conclusion

In this study we found that more patients prefer to receive their follow up MDR-TB DOT supervision from peripheral facilities, and in addition, show a better adherence to the treatment protocol compared to those at the central initiating facility. Younger people and those with household contacts screened also had better adherence to the treatment protocols. This highlights areas for targeted interventional programs for Drug Resistant TB in resource-limited settings. Furthermore, it highlights areas for further research, to understand why central

facilities might not be performing as expected. In general, a very low adherence rate was noted all round and therefore there is still a need to tackle non-adherence to treatment protocols more aggressively, otherwise this represents a potential public health risk to the general population.

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Conflict of interest

None declared.

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Patient and health system delay among TB patients in Ethiopia: Nationwide mixed method cross-sectional study

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Abstract

Background: Effective tuberculosis (TB) control is the end result of improved health seeking by the community and timely provision of quality TB services by the health system. Rapid expansion of health services to the peripheries has improved access to the community. However, high cost of seeking care, stigma related TB, low index of suspicion by health care workers and lack of patient centered care in health facilities contribute to delays in access to timely care that result in delay in seeking care and hence increase TB transmission, morbidity and mortality. We aimed to measure patient and health system delay among TB patients in Ethiopia.

Methods: This is mixed method cross-sectional study conducted in seven regions and two city administrations. We used multistage cluster sampling to randomly select 40 health centers and interviewed 21 TB patients per health center. We also conducted qualitative interviews to understand the reasons for delay.

Results: Of the total 844 TB patients enrolled, 57.8% were men. The mean (SD) age was 34 (SD ± 13.8) years. 46.9% of the TB patients were the heads of household, 51.4% were married, 24.1% were farmers and 34.7% were illiterate. The median (IQR) patient, diagnostic and treatment initiation delays were 21 (10–45), 4 (2–10) and 2 (1–3) days respectively. The median (IQR) of total delay was 33 (19–67) days; 72.3% (595) of the patients started treatment after 21 days of the onset of the first symptom. Poverty, cost of seeking care, protracted diagnostic and treatment initiation, inadequate community based TB care and lack of awareness were associated with delay. Community health workers reported that lack of awareness and the expectation that symptoms would resolve by themselves were the main reasons for delay.

Conclusion: TB patients' delay in seeking care remains a challenge due to limited community interventions, cost of seeking care, prolonged diagnostics and treatment initiation. Therefore, targeted community awareness creation, cost reduction strategies and improving diagnostic capacity are vital to reduce delay in seeking TB care in Ethiopia.

Keywords: Tuberculosis, Patient delay, Health system delay, Ethiopia

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Background

Tuberculosis (TB) has infected billions and has claimed the lives of millions. Despite the advances in knowledge about the importance of early case finding and treatment, millions of TB cases are being missed by the health system which has led to sustained transmission and increased the pool population at risk of acquiring and developing TB [1, 2]. It is estimated that one active TB case can infect about 10–15 healthy individuals leaving them with 5–10% life time risk of developing active TB [3]. Therefore, programme interventions that ensure early identification of index TB cases and support initiation of prompt treatment with the right dose, quality and duration are required to curb the epidemic.

Effectiveness of the National TB Programme (NTP) depends on its capacity to make early case finding and provision of standard treatment. The diagnostic and treatment services should be decentralized and be accessible to community to seek care. Health seeking behavior is the result of a complex interplay between community awareness, access and availability of the services, cost related to seeking care and sociocultural factors including stigma and beliefs. Factors that affect health seeking behavior lead to delay in seeking care and hence increase TB transmission, mortality and remain a challenge to TB programme performance [4, 5]. Measuring the delay in seeking and getting care is a proxy indicator for good programme performance in reaching and serving the community.

Delay is measured from the time of developing the first symptoms to the time of initiating treatment and is categorized by patient and health facility delay. Patient delay is the time between the onset of the first TB symptom to the time of seeking care while health facility delay is the duration between the first contact with health facility to the time of initiating treatment. Total delay is the sum of TB patient and health facility delays. Treatment delay is measured by the duration from the time of diagnosis to when TB patient started treatment.

Studies reported that delays in seeking care are associated with low awareness about TB, rural residence, high stigma [6], gender [7–10], number and type of facilities visited [11–13], cost of seeking TB care [14], poverty, comorbidity with HIV [15], socioeconomic status [16] and cultural barriers [17]. Total patient delay was more than ten weeks in Sub Saharan Africa [12, 18–20], about seven weeks in Asia - highest in Pakistan and Vietnam nearly doubled [21–24] and about six weeks in Latin America [25]. Though the duration of delay is shorter, it was also reported from low incident states, minority groups and natives due to low index of suspicion about TB [26, 27]. Unfortunately, after patients sought care and arrived at health facilities, there were also further diagnostic and treatment delays [28].

Studies have shown that patient delay contributed more to total delay than did health system delays. However, health system delay has been reported to be longer in smear negative, extra pulmonary TB (EPTB) and among those who visited non TB service providing facilities [29–31]. This could be due to the severity of symptoms TB patients present with that resulted in repeated visits to health facilities, led to protracted diagnostic procedures, and further delayed due to unavailability of diagnostic facilities required to confirm TB diagnosis [32–34].

Ethiopia has been implementing TB prevention and control for about a quarter century. It is successfully treating more than 90 % of enrolled drug sensitive cases [2].

With rapid expansion and decentralization of health services to the community using health extension workers (HEWs), access to TB care has increased and community awareness is expected to also increase.

Studies from Ethiopia reported delays to be associated with educational status, poverty, awareness about TB and accessibility of TB services [35, 36] with higher proportion of health system delay from northern Ethiopia [37]. However, most studies were limited to specific population groups and quantitative designs. In this study, we aimed to measure nationwide delay and the associated factors using a mixed method study using qualitative and quantitative data to understand the context and generate an evidence base to advise policy and decision making at the National TB Programme of Ethiopia.

Methods

Study setting and population

Ethiopia is a high TB burden country with a population of more than 100 million. 85% of the population lives in rural areas. Ethiopia is administratively divided into nine regional states and two city administrations. The National TB Programme started DOTS in 1995. Currently 256 hospitals and 3390 health centers provide diagnostic and/or treatment TB services. More than 15,000 health posts provide community based TB services. HEWs are female village residents who completed at least grade ten who received one-year training to provide primary health care to a community of 5000 people. They provide TB services from the health posts under disease prevention and health promotion which includes awareness creation, identifying presumptive TB cases and referral, providing DOT, and retrieving absentees and defaulters [38].

Study design and sampling

This is a mixed method study conducted from October to November, 2017 in the nine Challenge TB supported regions of Ethiopia that covers 92% of the national

population. Challenge TB project is USAID's global flagship TB control support mechanism designed for 2014 to 2019.

We used a multistage cluster sampling technique to randomly select the zones, districts and kebeles for the study. From six regions and two city administrations, we randomly selected 32 districts and eight sub cities/districts respectively. A health center was randomly selected from each district or sub city with a total of 40 health centers included in the study. From each randomly selected health center, 21 TB patients were consecutively enrolled from each health center. We also conducted qualitative interviews to understand the reasons for delay. The details of the methods are described in a published paper on Knowledge Attitude and Practice about TB in Ethiopia in 2017 [39].

Operational definition

Patient delay was defined as the time between the first symptoms to date of seeking health care and operationally defined as more than 2 weeks. Diagnostic delay is the interval between first visit to health facilities for TB diagnosis to date of diagnosis for TB. Treatment delay was considered if TB treatment was initiated 1 week or longer after patient was diagnosed with TB. Facility delay is the time between the first visit to treatment initiation. Total delay is the sum of TB patient and facility delay, that is, starting treatment 3 weeks after the onset of symptoms.

Quantitative studies

Single population proportion formula was used to estimate the sample size using EDHS 2011 KAP report [7], assuming that 50% of the study participants will have delay of at least 2 weeks to seek TB care. We used design effect of 2 and added 10% to compensate for non-response rate. 844 TB patients were enrolled from 40 health centers.

Qualitative studies

We conducted 18 Focus Group Discussions (FGD). Two FGDs, one for women and one for men, were conducted in the selected kebeles in the respective regions. The kebele administrators assisted in the identification of participants of the FGDs from the general population.

Data collection tools and methods

The questionnaires for the study were adopted from the WHO guide for KAP [14]. The questionnaires were initially prepared in English and translated into regional languages and translated back to ensure the quality. FGDs were developed for this study and were conducted in local languages using pretested, semi-structured in-depth interviews (IDI) and open ended topic guides for FGDs. Two data collectors were deployed per site to conduct FGDs and IDIs. 18 FGD sessions and 76 IDIs were conducted and audio recorded. Tablets were used for data collection using a web-based data tool using CSPro software.

Data management and analysis

Quantitative data

Data was extracted from the web-based system and exported to SPSS version 25 for analysis. Mean, median and interquartile range was used to describe the data. Binary logistic and multivariate logistic regression, for independent variables with $p < 0.25$, were used, which includes marital status, wealth index, gender, travel time to health institution, setting and region to construct multivariate model. Addition of other variables like occupation and education compromised model fitness.

Qualitative data

Was imported to Open Code software and analyzed using thematic content analysis technique. Direct verbatim and results from the coding and categorization were used to develop the narrative, triangulated and synthesized with the quantitative results [39, 40].

Data quality assurance

We selected and trained experienced data collectors. Pretested questionnaires were used for data collection. Supervisors were assigned and conducted random data and household checks, and reviewed the questionnaires. The CSPro expert regularly checked for completeness and errors.

Ethical considerations

Ethical clearance was obtained from the Ministry of Science and Technology. We obtained support letters from the Federal Ministry of Health to the regions and research areas. Ethics review committee approved informed verbal consent to be obtained from the study participants as most of the study participants are from rural and cannot read and write. We obtained informed consent from the study participants.

Results

Socio-demographic and economic characteristics of TB patients

A total 844 TB patients were interviewed. The mean (SD) of age was 34 (13.8) years. Of the total study participants, 57.8% were men, 46.9% were the heads of the household, 51.4% were married, 34.7% were illiterate and 24.1% were farmers (Table 1).

The mean family size and number of households per sleeping room was 4.5 and 3.6 respectively. Of the study

Table 1 Socio-demographic and economic characteristics of TB patients

Variables (***N*** = 844)	Categories	#	%
Gender	Male	488	57.8
	Female	356	42.2
Age in years[a]	18–24	251	29.7
	25–34	246	29.1
	35–44	164	19.4
	45–54	93	11.0
	55–64	52	6.2
	> 60	38	4.5
Relationship to the head of the HH	Head	396	46.9
	Spouse	189	22.4
	Son/Daughter	222	26.3
	Other relative	33	3.9
	Non-relative	4	0.5
Religion	Orthodox Christian	472	55.9
	Muslim	175	20.7
	Protestant	186	22.0
	Catholic	7	0.8
	Other	4	0.5
Marital Status	Married	434	51.4
	Never married/never lived together	283	33.5
	Divorced/ Separated	66	7.8
	Widowed	57	6.8
	Living together	4	0.5
Educational Status	Not able to read and write	292	34.7
	Read and write only	40	4.7
	Primary	263	31.2
	Secondary	163	19.3
	Above secondary	85	10.1
Occupation	Employed	102	12.1
	House wife	114	13.5
	Farmer	203	24.1
	Daily laborer	103	12.2
	Trader	85	10.1
	Student	109	12.9
	No job/dependent	102	12.1
	House maid	18	2.1
	Other	8	0.9
Wealth Quintile	Lowest	168	19.9
	Second	169	20.0
	Third	175	20.7
	Fourth	163	19.3
	Highest	169	20.0

[a]Range: 18–85 years; Mean (SD): 34 (13.8) years

participants, 37.4% had at least one child under 5 years old in their household.

Patient delay

The median (IQR) patient delay was 21 days (10–45) with signs and symptoms of TB before they first sought health care. 69.9% (575) of the patients sought health care after 2 weeks of onset of symptoms.

Health system delay: diagnostic and treatment delay

The median (IQR) number of days from the first day of seeking care to diagnosis (diagnostic delay) was 4 (2–10) days. The median (IQR) value of the number of days from diagnosis to treatment initiation was within 2 (1–3) of diagnosis. The median (IQR) for the total days spent between seeking health care and treatment initiation was 6 (3–15) days. However, 44.1% (363) of the patients started treatment after 7 days of first visit. There was significant regional variation of facility delay ($P < 0.001$) as shown in Table 2.

Total delay

The median (IQR) between first onset of symptoms was 33 (range 19–67) days for TB patients and 72.3% (595) of the TB patients initiated TB treatment after 21 days of the onset of the first symptom.

Factors associated with patient delay

Compared to the poorest, 42% TB patients in the second and 61% TB patients in the fifth wealth quintiles had low odds of being delayed in seeking care after the onset of symptoms. TB patients from rural areas had 40% low odds of being delayed. There was regional variation of delay in seeking care ($p < 0.05$) as shown in Table 2. The median (IQR) travel time from the patient's home and the health facility was 20 (15–30) minutes (range: 1–120).

The main reasons given for delay in seeking health care were lack of awareness of the severity of the symptoms in 84.4%, seeking care from other providers (drug vendors, traditional or spiritual healers) in 22.8% (40.4% of these visited private drug vendors), inadequate community referral (only 12.5% of the TB patients were initially seen and referred by HEWs) and referral for treatment initiation in 69.7% of the cases. Most family members (61.5%) and patients (59.2%) indicated that they could reduce delay of seeking care. 25.6% indicate that delay could be reduced by the health system (Table 3).

Factors associated with delays in seeking care and initiating treatment: qualitative findings

Lack of community awareness

Community awareness about TB is increasing within the communities of Ethiopia due to the community-based

Table 2 Factors associated with patient delay among TB patients in Ethiopia

Variables		Delay # (%)	No delay # (%)	COR (95% CI)	AOR(95%CI)
Gender	Male	340 (70.8)	140 (29.2)	1.12 (0.83–1.51)	1.19 (0.85–1.65)
	Female	235 (68.5)	108 (31.5)	1	1
Marital status	Married	299 (70.0)	128 (30.0)	1	1
	Divorced	44 (68.8)	20 (31.3)	0.94 (0.53–1.66)	1.05 (0.57–1.91)
	Widowed	44 (78.6)	12 (21.4)	1.57 (0.8–3.07)	1.73 (0.85–3.51)
	Not married	188 (68.1)	88 (31.9)	0.92 (0.66–1.27)	0.97 (0.68–1.38)
Wealth	Lowest	119 (75.3)	39 (24.7)	1	1
	Second	109 (66.5)	55 (33.5)	0.65 (0.4–1.06)	0.58 (0.34–0.98)[a]
	Third	129 (74.6)	44 (25.4)	0.96 (0.58–1.58)	0.82 (0.47–1.42)
	Fourth	120 (73.6)	43 (26.4)	0.92 (0.55–1.51)	0.7 (0.39–1.27)
	Highest	98 (59.4)	67 (40.6)	0.48 (0.3–0.77)	0.39 (0.21–0.71)[a]
Setting	Rural	236 (69.4)	104 (30.6)	0.96 (0.71–1.3)	0.6 (0.4–0.89)[a]
	Urban	339 (70.2)	144 (29.8)	1	1
Travel time to health facility	<=20 min	297 (71.1)	121 (28.9)	1	1
	> 20 min	278 (68.6)	127 (31.4)	0.89 (0.66–1.2)	0.84 (0.6–1.17)
Region	Oromia	103 (61.3)	65 (38.7)	1	1
	Amhara	124 (72.9)	46 (27.1)	1.7 (1.08–2.69)	1.62 (1.003–2.63)[a]
	SNNP	139 (85.3)	24 (14.7)	3.66 (2.15–6.23)	3.78 (2.19–6.52)[a]
	Tigray	57 (66.3)	29 (33.7)	1.24 (0.72–2.14)	1.2 (0.67–2.11)
	Benshangul Gumuz	34 (81.0)	8 (19.0)	2.68 (1.2–6.15)	2.4 (1.03–5.6)[a]
	Gambella	13 (46.4)	15 (53.6)	0.55 (0.25–1.22)	0.37 (0.16–0.88)[a]
	Addis Ababa	46 (56.1)	36 (43.9)	0.81 (0.47–1.38)	0.79 (0.43–1.46)
	Dire Dawa	28 (66.7)	14 (33.3)	1.26 (0.62–2.57)	1.17 (0.54–2.53)
	Harari	31 (73.8)	11 (26.2)	1.78 (0.84–3.78)	2.13 (0.95–4.75)

[a]Statistically significant; Delay: seeking care after 2 weeks since the onset of symptoms

initiative of using women community HEWs that provide health education in the communities. However, the level of awareness did not reach an adequate level for the community to seek care as early as possible.

"… The awareness of the community on TB has not reached the expected level" reflecting the inadequacy of their knowledge despite the efforts …." (SNNPR/ woreda TB focal/FGD).

Most participants reported delayed visit to health institutions after the onset of symptoms. The main reasons were lack of awareness about TB, considering cough to be due to common cold rather than tuberculosis, postponing seeking care until they were seriously ill, fear of screening for HIV, starting self-treatment of cough, and due to household and social responsibilities.

"… on average, TB patients seek treatment after two to three weeks of coughing …." (Tigray/ HEW).

"The problem here is that TB patients delay to go to the health facility simply because they think the cough is due to common cold." (HEW/BG).

Diagnostic capacity of public health facilities

TB patients usually seek care from public health facilities. However, when they are not diagnosed they tend to visit alternative services. A few participants reported that TB patients visit holy water, traditional healers, religious sites or procure drugs from illegal drug sellers.

"TB patients first seek care from health centers. If there is no improvement with medical care given at the health center, they seek care from holy water at church or well-known monastery." (HEW/Amhara).

"…. There are also some health professionals who sell drugs of the health center to another individual who sell anti TB drugs behind closed doors. For example, there is one individual in.... kebele who sells drugs

Table 3 Reasons why TB patients delaying seeking health care in Ethiopia

Variables		#	%
Reasons for delay in seeking health care	Not aware of the severity of the symptoms	320	84.4
	Fear of rejection/losing job	25	6.6
	Fear that treatment is expensive	32	8.4
	Lack of time	29	7.7
	Difficult access to health center/transportation issue	19	5.5
	Not having a previous satisfactory experience with the health system	20	5.3
	Feeling as if not delayed in seeking treatment for the symptoms	24	6.3
	Others	7	1.8
Seek advice from private facilities and traditional services		188	22.8
	Private drug vendor	76	40.4
	Religious leader	65	34.6
	Traditional healer	39	20.7
	Others	8	4.3
Initially seen by HEW and referred		103	12.5
Health facility of the first diagnosis	In the same health facility contacted first	249	30.3
	Referred from government hospital	422	51.3
	Referred from government health center	50	6.1
	Referred from private health facility	100	12.2
	Referred from NGO health facility	2	0.2
Who do you think can better reduce the delay in the diagnosis and treatment	The patient	487	59.2
	The family	506	61.5
	The health system	211	25.6
	The government	14	1.7
	Others	7	0.9

behind the closed doors. TB patients in this kebele buy anti TB drugs from this illegal person …" (Amhara/ FGD).

Cost of seeking care

A few patients reported that shortage of money or cost of seeking care prohibited them from seeking care early from public health facilities.

"… due to shortage of money some people go to church to treat TB with holy water. They also visit traditional healers." (FGD/BG).

Seeking care in private facilities

TB services were decentralized to private sectors late, which has now improved. This has led patients to seek care.

"As it is known previously, TB treatment service was not given by private health institutions. But now, in 2010 there are 10 private health institutions which provide the service after checking them whether they fulfil the criteria to give the service." (TB-HIV office/ Gambella).

Limited access or inadequacy of community TB care

Most participants reported that TB patients have difficulty visiting a health center for daily doses as most health posts do not treat TB. This is worsened by the lack of transportation.

"...The other point is, all HEWs are not providing DOT service and only 60-70% of the health centers are providing the service which put burden on the local community. Since people are coming from long distances, they default the treatments and that in turn creates a lot of MDR-TB cases in the zone …." (SNNPR/Zone TB focal).

The number of HEWs in each health post was reported to be inadequate, considering the volume of work they are expected to do.

"Health extension workers are exhausted with their work because of having multiple workloads in addition to TB package. Due to this problem, the referral linkage from health extension workers to health centers is weak." (Woreda/TB-HIV officer).

Inadequate commitment of HEWs to provide TB service to their community and failure to report their performance contributed to delay seeking care and treatment.

"The most challenging thing is the health extension workers are not working hard in the community. In some kebeles, they often forget to report on the work they have done." (Woreda TB focal/Gambella).

Poverty

Most participants reported that TB patients are poor and do not benefit from TB services due to the onerous visits and related costs besides the complex socioeconomic problems.

"… poor people get less nutritional food which exposes them to develop TB; … poor people are discriminated from social life; …. poor people have lack of knowledge; …. poor people delay visiting health facilities when they have symptoms of TB; …. poor people live in crowded houses, etc." (Amhara region/HC).

Delay in getting diagnosis

Most informants expressed that it takes longer to initiate TB treatment more in cases of EPTB and MDR-TB.

"… I didn't receive care early. It was not because of my fault rather it was because the health professionals failed to diagnose the disease. I don't believe there is good doctor in Ethiopia. I tried my very best by going to private and government health facilities, but it took them very long time to confirm that I have TB …" (Dire Dawa/TB patient).

Shortage of health professionals including laboratory professionals was one of the reasons for delaying diagnosis.

"Nearly twenty percent of health institutions do not have laboratory technologists." (TB/HIV officer/RHB).

"The problem related to shortage of laboratory professionals is very critical. We don't know how to solve it." (Zone/TB focal/SNNPR).

Delay in initiating treatment

Delay in diagnosis contributed to delay in initiating treatment for diagnosed TB cases. This is especially true for EPTB and MDR-TB.

"I didn't receive care early. It was not because of my fault rather it was because the health professionals failed to diagnose the disease. I don't believe there is good doctor in Ethiopia. I tried my very best by going to private and government health facilities but it took them very long time to confirm that I have TB." (DD/TB patient).

Discussion

Early diagnosis and timely initiation of treatment plays a key role in reducing disease transmission, disease severity and risk of death [20, 21]. We report national level delay in seeking diagnosis and initiation of treatment in Ethiopia. Patients delayed seeking care for 21 days and facility delayed diagnosis for 6 days and treatment for 6 days making total delay of 33 days. This is substantiated by qualitative results from patients and health care workers who identified lack of awareness, cost of seeking care and other socioeconomic factors to influence patient delays.

Compared to delay studies conducted in Ethiopia, we report shorter patient delay of 31 days from northern Ethiopia [41], 30 days reported from Hadiya zone in southern Ethiopia [36], 60 days in Addis Ababa [35] and more than 2 months pretreatment duration from Sidama in southern Ethiopia [42], but longer than study from southern Ethiopia that reported 4 days [43]. There is much reduction in the overall delay as a result of increased coverage of health service, better awareness, difference in the study period and changes in socioeconomic conditions. Delays are longer among elderly and patients with EPTB and smear negative TB cases which could be due to the limited diagnostic capacity to detect TB among the elderly, complex diagnostic pathways and delayed health seeking.

Compared to studies from SSA countries, patient delays are shorter in Ethiopia though higher than 2 weeks reported from Cameroon [44] and similar to 3 weeks reported from Lagos, Nigeria [18] and shorter than reports from Uganda, rural Nigeria, and other low incidence states which is in the range of 4–8 weeks [12, 19, 26]. Patients' residence, age, distance from health facilities, awareness about TB as a curable disease and fear of testing for HIV were the main reasons for delay.

Women had high odds of longer delays compared to men possibly due to higher stigma, lower priority or attention paid to them by the community, socioeconomic problems and domestic responsibilities they shoulder [8, 24]. This could be complex in settings where there is an inadequately decentralized heath system and gender norms favor men for accessing health services. Hence, gender-sensitive TB services should be identified and designed to address such variations in service delivery.

Patients from urban setting had lower odds of shorter delay compared to rural areas [43] mainly due to better awareness about TB, access to services, better education status and socioeconomic condition. However, in urban slums, urban poverty could be worse for TB patients. Contrary to other studies, we report longer delay in urban areas. This could be due to diagnostic pathways related to diagnosis of smear negative and EPTB and HIV [15, 45, 46]. In addition, 85% of the Ethiopian population lives in rural areas and this may have under represented the urban TB patients as we did not estimate the sample size to analyse urban-rural differences.

Due to low awareness about the disease, about the severity and about availability of services, patients ignore TB symptoms and remain at home or visit traditional or private pharmacies. Moreover, visiting health facilities that do not provide diagnostic services, have inadequate technical capacity, and lack diagnostic facilities like chest x-ray, contributes to the delay.

Emerging themes of the qualitative study reported by TB patients, program managers and community showed that lack of awareness, access to informal or illegal drug sellers, inadequate service provision, fear of knowing one is HIV positive, poverty and delay of service provision due to longer waiting time [8, 15, 34] led to delayed TB care.

Patients from high income countries generally have lower delays in seeking care due to the health infrastructure, improved awareness and health seeking. However, a systematic review indicated similarities [47]. This indicates the importance of reviewing case finding strategy and making pro-poor strategies in their respective contexts. Minorities and disadvantaged people in developed countries still have more delays [16].

In resource constrained settings, poverty and inadequate service decentralization complicate patient pathways. Decentralization of services with adequate technical and diagnostic capacity could facilitate early diagnosis. However, stigma, distance and related cost still remain a challenge to the patients to seek diagnosis and initiate treatment [48].

In the era of the End TB Strategy, reducing patient and household costs of seeking care is one of the key components and yet cost of seeking care is high in Ethiopia [43, 49]. Thus, patient insurance mechanisms, waiver services and possibility of reimbursing costs related to seeking TB care could be potential interventions to improve health seeking in resource-constrained settings. Moreover, decentralization of services to the community, early identification of cases and linking to care appear feasible and cost effective options. There is a community-based health insurance system which covers cost of seeking care for poor TB patients. Generally, understanding patient pathway of seeking care is important to program TB services, reduce delay and reduce cost [34, 50].

In the Ethiopian setting, engagement of the HEWs could be a cost effective model (women residing in villages who were trained and employed by the government to provide health care in the community). However, there is limited disclosure to HEWs and their engagement is low compared to the coverage of the HEWs in the country, more than 40,000 HEWs. Generally, mechanisms that reduce the distance between the community, patient and diagnostic units, bringing treatment units in the proximity of the patients at health posts or households and strengthening referral linkages are required to ensure timely diagnosis and prompt initiation of treatment.

The limitation of the study was that it did not consider subnational variations of delay and sample size in the regions was not adequate to measure why delays varied in the regions. Overall delays are likely to be longer since we did analyse the delays by type of tuberculosis. It is likely that smear-negative and extra-pulmonary TB patients would have experienced longer delays due to diagnostic challenges. Patient pathway analysis which could have helped the NTP in designing interventions to improve health seeking is beyond the scope of the study.

Conclusion

TB patients delay in seeking care remained a challenge, though there is improvement over time. The NTP therefore should increase community engagement to increase awareness about TB, design interventions that reduce cost of seeking TB diagnosis and treatment, and improve intra and interfaculty referral systems to ensure timely diagnosis and treatment initiation. Large scale patient pathway analysis is recommended to understand context-specific factors affecting timely health seeking and design targeted high impact interventions to reduce patient and health system delay in Ethiopia.

Abbreviations

DOTS: Directly Observed Treatment, Short Course; EDHS: Ethiopian Demographic Health Survey; EPTB: Extra Pulmonary Tuberculosis; FGD: Focus Group Discussion; HEWs: Health Extension Workers; HIV: Human Immunodeficiency Virus; IDI: In Depth Interview; NTP: National Tuberculosis Programme; TB: Tuberculosis; WHO: World Health organization

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Authors' contributions

DJ and PS designed the study. DGD supervised the data collection, data analysis and interpretation. DGD drafted the manuscript was reviewed in relation to data analysis and interpretation by DJ and PS. All authors reviewed and approved the submission of the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Ethics approval and consent to participate
This study was approved by the Ethiopian Science and Technology Commission, Ethics Review Board. We have also obtained a support letter from the Federal Ministry of Health and Regional State Health Bureaus to conduct the study. The study participants were recruited to the study after obtaining informed verbal consent.

Consent for publication
Not applicable.

Competing interests
Authors declare no conflict of interest.

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Modeling the likely economic cost of non-adherence to TB medicines in the Philippines

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SUMMARY

SETTING: The Philippines has a population of over 90 million people and is one of the 22 highest TB burden countries in the world.

OBJECTIVE: To understand the economic cost of non-adherence to TB medicines due to loss to follow up and stock-outs in the Philippines.

DESIGN: Data were collected on the economic costs of non-adherence to TB medicines and a model was developed to show those costs under different scenarios.

RESULTS: The model showed that as many as 1958 and 233 persons are likely to have died as a result of DS-TB and MDR-TB loss to follow up, respectively, and 588 persons are likely to have died as a result of TB medicine stock outs. The related economic impact in each case is likely have been to be as much as US$72.2 million, US$13.4 million and US$21.0 million, respectively.

CONCLUSION: The economic costs of non-adherence to TB medicines due to loss to follow-up and stock-outs represent a significant economic burden for the country and it is likely that the cost of addressing these problems would be much less than this burden and, therefore, a wise investment.

KEY WORDS: tuberculosis; treatment adherence; drug supply; loss to follow-up

TB IS A MAJOR CAUSE OF ILLNESS and death and places a huge social and financial burden on the people who have the disease, as well as on their families and communities. The economic impact of TB is also extremely high, making it a significant contributor to world poverty. TB absorbs an estimated US$12 billion from the incomes of the world's poorest communities and, in some countries, loss of productivity attributable to TB represents approximately 4–7% of gross domestic product.[1]

One of the key elements of successful TB control programs is adherence to treatment, which is a cornerstone of most international and national policies and guidelines.[2–6] The risk of non-adherence is high because treatment is long: at least 6 months for drug-susceptible TB (DS-TB) and at least 18 months for multidrug-resistant TB (MDR-TB; defined as TB resistant to at least isoniazid and rifampin). Non-adherence results in increased length and severity of illness, death, disease transmission, and drug resistance. This has economic consequences in terms of cost to the health system as well as cost to the persons with TB, such as lost income for patients and their families.[7,8]

A common cause of non-adherence is treatment interruption, which may range from short, intermittent periods of days to longer periods of weeks or months, and may even result in complete discontinuation of treatment. Treatment interruption can result from service delivery issues,[5] such as stock-outs of TB medicines, but is often because patients decide to stop treatment. This can be for financial reasons, such as inability to stop work or transport costs. However, DS-TB patients commonly report stopping treatment because they feel better after a few months and decide that there is no need to continue; DR-TB patients often report stopping because of the painful daily injections and side effects.[9]

Information on TB drug stock-outs globally is not easy to find, but they are believed to be a major issue, with shortages reported in several countries, including the United States. In 2007, for example, 10 of the then 22 high-burden countries reported first-line drug stock-outs at some level.[10] Loss to follow-up (LTFU) is also a major issue in many countries, exceeding 10% in general in 5 of the 30 high-burden countries. LTFU has been reported at respectively 19% and 31% for multidrug-resistant TB (MDR-TB) patients in India and Indonesia, and is also high in patients with extensively drug-resistant TB (XDR-TB; defined as MDR-TB with additional resistance to any fluoroquinolone and at least one of the three second-line anti-tuberculosis injectable drugs: capreomycin, kanamycin or amikacin) in some countries.[11]

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In several countries, the LTFU rate is not known because treatment outcomes are not properly measured.

The Philippines, with its population of over 90 million people, is among the 22 countries with a high burden of TB, including MDR-TB.[12,13] In recent years, data from the National Tuberculosis Control Program (NTP) has indicated problems of LTFU, which is defined in the Philippines as an interruption of treatment of ≥2 consecutive months. This has been a significant issue with a reported LTFU rate of 4% in DS-TB patients in 2013 and 36% in DR-TB patients in 2012.[14] A study of a cohort of MDR-TB patients who started treatment in 2014 found an LTFU rate of 29%, indicating that there may have been a reduction since 2012, but that the number of patients remains significant.[14] High LTFU rates in MDR-TB patients are especially worrying because some have XDR-TB or pre-XDR-TB (defined as resistance to isoniazid and rifampicin and either a fluoroquinolone or a second-line injectable agent but not both) when treatment begins; additional drug resistance is sometimes acquired during treatment; and many of those lost to follow-up are culture-positive at last contact, enabling community transmission of strains with more extensive resistance.

NTP data and several studies also indicated problems with stock-outs of some DS-TB medicines, which result in treatment interruption. A 2015 supply chain study, for example, found that stock-outs of first-line medicines resulted in delays in starting treatment, treatment interruptions, and patients having to buy medicines from third-party pharmacies.[15] Interruption of treatment due to stock-outs can lead to LTFU when patients decide not to return. Stock-outs of DR-TB medicines were not identified as an issue because these are purchased and distributed with assistance from international donors.

This study of the health, mortality, and economic impact of LTFU and stock-outs was conducted at the request of the Philippines NTP to provide evidence to justify greater investment in addressing these challenges.[16] The study focused on LTFU in patients with DS- and MDR-TB, and stock-outs of DS-TB medicines.

STUDY METHODS

Data were obtained from three sources: a global literature review, a review of NTP documents and records, and interviews with an expert panel of nine doctors, pharmacists, and NTP staff. Members of the panel were selected by the NTP as representative of national-level policy makers and facility-level service providers. The data and their sources are shown in Table 1.

Algorithms were developed based on the information received and these were modeled in a spreadsheet-based tool. The model used a simple multiplication across different probabilities based on data from multiple sources.

An example of the resulting decision trees is shown for MDR-TB LTFU in the Figure and the related probabilities are given in Table 2. For example, the rate of 5% treated in the private sector under MDR-TB LTFU means that 5% of those patients who were lost to follow-up were assumed to have subsequently gone to the private sector for treatment. Only the mean value of probability was collected for each node—minimum and maximum values were not collected. The models quantify the likely impact of the treatment interruption in terms of subsequent treatment or non-continuation of treatment and in terms of provider costs, household out-of-pocket (OOP) costs, and productivity losses. The models show the additional health and cost outcomes of each specific type of treatment interruption, excluding the health and cost outcomes that would have been incurred if treatment had not been interrupted.

Four types of economic cost are included in the model: 1) the cost to the service provider for treating TB; 2) the OOP cost to the patient for diagnosis and treatment; 3) the loss of productivity for the patient and household due to illness; and 4) the lifetime loss of productivity due to premature death. Philippines data were not available for the cost of diagnosis and treatment of TB (excluding medicines), MDR-TB patient OOP costs and the numbers of productive days lost due to illness, and instead we used Indonesia data. International data were used to estimate the average life span of a person who contracts active TB.[17]

Each decision made as a result of the treatment interruption has an impact on the economic cost. For example, people who decide to buy medicines in the private sector incur an OOP expense that they would not have incurred in the public sector, where medicines are free of charge. They may also incur a higher risk of developing drug resistance due to poor-quality medicines or incorrect dosages or combinations. People who die as a result of non-adherence to treatment due to stock-outs or LTFU have an economic impact in the form of a loss of productivity due to premature death.

A major cost element relates to the loss of productivity due to premature death. For this calculation, we assumed that the average age at which patients become ill with DS-TB is 39 years (42 years for MDR-TB), and that untreated patients would live for 3 years, meaning that premature death would take place at the age of 42 years (45 years for MDR-TB). Assuming a person is normally productive until the age of 65, 23 years of productive life would be lost (20 years for MDR-TB). An annual discount rate of 3% was applied to the cost of the years of life lost.

Table 1 Key variables and sources (all costs in 2016 US dollars)

Description	Figures	Source
Length of intensive treatment		
DS-TB	2 months	Expert panel (see Acknowledgements)
MDR-TB	6 months	Expert panel
Length of continuation treatment		
DS-TB	4 months	Expert panel
MDR-TB	12 months	Expert panel
Length of treatment before interruption		
DS-TB (LTFU and stock-outs)	3 months	Expert panel
MDR-TB	4 months	Expert panel
Average length of interruption		
DS-TB LTFU	3 months	Expert panel
DS-TB stock-outs	1 month	Expert panel
MDR-TB	5 months	Expert panel
Period that patients remain infectious after starting treatment		
DS-TB	1 month	Expert panel
MDR-TB	4 months	Expert panel
Period of life left when a person does not continue treatment	3 years	Tiemersma et al., 2011[17]
Cost of private-sector treatment per month, US dollars		
Consultation	8.79	Expert panel
Diagnostics	6.50	Expert panel based on information from SIAPS/Philippines
DS-TB medicines	13.24	Expert panel based on information from SIAPS/Philippines
MDR-TB medicines	NA	Not available in private sector
XDR-TB medicines	NA	Not available in private sector
Public-sector provider cost* per course of treatment, US dollars		
DS-TB Category 1	183	Indonesia patient costs study;[18] Philippines medicine costs from SIAPS/Philippines
MDR-TB	6188	NTP estimate for Global Fund (excludes hospitalization)
XDR-TB	7647	NTP estimate for Global Fund (excludes hospitalization)
Patient out-of-pocket cost per course of treatment, US dollars		
DS-TB	100	No data from the Philippines. Indonesia economic burden study[19]
MDR-TB	1473	Tupasi et al., 2006[20]*
XDR-TB	1768	MDR-TB figure of US$1473 extrapolated from 20 to 24 months
Productive days lost due to illness		
Treated DS-TB	81	Collins et al., 2013[19]
Untreated DS-TB	792	Collins et al., 2013[19]; expected to live for 3 years: 36 months x 22 days
Treated MDR-TB	132	Intensive period: 6 months x 22 days
Untreated MDR-TB	792	Collins et al., 2013[19]
Treated XDR-TB	528	24 months
Untreated XDR-TB	792	Same as untreated MDR-TB
Productive days per month	22	
Years of life lost		
DS-TB	23	Average age at which patient contracted DS-TB is 39;† would live for 3 years if untreated (Tiemersma et al., 2011[17]); age at which patient ceases to be productive is 65 years
DR-TB	20	Average age at which patient contracted MDR-TB or XDR-TB is 42 (NTP);‡ would live for 3 years if untreated (Tiemersma et al., 2011[17]); age at which patient ceases to be productive is 65 years
Productivity loss per day, US dollars	6.59	Minimum wage: highest PHP481 per day Manila, lowest PHP217 (March 2016); assumed average of PHP300. Source (accessed 14 April, 2016 (median rate);§ http://www.nwpc.dole.gov.ph/pages/statistics/stat_current_regional.html
Discount rate, %	3	
Pesos to US$	45.49§	

* Costs were for clinic visits, hospitalization, and, in some cases, board and lodging. The figure was updated for inflation.
† Costs of diagnostics, medicines, ancillary medicines, clinicians, nursing, and facility operations.
‡ Because the age at which a person contracts TB affects the value of the productive years of life lost, it would be better to use the median for each quartile of patients. Consideration should be given to removing children from the data set before determining the medians. Unfortunately, none of these figures were available at the time of writing.
§ 1 Peso = US$0.021981 Forex Currency Converter, 2015.
DS-TB = drug-susceptible tuberculosis; MDR-TB = multidrug-resistant TB; LTFU = loss to follow-up; SIAPS = Systems for Improved Access to Pharmaceuticals and Services; NA = not available; NTP = National TB Program; XDR-TB = extensively drug-resistant TB; DR-TB = drug-resistant TB.

Due to a lack of sufficient data and the desire to keep the analysis as simple as possible, we did not take into account sporadic treatment interruption of less than 2 months; delays in starting treatment; extra pulmonary TB; the impact of missing some, but not all of the combinations of medicines; stock-outs of vitamin B complex vitamins and medicines for side effects; and the presence of comorbidities such as HIV or diabetes.

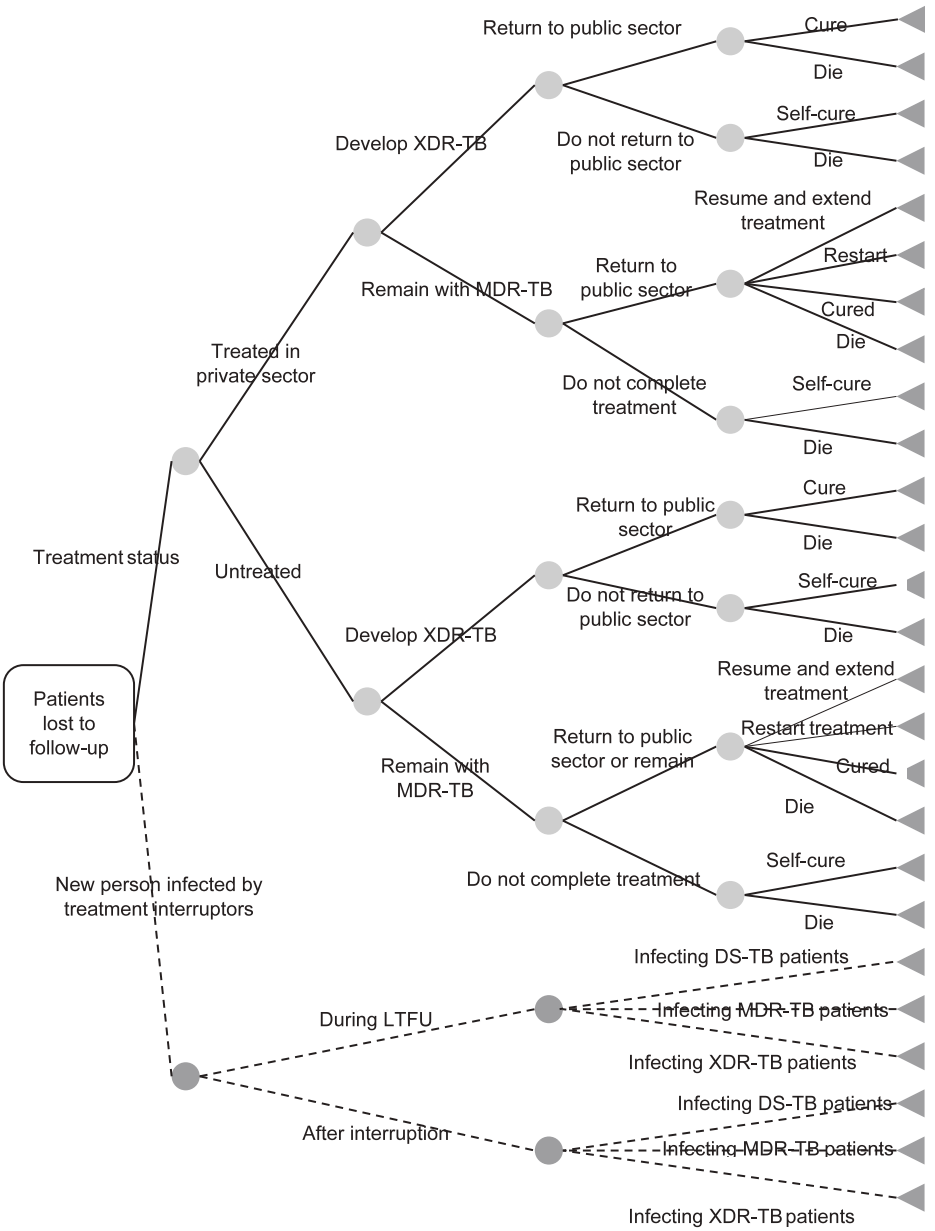

Figure MDR-TB LTFU decision tree. XDR-TB = extensively drug-resistant tuberculosis; MDR-TB = multidrug-resistant TB; LTFU = loss to follow-up; DS-TB = drug-susceptible TB.

We also did not take into account that persons infected by non-adherent patients might develop drug-resistant TB and infect additional persons, or that patients who were not infectious at the time the interruption started and who do not return to treatment are likely to become infectious again. Also, we did not include the premature mortality costs for persons infected by patients because of the lack of certainty of the length of time that it takes for persons to be infected, the proportion of persons who will develop active TB, and the time that that would take.

Other potential studies that were not explored relate to reported shortages of DS-TB Category 2 intensive phase kits needed for retreatment cases and shortages in pediatric TB medicines. We also did not model the costs of retreatment related to LTFU because the Expert Panel felt that very few of these patients are reportedly lost since they are afraid of the impact of not adhering to their medicines.

The data used in this study were obtained from the documents and records and interviews with government officials. As the study did not involve interviews with patients or other human subjects or the use of patient records, ethical review was not required.

RESULTS

DS-TB patients lost to follow-up

In 2014, 8870 patients with DS-TB were reported by the NTP as lost to follow-up. Based on the model, the

Table 2 Data and sources for decision trees*

	Probability (%)		
	MDR-TB LTFU	DS-TB LTFU	DS-TB stock-out
Patients LTFU treatment status			
Treated in private sector	5	10	72†
Develop XDR-TB | MDR-TB | MDR-TB	90	10	10
Return to public sector	80‡	70‡	70‡
Cured	50	87§	87§
Die	50	13§	13§
Do not return to public sector	20‡	30‡	30‡
Self-cure	0	0	0
Die	100	100	100
Remain with MDR-TB | DS-TB | DS-TB	10	90	90
Return to public sector or remain in treatment in private sector	80‡	70‡	70‡
Resume and extend treatment	0	0	100
Restart treatment	100	100	0
Cured	87§	98¶	98¶
Die	13§	2¶	2¶
Do not complete treatment	20‡	30‡	30‡
Self-cure	0	30#	30#
Die	100	70#	70#
Untreated	95	90	28†
Develop XDR-TB | MDR-TB | MDR-TB	40	10	10
Return to public sector	80‡	70‡	70‡
Cured	50	87§	87§
Die	50	13§	13§
Do not return to public sector	20‡	30‡	30‡
Self-cure	0	0#	0#
Die	100	100#	100#
Remain with MDR-TB | DS-TB | DS-TB	60	90	90
Return to public sector or remain in treatment in private sector	80‡	70‡	70‡
Resume and extend treatment	0	0	100
Restart treatment	100	100	0
Cured	87§	98¶	98¶
Die	13§	2¶	2¶
Do not complete treatment	20‡	30‡	30‡
Self-cure	0	30#	30#
Die	100	70#	70#
New persons infected by treatment interruptors			
During LFTU period			
Infecting DS-TB patients	0	0	0
Infecting MDR-TB patients	50	2	2
Infecting XDR-TB patients	2	0	0
After interruption period			
Infecting DS-TB patients	0	0	0
Infecting MDR-TB patients	20	30	30
Infecting XDR-TB patients	20	0	0
Proportion of persons infected who develop active TB	10	10	10

* Sources are all expert panel except for the following.
† Brown et al., 2015.[15]
‡ Tupasi et al., 2016;[9] MDR-TB figure adjusted by expert panel.
§ National Tuberculosis Control Program, 2012.[21]
¶ National Tuberculosis Control Program, 2014.[22]
# Tiemersma et al., 2011.[17]
MDR-TB = multidrug-resistant tuberculosis; LTFU = loss to follow-up; DS-TB = drug-susceptible TB; XDR-TB = extensively drug-resistant TB.

likely impact of this LTFU is that 887 of these patients would have developed MDR-TB through poor-quality private sector treatment, poor adherence, or discontinuation of treatment. These 887 patients are likely to have infected an additional 245 people with MDR-TB. In addition, 1958 patients and persons infected by these patients are likely to have died (Table 3).

The total additional economic cost resulting from this LTFU is likely to have been as much as US$72.2 million, comprised of US$5.8 million for additional service delivery costs and US$66.4 million for additional household costs (Table 3). This works out to a cost of approximately US$8000 per patient who interrupted treatment, meaning that an investment of up to that amount to prevent LTFU for one patient would have resulted in a net saving to society.

MDR-TB patients lost to follow-up

A study of a 2012 cohort of patients with MDR-TB found that 29% were lost to follow-up.[9] We applied that percentage to the 2680 patients with MDR-TB treated in 2014, which gave an assumption that 777 MDR-TB patients would have been lost to follow-up.

Table 3 Impact on morbidity, mortality and economic costs of treatment interruption

	DS-TB LTFU at 3 months	MDR-TB LTFU at 5 months	DS-TB stock-outs at 1 month
Number of patients whose treatment was interrupted	8 870	777	2 663
Impact on morbidity and mortality			
Patients who are likely to have developed MDR-TB as a result of the interruption	887	0	266
Patients who are likely to have developed XDR-TB as a result of the interruption	Not estimated	330	Not estimated
Patients who are likely to have died as a result of the interruption	1 958	233	588
Additional persons who are likely to have developed DS-TB as a result of the interruption	0	0	0
Additional persons who are likely to have developed MDR-TB as a result of the interruption	245	474	63
Additional persons who are likely to have developed XDR-TB as a result of the interruption	Not estimated	19	Not estimated
Economic impact			
Total additional healthcare system costs (2016 US$), million	5.8	4.5	1.5
Total additional patient costs (2016 US dollars), million	66.4	8.9	19.5
Total additional societal cost (2016 US dollars), million	72.2	13.4	21.0
Average additional healthcare system cost per patient who interrupted treatment (2016 US dollars)	655	5 733	573
Average additional patient cost per patient who interrupted treatment (2016 US$)	7 485	11 562	7 309
Average additional societal cost per patient who interrupted treatment (2016 US$)	8 141	17 296	7 882

DS-TB = drug-susceptible tuberculosis; LTFU = loss to follow-up; MDR-TB = multidrug-resistant TB; XDR-TB = extensively drug-resistant TB.

Based on the model, the likely impact for the 777 patients is that 330 would have developed XDR-TB through poor-quality private sector treatment, poor adherence, or through discontinuation of treatment (Table 3). These 330 patients are likely to have infected an additional 19 people with XDR-TB. In addition, the MDR-TB patients who were still infectious at the time of interruption are likely to have infected an additional 474 persons with MDR-TB. Plus, 233 people are likely to have died as a result of the LTFU.

The total additional economic cost resulting from this LTFU is likely to have been as much as USD13.4 million, comprised of USD4.5 million for additional service delivery costs and US$8.9 million for additional household costs (Table 3). This works out to approximately US$17 000 per patient who interrupted treatment, meaning that an investment of up to that amount to prevent the LTFU for one patient would have resulted in a net saving to society.

DS-TB medicine stock-outs

Based on the results of a sample patient survey conducted in early 2014, as many as 2663 patients with DS-TB may have been unable to obtain medicines from the public sector for a month or more. Based on the model, the likely impact of this stock-out is that 266 of these patients would have developed MDR-TB because of poor-quality private sector treatment, poor adherence, or discontinuation of treatment (Table 3). These 266 patients are likely to have infected an additional 63 people with MDR-TB. In addition, 588 patients and persons infected by these patients are likely to have died.

The total additional economic cost resulting from the stock-out is likely to have been as much as US$21.0 million, comprised of US$1.5 million for additional service delivery costs and US$19.5 million for additional household costs (OOP costs and productivity losses) (Table 3). This works out to a cost of approximately US$8000 per patient who interrupted treatment, meaning that an investment of up to that amount to prevent the stock-out for one patient would have resulted in a net saving to society.

One-way sensitivity analysis was carried out on key single variables for each model to see which had the greatest influence on total costs and additional costs. The degrees of change are hypothetical, except for the change in the variable for length of treatment for MDR-TB before interruption from 4 to 7 months, which is based on the number of months identified in the 2016 study by Tupasi et al.[9] Variables were separated into key assumptions used in the analysis and key decisions made in the model (Table 4). Changes in key assumptions that have the most impact on total additional costs are the proportion of patients with MDR-TB lost to follow-up who are infectious at the time of interruption, where a reduction from 50% to 25% results in a reduction of 19.0% of total additional cost, and the number of patients per month infected with active TB, where an increase from 0.1 to 0.2 results in an increase in total additional cost of 27.9%. These results show that, for MDR-TB patients, attention should be focused on preventing LTFU while patients are still infectious.

Table 4 Sensitivity analysis

		DS-TB LTFU			DR-TB stock-outs			MDR-TB LTFU		
	Base data sources	Base	Sensitivity change	Impact on additional cost %	Base	Sensitivity change	Impact on additional cost %	Base	Sensitivity change	Impact on additional cost
Key assumptions										
Months before interruption	*	3	4	+4.4	3	4	+5.2	4	7	+4.4
Length of treatment interruption	*†	3	4	+0.2	3	4	+0.2	5	3	–9.2
Patients who have undiagnosed MDR-TB/XDR-TB at start of LTFU, %	*	2	4	+2.9	2	4	+2.6	2	4	+1.8
Patients who are infectious at the time they interrupt treatment, %	*	0	10	+0.3	0	10	+2.7	50	25	–19.0
Patients per month infected with active TB by patients who interrupted treatment	*	0.1	0.2	+2.9	0.1	0.2	+4.0	0.1	0.2	+27.9
Key decisions										
Patients treated in the private sector during interruption period, %	*†	10	20	−0.1	72	36	+1.8	5	10	+2.3
Patients treated in private sector during interruption period who develop MDR-TB/XDR-TB, %	*	10	20	+1.5	10	20	+13.1	90	45	–5.5
Patient untreated during interruption period who develop MDR-TB/XDR-TB, %	*	10	20	+14.6	10	20	+6.2	40	20	–16.7
Patients with DS-TB treated in private sector who return to public-sector treatment, %	‡	70	35	+87.4	70	35	+94.8	NA	NA	NA
Patients with MDR-TB treated in private sector who return to public-sector treatment, %	‡	70	35	+9.8	70	35	+12.4	80	40	+62.2
Patients with XDR-TB treated in private sector who return to public-sector treatment, %	*	NA	NA	NA	NA	NA	NA	80	40	+6.9

* Expert panel.
† Brown et al., 2015.[15]
‡ Tupasi et al., 2016.[9]
DS-TB = drug-susceptible tuberculosis; LTFU = loss to follow-up; DR-TB = drug-resistant TB; MDR-TB = multidrug-resistant TB; XDR-TB = extensively drug-resistant TB.

DISCUSSION

The results of the three case studies show that TB treatment interruption can have a significant impact on morbidity and mortality, causing many people to develop MDR-TB and XDR-TB, and resulting in many new infections and deaths. The economic impact on the health services, families, and society in general is equally devastating, running into many millions of US dollars.

The analysis was subject to some limitations. One was that the data on the number of patients who experienced stock-outs and the length of those stock-outs were derived from patient surveys in that study,[15] and the number of responses was quite small. Another was that there are no estimates for the Philippines for the numbers of persons infected by an active TB case in 1 year, the proportion of these persons who develop active TB, or how long that would take. We, therefore, used international estimates but figures for the Philippines may be quite different.

These results are only approximate figures because some of the assumptions were based on estimates provided by the expert panel in the absence of data. However, due to the fact that the abovementioned areas were not taken into account, it is likely that the economic impact shown in this study is underestimated.

A systematic global literature review could not find any research on the impact of treatment interruption; additional research would, therefore, be highly beneficial, both in the Philippines and globally to provide a more robust evidence base.

Finally, it should be noted that this was a preliminary model intended to lead to further research. It was developed as a simple way of providing data for rapid decision-making on treatment interruption in lower-middle-income countries where data are limited.

CONCLUSIONS

The results of the analysis indicate that the reduction of prioritization LTFU should be prioritized through better education and case management, especially in regions where LTFU is high, and to improving supply

chain management to prevent stock-outs. It is clear from these case studies that the cost of treatment interruption in the Philippines is significant and that investing additional resources to resolve the causes of these problems is likely to be extremely worthwhile.

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RÉSUMÉ

CONTEXTE : Les Philippines ont une population de plus de 90 millions et sont l'un des 22 pays les plus affectés par la TB dans le monde.

OBJECTIF : Comprendre le coût économique de la non-adhérence aux médicaments de la TB, liée aux pertes de vue et aux ruptures de stock aux Philippines.

SCHÉMA : Des données ont été recueillies sur le coût économique de la non-adhérence aux médicaments TB et un modèle a été élaboré pour mettre en évidence ces coûts dans différents scénarios.

RÉSULTATS : Le modèle a montré que jusqu'à 1958 et 233 personnes respectivement atteintes de TB sensible aux médicaments et TB multirésistante étaient susceptibles d'être décédées car perdues de vue et 588 personnes étaient susceptibles d'être décédées à cause de ruptures de stock de médicaments TB. L'impact économique correspondant dans chaque cas est susceptible d'avoir atteint 72,2 millions $US, 13,4 millions $US et 21,0 millions $US, respectivement.

CONCLUSION : Le coût économique de la non-adhérence aux médicaments de la TB à cause de pertes de vue et de ruptures de stock représente un poids économique significatif pour le pays et il est probable que le coût du traitement de ces problèmes serait bien inférieur à ce fardeau et serait donc un judicieux investissement.

RESUMEN

MARCO DE REFERENCIA: Filipinas, con una población de más de 90 millones de habitantes, es uno de los 22 países del mundo con una carga alta de TB.

OBJETIVO: Comprender el costo económico del incumplimiento del tratamiento de la TB debido a pérdidas durante el seguimiento y desabastecimientos en Filipinas.

MÉTODO: Se recogieron datos sobre los costos económicos del incumplimiento del tratamiento de la TB y se creó un modelo que permitía demostrar estos costos en diferentes situaciones hipotéticas.

RESULTADOS: El modelo puso de manifiesto la posibilidad de que hubiesen fallecido hasta 1958 personas por TB sensible y hasta 233 personas por TB multirresistente por pérdidas durante el seguimiento y 588 personas por desabastecimientos de fármacos antituberculosos. El impacto económico en cada caso pudo alcanzar hasta 72,2 millones, 13,4 millones y 21,0 millones de dólares, respectivamente.

CONCLUSIÓN: Los costos del incumplimiento del tratamiento de la TB debido a las pérdidas durante el seguimiento y los desabastecimientos representan una carga económica considerable para el país; es posible que la solución de estos problemas tenga un costo muy inferior a la carga y constituya una inversión acertada.

PLOS ONE

RESEARCH ARTICLE

Active household contact screening for tuberculosis and provision of isoniazid preventive therapy to under-five children in Afghanistan

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Abstract

Objectives

This observational study analyzed the performance of the National TB Control Program (NTP) in Afghanistan in household contact screening from 2011 to 2018 and its use as an entry point for isoniazid preventive therapy (IPT), as well as the IPT completion rates for children under age five.

Methods

From 2011 to 2018, the Afghanistan NTP released guidelines for passive and active contact screening of bacteriologically confirmed TB cases. Health workers were trained in contact screening. Presumptive TB cases gave sputum for AFB smear microscopy; other diagnostics were used if patients could not produce sputum. Children under five (excluding those with active TB) were treated for latent TB infection. We calculated the yield and the number needed to screen and number needed to test to find a case of TB, as well as the rates of IPT initiation and completion.

Results

From 2011 to 2018, 142,797 bacteriologically confirmed TB cases were diagnosed in Afghanistan. The number of household members eligible for screening was estimated to be 856,782, of whom 586,292 (81%) were screened for TB and 117,643 (20.1%) were found to be presumptive TB cases. Among the cases screened, 10,896 TB cases (all forms) were diagnosed (1.85%, 95% CI 1.82–1.89), 54.4% in females. The number needed to screen to diagnose a single case of TB (all forms) was 53.8; the number needed to test was 10.7. Out of all children under five, 101,084 (85.9%) were initiated on IPT, and 69,273 (68.5%) completed treatment.

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Competing interests: None declared.

Conclusions

Program performance in contact screening in Afghanistan is high, at 81%, and the yield of TB is also high—close to 10 times higher than the national TB incidence rate. IPT initiation and completion rates are also high as compared to those of many other countries but need further improvement, especially for completion.

Introduction

Tuberculosis (TB) is a major global public health problem and represents 1 of the top 10 causes of death globally. In 2018, an estimated 10 million people developed TB disease, which caused death in 1.5 million people [1]. In 2018, a total of 7 million new TB cases were notified by national health authorities and reported to the World Health Organization (WHO), but more than 3 million TB cases were missed [1]. Although Afghanistan is not on WHO's list of the 30 high-TB-burden countries, the incidence of TB is as high as in some of the high-burden countries, with a rate of 189 per 100,000 population, which has remained the same since 2000, although treatment coverage has greatly improved, from 19% in 2000 to 69% in 2018. In 2018, Afghanistan reported 48,420 TB cases out of the estimated 70,000 incident cases [1].

One strategy to increase case detection is contact screening of bacteriologically confirmed TB index cases. In 2011, the National TB Control Program (NTP) of Afghanistan initiated passive household contact screening, whereby bacteriologically confirmed index TB patients are counseled to bring their contacts for screening, and active household contact screening was also implemented in selected provinces [2]. In 2014, active household contact screening was expanded to Kabul and in 2015 further expanded to another five provinces. Contact screening was also used as an entry point to implement isoniazid preventive therapy (IPT) for children under five.

Although contact screening is a high-yield intervention recommended by WHO [3], its yield differs based on the country disease burden, diagnostic methods used, and health workers' capacity. The reported yield of contact screening ranges from 656 per 100,000 population [4] to 1,788 per 100,000 population in Viet Nam [5], 914 per 100,000 in Peru [6], 610 per 100,000 in Ethiopia [7], and 2,200 per 100,000 in Pakistan [8]. In an Afghanistan study of household contact screening that reported only on smear-positive cases, the yield was 1,880 per 100,000 population in the first year and decreased to 1,400 per 100,000 in the second year of intervention [9]. The yield was almost 10 times higher than the national estimated incidence of 189 per 100,000 population for Afghanistan [1].

This article analyzes the routine contact screening performance of the Afghanistan NTP from 2011 to 2018, with a focus on how contact screening helped expand IPT for children under five.

Methods

Setting

The Afghanistan NTP was initiated in 1954 by the Ministry of Public Health (MOPH), and the directly observed treatment short course (DOTS) strategy was introduced in 1997 but not rolled out nationwide until 2002 due to the security situation in the country [2]. The TB control program is integrated into primary and secondary health services through the Basic Package of Health Services and Essential Package of Hospital Services. Currently 2,627 health

facilities in the country provide DOTS services, and 883 laboratories carry out sputum microscopy (MOPH, National TB Report 2018). The TB program has been relatively well funded through the Global Fund, USAID, and other major donors; this support has built capacity in the health care system to diagnose and manage the TB prevention and control program. The relative improvement in the country's security situation also provided an opportunity to strengthen the TB program.

The national reporting system collected the results of routine contact screening for all 34 provinces from 2011 to 2018, following the implementation policy of the NTP. This study presents this programmatic experience, including only the public sector since the private sector was not engaged in contact screening and IPT administration. Before 2011, there was no contact screening policy or reporting. The national guidelines recommend both active and passive contact screening of the household members of bacteriologically confirmed index TB patients [10]. After a new index TB patient is identified and registered for treatment, TB experts counsel the index patient to bring his/her contacts to the health facility for screening, which is the passive screening approach, or a health worker or a community health worker (CHW) visits the house of the index TB patient to screen all household members, which is the active screening approach [10, 11].

The health worker, per the national guideline, asks each family member of the index TB patient if s/he has signs and symptoms of TB (productive cough for more than two weeks, weight loss, fever, and loss of appetite). Identified presumptive TB cases then give spot sputum, which is transported to an acid-fast bacilli (AFB) smear microscopy center on the same day. For the morning and spot sputum collection, the person with presumptive TB is asked to go to the health facility. At the health facility, people with presumptive TB are asked again about symptoms and signs, receive physical exams, and give sputum. If the sputum smear or GeneXpert test is negative, but there is a high degree of suspicion of TB or another disease, other investigations, such as chest x-rays, are undertaken. Per the national guidelines, two smears should be positive to support a diagnosis of TB. If only one smear out of three is positive, the doctor decides whether other investigations are warranted and starts treatment with a broad-spectrum antimicrobial. If abnormalities are present in the chest x-ray and the symptoms persists after antibiotic treatment, the patient is diagnosed as having pulmonary TB and anti-TB treatment starts. Extrapulmonary TB is diagnosed with a combination of histology, cytology, x-ray investigations, and clinical decisions [10].

The presumptive TB cases diagnosed with TB are enrolled for treatment, and children under the age of five in whom active TB has been ruled out are started on IPT for six months. IPT administration is demonstrated to the index TB patients, who administer IPT to children at home, and verified by CHWs when they provide directly observed treatment (DOT) to the index TB patient at home.

Data collection and analysis

We collected the data from the NTP's annual and quarterly reports for 2011–2018. The national database since 2011 reports the number of all forms of TB diagnosed, number of bacteriologically confirmed TB cases, number of contacts screened, screening results (i.e., presumptive TB cases), number of children under five registered and put on IPT, and IPT completion rate. The database does not disaggregate the number of contacts screened by age for all years, so this information is not included in the analysis. The sex difference in performance was analyzed to see if there is a gender difference in services as well as disease burden, in order to inform future recommendations. The NTP, provincial health offices, and NGOs supporting the TB program carried out quarterly data quality assurance, and the quality of data has

improved over time. Individual data were entered into registers, and health facilities reported indicator-level aggregated data to provinces, which in turn aggregate the data and report it to the NTP manually. In Afghanistan there are two CHWs, one male and one female, for a population of 1,000–1,500, and most DOT is administered by CHWs. We aggregated the data by year and calculated the number needed to screen (NNS) to obtain a presumptive TB case and number needed to test (NNT) to diagnose a single case of TB. We calculated the 95% confidence intervals and *p* values using OpenEPI Software (Dean AG, Sullivan KM, Soe MM, OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version 3.01, available from www.OpenEpi.com, updated 6 April 2013, accessed 23 Oct. 2019) and MedCalc software (Ostend, Belgium, Version 19, available from MedCalc.net, updated Aug. 2019).

Definition of terms

We defined "bacteriologically confirmed index TB case" as a patient diagnosed with AFB sputum-smear microscopy as positive or any patient diagnosed positive with GeneXpert. A household contact per WHO's definition is "A person who shared the same enclosed living space for one or more nights or for frequent or extended periods during the day with the index case during the 3 months before commencement of the current treatment episode" [3]. A presumptive TB case is defined as having cough for two weeks or more, night sweating, and loss of weight, and, for children, failure to thrive. The NNS is defined as the number of contacts that have to be screened to detect a single case of presumptive TB, and the NNT is the number of presumptive TB cases that have to be evaluated to diagnose a single TB patient. IPT completion is defined as the completion of more than 95% of the prescribed dose of isoniazid, ascertained by TB focal persons by counting the pills in a blister pack, and DOT by CHWs when they observe the treatment of the index case.

Ethical considerations

We obtained approval from the Afghanistan NTP to use the data collected and aggregated in the MOPH Management Information System database, and no additional ethical approval was required because we used de-identified data collected from routine programmatic reports of the NTP.

Results

We analyzed a total of 298,332 TB cases between 2011 and 2018, and of those 142,797 (47.8%) were bacteriologically confirmed TB cases. Those bacteriologically confirmed TB cases were used as the index TB patients for the household contact screening. Based on data from the national census about average household size, the number of household contacts for each index TB patient was estimated to be six [12].

The yield of TB screening

From 2011 to 2018, 586,292 household contacts were screened for TB, of whom 291,995 (49.8%) were females. Out of those screened, 117,643 (20.1%, 95% CI 19.96–20.07) were identified as presumptive TB cases. The presumptive TB cases identified totaled 55,255 (18.8%) in males and 62,388 (21.3%) in females ($p < 0.0001$). A total of 10,896 (1.8%, 95% CI 1.82–1.89) TB cases were diagnosed among all those screened, and out of those in whom TB (all forms) was diagnosed, 6,271 (57.5%, 95% CI 56.6–58.5) were bacteriologically confirmed TB patients (Table 1 and Fig 1).

Table 1. Trends and yield of household contact investigation.

Year	All TB Cases Notified	Bacteriologically Confirmed TB Cases (%)	Estimated No. HH Contacts to Be Screened[a]	No. (%) HH Contacts Screened	No. (%) Presumptive TB Cases	No. (%) TB (All Forms) Diagnosed among HH Contacts	No. (%) Bacteriologically Confirmed TB among HH Contacts
2011	28,167	15,103 (53.6)	90,618	44,259 (49)	16,145 (36.4)	822 (1.8)	606 (73.7)
2012	29,578	14,464 (48.9)	86,784	44,766 (52)	7,939 (17.7)	610 (1.3)	350 (57.3)
2013	31,622	15,670 (49.5)	94,020	48,122 (51)	8,274 (17.2)	788 (1.6)	390 (49.4)
2014	32,712	16,182 (49.4)	97,092	53,189 (55)	9,403 (17.6)	770 (1.4)	469 (58.3)
2015	37,001	17,975 (48.5)	107,850	61,678 (57)	13,367 (21.7)	1,062 (1.7)	580 (54.6)
2016	43,046	19,948 (46.3)	119,688	85,755 (72)	15,569 (18.1)	1,544 (1.8)	894 (57.9)
2017	47,406	21,316 (44.9)	127,896	125,350 (98)	22,499 (17.9)	2,443 (1.9)	1,511 (63.4)
2018	48,800	22,139 (45.3)	132,834	123,173 (93)	24,447 (19.8)	2,857 (2.3)	1,471 (51.4)
Total	298,332	142,797 (47.8)	856,782	586,292 (81)	117,643 (20.1)	10,896 (1.8)	6,271 (57.5)

Notes: HH = household.

[a]The average number of household members in Afghanistan is reported to be six.

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Out of all those screened, 4,963 (1.7%) of the males and 5,933 (2.03%) of the females were diagnosed with TB (all forms) ($p < 0.001$) (Table 2). In terms of yearly performance, the number of all forms of TB diagnosed progressively increased, from 28,167 in 2011 to 48,800 in 2018, which is a 73% increase (chi-square for trend = 269.2, $p < 0.01$). The number of bacteriologically confirmed cases also increased, from 15,103 in 2011 to 22,139 in 2018—an increase of 46.5%. Parallel to case detection, the number of index case household members screened also increased gradually, from 49% in 2011 to 93% in 2018 (chi-square for trend = 130.9, $p < 0.01$). The average yield of all forms of TB diagnosed was 1.8%, and it is only in 2018 that the rate was higher, at 2.3% (Table 1).

The proportion of presumptive TB cases identified was 18.8% (95% CI 18.63–18.92) for males and 21.4% (95% CI 21.2–21.5) for females ($p < 0.0001$). The NNS to identify a single presumptive TB cases was 53.8, and the NNT to diagnose a single case of all forms of TB was 10.8. The NNS for bacteriologically confirmed TB cases was 93.5 and the NNT was 18.7 (Table 3).

Isoniazid preventive therapy

Contact screening was used as an entry point for identifying eligible children under the age of five for IPT. Out of the 586,292 household members of index TB patients screened for TB from 2011 through 2018, 117,593 children under five were eligible for IPT. Of those, 101,084 (85.9%) were initiated on IPT and 69,273 (68.5%) completed treatment. IPT coverage increased from 73% of the eligible children in 2011 to 94% in 2018. IPT completion also improved from 46% in 2011 to 74% in 2018 ($p < 0.0001$) (Table 4). In terms of sex, 59,873 children (50.9%) were females, and the number of male and female children who completed the full six months of IPT were 34,293 (68%) and 34,980 (69%), respectively ($p < 0.005$).

Discussion

The Afghanistan NTP increased the screening of household contacts of bacteriologically confirmed index TB patients from 49% in 2011 to 93% in 2018 ($p < 0.0001$). The overall number of presumptive TB cases identified was 20.1%, which is higher than the numbers of presumptive TB cases reported in Ethiopia (6.1% and 11%) [7,13], and the 3% reported in Pakistan [8], 7.5% in Accra, Ghana [9], and 3% in another Afghanistan study [7]. The yield of all forms of

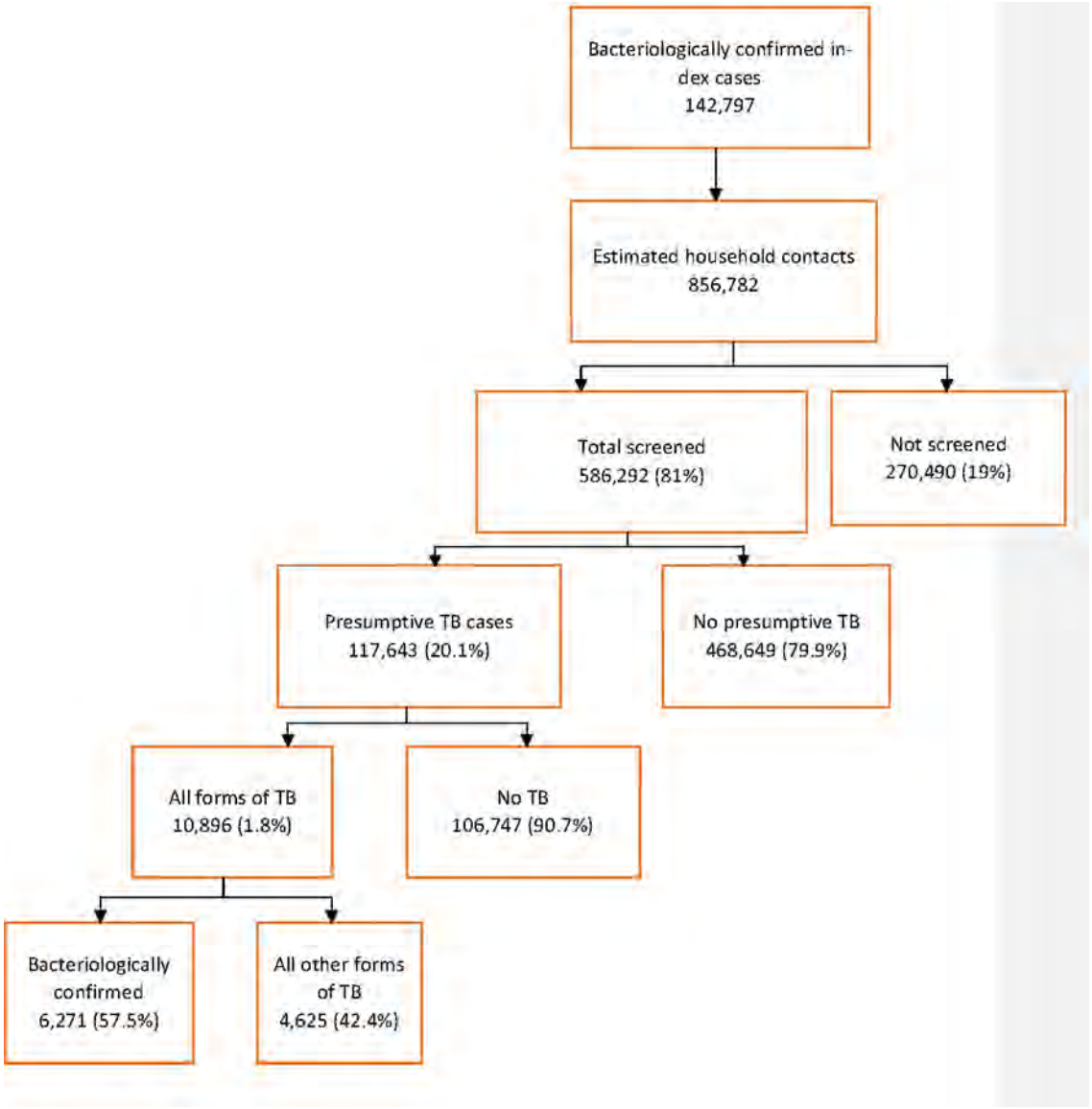

Fig 1. Total screened, and yield of TB, Afghanistan (2011–2018).

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TB was 1.8%, which is close to 10 times higher than the estimated national incidence of TB, at 189 per 100,000, and is closer to the 1.6% reported in another study in Afghanistan [9] and the 1.7% reported in Viet Nam [5]. Furthermore, the yield of 1.8% found in this study was higher than the 0.65% in Ghana [14], 0.17% in Viet Nam [5], and 0.9% in Peru [6], but lower than the 3.6% that WHO reported [3], lower than the 3.9% reported in South Africa [15] and lower than the 2.5% reported in Ethiopia [7]. In a 21-year retrospective study in Birmingham, UK, the TB yield among smear-positive contacts screened was 7.0 [16]. The high number of presumptive TB cases identified in the routine program of Afghanistan is relatively low when considered as a proportion of all forms of TB diagnosed. It might be that health workers included people with signs and symptoms of TB but less than two weeks of history in screening; another reason for the relatively low yield could be the use of microscopy, a low-sensitivity diagnostic tool, in the majority of cases.

Table 2. Yield of screening of household contacts of TB index cases by sex.

Year	No. HH Contacts Screened		Ratio (F/M)	No. Presumptive TB Cases (%)		No. TB (All Forms) Diagnosed among HH Contacts Screened (%)		No. and Proportion of Bacteriologically Confirmed TB among all Forms of TB Diagnosed	
	M	F		M	F	M	F	M	F
2011	21,665	22,594	1.04	7,554 (34.9)	8,591 (38.0)	340 (1.6)	482 (2.1)	222 (65.3)	384 (79.6)
2012	22,339	22,427	1.00	3,713 (16.5)	4,226 (18.8)	253 (1.1)	357 (1.6)	139 (54.9)	211 (59.1)
2013	23,536	24,586	1.04	3,872 (16.5)	4,402 (17.9)	359 (1.5)	429 (1.7)	164 (45.6)	226 (52.7)
2014	27,422	25,767	0.94	4,372 (15.9)	5,031 (19.5)	359 (1.3)	411 (1.6)	192 (53.4)	277 (67.3)
2015	30,746	30,932	1.01	6,189 (20.1)	7,178 (23.2)	485 (1.6)	577 (1.9)	235 (48.4)	345 (59.8)
2016	43,142	42,613	0.99	7,312 (16.9)	8,257 (19.4)	669 (1.5)	875 (2.0)	353 (52.7)	541 (61.8)
2017	64,072	61,278	0.96	10,619 (16.6)	11,880 (19.4)	1,161 (1.8)	1,282 (2.1)	673 (57.9)	838 (65.3)
2018	61,375	61,798	1.01	11,624 (18.9)	12,823 (20.7)	1,337 (2.2)	1,520 (2.5)	672 (50.2)	799 (52.5)
Total	294,297	291,995	0.99	55,255 (18.8)	62,388 (21.4)	4,963 (1.7)	5,933 (2.0)	2,650 (53.4)	3,621 (61.0)

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Table 3. Yield of contact screening by sex.

Characteristics	Male	Female	Total	*P* Value
Total contacts screened	***294,297***	***291,995***	***586,292***	
Presumptive TB cases	55,255	62,388	117,643	
Proportion	18.8 (18.63–18.92)	21.4 (95% CI 21.2–21.5)	20.0 (95% CI 19.96–20.17)	
NNS	5.3	4.6	4.9	
All forms of TB	***4,963***	***5,933***	***10,896***	
Proportion	1.6	2.0	1.8	< 0.0001
NNS	59.2	44.1	53.8	
NNT	11.1	10.5	10.8	
Bacteriologically confirmed total	***2,650***	***3,621***	***6,271***	
Proportion	53.4	61.0	57.5	< 0.0001
NNS	111.0	80.6	93.5	
NNT	20.8	17.2	18.7	

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Table 4. IPT enrollment and completion rate for children under age five.

Year	No. HH Contacts under 5 Years Eligible for IPT	No. (%) HH Contacts under 5 Years Who Started IPT	No. (%) HH Contacts under 5 Years Who Completed IPT
2011	8,534	6,199 (73%)	2,823 (46%)
2012	8,934	7,461 (84%)	4,808 (64%)
2013	10,620	7,690 (72%)	4,924 (64%)
2014	11,919	8,792 (74%)	6,046 (69%)
2015	11,799	10,164 (86%)	7,737 (76%)
2016	17,215	15,417 (90%)	10,387 (67%)
2017	24,656	22929 (93%)	16,049 (70%)
2018	23,916	22,432 (94%)	16,499 (74%)
Total	117,593	101,084 (85.9%)	69,273 (68.5%)

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The other factor that should be studied is the lack of clear international guidelines about the definition of a contact. Contact screening is currently limited to the household members living under one roof, but in a traditional society like Afghanistan's extended family members have very close daily interactions. In a study in Pakistan, screening of household contacts and neighbors within 50 m of the radius of the index TB cases yielded rates of 22.3% and 19.1% of all forms of TB, respectively [8]. Given similarities between the community structure in Pakistan and Afghanistan, we recommend including neighbors in contact screening.

We found a significant difference between females and males ($p < 0.0001$) in the number of all forms of TB diagnosed, which is consistent with another Afghanistan study in which the diagnosed female-male ratio was 2.1 [9], while studies in Tanzania and England (London) did not show any difference between males and females [17–18].

The NNS to obtain a presumptive case of TB (all forms) was 53.8 and the NNT was 10.7. The NNS is lower than the NNS of 424 and 378 reported in the Afghanistan study [9]. In Ethiopia, the NNS and NNT were 40 and 2.4, respectively, and in Ghana, the NNS was 154 and the NNT was 8, respectively [7,14]. The NNT depends mainly on the incidence of the disease in a country, the quality of screening, and the screening tool used, so the differences among countries can be explained by these factors, but we do not know why the NNT in the other Afghanistan study was so high [9]. A different geography with a different disease burden or the capacity of the professionals involved in TB screening and diagnosis could be factors. The introduction of GeneXpert in recent years might also be a factor in the difference in results between our study and the other Afghanistan study.

The rate of bacteriologically confirmed cases in this analysis was 57.5%, which is close to the 61% reported by WHO [1]. The yield could have been higher if x-rays had been used as a screening tool and GeneXpert used as a diagnostic tool for all. As an example, in a study in Zambia, out of all contacts screened with chest x-ray, 53.6% had abnormal chest x-rays, and out of those, TB (all forms) was diagnosed in 32%; 19% of them were bacteriologically confirmed, but 8% had no symptoms [19]. Chest x-ray is highly sensitive, and most of the TB cases identified in national prevalence surveys and focal studies were found by chest x-ray rather than by symptomatic screening alone [17–20]. GeneXpert is also a more sensitive and specific tool for TB diagnosis [20,21]. In the future, the introduction of chest x-ray and GeneXpert for screening and diagnosis of TB, respectively, will help to increase case detection in Afghanistan.

Contact screening was used as an entry point for IPT initiation of children under age five who were contacts of bacteriologically confirmed TB patients. According to the 2018 WHO report, Afghanistan reported 100% initiation of IPT for the year 2017 [1], while we report 93% because of updates after the data were submitted to WHO. Afghanistan is one of the few countries with a high TB incidence rate to achieve this result [1]. The completion rate for six months of IPT is also very high, with an average of 68.5% from 2011 through 2018. To our knowledge, there is no nationwide report of completion of treatment for latent TB infection on this scale except from Mozambique [1], and the reports for various smaller groups ranged from 6% to 94% [22]. We attribute the high rate of completion to the counseling of parents on the importance of IPT, including health workers' encouragement of parents to complete children's IPT; good follow-up with patients who missed a day of treatment; and uninterrupted supply of isoniazid. The mandatory implementation of contact registration and screening of all index TB patients in Afghanistan increased case notification and served as an entry point to find IPT-eligible children. Another advantage is that the treatment of index TB patients is observed daily, so the health worker can ask them to bring all contacts for screening. CHWs visit index TB patients at home, providing another opportunity to screen all contacts and to supervise IPT.

Limitations

Because the data for this study were collected from routine reports, and health facility registers do not include the number of household members, the denominator used to calculate the target for screening was the national average household size. Using that number might have inflated or underestimated the actual number of contacts screened. Furthermore, GeneXpert has been used since 2015 as a diagnostic method in a very small number of health facilities, but this study did not capture the results by diagnostic type for bacteriologically confirmed TB cases.

Conclusions

This study found that contact screening of household members of TB index cases in Afghanistan is very high by global standards, and the yield of TB is also close to 10 times higher than the national estimated TB incidence from 2011 through 2018 [1]. We recommend following contacts for two to three years, since most contacts who develop TB disease do so within this time period. IPT initiation and completion rates are very high, and along with the extension of contact screening to neighbors, IPT targets should also be revised. Shifting from IPT to rifapentine- or rifampicin-based shorter TB preventive treatment for latent TB infection [23] will further improve treatment completion, and the country should revise its policy to extend preventive treatment to all eligible contacts of all ages.

Supporting information

S1 File.
(XLS)

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Factors Determining Treatment Success in Children with Drug-Sensitive Tuberculosis in Ethiopia: A Three-Year Retrospective Analysis

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Abstract. This study in the Amhara and Oromia regions of Ethiopia assessed the outcomes of tuberculosis (TB) treatment among children younger than 15 years. Retrospective data were collected on treatment outcomes and their determinants for children with TB for the cohorts of 2012–2014 enrolled in 40 hospitals and 137 health centers. Chi-square tests, *t*-tests, and logistic regression were used for the analysis. Of 2,557 children registered, 1,218 (47.6%) had clinically diagnosed pulmonary TB, 1,100 (43%) had extrapulmonary TB, and 277 (8.9%) had bacteriologically confirmed TB. Among all cases, 2,503 (97.9%) were newly diagnosed and 178 (7%) were HIV positive. Two-thirds of the children received directly observed treatment (DOT) in health centers and the remaining one-third, in hospitals. The treatment success rate (TSR) was 92.2%, and the death rate was 2.8%. The childhood TSR was high compared with those reported in focal studies in Ethiopia, but no national TSR report for children exists for comparison. Multivariate analysis showed that being older—5–9 years (adjusted odds ratio [AOR], 95% CI: 2.53, 1.30–4.94) and 10–14 years (AOR, 95% CI: 2.71, 1.40–5.26)—enrolled in DOT in a health center (AOR, 95% CI: 2.51, 1.82–3.48), and HIV negative (AOR, 95% CI: 1.77, 1.07–2.93) were predictors of treatment success, whereas underdosing during the intensive phase of treatment (AOR, 95% CI: 0.54, 0.36–0.82) was negatively correlated with treatment success. We recommend more research to determine if intensive monitoring of children with TB, dosage adjustment of anti-TB drugs based on weight changes, and training of health workers on dosage adjustment might improve treatment outcomes.

INTRODUCTION

Globally, there were an estimated 10 million incident tuberculosis (TB) cases in 2018, of which 11% would be expected to be children younger than 15 years. In 2018, 7 million people with TB were notified worldwide. Childhood TB accounted for 8% of all the notified TB globally. According to the same WHO 2019 report, Ethiopia, one of the 30 high TB-burden countries, notified 113,613 new and relapse cases in all age-groups in 2018. Childhood TB accounted for 10% of all the notified TB cases in Ethiopia, but high proportion of missed cases was reported in the 0–4 age category.[1] In 2018, Ethiopia also reported a treatment success rate (TSR) of 96% for the cohort of new TB cases of all ages registered in 2017.[1] Although there are no global data on the TSR for children as a point of comparison, focal studies in Ethiopia have reported a TSR of 78.9% in the northern part of the country,[2] 63.0% in the south,[3] and 85.5% in Addis Ababa.[4,5] In Cape Town, South Africa, a TSR of 89.5% for children younger than 15 years has been reported.[6]

Tuberculosis surveillance data for children in many countries are lacking, and there are few epidemiologic studies.[7] In Ethiopia, the true burden of childhood TB is unknown because of poor case ascertainment, absence of active case finding, and limited surveillance data. Ethiopia launched a national childhood TB road map in 2015 that prioritized childhood TB interventions to be incorporated into Integrated Management of Neonatal and Childhood Illnesses nationally, although that strategy had been implemented through the Help Ethiopia Address Low TB Performance (HEAL TB) project since 2011. The road map recommends strengthening routine TB screening in clinics and offers guidance on the delivery of quality childhood TB care and treatment services.[8] The available studies of the epidemiology and treatment outcomes of childhood TB in Ethiopia have focused on a few health facilities or urban settings.[2,5,9,10]

Child-specific performance data are important for understanding the situation in children, exploring the factors associated with program success, and fostering evidence-based decision-making at the policy, planning, and program implementation levels. However, the national health management information system routinely reports aggregated treatment outcomes for all age-groups. Because evidence on the treatment outcomes of children who start treatment for TB in Ethiopia is limited, this study aims to assess the childhood TB TSRs and associated factors in two major agrarian regions of Ethiopia.

MATERIALS AND METHODS

The setting. Data on childhood TB treatment outcomes were collected in the Amhara and Oromia regions of Ethiopia, which, with a total population of 55 million, account for 60% of the country's population.[11] In the two regions, there were 121 public hospitals and 2,195 health centers providing TB prevention, control, and treatment services (Regional Health Bureaus, unpublished report, 2017). In this study, 40 hospitals and 137 health centers with high TB patient loads (a minimum of 10 childhood drug-sensitive TB cases per year) were included. Children with multidrug-resistant TB (MDR-TB) were excluded because they were treated in selected MDR-TB centers. The HEAL TB project, funded by the U.S. Agency for International Development and managed by the Management Sciences for Health, provided comprehensive TB program support in the Amhara and Oromia regions of Ethiopia from 2011 through 2016. Technical and financial support included the preparation of a childhood TB policy, road map, and training manual. The policy and materials were implemented through training of health workers, continuing medical education of clinicians, demonstration of sputum sample collection

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in children, distribution of childhood TB job aids, supervision, and mentoring.

Study design and data collection. We analyzed 3 years of retrospective data for the cohort of TB patients aged 0–14 years who were enrolled in first-line anti-TB treatment during 2012–2014. We extracted relevant data from the health facilities' TB registers, which include type of health facility, age, gender, TB type, drug dose correctness, HIV test result, and treatment outcome. A semi-structured data collection tool was used to extract patient information from the TB unit registers. Trained health workers with a BSc degree were involved in the data collection.

Data quality. Each reporting health facility has a data quality assurance mechanism led by a performance monitoring team responsible for all health-related data.[12] Data collectors clarified any inconsistency or incompleteness noted during data extraction by consulting the health worker in charge and reconciled the data with the information on the TB patient card kept in the TB clinic.

Data analysis. The data collected via the extraction sheet were entered into MS Excel and later imported to SPSS (IBM SPSS Statistics for Windows, version 20, IBM Corp., Armonk, NY) for analysis. Frequencies and proportions were calculated to describe background characteristics and treatment outcomes. Chi-square test and *t*-test for comparison of proportions were computed to compare the association between categorical variables. Logistic regression analysis was used to assess the covariates associated with successful TB treatment. Covariates with *P*-values less than 0.25 in bivariate analysis were included in the logistic regression model. Odds ratios and 95% CIs were used to present the results of logistic regression. *P*-values of less than 0.05 were considered statistically significant.

Operational definitions. A bacteriologically confirmed TB case refers to a patient from whom at least one biological specimen is positive for *Mycobacterium TB* using smear microscopy, GeneXpert MTB/RIF (Cepheid, Sunnyvale, CA), or culture.[13] A clinically diagnosed TB case refers to a patient who does not fulfill the criteria for a bacteriologically confirmed TB case but has been diagnosed with active TB by an experienced clinician who has prescribed a full course of TB treatment. This definition includes cases diagnosed on the basis of X-ray abnormalities or suggestive histology, and extrapulmonary cases diagnosed without confirmation that *Mycobacterium TB* is present.

The standard TB treatment outcome described in the WHO definitions and reporting framework for TB was used (cured, treatment completed, treatment failure, death, lost to follow-up, transferred out, and not evaluated). Treatment success is defined as either a completion of treatment by a TB patient, with smear- or culture-negative results for bacteriologically confirmed cases, or without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not performed or because results are unavailable.[14] Over- and underdosing for pediatric TB treatment is based on the weight of the child recommended in the national guidelines; deviation from the standard for any dose in the intensive or continuation phase is considered over- or underdosing.[15]

Ethical considerations. The Ethical Review Committees of Oromia and Amhara Regional Health Bureaus reviewed and approved the proposed research, including the use of routinely available data and dissemination of the findings. We also obtained permission from the heads of the respective health facilities before extracting the data from TB registers. The data extracted from the registers did not include any personal identifying information.

RESULTS

A total of 2,557 children (aged 0–14 years) were enrolled for treatment in the 40 hospitals and 137 health centers. One-fourth of the patients were children younger than 5 years (4.7% younger than 1 year and 22.3% aged 1–4 years), whereas 30.4% were aged between 5 and 9 years and the remaining 42.6% were children aged 10–14 years, with a median age (interquartile range) of 8 (4–12) years. The results showed that 853 (33.4) were males, 827 (32.4) females, and 34.2% did not have information about gender on their records. Most of the children, 1,788 (69.9%), were treated in health centers, and the remaining children, 769 (30.1%), were treated at hospitals. The clinically diagnosed TB cases constituted 1,218 (47.6%), extrapulmonary TB 1,100 (43%), and only 227 (8.9%) were bacteriologically confirmed TB (all were from sputum samples); 97.9% were newly diagnosed TB cases; and 88.4% were HIV negative. Appropriate doses of TB drugs were provided to 83.1% and 82.4% of the patients during the intensive and continuation phases, respectively (Table 1).

The overall TSR was found to be 92.2% (6.9% cured and 85.3% treatment completed). The unsuccessful treatment

TABLE 1
Characteristics of children with TB enrolled on treatment

Characteristic	Number (%)
Type of TB	
Bacteriologically confirmed	227 (8.9)
Clinically diagnosed pulmonary	1,218 (47.6)
Extrapulmonary	1,100 (43.0)
No record	12 (0.5)
Category of TB	
New	2,503 (97.9)
Relapse	11 (0.4)
Treatment failure	6 (0.2)
Transferred in	5 (0.2)
Other	17 (0.7)
No record	15 (0.6)
HIV test result	
Reactive	178 (7.0)
Nonreactive	2,261 (88.4)
No record	118 (4.6)
Drug dose, intensive phase	
Appropriate	2,126 (83.1)
Overdosage	121 (4.7)
Underdosage	284 (11.1)
No record	26 (1.0)
Drug dose, continuation phase	
Appropriate	2,108 (82.4)
Overdosage	80 (3.1)
Underdosage	121 (4.7)
No record	248 (9.7)
Treatment outcome	
Cured	175 (6.9)
Treatment completed	2,167 (85.3)
Died	72 (2.8)
Treatment failure	3 (0.1)
Lost to follow-up	28 (1.1)
Transferred out	85 (3.3)
Not evaluated	11 (0.4)

TB = tuberculosis.

outcomes included death (2.8%), failure (0.1%), lost to follow-up (1.1%), transferred out (3.3%), and not evaluated (0.4%). The TSRs for the cohort of patients who finished treatment in 2012, 2013, and 2014 showed an increasing trend: 86.9%, 93.3%, and 96.6%, respectively (chi-square for trend = 36.86, $P < 0.01$). A cure rate of 74.4% and a TSR of 93.3% were achieved among bacteriologically confirmed TB cases (Table 1).

The patients who were diagnosed and started treatment in hospitals had relatively lower treatment success than those in health centers (86.5% versus 94.6%, $P < 0.001$). Children younger than 1 year had the lowest TSR (83.5%; 95% CI: 75.4–89.3%), 1–4 years (88.0%; 95% CI: 85.1–90.5%), 5–9 years (93.7%; 95% CI: 91.7–95.2%) and, whereas the 10- to 14-year age-group had the highest TSR (94.1%; $P < 0.001$). The TSR among HIV-positive children was 88.2%, compared with a TSR of 93% in HIV-negative patients ($P < 0.05$). More deaths and loss to follow-up were reported in hospitals than health centers (4.3% versus 2.2% [$P < 0.01$] and 2.6% versus 0.5% [$P < 0.001$], respectively). Similarly, a higher death rate was observed in children younger than 1 year (8.3%), whereas the lowest was reported in the 5- to 9-year age-group (1.9%) ($P < 0.001$). Clinically diagnosed pulmonary TB had a 3.8% mortality (95% CI: 0.7–4.4%) compared with 1.8% (95% CI: 2.8–5.0%) in bacteriologically confirmed TB. The death rate among HIV-positive patients was 8.4%, whereas the corresponding rate among HIV-negative patients was 2.3% ($P < 0.001$). The transferred-out rate was 5.1% in the hospitals as compared with 2.6% in the health centers ($P < 0.001$) (Table 2).

Multivariate analysis showed that belonging to age-groups 5–9 and 10–14 years (adjusted odds ratio [AOR], 95% CI: 2.53, 1.30–4.94; and 2.71, 1.40–5.26, respectively), follow-up at a health center (AOR, 95% CI: 2.51, 1.82–3.48), and HIV-negative status (AOR, 95% CI: 1.77, 1.07–2.93) were significant predictors of successful TB treatment outcomes. Patients with reported drug underdosage in the intensive phase of treatment had a 46% reduction in their treatment success compared with appropriately dosed groups (odds ratio, 95% CI: 0.54, 0.35–0.81). Region and type of TB did not show statistically significant associations with successful TB treatment (Table 3).

DISCUSSION

The TSRs among children with TB who received first-line anti-TB drugs in the study period were higher than others previously reported in Ethiopia.[4,5,9] Treatment success rates for childhood TB reported in different settings include 45% in Malawi,[16] 72% in Thailand,[17] 91.7% in Iran,[18] and 95% in India.[19] The TSR in this study is higher than those in reports from Ethiopia in different settings: a TSR of 85.5% in urban health centers in Addis Ababa,[4] 85.5% in a referral hospital in Addis Ababa,[5] 83.2% in a referral hospital in southern Ethiopia,[9] and 66.4% in a rural hospital in southeast Ethiopia.[10] The proportion of children with bacteriologically confirmed TB, 8.9%, is substantially lower than the corresponding proportion in those aged ≥ 15 years in Ethiopia (27.7%),[20] but similar to the proportion in children in other reports in Ethiopia.[4] The observed improvement in TB treatment success might be attributable to ongoing trainings in the regions on comprehensive programmatic and clinical management of TB/HIV, continuing medical education on childhood TB, strengthening of laboratory support, and close mentorship at district health offices as well as health facilities.[21]

We observed an increasing trend in the TSR over the 3-year period, which is probably related to the improvements in TB prevention and control efforts as well as the quality of TB-related health services in the specified period. For bacteriologically confirmed TB cases, the cure rate was found to be 74.4%, which falls within the range of the national target of 72–77% in the specified years.[22]

TABLE 2
Tuberculosis treatment outcome by background and clinical characteristics

	Treatment outcome, *n* (%)					
	Successful treatment*	Died	Rx failure	Lost to follow-up	Transferred out	Not evaluated
Region (*N*)						
Amhara (1,285)	1,199 (93.3)	34 (2.6)	1 (0.1)	7 (0.5)	33 (2.6)	11 (0.9)
Oromia (1,256)	1,143 (91.0)	38 (3.0)	2 (0.2)	21 (1.7)	52 (4.1)	0
Type of health facility (*N*)						
Hospital (764)	661 (86.5)	33 (4.3)	2 (0.3)	20 (2.6)	39 (5.1)	9 (1.2)
Health center (1,777)	1,681 (94.6)	39 (2.2)	1 (0.1)	8 (0.5)	46 (2.6)	2 (0.1)
Gender (*N*)						
Male (853)	795 (93.2)	19 (2.2)	2 (0.2)	4 (0.5)	26 (3.0)	7 (0.8)
Female (827)	777 (94.0)	23 (2.8)	0	4 (0.5)	19 (2.3)	4 (0.5)
No record (861)	770 (89.4)	30 (3.5)	1 (0.1)	20 (2.3)	40 (4.6)	0
Age (years) (*N*)						
< 1 (109)	91 (83.5)	9 (8.3)	0	3 (2.8)	5 (4.6)	1 (0.9)
1–4 (569)	501 (88.0)	26 (4.6)	1 (0.2)	10 (1.8)	29 (5.1)	2 (0.4)
5–9 (774)	725 (93.7)	15 (1.9)	0	8 (1.0)	22 (2.8)	4 (0.5)
10–14 (1,089)	1,025 (94.1)	22 (2.0)	2 (0.2)	7 (0.6)	29 (2.7)	4 (0.4)
HIV status (*N*)						
Positive (178)	157 (88.2)	15 (8.4)	0	1 (0.6)	4 (2.2)	1 (0.6)
Negative (2,257)	2,097 (92.9)	51 (2.3)	3 (0.1)	23 (1.0)	74 (3.3)	9 (0.4)
Unknown (106)	88 (83.0)	6 (5.7)	0	4 (3.8)	7 (6.6)	1 (0.9)
Type of TB (*N*)						
Bacteriologically confirmed (227)	212 (93.4)	4 (1.8)	2 (0.9)	4 (1.8)	5 (2.2)	0
Clinically diagnosed pulmonary (1,216)	1,099 (90.4)	46 (3.8)	1 (0.1)	17 (1.4)	51 (4.2)	2 (0.2)
Extrapulmonary (1,098)	1,031 (93.9)	22 (2.0)	0	7 (0.6)	29 (2.6)	9 (0.8)

TB = tuberculosis.
* A sum of those cured and those who completed treatment.

TABLE 3
Factors associated with successful TB treatment in children

Variable	Number (*N* = 2,423)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (years)			
< 1	89	Reference	Reference
1–4	528	1.48 (0.78–2.79)	1.41 (0.74–2.69)
5–9	744	**2.76 (1.45–5.26)**	**2.53 (1.30–4.94)**
10–14	1,062	**3.11 (1.66–5.83)**	**2.71 (1.40–5.26)**
Region			
Amhara	1,254	Reference	Reference
Oromia	1,169	0.74 (0.55–1.01)	1.07 (0.77–1.49)
Type of health facility			
Hospital	737	Reference	Reference
Health center	1,686	**2.72 (2.00–3.69)**	**2.51 (1.82–3.48)**
Type of TB			
Bacteriologically confirmed	219	Reference	Reference
Clinically diagnosed pulmonary	1,146	0.74 (0.42–1.30)	1.09 (0.60–1.98)
Extrapulmonary	1,058	1.18 (0.65–2.11)	1.34 (0.73–2.45)
HIV test result			
Reactive	177	Reference	Reference
Nonreactive	2,246	**1.76 (1.09–2.86)**	**1.77 (1.07–2.93)**
Dose during intensive phase			
Appropriate	2,031	Reference	Reference
High	116	0.86 (0.42–1.73)	0.88 (0.43–1.79)
Low	276	**0.51 (0.34–0.76)**	**0.54 (0.36–0.82)**

TB = tuberculosis. Bold values indicate significant associations.

Hospitals were found to have a relatively lower TSR than health centers. The reasons could be that severely and critically ill patients are referred to and managed in hospitals. Hospitals had more deaths and transfer-outs, which contributed to the lower TSR. Most of the patients had follow-up and adherence support at health centers, serving up to 25,000 people, with the support of satellite health posts, which are located in the community very close to patients. Hospitals need to consider transferring stable patients to health centers for directly observed treatment because the results showed that treatment outcomes in health centers are good, possibly because of lower workloads that facilitated close follow-up. In addition, more patients were lost to follow-up and transferred out in the hospitals, which might have contributed to lower TSRs. Hospitals do not form part of the primary healthcare network in Ethiopia, which works closely with the community via health extension workers (HEWs) to trace children lost to follow-up. Furthermore, hospitals need to devise a mechanism to track the treatment outcomes of transferred-out patients, especially by working closely with the HEWs. The use of digital technology in this regard could be a viable option.[23] The national childhood TB road map recommends developing integrated family- and community-centered strategies to provide comprehensive and effective services at the community level,[15] so treatment follow-up and adherence support in health posts for children on TB treatment need to be strengthened.

Treatment success in children undergoing TB treatment depends on the quality of diagnosis and treatment follow-up and of adherence counseling of patients and their families. In our study, underdosage (11.1%) and overdosage (4.7%) were noted in the intensive phase and the continuation phase of treatment (3.1% overdosage and 4.7% underdosage, respectively). Lack of knowledge, failure to monitor patients' weight, and poor dose adjustment based on children's weight changes are the likely reasons for inappropriate dosing, which needs further exploration. A multicountry study in Africa reported significantly higher underdosage and overdosage of individual anti-TB drugs than those found in this study.[24]

Overall, deaths, loss to follow-up, and transfer-outs contributed to most of the unfavorable treatment outcomes. More deaths and loss to follow-up were observed in patients followed in hospitals, infants younger than 1 year, and HIV-positive cases. Being older, HIV negative, and followed up in health centers were associated with good treatment success, whereas drug underdosing in the intensive phase was a negative predictor of successful TB treatment. Other factors that play a role in poor treatment outcomes could be delayed TB diagnosis in children, severity of illness, and poor compliance with drug treatment among infants.

Despite the strengths of this study, including reporting previously unavailable evidence on the treatment outcomes of a large number of children with TB from diverse settings, the following limitations should be noted. The data were incomplete because of the retrospective nature of this study, although that issue did not affect the analysis significantly. Some important covariates, such as socioeconomic status, comorbidities, access to health services, health-seeking behavior, and acceptability of the drugs (tablets) to children, were missing because we used the standard national health facility registers devised for routine reporting purposes, which lack those data. A comparison of the result with a baseline was also lacking because there was no nationally disaggregated data on TSRs by age. Another limitation is the exclusion of health facilities with fewer than 10 reported childhood TB patients, because of resource shortages.

CONCLUSION

The TB TSRs in this study were higher than the national targets for all age-groups as well as the TSRs reported in other studies in the country and the region. Nevertheless, more attention to younger children, hospital settings, and HIV coinfected patients is needed to improve treatment success

through better-quality patient care and adherence support and closer monitoring of treatment. Intensive monitoring of children with TB in terms of weight measurement at each follow-up visit, dosage adjustment of anti-TB drugs based on weight changes, and training of health workers on dosage adjustment by child weight could improve treatment outcomes. We recommend a prospective study to understand the contributions to treatment outcomes of social determinants, comorbid conditions, access to health services, new pediatric formulations, and factors related to patient care. We also recommend disaggregation of data by age in the national reporting system.

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Driving the usage of tuberculosis diagnostic data through capacity building in low- and middle-income countries

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Background: Connectivity platforms collect a wealth of data from connected GeneXpert instruments, with the potential to provide valuable insights into the burden of disease and effectiveness of tuberculosis programmes. The challenge faced by many countries is a lack of training, analytical skills, and resources required to understand and translate this data into patient management and programme improvement.

Objective: We describe a novel training programme, the tuberculosis Data Fellowship, designed to build capacity in low- and middle- income countries for tuberculosis data analytics.

Methods: The programme consisted of classroom and remote training plus mentorship over a 12-month period. The focus was on skills development in Tableau software, followed by training in exploration, analysis, and interpretation of GeneXpert tuberculosis data across five key programme areas: patient services, programme monitoring, quality of testing, inventory management, and disease burden.

Results: The programme was piloted in six countries (Bangladesh, Ethiopia, Ghana, Malawi, Mozambique) in July 2018 and Nigeria in September 2018; 20 participants completed the training. A number of key outputs have been achieved, such as improved instrument utilisation rates, decreased error rates, and improved instrument management.

Conclusion: The training programme empowers local tuberculosis programme staff to discover and fix critical inefficiencies, provides high-level technical and operational support to the tuberculosis programme, and provides a platform for continued sharing of insights and best practices between countries. It supports the notion that connectivity can increase efficiencies and clinical benefits with better data for decision making, if coupled with commensurate capacity building in data analysis and interpretation.

Keywords: tuberculosis; GeneXpert; diagnostic data; monitoring and evaluation; data analysis; programmatic.

Introduction

Tuberculosis has been declared a global public health emergency. An estimated one-third of the world's population is infected with tuberculosis; 10 million people developed tuberculosis disease in 2017 alone,[1] a number that may be underestimated due to under-reporting and lack of reliable data. The widespread implementation of the Xpert® MTB/RIF assay (Cepheid, Sunnyvale, California, United States) for detection of *Mycobacterium tuberculosis* and rifampicin resistance as a first-line tuberculosis diagnostic, has been hailed as the most significant advancement in decades, becoming the first molecular assay to provide a tuberculosis and first-line drug resistance diagnosis in just 2 hours. Following widespread adoption of this technology, the World Health Organization's Agenda for Action on Digital Health for the End Tuberculosis Strategy called for 100% of all sites using rapid tuberculosis diagnostic instruments to be connected by 2020,[2] becoming the first to recognise the role of digital health in the fight against tuberculosis. Over the past 2 to 3 years, numerous countries have begun adopting connectivity platforms to help monitor and manage their GeneXpert fleet by collecting the vast amounts of rich clinical diagnostic and operational data produced by the instrument. Rarely before has such a rich data resource been both produced by a diagnostic instrument and been made available via connectivity platforms, at scale, for analysis. As yet, it remains largely untapped.[3] If these data can be analysed, interpreted and translated into appropriate recommendations and actions, they

have the potential to provide significant transformative impact on the management and effectiveness of infectious disease programmes worldwide.

GxAlert® (SystemOne, LLC, Northampton, Massachusetts, United States) is currently collecting data from GeneXpert platforms in 43 countries running Cepheid's Xpert MTB/RIF assay. GxAlert is a connectivity platform that integrates directly with diagnostic instruments to collect and send a digital copy of test results and associated instrument metadata to an in-country or GxAlert server. From there, results can be sent and accessed via short message service and email alerts, Microsoft Excel (Microsoft Corp, Redmond, Washington, United States) reports and web dashboards. The type of data being collected includes not only the diagnostic result, but also information on when and where the test was run and by whom, demographic information about the patient (through an application called GxConnect), reagent lot numbers, probe data, cycle thresholds as well as instrument operational data such as instrument failures, inventory consumption and instrument downtime. From these data, critical insights can be gained or inferred about the tuberculosis programme and can help shed light on both clinical and operational return on investment. Data can also provide useful information on testing coverage, disease status and trends, circulating strains and drug resistance profiles, instrument utilisation rates, training needs, supply chain, inventory, and quality of the testing programme.[4]

But there is a challenge: even though countries now collect this type of data in large volumes, it is a new arena for them. Most high-disease burden countries lack the tools, resources and expertise required to analyse, understand and translate these data into improved programme and patient outcomes. A recent study by the Foundation for Innovative Diagnostics (FIND), found that despite large investments by donors to implement electronic data management systems, there is limited usage of the data to improve service delivery, mainly due to a lack of understanding and awareness of what data means.[5] As a result, tuberculosis programmes are accumulating but not using the data being collected to drive decision making. This becomes apparent when one considers the various challenges still hindering tuberculosis programmes today, including gross under-utilisation of instruments,[3,6,7,8] high unsuccessful test and error rates (loss of tests),[9,10] cartridge stock-outs, instrument breakdowns, and lack of adequate module replacements and maintenance of instruments.[11]

There is a dire need to build capacity in health data analytical skills amongst staff within national tuberculosis programmes (NTPs) in order to bolster the usage of data. To address this need, we designed a novel training programme to develop the expertise and skills required for the analysis and understanding of connected diagnostic data.

The Tuberculosis Data Fellowship programme

The TB Data Fellowship (TDF) programme was initiated in 2018 through a joint collaboration between SystemOne and Management Sciences for Health, with the support of the Tableau Foundation. Designed to build the foundation for sustainable in-country capacity, the programme aimed to enhance the understanding of tuberculosis data and its translation into actionable outputs. Achieving these goals required a new cadre of healthcare worker to be trained, one with the ability to understand and interpret the vast amounts of diagnostic and operational data being collected through connected diagnostic systems.

For the pilot programme, staff from the NTPs, national tuberculosis reference laboratories and ministries of health from several countries using the GxAlert connectivity platform were invited to apply. Countries invited included Bangladesh, Ethiopia, Ghana, Malawi, Mozambique and Nigeria. The selection criteria for the programme included a minimum of 2 years' work experience in the field of tuberculosis, and more specifically the GeneXpert tuberculosis programme, and at least 6 months of work experience with GxAlert software. Participants also had to have experience working in Excel.

Informatics infrastructure

The programme leveraged the existing connectivity infrastructure, GxAlert, to gain access to live Xpert MTB/RIF data. In addition, each participant was provided with a Tableau Desktop and Tableau Online licence (Tableau, Seattle, Washington, United States). Tableau is a powerful data visualisation and analytics software package that is specifically aimed at helping people understand large amounts of data through the creation of structured storyboards, dashboards and visual representations. SystemOne developed the server architecture to enable participants to extract live country data from GxAlert and to import it into Tableau (Figure 1). This allowed participants to safely interact with data, enforce the necessary patient privacy and country-specific data permissions, and generate visualisations to allow them to share this with the NTP, neighbouring disease programmes, the ministry of health or donors, via Tableau Online (Figure 1).

Training structure

Two pilot training programmes were undertaken: the first accepted participants from five countries supported by the global Challenge TB project, funded by the United States Agency for International Development. The first countries were Bangladesh (n = 2), Ethiopia (n = 2), Mozambique (n = 2), Ghana (n = 1) and Malawi (n = 1). The second programme accepted participants from Nigeria only (n = 12). The training lasted 12 months and was structured in two parts: a 1-week in-person classroom training followed by an 11-month remote training and mentorship.

Classroom training

The in-person classroom training consisted of a 1-week intensive centralised training, the first of which was held in

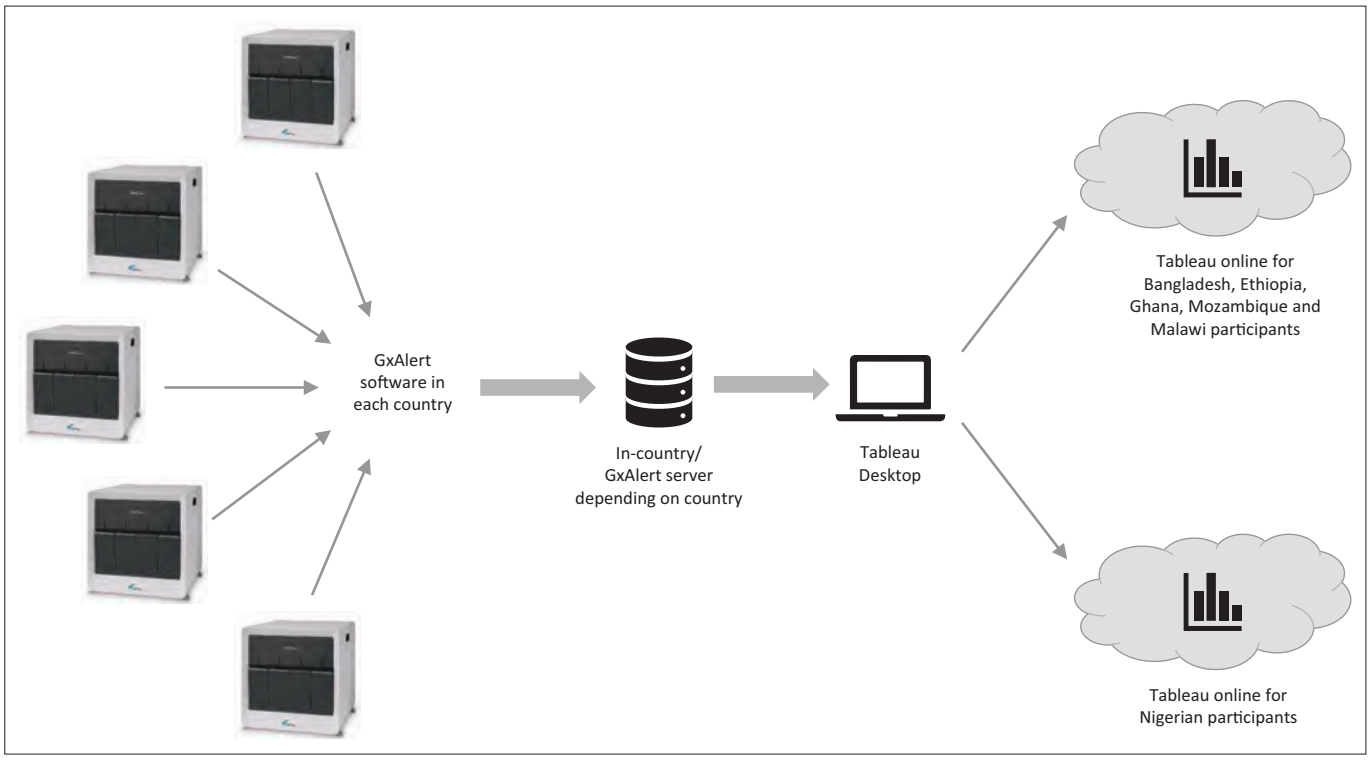

FIGURE 1: General informatics infrastructure and data flow for TB Data Fellowship programme. Live Xpert MTB/RIF data from each country is collected via GxAlert and stored on a in-country or private cloud hosted GxAlert server (depending on country preference). Each data fellow is able to download an extract of their own country data to Tableau Desktop in order to create various graph-like visualisations and basic analytics. Once analysis is complete, data fellows could choose to publish a subset of these visualisations, unlinked to the data source, via a community folder on Tableau Online, allowing them to share insights, ideas and graphics with other data fellows, the ministry of health or NTP.

Johannesburg, South Africa from 9–13 July 2018, and the second in Abuja, Nigeria from 24–28 September 2018. During the first three days of each session, participants were trained extensively on Tableau Desktop v2018.1 software (Tableau, Seattle, Washington, United States). This was followed by two days of training on how to integrate and interpret GxAlert tuberculosis data in Tableau, perform basic data analysis, and prepare visualisations to improve the interpretation and reporting of tuberculosis data.

Remote training and mentorship

For 11 months following the classroom training, participants received monthly training and mentorship remotely via 2-hour Skype sessions as two separate groups, depending on which classroom training session they attended. SystemOne designed these sessions to allow in-depth data analysis and development of visualisations to improve understanding, with a focus on the development of data-driven recommendations for programmatic improvement. To promote a platform for sharing of data, insights and best practices, each month participants were required to complete assignments and publish their developed visualisations and insights on the Tableau online server for the entire group to see. This encouraged collaboration among members of the groups.

Focus areas of the training

Through the 12-month programme, participants were taught how to understand GeneXpert tuberculosis diagnostic and operational data being collected by the GxAlert platform and to translate this data into insights about their respective tuberculosis programmes (Table 1). They identified programme gaps and appropriate intervention needs in different programme areas (Table 1), while learning how to lower operating costs (by reducing supervision frequency and troubleshooting services), improve the quality of the programme and manage the programme more effectively.

Key insights from the programme

The training has yielded new country-level insights and programme improvements due to improved data use and decision making as demonstrated by numerous technical reports, conference abstracts and presentations. For example, in Bangladesh, participants have used data about instrument utilisation rates to influence the NTP to improve referral mechanisms for underperforming sites and further optimise GeneXpert placement within their NTP to better meet testing demand.[12] These insights have also helped the NTP plan for future placement of additional GeneXpert machines. In Ethiopia, analysis of instrument utilisation and subsequent proactive monitoring have led to an improvement in utilisation, from 28% to 75%.[13] Such dramatic improvements can translate immediately into programme return on investment – whereby tuberculosis programmes can make existing resources go much farther than expected and deploy resources more effectively when receiving future grants or allocating domestic budgets.

TABLE 1: Key topics covered during the 2018 TB Data Fellowship training.

Area	Data collected	Topics covered
Disease burden	• MTB/RIF results • Probe data • Semi-quantitative values (cycle thresholds)	• TB positivity and RIF positivity rates and trends • Diagnostic algorithm adherence • Epidemiological characteristics of circulating strains • Identification of 'hotspots' to inform design of targeted case-finding and interventions
Patient services	• Demographic data (age, sex, treatment history, etc.)	• Identify which populations are underserved • Identify where interventions are working • Identify where interventions are needed • Tailoring diagnostic and treatment strategies • Improved reporting against key programme indicators
Programme monitoring	• Testing numbers • Instrument and module serial numbers • Geographic locations of laboratories	• Monitoring of test numbers and trends • Growth of testing fleet and placement, gaps, absorption by the health system • Instrument and module status and downtimes • Instrument and module utilisation rates • Monitoring progress towards testing targets
Quality monitoring	• Error, invalid and no results • Error codes • External quality assurance and proficiency testing results	• Monitoring error, invalid and no result rates and trends • Reportable versus unreportable results (loss of tests) and wastage • Monitoring quality of the programme • Error code interpretation to target specific intervention needs, for example, re-training needs, power needs, environmental issues • Identifying sites needing support and supervision • Identifying specific users needing support • Identify sites performing quality assurance and monitoring quality of testing
Inventory tracking	• Reagent lot numbers • Reagent expiry dates	• Monitoring of levels of reagents and consumable stock and expiry • Forecasting • Prevention of stock-outs • Supply chain improvement • Identification of reagent lot numbers with high invalid or error rates • Cartridge age and relationship to invalid or error rates

Note: Several areas of learning were covered during the 12-month programme held for Bangladesh, Ethiopia, Ghana, Mozambique, Malawi and Nigerian participants.

MTB, *Mycobacterium tuberculosis*; RIF, rifampicin; TB, tuberculosis.

By teaching participants how to monitor unreportable test rates or the number of tests resulting in errors, no results and invalid results, programme efficiency and response speed can be improved. Unreportable or unsuccessful tests do not provide a clinically valid result to the patient and thus need to be repeated. Besides the cost in 'lost' cartridges, when one considers that the actual cost per test performed has been estimated at $23.00 (United States dollors [USD]) and the cost per diagnosis at $99.00 USD,[14] unsuccessful tests represent a significant cost to the health system. The majority of unsuccessful tests are due to error results and can, to a large extent, be corrected. Unfortunately, countries seldom know how to interpret error codes to inform appropriate corrective actions. The TDF helped participants categorise error codes according to their suspected sources and, through doing this, identify the most frequent types of errors to troubleshoot while pinpointing the sites needing supervision and follow-up. This real-time support is less costly compared to conventional monitoring, which requires a person to visit sites to troubleshoot issues, without any understanding of which issues pertain to which sites. Across all participating countries, the majority of errors were user or technical errors. These errors are associated with incorrect specimen processing or volumes added to the cartridge.[15] For example, in Ghana, up to 67% of error results were identified as user related, and this insight has led to the introduction of refresher training and targeted supervision for sites.[16] The same issue was identified in Nigeria and Bangladesh, where both programmes have managed to reduce their national error rates due to targeted supervision, refresher training for laboratory staff and regular feedback to laboratories aimed at addressing the high incidence of these user related errors.[12,17]

Another focus area of the TDF training that has led to significant programmatic improvement is the monitoring of testing fleet and instrument downtime. A challenge faced by many tuberculosis programmes is that GeneXpert instruments are often located at remote facilities, leading to delays in maintenance and replacement of broken modules. By monitoring trends in how instruments report in real-time through connectivity tools, the Bangladesh NTP are now identifying directly when modules are down or instruments require calibration. Through this real-time monitoring of instrument performance, Bangladesh has managed to reduce instrument maintenance turn-around time from anywhere between 5 and 14 months to just 2 weeks, and is now also maintaining 90% module functionality.[12]

Ethical considerations

Ethical clearance was not required for this study.

Discussion

Various connectivity solutions exist to collect diagnostic data, some of which have already been adopted widely. Connectivity tools can play a major role in addressing many of the challenges that tuberculosis programmes face by facilitating the central collection and aggregation of diagnostic instrument data so that it can be analysed. However, the introduction of connectivity tools is not sufficient to ensure improved programme management. Well-functioning health systems need to utilise this data at all levels in order to drive evidence-based decisions and interventions to improve the quality of care provided.[18]

To our knowledge, the TDF programme is the first of its kind to build capacity and resources in low- and middle-income countries for the analysis of tuberculosis data collected from connected diagnostics. To address sustainability, the programme provided participants with the much-needed tools required to drive data analytics, counting on participants to lead the ongoing analysis of tuberculosis-related health data from the national GeneXpert programme in their respective countries. We chose Tableau software as a data analytics and visualisation tool, because it enables users to explore, manipulate and create visual representations of large amounts of data in order to produce insights as well as to communicate those insights to a broader audience. We leveraged an existing connectivity footprint, namely the GxAlert system (SystemOne, LLC, Northampton, Massachusetts, United States), to gain access to GeneXpert tuberculosis data within each respective country, but the programme is translatable to any connectivity platform collecting tuberculosis GeneXpert data. While the initial pilot

programme focused on tuberculosis, the intent is to expand into related disease streams and diagnostics within the ministry of health, such as HIV. By providing an online tool (Tableau Online) where participants could post their visualisations and insights, the programme also provides a platform whereby countries can share best practices and help to create value.

The TDF programme has already seen rapid development and analysis of country key performance indicators leading to immediate publications, programme engagements and strengthening.[12,13,16,17] By using the data to recognise programme gaps and identify needs, issues and priorities, participants have been equipped to help develop their national strategies, address challenges and inform data-driven decision making.

Conclusion

The programme empowers local ministry of health, NTP and national tuberculosis reference laboratory staff to lead the analysis of tuberculosis-related data, discover and fix critical inefficiencies, and provide high-level technical and operational support to tuberculosis programmes. Through data-driven, actionable recommendations, the TDF helps to strengthen, improve and complement NTPs in low- and middle-income countries and, ultimately, improve healthcare delivery.

Lessons learned
• Delivery of test data in a timely manner through connectivity platforms is critical to successful reporting and monitoring of tuberculosis programmes.
• Countries lack the capacity and experience in interpretation of diagnostic instrument data to be able to translate it into targeted interventions to improve programme performance.
• Selection of participants for this type of training needs to be more targeted to specific positions within the ministry of health and NTP programme to ensure better skills transfer.
• There was a decline in participant engagement toward the end of the 12-month training programme. In future, training should be accelerated towards a 3–6 month programme in order to avoid any decline.
• There is a need for institutionalisation of this kind of training by the World Health Organization, ministry of health, donors, implementers and partners, as connectivity becomes one of the cornerstone tools in data capture and management.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

N.G. was the project leader, and N.G., A.U.N. and B.C. were responsible for project design. N.G. wrote the article, and A.U.N., B.C. and C.M. contributed to the conceptualisation, design, development and editing of this article.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Disclaimer

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RESEARCH ARTICLE

Evaluating the integration of tuberculosis screening and contact investigation in tuberculosis clinics in Ethiopia: A mixed method study

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Abstract

Background

Aligned with global childhood tuberculosis (TB) road map, Ethiopia developed its own in 2015. The key strategies outlined in the Ethiopian roadmap are incorporating TB screening in Integrated Maternal, Neonatal and Child Illnesses (IMNCI) clinic for children under five years (U5) and intensifying contact investigations at TB clinic. However, these strategies have never been evaluated.

Objective

To evaluate the integration of tuberculosis (TB) screening and contact investigation into Integrated Maternal, Neonatal and Child Illnesses (IMNCI) and TB clinics in Addis Ababa, Ethiopia.

Methods

The study used mixed methods with stepped-wedge design where 30 randomly selected health care facilities were randomized into three groups of 10 during August 2016-November 2017. The integration of TB screening into IMNCI clinic and contact investigation in TB clinic were introduced by a three-day childhood TB training for health providers. An in-depth interview was used to explore the challenges of the interventions and supplemented data on TB screening and contact investigation.

Results

Overall, 180896 children attended 30 IMNCI clinics and145444 (80.4%) were screened for TB. A total of 688 (0.4%) children had presumptive TB and 47(0.03%) had TB. During the

Competing interests: The authors have declared that no competing interests exist.

pre-intervention period, 51873 of the 85278 children (60.8%) were screened for TB as compared to 93570 of the 95618 children (97.9%) in the intervention (p<0.001). This had resulted in 149 (0.30%) and 539 (0.6%) presumptive TB cases in pre-intervention and intervention periods (p<0.001), respectively. Also, nine TB cases (6.0%) in pre-intervention and 38 (7.1%) after intervention were identified (p = 0.72). In TB clinics, 559 under-five (U5) contacts were identified and 419 (80.1%) were screened. In all, 51(9.1%) presumed TB cases and 12 (2.1%) active TB cases were identified from the traced contacts. TB screening was done for 182 of the 275 traced contacts (66.2%) before intervention and for 237 of the 284 of the traced (83.5%) under intervention (p<0.001). Isoniazid prevention therapy (IPT) was initiated for 69 of 163 eligible contacts (42.3%) before intervention and for 159 of 194 eligible children (82.0%) under intervention (p<0.001). Over 95% of health providers indicated that the integration of TB screening into IMNCI and contact investigation in TB clinic is acceptable and practical. Gastric aspiration to collect sputum using nasogastric tube was reported to be difficult.

Conclusions

Integrating TB screening into IMNCI clinics and intensifying contact investigation in TB clinics is feasible improving TB screening, presumed TB cases, TB cases, contact screening and IPT coverage during the intervention period. Stool specimen could be non-invasive to address the challenge of sputum collection.

Introduction

There were an estimated 1.1 million children with TB globally, and this is about 11% of the estimated 10 million total TB cases in 2018 [1]. TB is one of the top 10 contributors to U5 mortality in TB endemic countries such as Ethiopia [2]. Ethiopia is one of the 30 high TB burden countries with an estimated TB incidence of 151/100,000 population in 2018 [1]. Accoridng to unpublished national TB report during July 2018-June 2019, there were 10,080 children less than 15 years among the 100,782 (10.0%) new TB cases where 2712 were children U5, representing 2.7% of total new cases in Ethiopia [3].

According to the 2019 global TB report, a third of estimated TB cases in Ethiopia were not detected [1]. Of the missed TB cases, 11,918 (20.0%) were estimated to be among children [3].

TB diagnosis in children is more difficult than in adults [4–6] due to the non-specific presentation of TB in children in the form of pneumonia, wheeze, and fever of unknown origin. In many developing countries, there is limited capacity, especially at the lower levels of the health care system, to suspect and diagnose TB in children. Also, systematic investigation of child contacts of adult pulmonary TB cases, an entry point to identify tuberculosis disease in children, is occasionally practiced. This causes a huge missed opportunity [7, 8]. Younger children rarely produce adequate sputum samples, reducing the possibility of utilizing rapid and sensitive TB diagnostic tools like GeneXpert for children [9].

In high TB burden settings like Ethiopia, there are opportunities to identify children with presumptive TB in the framework of IMNCI clinics or integrated community case management (ICCM). Though these clinics prioritize the identification and management of acute childhood diseases; such as diarrhea, malnutrition, pneumonia and fever, TB is likely affecting a number of children evaluated in these clinics. Besides, TB could be masked by symptoms of

these accute ilnessses [10]. Therefore, these clinics could harbour missed TB cases in children [11]. Yet an important step towards improving identification, prevention and management of TB in children is the provision of integrated care in IMNCI and ICCM platforms [12].

Accordingly, Ethiopia was the first African country to develop a national childhood TB roadmap following the global childhood TB road map in 2015 [13–15]. The key strategies outlined in the Ethiopian roadmap is integrating TB screening, diagnosis and prevention services into IMNCI clinics at the primary health care level and intensifying contact investigations at the TB clinics. These strategies can increase TB case detection in children and provide an opportunity to provide IPT [13, 15, 16]. The federal ministry of health of Ethiopia (FMOH) started implementing both strategies in Addis Ababa as a pilot before scaling up. This provided an opportunity to evaluate these interventions through implementation research.

Materials and methods

Settings

The study was carried out in Addis Ababa, the capital city of Ethiopia, with an estimated population of 3.9 million in 2017/2018 [17]. According to unpublished national TB report of 2018/2019, a total of 4,070 TB cases (116 /100, 000) were notified in Addis Ababa, of whom 191 (4.7%) were children less than 15 years of age [3].

Health centers are the first entry point to the formal health system, and they are the centerpiece of primary health care services in Ethiopia. One of their key roles is the provision of curative IMNCI services, such as treating children with diarrhea, pneumonia, and malnutrition. Cough triage, TB screening, diagnosis, and treatment are part of the TB service provided at the primary health care level with little focus on childhood TB.

Study design

A mixed method study was adopted to evaluate the programmatic intervention outlined below. For the quantitative part, a stepped-wedge design was applied as this is an optimal design to evaluate phased in interventions [18]. In depth interview and field notes (qualitative data) supplemented the quantitative data collection. For the stepped wedge design, the units of comparison were groups of randomly assigned health facilities that moved over to the intervention together. Allocation was not concealed, but clinicians, and TB and IMNCI officers were blinded to the order of entry into the intervention till each group of health centers were enrolled to the interventions [19].

The study was undertaken over a period of 16 months, and facilities transitioned in four-month intervals from pre-intervention to intervention period (Fig 1).

Sampling

Initially, all of the 100 health centers in Addis Ababa were listed with their annual patient load in the IMNCI clinic. Fifty health centers that reported more than 500 U5 children per year were included in the sampling frame. From these, 30 were randomly selected as the study health facilities. Subsequently, the 30 facilities were randomly assigned to three groups, each with 10 health centers, which started the intervention phase by phase.

Health care workers from each group of 10 health centers were trained and made ready to start the intervention at four-month interval (Fig 1). Preparation for and initiation of the interventions were during the fourth month of the previous phase and the first month of the upcoming phase.

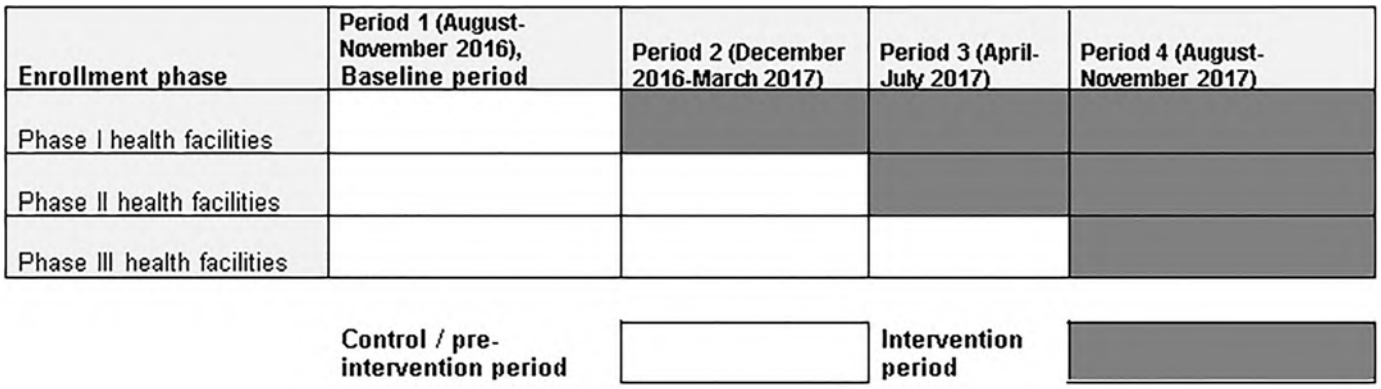

Fig 1. Schematic representation of the stepped wedge design of the implementation study in 30 health centers in Addis Ababa, August 2016-November 2017. Fig 1 shows the four periods, each with the length of four months. The first period (August- November 2016) was the baseline period where all health facilities served as control. December 2016-March 2017 was phase I where the first group of 10 health facilities (phase I health facilities) were enrolled into intervention. During this phase the rest of 20 health facilities served as control in the control period. April-July 2017 was a period when the second group of 10 health facilities (phase II) were enrolled into intervention. Here, phase I &II health facilities served as intervention health facilities in the intervention period, whereas the remaining 10 health fasciitis (phase III facilities) served as a control in the control period. Finally, in August-November 2017 phase III facilities entered the intervention.

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Interventions

The interventions consisted of the integration of TB screening into IMNCI clinics, and enhanced childhood TB case finding in the TB DOT unit (TB DOTS) clinics through contact investigation. To guide the intervention, desk reference materials in the form of pediatric TB job aids, updated IMNCI registers with a TB screening column and registers for contact investigation and IPT provision were developed and supplied. Sensitization on the implementation study was conducted for child-health and TB program officers and heads of the study health facilities. This was followed by a three-day basic childhood TB training for health care providers from the IMNCI and TB DOTS clinics to introduce the intervention. Nasogastric (NG) tubes were provided to each study health facility. Research physicians demonstrated and mentored Health care workers (HCWs) on how to perform the nasogastric aspiration (NGA) procedure. Onsite coaching of health providers followed classroom demonstration till the HCWs confidently carried out the procedure. The research team also monitored the performance of each study health facility and record keeping practice monthly.

TB screening and diagnosis, and contact tracing were based on the existing national guidelines and algorithms [20]. A child was identified as a presumptive TB case if cough, fever, failure to gain weight or contact history was reported. As per national policy, all children with presumed TB cases received GeneXpert MTB/Rif (GXP) as a primary diagnostic test. If the GXP was negative, contact history with an infectious pulmonary TB (PTB) case, suggestive chest X-ray and the presence of clinical signs of TB were used as criteria to diagnose TB in a child. The presence of at least two of these made a clinical diagnosis of TB in children. Those children identified to have active TB cases were started on TB treatment at TB DOTS clinic. To enhance contact tracing, all U5 contacts of PTB index cases identified at the TB DOTS clinics underwent evaluation for TB as outlined above. As part of contract tracing, children with screen negative or non-presumed TB case, thus without suggestion of TB, were eligible for prophylaxis and offered IPT (S1 Fig).

Data collection

Baseline data collection started in all study sites to document the practice of TB screening over a four-month period before the first group of 10 health facilities entered to the intervention. This baseline assessment was carried out using key outcome indicators, such as the number of presumed TB cases identified, the number of NGA undertaken, the number of TB cases identified at IMNCI clinics, the number of eligible contacts traced and screened, and the number of eligible U5 contacts started on IPT. During the project implementation, the researchers provided a standardized set of tools to capture the childhood TB data. From the study health facilities, HCWs were recruited and trained as data collectors. At the end of every fourth month, the trained HCWs collected data from the records of the study health facilities.

In addition, in-depth interviews (IDIs) were performed with 30 HCWs and 11 heads of study health facilities. Those on duty on the interview day were selected. The study coordinator conducted the IDIs until saturation, i.e. until no new information or views were obtained from subsequent interviews.

The IDIs were conducted twice during the project period, at the beginning (August-November 2016) and at the end (August-November 2017). IDIs were guided by a developed interview guide inquiring about the advantages and barriers of integration of TB screening into IMNCI and contact investigation to TB clinics. The study coordinators kept field notes of the observation during the data collection. The IDI and field notes were captured in English, though the interview was conducted in the local language, Amharic, for convenience.

At the end of the study, assessment on the feasibility of integration of TB screening into IMNCI and intensified contact investigation in TB clinics was done through a structured questionnaire among the selected set of 190 parents/caretakers, 80 health care providers and 30 heads of the study health facility. The data collectors interviewed the parents and caretakers when they showed up at IMNCI and TB clinics with their children, and the HCWs while on duty.

Data quality

Data collectors attended a one day training on how to extract data using the checklist. The researchers checked data consistency everymonth during mentoring visits and every quarter during supportive supervision to the study sites. The supervision was undertaken jointly with the staff from KNCV Tuberculosis Foundaiton, the national TB program (NTP) and the Maternal and Child Health Unit of FMOH and Addis Ababa regional Health bureau (AARHB). Double data entry was done for all extracted data. The quality control of this process was performed by the study coordinator. Before data analysis was commenced, data cleaning and validation of the entered data was done by checking for data completeness, presence of outliers and inconsistencies. The summary of findings from IDIs, and field notes of observation at the health facilities were re-checked with IDI participants.

Data analysis

Data entry for the quantitative part was done using EPI info (Version 7.2.2.16; Atlanta, Georgia: Centers for Disease Control and Prevention; 2018). Data analysis was done using STATA (Version 13; College Station, Texas: Stata Corp; 2013).

The main indicators such as the proportion of children screened for TB from patients at IMNCI clinics, the proportion of presumed TB cases and TB cases identified from the screened, the proportion of presumptive TB cases with NGA procedure done and the coverage of IPT (number of children started on IPT/number of children eligible for IPT) were compared using the two sample proportion test over the 16 months control and 16 months

intervention period. The mean number of children screened, identified with presumptive TB and detected to have active TB during the control (pre-intervention) period and the intervention period per the study site was also compared using two samples mean comparison test or t–test. The 95% CI and p-value (less than 0.05) were used to assess statistical significance.

The manual theme-based word data analysis was done based on the IDIs and field notes. Subsequently, the quantitative and qualitative findings were triangulated. Eventually, the feasibility (acceptability and practicality) of the integration of childhood TB screening to U5 clinics was described quantitively using frequency and proportion.

Ethical considerations

Ethical clearance was obtained from the Ethical Review Board of Addis Ababa City Health Bureau (AACHB). Support letters from AACHB to the sub-cities health bureaus, and then from sub-cities to the study health facilities were written to obtain permission to conduct the study and gain access to the childhood TB data of each the study participants. After the heads of the study facilities were briefed on the aim and methodology of the study, they provided a permission to include their health facility in the study. As this was a routine strategy being evaluated, no written consent was obtained for each child to take part in the study. The ethics committee waived the requirement for informed consent, and the data of each child was anonymized as well. Children diagnosed with TB were provided with TB treatment, and children eligible for preventive therapy were provided with IPT per the national guidelines.

Results

Over the 16 months period, a total of 181,455 children attended the 30 health facilities. Of these, 145,862 (80.4%) were screened for TB where 739 (0.4%) were presumed TB cases and 59 (0.03%) were TB cases. Over the study period, 125 successful NGA procedures were performed, and 12 (9.6%) of these were confirmed to be MTB by GXP. That is, only 12 of the 59 TB cases (20%) were bacteriologically confirmed.

A total of 559 U5 contacts were traced from the 1603 index cases, an average of one contact per three index cases. From the traced contacts, 419 (80.1%) were screened for TB. Three hundred fifty-seven were eligible for IPT, of whom 228 (63.9%) were started on IPT (Table 1).

IMNCI clinic

Of 180,896 children seen at IMNCI, 85,278 (47.1%) visited the study health facility during the pre-intervention period while 95,618 (52.9%) of them were seen during the intervention. A total of 145,443 (80.4%) of these children were screened for TB. TB screening was undertaken for 51,873 (60.8%) of children during the pre- intervention period and for 93,570 (97.9%) of the children under the intervention ($p<0.001$). From the overall screened children at IMNCI clinics, 688 (0.5%) children had presumptive TB cases where149 presumptive TB cases (0.3%) were identified among children screened duringthe control period while 539 (0.6%) were detected among children screened during the intervention ($p<0.001$). NGA was performed in 105 (15.3%) of the presumed TB cases. The procedure was carried out for 18 (12.1%) of the presumed TB cases identified during the pre- intervention and, it was done for 87 (16.1%) of the presumed TB cases during the intervention period ($p = 0.22$). A total of 47 TB cases were identified from the 688 presumed TB cases (6.8%). Nine (6.0%) were from the presumed TB cases detected before the intervention while 38 (7.1%) were from the presumed children detected under the intervention period ($p = 0.67$) (Table 1 and Fig 2).

Table 1. TB screening, identification of presumptive TB and TB cases, and contact investigation and TB preventive therapy efforts in the 30 study facilities in Addis Ababa Ethiopia, August 2016- November 2017.

Ser No.	Variables	Overall frequency (proportion)	Control period Frequency (proportion)	Intervention period Frequency (proportion)	Two-sample test of proportion, p-value (intervention vs control period)
1	**Overall (IMNCI unit and TB DOTS)**				
1.1	Children in attendance	181,455	85553	95902	
1.2	Children screened for TB (proportion screened)	145,862 (80.4%)	52055 (60.80%)	93807 (97.90%)	<0.001
1.3	Presumptive cases identified (proportion from screened)	739 (0.5%0	154 (0.3%)	585 (0.6%)	<0.001
1.4	NGA procedure carried out (proportion of those with presumptive TB)	125 (1.0%)	18 (11.7%)	107(18.1%)	0.06
1.5	TB cases detected (proportion from presumed TB cases)	59 (8.0%)	11 (7.1%)	48 (8.2%)	0.66
2	**IMNCI unit**				
2.1	children participated	180,896	85278	95618	
2.2	children screened for TB (proportion screened)	145443 (80.4%)	51873 (60.8%)	93570 (97.9%)	<0.001
2.3	presumptive cases identified (proportion from screened)	688 (0.5%)	149 (0.3%)	539 (0.6%)	<0.001
2.4	NGA procedure carried out (proportion of those with presumptive TB)	105 (15.3%)	18 (12.1%)	87 (16.1%)	0.22
2.5	TB cases detected (proportion from presumed TB cases)	47 (6.8%)	9 (6.0%)	38 (7.1%)	0.67
3	**TB DOTS**				
3.1	Number of index cases	1,603	684	919	
3.2	U5 contact children traced	559	275	284	
3.3	contacts screened (proportion screened)	419 (75.0%)	182 (66.2%)	237 (83.5%)	<0.001
3.4	Presumptive TB cases identified (proportion from screened)	51 (12.2%)	5 (2.7%)	46 (19.4%)	<0.001
3.5	NGA procedure done (proportion of those with presumptive TB)	20 (39.2%)	0 (0%)	20 (43.5%)	NA
3.6	TB cases detected (proportion from presumed TB cases)	12 (23.5%)	2 (40.0%)	10 (21.7%)	0.36
3.7	Eligible U5 children eligible for IPT	357	163	194	NA
3.8	Children started on IPT (proportion from eligible)	228 (63.9%)	69 (42.3%)	159 (82.0%)	<0.001

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TB DOTS clinic

Of the 1603 index cases at TB DOTS clinics, 684 (42.7%) were identified in the pre-intervention and 919 (53.3%) during the intervention period ($p<0.001$). TB screening was done for 182 of the 275 traced contacts (66.2%) before the intervention and for 237of the 284 traced (83.5%) after the intervention ($p<0.001$). Overall, 51 of the screened contacts in TB DOT (12.2%) had presumed TB cases, five (2.7%) among the screened before the intervention and 46 (19.4%) after the intervention ($p<0.001$). Before the intervention, no NGA procedures were undertaken in the TB DOTS clinic while 20 NGA procedures were performed during the intervention period. A total of 12 TB cases, 23.5% among the presumed TB cases, were identified in the TB DOTS clinic during the study period, two (40%) were among the presumptive TB cases before the intervention and 10 (21.7%) under the intervention ($p = 0.36$). IPT was

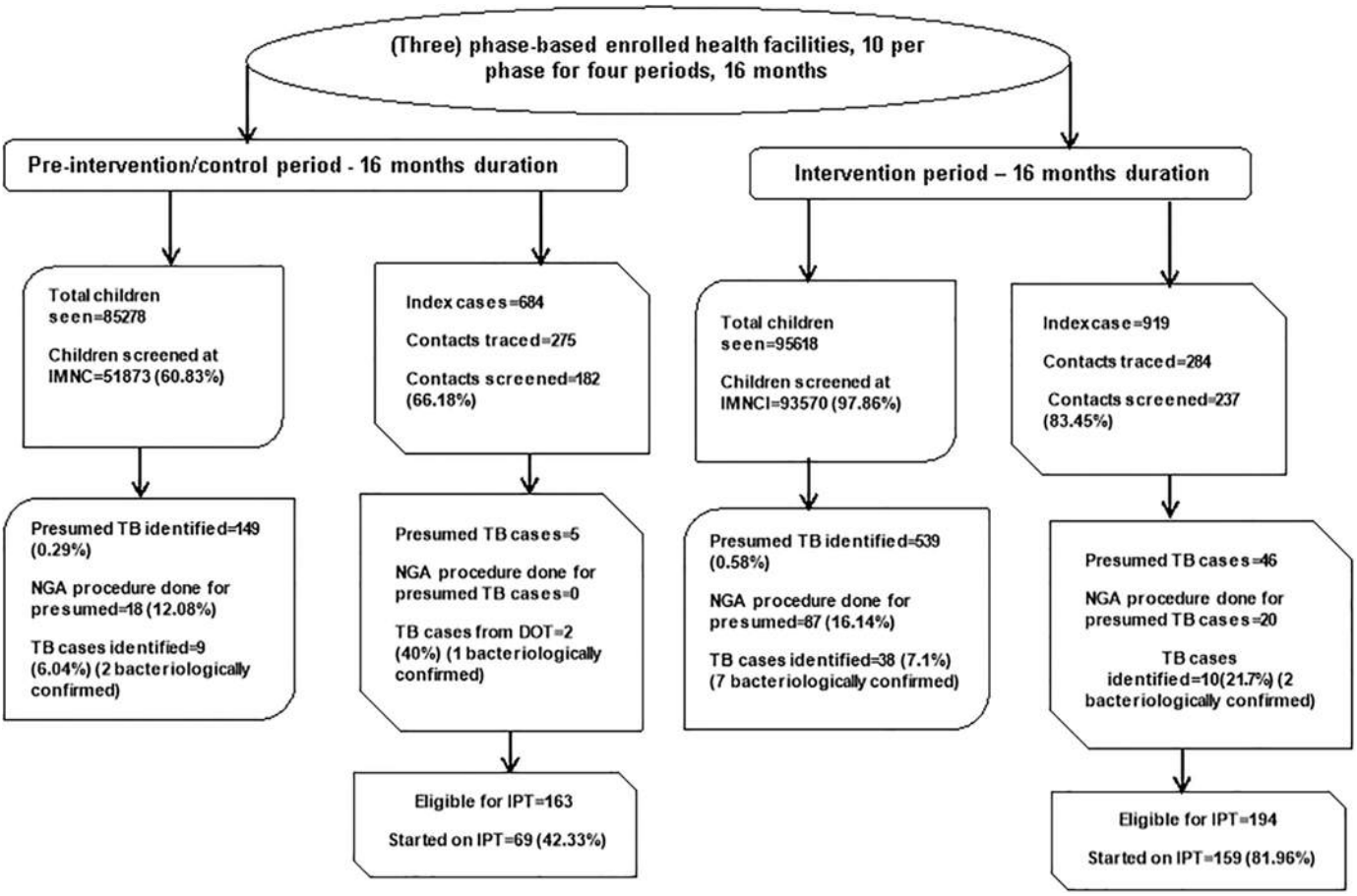

Fig 2. Summary of the findings: TB screening, evaluation, and diagnosis at IMNCI; and contact tracing, screening, and initiation of TB preventive therapy at TB DOTS in Addis Abba Ethiopia, August 2016-November 2017. Fig 2 shows the flow of TB screening and contact investigation activities based on the control and intervention period. For each period, there was TB activities at IMNCI and TB DOTs clinics. At IMNCI clinic, TB screening, identified presumed TB cases and TB cases were reported. At TB DOTS, number of index cases, contacts traced and screened, and IPT coverage were reported.

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initiated for 69 (42.3%) of eligible U5 children in the control period as compared to 159 (82.0%) during the intervention ($p<0.001$) (Table 1 and Fig 2). The details of TB activities at IMNCI and TB DOTS clinics in the 30 health facilities are described in S1 Table.

Table 2 shows the difference in the mean of children screened, presumed TB case identified, NGA procedure done, contacts traced, contacts screened and put on IPT in each study health facility during the pre-intervention and intervention periods. During the intervention period an average of 697 more children in each study health facility were screened ($p<0.001$). An average of eight more children with presumptive TB were identified ($p<0.001$), two more NGA procedures were done ($p<0.001$) and 01 more TB cases were identified ($p<0.001$) during the intervention period as compared to the pre-intervention in each study health facility. At IMNCI clinics, the mean difference in the number of children screened for TB, identified presumptive TB cases, performed number of NGA procedures and notified TB cases during the intervention period, as compared to the pre-intervention period, was statistically significant ($p<0.001$). In addition, the proportion of U5 children screened for TB was increased by 47.2% (95% CI 39.5%-54.9%) after intervention, by 47.3% (95% CI 39.6–55.0%) at the IMNCI clinics and by 27.9% (95% CI18.7–37.0%) at TB-DOTS. Also, IPT coverage was increased by 42.2% (95% CI 27.8–56.6%) after the intervention (Table 2). Further study health facility based

Table 2. Comparison of TB activities during the pre-intervention/control and intervention period per the study facility in Addis Ababa, Ethiopia, August 2016-November 2017.

Ser No.	Variables	Mean Difference per study health facility (after and before intervention)	95% Confidence Interval of mean difference		t-value	Sig. (2-tailed)
			Lower	Upper		
1	**Overall comparison**					
1.1	Total children involved	172	-128	471.7	1.1	0.26
1.2	Total screened	697.9	400.6	991.1	4.7	<0.001
1.3	Total presumptive TB case	7.6	5.1	10.03	6.04	<0.001
1.4	Total NGA procedure done	1.5	0.7	2.3	3.5	<0.001
1.5	Total TB cases identified	0.6	0.3	0.9	4.3	<0.001
1.6	% screened	47.2	39.5	54.9	12.1	<0.001
2	**IMNCI unit**					
2.1	No of U5 (IMNCI) children involved	172.3	-127.1	471.7	1.1	0.26
2.2	% screened at _IMNCI	47.3	39.6	55	12.1	<0.001
2.3	NGA done at IMNCI	1.2	0.4	1.9	2.9	<0.001
2.4	TB cases at IMNCI	0.5	0.2	0.7	4	<0.001
3	**TB DOTS unit (Contact investigation and preventive therapy)**					
3.1	% Contact screened	27.9	18.7	37	6.03	<0.001
3.2	%IPT coverage	42.2	27.8	56.6	5.8	<0.001

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detail of TB activities at IMNCI and TB DOTS based on the control and intervention periods is shown in S2 Table.

Challenges of childhood TB integration into under-five clinics

Health care providers usually refer children with presumptive TB to higher level health facilities. Because of the shortage of skilled manpower to diagnose TB in children, 22 of the 30 health facilities (73.0%) indicated to send children to higher level hospitals for evaluation and confirmation of TB during the baseline assessment. In addition to the non-specific presentation of TB in a child, this referral is mainly due to the lack of skilled HCWs to carry out the procedure of NGA. This was justified as,

> *"The failure to get a child with textbook symptoms and signs of TB. . . and few staff with the skill of conducting nasogastric aspiration could be ascribed to the difficulty of identifying TB among the children"*
>
> *M, 38, Head of a health center.*

The turnover of trained HCW in the IMNCI clinics was also pointed out as one of the challenges. In addition, HCWs reported to be overstretched due to the large number of U5 visits compromising quality of care and attention for TB screening. One of the participants stated,

> *". . . HCWs could be busy dealing with many U5 visits . . . There is a limited training on childhood TB for health care workers on the newly updated childhood TB diagnostic algorisms."*
>
> *Female (F), 30, head of a health center.*

Irrespective of the intervention, the health care providers indicated to have a low index of suspicion for presumptive TB cases of childhood TB. This was thought partly because a chronic cough was rarely identified in children through regular follow-up. Though the IMNCI guidelines indicate that parents should come back for follow up if the cough does not improve within two weeks, this often does not happen. Parents with children having respiratory tract infections usually seek for better care at private clinics or higher-level facilities, making it impossible to strict follow-up of pneumonia, malnutrition or URTI at health centers as per the IMNCI guidelines. The head of one of the study health facility described this as follows,

"If a child does not improve with common treatment as recommended by IMNCI, s/he is likely to be taken to private clinics . . .. and may not return to the IMNCI clinic. . . Families prefer to take the child (that does not improve) to hospital if the child has a cough or other signs and symptoms indicative of the presumed TB case; hence, difficult to observe chronic cough in kids"

M, 40, head of health center.

Therefore, in most cases, one cannot retain children long enough for further investigations or for subsequent screening to identify presumptive TB cases.

Feasibility of integrating childhood TB into IMNCI

Acceptability. At the study health facilities, more than 95.0% of the parents/guardians, health care providers and heads of the health facilities indicated they were comfortable with an integrated service delivery of TB screening and evaluation at IMNCI clinics and contact investigation at TB DOTS clinics. More than 94.0% of the clients and HCWs, and all facility heads said that they had a positive perception of the integration and none of them had negative feeling related to the integration of TB screening.

Practicality. Both the health care providers (95.0%) and the heads of the health facilities (100.0%) indicated that the implementation of TB symptom screening and contact investigation at IMNCI and TB DOTS clinics was easy to put in practice. (Table 3).

Discussion

We showed that the integration of TB screening into IMNCI and enhanced contact investigation at TB DOTS clinics is feasible, resulting in improved TB screening from 60.8% to 97.9%, identification of presumed TB cases from 0.3% to 0.6% and TB case detection from 7.1% to 8.2%. An additional 37 children with TB were diagnosed in the 30 clinics as part of the 16-month intervention. Enhancing contact investigation and improving the link between the TB DOTS clinic and the IMNCI clinic brought about 90 additional children accessing IPT and an additional 8 TB cases being detected over the study period reducing the potential of missed TB cases. In addition, the proportion of contacts screened was improved from 66.2% to 83.5%, while the coverage of IPT was increased from 42.3% to 82.0%. Nevertheless, challenges were also reported; the key ones being frequent turnover of trained staff and difficulty of obtaining sputum samples from young children with presumptive TB. High staff turnover is a common problem in developing country settings [21] and should be addressed as part of the further roll out of this intervention and in the general health care system. The difficulty of obtaining sputum samples has been previously reported [6] and is known for U5 children. At present, stool, which is easier to obtain and not invasive is being considered as an alternative sample for diagnosis of TB in children [22, 23] and investigated in a follow up project [24] in Ethiopia.

Table 3. The assessment of feasibility of integrating TB screening and contact investigation activities into IMNCI and TB DOTS clinics, August 2016- November 2017 Addis Ababa.

Ser No.	Feasibility	Clients who responded yes (N = 190)	Service providers who responded yes (N = 80)	Heads of the study health facilities who responded yes, (N = 30)
1	**Acceptability (Y/N)**			
1.1	Satisfied with availability of TB screening and contact investigation services at the same place as IMNCI and TB DOTs services	95.0	95.7	95.2
1.2	Is it appropriate to integrate TB screening and contact investigation services with IMNCI and TB DOTs services	94.7	90.9	100.0
1.3	Perceived positive effects of integrated TB screening and contact investigation services on IMNCI and TB DOTs services	94.4	95.2	100.0
2	**Practicality (Y/N)**			
2.1	Is it practical to implement TB symptom screening, clinical evaluation, and treatment for TB	NA	95.2	100
2.2	Are the suggested process, tools, and SOPs for TB management in IMNCI and TB DOTs setting easy to adopt	NA	94.7	100
2.3	Is delivery of integrated TB services through IMNCI and TB DOTs sustainable considering cost and human resources?	NA	86.4	89
2.4	Do integrated TB screening and contact investigation services disrupt implementation of routine IMNCI and TB DOTs services?	NA	14.3	17

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At the end of the study period, TB screening was conducted for over 98% of all children that attended the IMNCI clinics. This is much higher than findings from Uganda, where 47.0% of those <15 years were screened for TB symptoms [25]. In the same Ugandan study, however, 15.0% of the screened children were identified as presumptive TB, which is much higher than the 0.6% in our study. The lower screening coverage in Uganda may have resulted in a more targeted group of presumptive cases partly explaining the much higher proportion of presumed TB cases observed, as the study included many self-reported presumed TB cases. In our study, the proportion of TB screening and identified presumed TB cases could have been improved further had it been not for the high workload and high turnover of trained staff. Addressing such challenges could potentially further enhance the diagnosis of TB in children. Hence, on-the-job orientation on the importance of universal screening and evaluation of sick children for TB should become a routine activity.

It was shown that about four times less presumed TB cases were identified in the pre-intervention period, suggesting opportunities are currently being missed in routine childhood TB activities. This is also reflected in a community-based study in Ethiopia which showed that under routine care, opportunities are being missed to diagnose TB. This is because all presumed TB cases are not being identified and referred to a corresponding health center by health extension professionals (HEPs) leading to underdiagnosis of TB cases [26, 27]. According to a study by Tulloch and colleagues in Ethiopia, presumed TB cases often are not evaluated for active TB diseases even though they have a chronic cough. This is contributing to the missed TB cases [28]. Identification of presumptive TB in children largely depends on contact history with infectious TB cases, recurrent and repeated pneumonia, and failure to respond to the standard therapeutic therapy [29–31]. Those in contact with undiagnosed chronic coughers in the neighborhood or school should be considered to find all TB cases in children. Also, it is essential to avoid pre-diagnostic lost to follow up among children potentially showing signs and symptoms of TB [32]. That is, if all presumed TB cases that are treated for other non-TB cases but are not responding to the treatment and become deteriorated, these could

systematically be followed by the initial health facility. Doing so, children with presumptive TB could more easily be identified and subsequently be evaluated for TB.

Twenty-nine additional TB cases were identified in the intervention period at the IMNCI units, showing the potential of missed childhood TB cases under current routine conditions. Similarly, a study in Pakistan found that systematic verbal screening combined with contact tracing with appropriate management services resulted in a three-fold increase in pediatric TB case notification, cases that might have otherwise been missed [33]. In our study, it is important to note that only 88 NGA samples were collected out of the 454 presumed TB cases that were eligible for NGA procedure. The lower NGA performance was mainly due to lack of skill in the health care workers. Yet, if specimen collection and handling protocols could be strictly adhered to, NGA GXP can be highly specific for diagnosis of PTB in children [34] and we could have identified more TB cases.

Our study indicated that 10% of the NGA test results were MTB detected, resulting in a bacteriologically confirmed diagnosis. This is similar to a study in Botswana whereby 121/1274 NG samples (9.5%) were confirmed by culture [35]. Other studies found lower levels of bacteriological confirmation; for example, a study in India found 5.8% [36]. The difference could be due to the specific settings, skill differences or characteristics of the study population.

Our study also showed that enforcing contact investigation in the TB DOTS clinic can serve to increase TB case detection and coverage of preventive therapy. There were an additional 17.3% of child contacts screened, 39.6% more children started on IPT and 8 more TB cases identified. Similarly, a facility-based study on childhood TB screening in rural Pakistan identified 390 additional children with TB through contact tracing [33]. Studies from the southern region of Ethiopia [37], Amhara and Oromia regions [38–40] have shown that contact tracing can serve as a good entry point for IPT provision. However, this has not been replicated in all countries as shown by a study in Botswana attributing the low coverage of IPT to a poor implementation of contact tracing [41]. A study in Tanzania, conducted a year after a training on childhood TB, indicated that three times as many trained as untrained health care providers reported having ever prescribed IPT to a child [42]. Hence, consistent and continuous capacity building of health care workers at primary health care facilities is needed to improve and sustain contact investigation and provision of IPT for TB. The need to prepare a standard counseling tool that could assist in explaining parents the benefits of contact tracing and IPT at TB DOTS clinic is suggested.

We also indicated that improving childhood TB screening and diagnosis is feasible and practical after an intense training and creation of awareness on childhood TB among health care providers at the primary health care units, and this is similar to other studies [42, 43]. However, the required capacity building should not be limited to the health facilities, but needs to also involve community health care workers [44] to facilitate the integration of childhood TB into the ICCM platform. The integration of childhood TB into the child health platform was shown to be acceptable retaining more children to care in Malawi [45]. In Pakistan, the introduction of the intensified childhood TB care into the national TB program policy improved TB case finding as well as treatment outcomes [46]. Also, our study demonstrated that trained and mentored clinicians at child health clinics could screen, confirm TB diagnosis and link to treatment, yet the extent of the practical integration at primary care units should be explored further. Besides, the facility and community level routine monitoring of the childhood TB integration into sick child platforms necessitates the coordination and collaboration work with primary health care unit director, HEWs and other community health workers.

Our study is one of a few studies evaluating the implementation of the integration of childhood TB screening into IMNCI clinics and contact investigation into TB DOTS units using a mixed method study. However, the findings should be interpreted cautiously because the

study did not evaluate the integration of TB screening and contact investigation at the other childhood clinics. Therefore, the positive results achieved with the current study could be further expanded by involving other childhood health services such as nutrition, vaccination or, pediatric inpatient units as well as at the community level.

Conclusions

This demonstration work suggested that the implementation of integration of childhood TB screening to IMNCI and intensified contact investigation at TB DOTS clinics could improve TB diagnosis, and is acceptable and practical in Ethiopia. We have shown that appropriately trained frontline health workers at primary heath care unit level can significantly improve childhood TB diagnosis. Collecting sputum samples to confirm TB in children is difficult and alternative samples such as stool, which are easier to collect without invasive procedures, could be considered. Finally, contact investigation should be enhanced as an entry point for increasing IPT coverage for U5 children. In addition to the IMNCI, further integration of childhood TB screening into other childhood clinics such as nutrition therapy, expanded program on immunization (EPI), maternal and child health (MCH), pediatric wards or in patients, and pediatric emergency department clinics in health facilities could be considered to increase the coverage of screening U5 children.

Supporting information

S1 Fig. The flow chart and the algorism of TB screening, TB diagnosis, contact tracing and screening in Addis Ababa health facilities, August 2016- November 2017. S1 Fig shows that presumed TB cases in children could show up at IMNCI/U5 or TB DOT clinic. In both clinics, history of contact to infectious TB cases (or PTB) is used to identify children exposed to TB infection. PTB are smear negative and smear positive TB cases around which contacts are traced to be screened for TB. Eligible U5 children for IPT service were those with non-presumed TB cases and those with no contraindication to INH.
(TIF)

S1 Table. Phase and period-based activities at IMNCI and TB DOTS clinics in the 30 health facilities, August 2016-November 2017, Addis Ababa. The table indicates the three phase health facilities (Phase I, II &III) enrolled to the study/intervention. Phase I means the first 10 health facilities that were enrolled to intervention during December 2016-March 2017. Phase II means the second batch of 10 health facilities enrolled to intervention and it was from April-July 2017. Phase III is the period when the last 10 of the health facilities got into the intervention and it is August- November 2017. Note that the period of August-November 2016 was where all health facilities served as a control or baseline. The darker box is for TB activities for the intervention period and the normal or white sections is data for the control/baseline period.
(DOCX)

S2 Table. Overall and average TB activities at IMNCI and TB DOT based on the control and intervention periods per each four months per study health facilities of Addis Ababa, Ethiopia, August 2016-November 2017. This table indicates the total/sum, the ranges, and the means with 95% CI of TB screening and contact investigation activities for the control and intervention period health facilities. The range and the mean are shown per the study health facilities over the four months period.
(DOCX)

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RESEARCH ARTICLE

Addressing the drug-resistant tuberculosis challenge through implementing a mixed model of care in Uganda

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Abstract

Worldwide, Drug-resistant Tuberculosis (DR-TB) remains a big problem; the diagnostic capacity has superseded the clinical management capacity thereby causing ethical challenges. In Sub-Saharan Africa, treatment is either inadequate or lacking and some diagnosed patients are on treatment waiting lists. In Uganda, various health system challenges impeded scale-up of DR-TB care in 2012; only three treatment initiation facilities existed, with only 41 of the estimated 1010 RR-TB/MDR-TB cases enrolled on treatment yet 300 were on the waiting list and there was no DR-TB treatment scale-up plan. To scale up care, the National TB and leprosy Program (NTLP) with partners rolled out a DR-TB mixed model of care. In this paper, we share achievements and outcomes resulting from the implementation of this mixed Model of DR-TB care. Routine NTLP DR-TB program data on treatment initiation site, number of patients enrolled, their demographic characteristics, patient category, disease classification (based on disease site and human immunodeficiency virus (HIV) status), on co-trimoxazole preventive therapy (CPT) and antiretroviral therapy (ART) statuses, culture results, smear results and treatment outcomes (6, 12, and 24 months) from 2012 to 2017 RR-TB/MDR-TB cohorts were collected from all the 15 DR-TB treatment initiation sites and descriptive analysis was done using STATA version 14.2. We presented outcomes as the number of patient backlog cleared, DR-TB initiation sites, RR-TB/DR-TB cumulative patients enrolled, percentage of co-infected patients on the six, twelve interim and 24 months treatment outcomes as per the Uganda NTLP 2016 Programmatic Management of drug-resistant Tuberculosis (PMDT) guidelines (NTLP, 2016). Over the period 2013–2015, the RR-TB/MDR-TB Treatment success rate (TSR) was sustained between 70.1% and 74.1%, a performance that is well above the global TSR average rate of 50%. Additionally, the cure rate increased from 48.8% to 66.8% (P = 0.03). The Uganda DR-TB mixed model of care coupled with early application of continuous improvement approaches, enhanced cohort reviews and use of multi-disciplinary teams allowed for rapid DR-TB program expansion, rapid clearance of patient backlog, attainment of high cumulative

enrollment and high treatment success rates. Sustainability of these achievements is needed to further reduce the DR-TB burden in the country. We highly recommend this mixed model of care in settings with similar challenges.

Introduction

Worldwide, Drug-resistant Tuberculosis (DR-TB) remains a big challenge with Multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) being the worst forms. DR-TB is said to occur when TB organisms can continue to grow in the presence of one or more anti-TB drugs. Different forms of DR-TB exist and these include; Mono resistance, Poly resistance, Rifampicin resistance (RR-TB), MDR-TB and XDR-TB. Mono-resistance: resistance to one first-line anti-TB drug only while Poly-resistance: resistance to more than one first-line anti-TB drug, other than both isoniazid and rifampicin. MDR-TB is defined as TB that is resistant to at least the two most powerful first-line medicines (Rifampicin and Isoniazid) while XDR-TB is a form of TB that addition to being resistant to Rifampicin and Isoniazid, is resistant to any Fluoro-quinolone and at least one of the injectable second-line drugs. Rifampicin resistance (RR-TB): resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs; includes any resistance to rifampicin in the form of mono-resistance, poly-resistance, MDR-TB, or XDR-TB [1–3]. In 2015 alone, about 580,000 people developed MDR-TB and about 9.7% of these cases had XDR-TB [4] while an estimated 250,000 people died of MDR-TB [1, 4]. Notable causes of DR-TB among others include; poor adherence to TB treatment, inappropriate or incorrect use of anti-TB drugs and the use of poor quality medicines [5]. Again, due to the growing availability of rapid diagnostics (Xpert MTB/Rif assay), the detection and diagnosis of DR-TB patients is on the increase. However, in most settings, the diagnostic capacity has superseded the DR-TB clinical management capacity thereby causing ethical challenges [6, 7]. Untreated MDR-TB fuels the generation and subsequent transmission of XDR-TB [2] and incident cases are predicted to increase [8]. In this regard, the emergence of DR-TB continues to threaten global efforts to eliminate TB and threatens to reverse the global progress made in TB control [9–12].

In Sub-Saharan Africa, a resource-limited setting, the true burden of DR-TB is unknown as most countries have not conducted drug-resistance surveys. To make matters worse, the treatment of patients with DR-TB is either inadequate or lacking [2, 13]. This precedent has resulted in DR-TB patients diagnosed being put on treatment waiting lists as affected countries try to establish or scale up PMDT treatment programs. The outcome of this is that most DR-TB patients are delayed to start treatment resulting in high morbidity and mortality [14–17].

Uganda is one of the "30 high burden TB/ Human immunodeficiency virus (HIV)" countries that collectively account for 90% of the global TB burden [18]. While the World Health Organization (WHO) had removed Uganda off the list of TB high burden countries (HBC) in 2015 [20], a recent Uganda population-based TB prevalence survey suggests that incidence and prevalence rates in the country are far higher than previously believed [19, 20], and that notification rates for drug-susceptible (DS) and DR-TB represent only a small proportion of actual cases [20]. In 2012, the Uganda National TB and Leprosy Programme (NTLP) had encountered several challenges in implementing TB control activities in the country, for example, there was limited capacity to rapidly clear the 300 RR-TB/MDR-TB patient backlogs. Consequently, in 2013, the NTLP was supported to overcome such challenges [20, 21]. Partners

provided both logistical and technical support to NTLP central unit, treatment sites and played a coordination role. Therefore, the objective of this descriptive review was to assess and share resulting from the achievements of the implementation of the Uganda mixed Model of DR-TB care.

Materials and methods

Study area

Uganda is a landlocked country, located in East Africa with a total population of 34.6 million and over 111 districts and one City [22]. Uganda is among the 30 high TB/HIV burden countries [18] with a TB prevalence and incidence at 253 cases per 100,000 and 234 cases per 100,000 respectively [19, 23]. The burden of RR-TB/MDR-TB is estimated at 1.4% among all new and 12.1% among previously treated TB cases [9, 11]. In 2012, Uganda notified about 310 out of an estimated 1010 RR-TB/MDR-TB cases. Of these, only 41 were enrolled on treatment, and about 300 RR-TB/MDR-TB patients awaited treatment during this period [17, 21]. The lack of treatment for most RR-TB/MDR-TB patients perpetuated an ongoing transmission posing a major threat to the community around these patients. During the same period, the NTLP was still grappling with a lack of a nationally agreed DR-TB scale-up plan coupled with a weak health care system. There was limited access to drug susceptibility test (DST), unreliable second-line drug (SLD) management system, with no contact tracing of contacts of index cases besides limited expertise in case management and poor access to treatment. More still, the country only had three DR-TB treatment initiation facilities [21, 24] and thus health workers often referred RR-TB/MDR-TB patients to these few treatment initiation sites. Furthermore, there were low levels of sputum follow up examinations; loss of specimens during transportation; drug stock-outs; lack of appropriate isolation spaces, and limited funding at both NTLP central unit and district levels. Due to high stigma towards RR-TB/MDR-TB patients and high mobility of populations, RR-TB/MDR-TB patient loss-to-follow-up was high [21].

Study design

Service delivery through a mixed DR-TB model of care. The above challenges and the need to expand the Programmatic Management of DR-TB (PMDT) program led to a paradigm shift. The NTLP and partners (USAID funded TRACK TB Project, Strengthening Uganda's Systems for Treating AIDS Nationally/SUSTAIN and The Global Fund to Fight AIDS, Tuberculosis, and Malaria/GFATM) designed and scaled up DR-TB service delivery [21]. A locally appropriate Uganda-specific mixed model of DR-TB treatment was designed and rolled by NTLP and partners to rapidly absorb the RR-TB/MDR-TB patient backlog to save lives and to curtail the ongoing DR-TB transmission [25]. This DR-TB mixed model of care involves brief periods of hospitalization (in-patient) followed a long period of ambulatory/clinic-based care. Patients who are severely ill or not within the immediate catchment area of the treatment initiation hospital are admitted for a short period of 1–8 weeks and thereafter are transferred for ambulatory care at a prepared peripheral directly observed therapy (DOT) follow up facility nearest to patients' homes. In this paper, we share experiences, implementation approach, achievements, and lessons/good practices from the implementation of the mixed DR-TB treatment model of care in Uganda starting from 2013 through 2017. This model may be ideal for both current and future PMDT programs in similar resource settings.

Interventions, innovations, and roll out of the DR-TB mixed model. Before the DR-TB program was scaled up, a baseline analysis was conducted that informed the DR-TB minimum package of interventions that were applied. These interventions included the strengthening of

health care provider skills, implementation of quality improvement and use of standard operating procedures, improving access to patient investigation/treatment monitoring tests, management of TB commodities, strengthening of data management, the performance of enhanced cohort reviews, improving TB Infection Control practices, facilitation to implement ambulatory care (Home visiting, contact tracing, follow up facility training/mentorship and drug delivery), general hospital administrative support and provision of patient psychosocial economic support including food and transport (incentives and enablers). This direct patient socio-economic support is reported to be associated with better treatment outcomes through enhancement of nutritional status, patient adherence, and compliance [26, 27].

NTLP was supported with logistical and technical support at both its central unit and at all DR-TB facilities. Human resource (HR) capacity and partner coordination at NTLP central unit was strengthened through the secondment of technical staff to lead NTLP continuous quality improvement (CQI) campaigns and overall partner coordination. Early implementation of continuous quality improvement campaigns through peer to peer mentorships, coaching, holding learning sessions contributed to improved quality of care and the building of multi-disciplinary teams of DR-TB experts in sites where few experts existed. Therefore, these teams of experts provided the day to day advisory services at both the national and regional levels. More still, initially, a toll-free helpline was established to support the linkage of peripheral regional site teams to the National DR-TB Panel for specialized advisory services until an Echo platform which a learning network, established by the Project ECHO (University of New Mexico) was introduced.

To ensure standardized DR-TB program implementation, DR-TB treatment guidelines, and other tools were developed and disseminated through National coordination committee (NCC) meetings at the central level while at the subnational level, this was achieved through performance and cohort review meetings. Conduction of enhanced cohort reviews also helped to validate program data, identify performance gaps and best practices. Therefore, these enhanced cohort reviews served as a vehicle for capacity building and programmatic implementation of continuous quality improvement (CQI) campaigns.

More human resource capacity at DR-TB treatment initiation was built based on a standardized curriculum and training materials including at Follow up health facilities (FUFs, defined as any health facility identified and accepted to offer DOT to DR-TB patients). Remodelling/construction of DR-TB wards to both expand admission ward space as well as improve TB infection control was supported. Community linkage facilitators (CLF) and district teams supported adherence enhancement through the provision of patient and family education on DR-TB disease, tracking of patients lost to follow-up (LTFU) as well as linking of diagnosed patients. The DR-TB program monitoring and evaluation system was strengthened through the development of an electronic web-based recording/reporting management system (DR-TB Management Information System). To strengthen the DR-TB drug and commodity supply chain, the QUAN TB tool was used [31] to improve ordering as well as monitoring of utilization of DR-TB commodities. Again, the installation of GeneXpert machines while ensuring internet connectivity to improve access to rapid DST (drug susceptibility testing) and to facilitate the real-time transmission of GeneXpert results through the GxAlert information system was done. To ensure a high DR-TB program quality, NTLP's central DR-TB core committee that is part of the national technical committee that oversees implementation, policy formulation, resource mobilization, implementation science and overall coordination of the PMDT program was set up and facilitated to hold regular coordination meetings during which action plans were drawn. For Treatment Initiation Sites (TISs) and, FuFs' roles see Table 1.

Table 1. Roles of treatment initiation sites and FuFs in DR-TB management.

Treatment initiation site (TIS)	Follow up Facility (FuF)
• Initiating and offering "start-to-finish" case management (monthly clinic reviews, monitoring and managing side effects, offering DR-TB expert Panel services, and conducting cohort reviews to assign treatment outcomes)	• Providing DOT to DR-TB patients on ambulatory care
	• Providing adherence counselling and education to patients and families
• Training and mentoring FuFs for ambulatory care	• Conducting patients' home visits for contact tracing, nutrition, and infection control assessments.
• Managing and supplying DR-TB commodities to all initiated/active patients	

DR-TB, Drug-resistant tuberculosis.

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Data management and analysis

We used the baseline program data collected in 2012 and the routine DR-TB program 2013–2017 data collected by NTLP from all the 15 sites to describe the achievements and outcomes of implementing the DR-TB mixed model in Uganda. Data on the following variables were collected; treatment initiation site, RR-TB/MDR-TB patients enrolled, sex, age, patient categories, disease type, HIV status, HIV integration, culture and smear results, 6-month interim outcomes, 12-month interim outcomes and 24-month final treatment outcomes based on Uganda NTLP guidelines [32]. The study endpoints for the six, twelve and 24-month outcome analysis were 12, 18 and 24 months after the closing day of the RR-TB/MDR-TB cohort enrollment respectively. Based on these study endpoints, RR-TB/MDR-TB cohort data from 2012 to 2017 for all the 15 treatment initiation facilities were collected and descriptive analysis was done using STATA version 14.2 (Stata Corp. 2015. Stata Statistical Software: College Station, TX: Stata Corp LP). Continuous data were summarized using medians while categorical data were computed as proportions. We presented the data in text, tables, and graphs. Results for trends were presented at p-value < 0.05 level of significance and 95% confidence interval. We considered the achievements and outcomes to be; the increase in the number of RR-TB/MDR-TB patient backlog cleared, an increase in the number of DR-TB initiation sites, an increase in cumulative number patients enrolled, an increasing percentage of HIV integration interventions and favourable six, twelve months interim and 24 months final treatment outcomes among 2013–2017 cohorts. The RR-TB/MDR-TB outcome measures were defined according to the Uganda NTLP 2016 PMDT guidelines [32].

Ethical considerations

We used routine NTLP program data [19, 23, 24] collected for routine patient care at all health facilities in Uganda with no patient interaction. The data did not carry any personal identifiers and third parties had no access to this data. Permission to use the data for this study was sought from the NTLP. The researchers did not anticipate any risk or benefit to the patients in the analysis of this information.

Results

The backlog of the 300 RR-TB/MDR-TB patients who were on the treatment waiting list was cleared by the end of 2014. The RR-TB/MDR-TB cumulative patient enrollment increased from 41 in 2012 to 1311 patients (Fig 1) in 2017. GeneXpert coverage increased from 24 GeneXpert machines in 2012 to 131 GeneXpert machines in 2017 (Fig 2). The operationalization of the Uganda DR-TB mixed model also allowed for the rapid expansion of the DR-TB

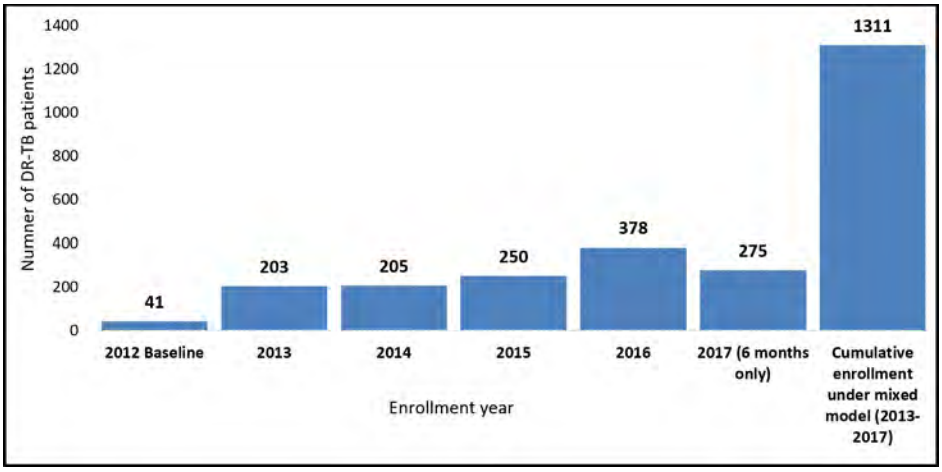

Fig 1. The number of RR-TB/MDR-TB patients enrolled by year.

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treatment and care program from 3 DR-TB treatment initiation sites at baseline in 2012 to 12 sites in 2013, 15 sites in 2017 (Fig 2).

Characteristics of patients enrolled for RR-TB/MDR-TB treatment

The characteristics of the RR-TB/MDR-TB patients enrolled for treatment from 2013 to 2017 are shown in Table 2 below. In this period, a total of 1,311 RR-TB/MDR-TB patients were enrolled; 64.4% (844/1311) were male. The majority of enrolled patients, 47.2% (619/1311), were in the young and productive age group of 15–34 years. 41.7% (547/1311) were aged 35–54 years, 7.6% (100/1311) were older than 54 years and 3.3% (43/1311) were under 15 years. The median age was 34 years, with a mean of 35.53 ± SD 12.78 years. Most patients, 98.5% (1291/1311) had pulmonary RR-TB/MDR-TB, and slightly more than half of the patients enrolled from 2013 through 2017 52.6% (690/1311) were HIV co-infected.

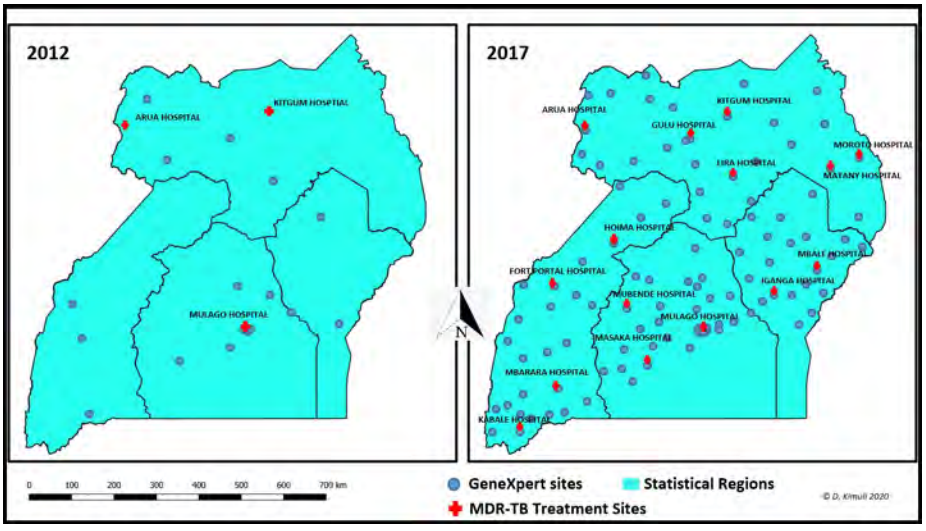

Fig 2. GeneXpert machines and DR-TB treatment sites in 2012 and 2017.

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Table 2. Characteristics of RR-TB/MDR-TB patients enrolled for treatment in 2012 and 2017.

Baseline characteristics	*2012 Baseline*	*2013*	*2014*	*2015*	*2016*	*2017*
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Total (N)	41	203	205	250	378	275
Sex						
Male	26(63.4)	126(62.1)	131(63.9)	168(67.2)	247(65.3)	172(62.6)
Female	15(36.6)	77(37.9)	74(36.1)	82(32.8)	131(34.7)	103(37.4)
Age (years)						
<15	2(4.9)	5(2.5)	3(1.5)	7(2.8)	12(3.2)	16(5.8)
15–34	13(31.7)	97(47.8)	88 (42.9)	132(52.8)	180(47.6)	122(44.4)
35–54	24(58.5)	91(44.8)	101(49.3)	96(38.4)	153(40.5)	106(38.5)
>54	2(4.9)	10(4.9)	13(6.3)	14(5.6)	33(8.7)	30(10.9)
Missing age	0(0.0)	0(0.0)	0(0.0)	1(0.4)	0(0.0)	1(0.4)
Pulmonary	39(95.1)	200(98.5)	201(98.1)	248(99.2)	373(98.7)	269(97.8)
Extra-pulmonary	2(4.9)	3(1.5)	4 (1.9)	2(0.8)	5(1.3)	6(2.2)
HIV status						
HIV-negative	28(68.3)	112(55.2)	96(46.8)	107(42.8)	167(44.2)	139(50.5)
HIV-positive	13(31.7)	91(44.8)	109(53.2)	143(57.2)	211(55.8)	136(49.5)

N/n = Number of patients.

HIV—human immunodeficiency virus.

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Treatment outcomes

Six-month interim treatment outcomes for RR-TB/MDR-TB patients enrolled from 2012 to 2016. Although the culture conversion rates initially improved at month six from 48.8% (20/41) in 2012 to 55.2% (112/203) in 2013 and 67.8% (139/205) in 2014, there was a drop off to 58.0% (145/250) in 2015 and 47.6% (180/378) in 2016 cohorts (Table 3).

Twelve-month interim outcomes for RR-TB/MDR-TB patients enrolled in 2012–2015. The culture conversion rates at 12 months initially improved from 29.3% (12/41) to 51.7% (105/203) in 2013 and 63.9% (131/205) in 2014 but again dropped to 48% (120/250) in 2015 (Table 4).

Final treatment outcomes for RR-TB/MDR-TB patients enrolled in 2012 and 2014. The original small cohort of 41 RR-TB/MDR-TB patients in 2012 cared for by partner organizations achieved a high level of treatment success of 78% (32/41), but the notable achievement under this NTLP led DR-TB mixed model is that NTLP managed to maintain high treatment success rates of 74.0% among both 2013 and 2014 cohorts and then 70.1% in the 2015 cohort in the face of the large rise in enrollment and rapid expansion to multiple sites across the country, within the public health system (Table 5). Evidence from other settings shows similar

Table 3. Six-month interim outcomes for RR-TB/MDR-TB patients enrolled from 2012 to 2016.

Interim outcomes at 6 months	*2012 Baseline*	*2013*	*2014*	*2015*	*2016*	*Total 2013–2016*
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Total	41	203	205	250	378	1036
Culture negative	20(48.8)	112(55.2)	139(67.8)	145(58.0)	180(47.6)	576(55.6)
Culture positive	1(2.4)	2(1.0)	1(0.5)	4(1.6)	2(0.5)	9(0.9)
Culture unknown	20(48.8)	89(43.8)	65(31.7)	101(40.4)	196(51.9)	451(43.5)

N/n = Number of patients.

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Table 4. Twelve-month interim outcomes for RR-TB/MDR-TB patients enrolled in 2012–2015.

Interim outcomes at12 months	*2012 Baseline*	*2013*	*2014*	*2015*	*Total 2013–2015*
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Total	41	203	205	250	658
Culture negative	12(29.3)	105(51.7)	131(63.9)	120(48.0)	356(54.1)
Culture positive	0(0.0)	2(1.0)	1(0.5)	0(0.0)	3(0.5)
Culture unknown	29(70.7)	96(47.3	73(35.6)	130(52.0)	299(45.4)

N/n = Number of patients.

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outcomes when patients are hospitalized for a brief period followed with ambulatory care so long as patient support and monitoring is done [28].

The proportion of RR-TB/MDR-TB patients that cured increased substantially from 48.8% in 2012 to 60% and above in 2013 to 2015 ($p = 0.03$), with a significant reduction in treatment completion rates from 29.3% to 3.3% ($p<0.05$) which points to improved quality of care. Overall, 1.1% (7/649) failed on treatment, with a slight increase in failure rate from 0% in 2012 to 1.7% in 2015 but this was not statistically significant ($p = 0.57$). Out of the 52.1% (338/649) HIV co-infected patients, 100% (338/338) were on both CPT and ART. However, HIV co-infection rates soared up from 31.7% in 2012 to 57.3% in 2015 ($p<0.05$), see Table 5.

Discussion

The most notable achievement under this NTLP led DR-TB mixed model is that NTLP managed to improve the percentage of patients that were cured from 48.8% in 2012 to 66.8% in

Table 5. Final treatment outcomes for RR-TB/MDR-TB patients enrolled in 2012 and 2015.

Final Treatment outcome	2012 Baseline	2013	2014	2015	P-value
	n (%)	*n (%)*	*n (%)*	*n (%)*	*(X^2)*
Total	41	203	205	241	
Cured[¥]	20(48.8)	122(60.1)	142(69.3)	161(66.8)	0.03
Completed[Ø]	12(29.3)	28(13.8)	10(4.9)	8(3.3)	<0.05
TSR[*]	32(78.0)	150(73.9)	152(74.1)	169(70.1)	0.63
Unfavorable	9(22.0)	53(26.1)	53(25.9)	72(29.9)	
• Lost to Follow up	4(9.7)	15(7.4)	22(10.7)	34(14.1)	0.16
• Died	2(4.9)	36(17.7)	30(14.6)	34(14.1)	0.20
• Failed Treatment	0(0.0)	2(1.0)	1(0.5)	4(1.7)	0.57
• Not evaluated	3(7.3)	0(0.0)	0(0.0)	0(0.0)	<0.05
Tested for HIV	41(100)	203(100)	205(100)	241(100)	
HIV-positive	13(31.7)	91(44.8)	109(53.2)	138(57.3)	<0.05
Started on CPT	13(100)	91(100)	109(100)	138(100)	
Started on ART	13(100)	91(100)	109(100)	138(100)	

N/n = Number of patients. [*]From 2015 cohort 9 patients were found not RR/MDR patients and thus eliminated from final treatment outcomes

¥Cured is a pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.

Ø Treatment completed is a TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.

[*]TSR (Treatment Success Rate) is the sum of cure rate and completion rate.

HIV—human immunodeficiency virus, CPT—Co-trimoxazole preventive therapy, ART–antiretroviral therapy, X^2 for the trend.

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2015. The NTLP also maintained high treatment success rates (TSR) of 74.0% among both 2013 and 2014 cohorts and 70.1% among the 2015 cohort. This rate was in comparison to the 78% TSR that was achieved among the original small cohort of 41 patients cared for by partner organizations under research setting in 2012. The achieved TSR was well above the global TSR average rate of 50% [4] and was achieved in the face of a high number of RR-TB/MDR-TB patient backlog (of 300 patients), large rise in enrollment and rapid expansion to multiple sites across the country within the public health system [24]. These high treatment success rates in 2013 through 2015 were possibly made possible through implementation of continuous quality improvement campaigns through peer to peer mentorships, coaching, holding learning sessions. These quality improvement campaigns contributed to improved quality of care and the building of multi-disciplinary teams of DR-TB experts. Besides, there was the conduction of enhanced cohort reviews which helped to validate program data, identify performance gaps and best practices. The quickly built DR-TB capacity through enhanced cohort reviews and early application of CQI approaches allowed for the rapid expansion of the DR-TB treatment initiation sites from three in 2012 to 12 in 2013 and subsequently to 15 from 2014 up to 2017. The significant rise in enrollment rates and in the proportion of cured RR-TB/MDR-TB patients over those who completed treatment attests to this built capacity and improved the quality of DR-TB care. Again, treatment models that embrace.

This rapid expansion in the number of DR-TB treatment initiation facilities and ambulatory care led to rapid clearance of the 300 RR-TB/MDR-TB patients who were on the waiting list since 2009 and the attainment of a cumulative RR-TB/MDR-TB enrollment of 1311 patients over five years (2013–2017) up from 41 enrolled in 2012. More still, widespread availability of GeneXpert machines enabled the identification of the 1311 RR-TB/MDR-TB cases despite a low GeneXpert utilization standing at an average of 6 tests per machine; there were 24 GeneXpert machines in 2012, 39 in 2013, 72 in 2014, 111 in 2015, 112 in 2016 and 131 in 2017. GeneXpert implementation is reported to improve early detection and to promote early treatment of RR-TB/MDR-TB [29–31].

According to Uganda PMDT guidelines, all newly diagnosed RR-TB/MDR-TB patients are started on a standard regimen - 6Km-Lfx-Cs-Eto-Z/14Lfx-Cs-Eto-Z until their DSTs are available at which point, their treatment becomes individualized based on observed resistance and side effects profiles [32]. Most patients responded well on this regimen as noticed through the improvement in the culture conversion rates between 2013 and 2015 compared to the 2012 baseline ($p< 0.05$). The majority of the patients had achieved culture conversion with only 0.9% (9/1036) still being culture positive. At 12 months, 54.1% (356/658) of the evaluated patients were culture-negative with only 0.5% (3/658) remaining culture positive. The high proportion of patients with no culture results at both six and 12 months outcome analysis across all the years is attributed to patient deaths, LTFU, and failures in sample referral system as well as failure to return culture and smear results to health facilities [21, 33]. Again, although decentralization of DR-TB treatment services was supposed to improve RR-TB/MDR-TB interim and final treatment outcomes, case holding was poorer in sites with big numbers of patient enrollment beyond site capacity. For instance, in 2016, an analysis of the performance at individual sites showed that sites which enrolled the highest number of patients had the highest number of deaths and patients Loss to follow up due to high volume of patients they have to manage [33]. Again, although these challenges were picked up by CQI assessments, addressing them could not be solved at once in a public health system.

Between 2013 and 2015, there were more patients that died while on treatment than were LTFU and failed treatment. Although one study attributed this death to TB-HIV co-infection [17], the high deaths and LTFU among the 2013 to 2015 cohorts could be attributed to; firstly, enrollment of critically ill patients as a result of being on a treatment waiting list for long before

the expansion of PMDT in 2013 [20] and secondly, rapidly expanding PMDT program to DR-TB sites that had limited capacity and prior experience in managing RR-TB/MDR-TB patients in the bid to rapidly clear the patient backlog and save lives [20].

Of the 1,311 RR-TB/MDR-TB patients enrolled on treatment from 2013 up to 2017, 64.4% (844/1311) were males. This finding of a higher RR-TB/MDR-TB burden among males is also reported in other settings and the available epidemiological literature suggests that this differential burden may be due to environmental and biological factors [34–39]. However, in Uganda, whether this observation is due to environmental, biological, social determinants or increased male's health-seeking behaviour remains to be fully established. Also, most of the patients were in the reproductive years, with pulmonary RR-TB/MDR-TB disease and were co-infected with HIV. This indicates a pressing need to identify and effectively manage RR-TB/MDR-TB patients with Pulmonary TB disease with a gender focus among men.

To reduce RR-TB/MDR-TB related mortality and DR-TB transmission, there is a need for early detection and prompt treatment of DR-TB patients. Again, the regularity in the provision of patient incentives and enablers under the Global Fund needs to be improved to lead to further improvement in RR-TB/MDR-TB treatment outcomes. Also, the increased emphasis on the provision of socio-economic support to improve treatment outcomes and overall quality of life is needed [12, 16, 40]. An improvement in the transportation of sputum samples to the central reference laboratory for testing, the turnaround time of results, and addressing logistical challenges is needed [20, 21, 23]. Therefore, more support should be extended to DR-TB sites to ensure that all data on baseline investigations, treatment monitoring including sputum smear and culture results and treatment outcomes are promptly and completely entered the DR-TB registers.

The strategies and approaches employed under this model are useful to most countries battling with the same problem of clearing backlog and expanding patient enrollment [25]. Available studies suggest that such DR-TB treatment models that embrace CQI approaches and decentralization of management of patients near or at home, are not only socially acceptable [27, 41] but are associated with favourable treatment outcomes; even among HIV co-infected and XDR-TB patients [42].

Due to the inherent nature of retrospective studies, this descriptive review had some limitations; some important study variables e.g. smear and culture monitoring results were unknown for a significant number of patients. Therefore, during study analysis, outcomes were assigned based on only records and monitoring data variables that were available in the DR-TB register. This has the potential of introducing a selection bias into our results, therefore, there is a need to strengthen data documentation especially now with the introduction of a web-based DR-TB management system. Finally, the absence of controls for such a review may lower the vigour for the conclusions drawn, however, this study may act as a benchmark for future studies.

Conclusions

In conclusion, this descriptive review indicates that the NTLP led DR-TB mixed model of care achieved high TSRs of 74.0% among both 2013 and 2014 cohorts and 70.1% among 2015 cohort in the face of a high number of RR-TB/MDR-TB patient backlog (of 300 patients), large rise in enrollment and rapid expansion to multiple sites across the country within the public health system. These achievements are attributed to the early implementation of CQI campaigns which contributed to improved quality of care and the building of the capacity of multi-disciplinary teams of DR-TB experts. Also, conduction of enhanced cohort reviews helped to validate program data, identify performance gaps and best practices. The use of this experience to foster national PMDT expansion as well as the sustainability of these

achievements is needed to further reduce the DR-TB burden in the country. However, due attention should be paid to the identified performance gaps for improvement. We propose this mixed model of care that applies a standardized minimum package of interventions in similar settings with similar challenges. This approach may have financial implications, so, the implied cost of the intervention may need to be investigated before the adoption. The financial analysis for the program was not considered for the scope of this study.

Supporting information

S1 Table. MDR-TB performance indicators: 2013–2017 against 2012 baseline.
(DOCX)

S1 Dataset. Program dataset MDR.
(XLS)

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Title: Incorporating Patient Reporting Patterns to Evaluate Spatially Targeted TB Interventions

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Abstract

Purpose: Tuberculosis is geographically heterogeneous and geographic targeting can improve the impact of TB interventions. However, standard TB notification data may not sufficiently capture this heterogeneity. Better understanding of patient reporting patterns (discrepancies between residence and place of presentation) may improve our ability to use notifications to appropriately target interventions.

Methods: Using demographic data and TB reports from Dhaka North (DNCC) and South (DSCC) City Corporations, we identified wards of high TB incidence and developed a TB transmission model. We calibrated the model to patient-level data from selected wards under four different reporting pattern assumptions and estimated the relative impact of targeted versus untargeted active case finding (ACF).

Results: The impact of geographically targeted interventions varied substantially depending on reporting pattern assumptions. The relative reduction in TB incidence, comparing targeted to untargeted ACF in DNCC, was 1.20, assuming weak correlation between reporting and residence, versus 2.45, assuming perfect correlation. Similar patterns were observed in DSCC (1.03 versus 2.08).

Conclusion: Movement of individuals seeking TB diagnoses may substantially affect ward-level TB transmission. Better understanding of patient reporting patterns can improve estimates of the impact of targeted interventions in reducing TB incidence. Incorporating high-quality patient-level data is critical to optimizing TB interventions.

Abbreviations and Acronyms

TB = tuberculosis

DNCC = Dhaka North City Corporation

DSCC = Dhaka South City Corporation

ACF = active case finding

Background

Tuberculosis (TB) is the leading infectious cause of morbidity and mortality worldwide. While the past few years have seen a large increase in TB control efforts in high burden countries, several studies have shown that TB burden is geographically heterogeneous, which can undermine the effectiveness of such interventions [1]. Therefore, when implementing TB interventions, it may be more effective to target areas of high TB incidence (i.e. “hotspots”) as opposed to the general population [2,3]. By distinguishing hotspots from the general population, spatial targeting concentrates interventions such as active screening, preventive therapy or vaccine campaigns within a geographically restricted population (e.g. neighborhood, subdistrict) to maximize the impact of the resources and effort spent in reducing disease incidence.

To estimate the spatial distribution of TB cases in a population, most models use standard TB notification data collected from TB reporting centers. However, such data, defined by the locations of these centers, may not necessarily reflect where individuals with TB live, where people become infected with TB, or where transmission frequently occurs (e.g. slums, workplaces, public transit, etc.) [4,5]. Considering that TB is an airborne disease, such mobility could have a substantial impact on the distribution of TB transmission and the effectiveness of spatially targeted TB control measures, particularly in urban areas and at smaller spatial resolutions [6,7].

Methods

Overview. In this study, we explored the effect of one measure of patient mobility, specifically discrepancies between patient reporting and residence, on the projected population-level impact of geographically targeted TB interventions [6]. Our primary outcome was the 10-year relative reduction in TB incidence through active case finding (ACF), comparing a hotspot-targeted strategy (approximately 50% coverage across high-incidence wards) to an untargeted strategy (10% population-wide coverage). A relative reduction greater than 1.0 indicates that a hotspot-targeted strategy would reduce TB incidence more than an untargeted strategy of equal intensity after 10 years of continuous implementation, while a relative reduction less than 1.0 would favor the untargeted strategy.

Generally, ACF – which may include combinations of symptom interviews, chest radiography, sputum smear and molecular testing – aims to detect infectious individuals earlier in their disease course to both avert transmission and improve treatment outcomes. We conceptualized ACF as an intervention that could reduce time-to-diagnosis by one-third in 10% of individuals with prevalent TB receiving the intervention each year [8,9]. We evaluated the impact of this stylized intervention using a previously published mathematical model of TB transmission in Dhaka, Bangladesh [6]. In this model, each ward’s population was stratified into three compartments: TB uninfected, latent TB infection, or active TB disease. Latently infected populations could develop active TB disease either via reactivation or via reinfection followed by primary progression.

Setting. Dhaka City Corporations, Bangladesh (population: 8.9 million in 2011) consisted of 90 wards as of 2018, divided into Dhaka North City Corporation (DNCC, 36 wards) and Dhaka South City Corporation (DSCC, 54 wards) [10]. Wards are the lowest administrative unit in Bangladesh, with an average population of 100,000 people.

Data source. In Bangladesh, patients report to TB reporting centers for treatment, which are located in nearly all wards. These centers notify the National TB Control Program of new TB

diagnoses using a standardized reporting form and provide TB treatment to patients via Bangladesh's Directly Observed Therapy, Short-Course (DOTS) program. We extracted ward-level TB notification data in 2014 and 2017 and used these to generate estimates of ward-level TB notification rates [6], calculated as the number of notified TB cases within each ward divided by the population of the ward (estimated using the 2011 national census and an assumed 5% annual growth rate). Wards with the highest TB notification rates (whose cumulative populations comprised approximately 20% of the total population in each city corporation: six wards in DNCC and 12 in DSCC) were selected for "geographic targeting". We compared the impact of ACF in these wards alone to ACF in Dhaka City Corporations as a whole, assuming that the additional number of people diagnosed and treated for prevalent TB was the same in both strategies.

To account for discrepancies between where TB cases are notified and where they live, we extracted the residential addresses of 3,512 patients diagnosed with TB from selected reporting centers in one DNCC ward and five DSCC wards between 2017 and 2018. For each of the six wards, we estimated the percentage of patients who reported TB in the same, adjacent, or distant (noncontiguous) wards from which they lived. We used the wards with the highest and lowest correlations between patient reporting and residence to inform two scenarios as described below.

Scenarios.

- *Strong Correlation scenario:* assumes 50% of patients report TB in their ward of residence, 37% report in adjacent wards and 13% report in distant wards.
- *Weak Correlation scenario*: assumes 18% of patients report TB in their ward of residence, 12% report in adjacent wards and 70% report in distant wards.

Additionally, we considered hypothetical scenarios of *perfect correlation* and *constant incidence* across all wards for purposes of comparison.

- *Perfect Correlation scenario:* assumes 100% of patients report TB in their ward of residence.
- *Constant Incidence scenario:* assumes TB notification rates are uniform across wards in DNCC and DSCC, regardless of reporting.

Sensitivity Analysis. We considered three different transmission levels that could reasonably reflect the observed epidemiology of TB in Dhaka: low (in which 56% and 44% of incident cases in DNCC were due to recent transmission and reinfection respectively; compared to 71% and 29% in DSCC), moderate (70% and 30% in DNCC; 82% and 18% in DSCC), and high (79% and 21% in DNCC; 88% and 12% in DSCC).

Results

The impact of geographically targeted interventions varied substantially depending on correlation between reporting and residence. Generally, the relative impact of hotspot-targeted ACF was greatest when the correlation between locations of reporting and residence was higher, regardless of transmission level. Assuming a moderate level of transmission, the relative reduction (RR) in TB incidence, comparing targeted to untargeted ACF in DNCC, was 1.20 for the weak correlation scenario, 1.82 assuming strong correlation, and 2.45 assuming perfect correlation (**Fig. 1)**. Similar patterns were seen in DSCC (1.03 versus 1.50 and 2.08). In the scenario of constant incidence (with no correlation between location of reporting and location of

residence), targeted ACF was consistently less effective than untargeted ACF (RR 0.88 in DNCC, 0.94 in DSCC). Assuming higher underlying TB transmission, these associations were more pronounced (for example, RR 1.90 for strong correlation scenario in DNCC).

Discussion

Using patient-level data from selected reporting centers in wards across Dhaka, Bangladesh, we explored how assumptions regarding patient reporting patterns could mask the underlying epidemiology of TB in an urban setting and thus affect the projected impact of geographically targeted TB interventions, such as active case finding. For example, we found that, if one neglects to account for underlying patient mobility and assumes that patients live strictly in the wards in which they are diagnosed with TB, interventions targeted to high-incidence wards might appear to be more effective than they will actually be in practice. Should significant discrepancies exist between available data and actual patterns of inter-ward mobility, a universal approach may be preferred to one that is targeted on the basis of those data. Conversely, if discrepancies between reporting and residence are minimal, the collection and integration of patient-level data into TB transmission models may refine our understanding of where TB hotspots (and contact networks of TB cases) are located and inform the targeted delivery and evaluation of TB interventions in these areas.

As with any modeling analysis, our study had certain limitations. We collected data from TB reporting centers; however, reported TB does not encompass all TB cases within a population, and such missed cases also contribute to transmission. Also, our patient-level data were sampled from only six wards and thus may not be representative of the entire population. A comprehensive assessment of reporting patterns across DNCC and DSCC could address this limitation. Furthermore, discrepancies between patient reporting and residence may not reflect the full scope of movement of individuals seeking TB diagnoses, particularly in urban settings; additional metrics of mobility, such as the purpose of migration, frequency and duration of travel, and mode of transportation, could be highly informative as well [7,11].

In summary, our results illustrate how a better understanding of patient reporting patterns can help improve the interpretation of notification data and thus the impact of targeted interventions, particularly in settings like Dhaka, Bangladesh, where the location of TB reporting centers may be used in lieu of patients' place of residence due to logistical challenges and available resources. In such situations, the ability to accurately identify high-incidence hotspots, assess reporting patterns and incorporate high-quality patient-level data (e.g. movement of individuals seeking TB diagnoses) at an appropriate and actionable spatial scale, such as at the ward level in Dhaka, Bangladesh, is critical to reducing TB incidence. Without such information, discrepancies between available notification data and actual mobility patterns may reduce the relative impact of geographically targeted interventions by a factor of 50% or more.

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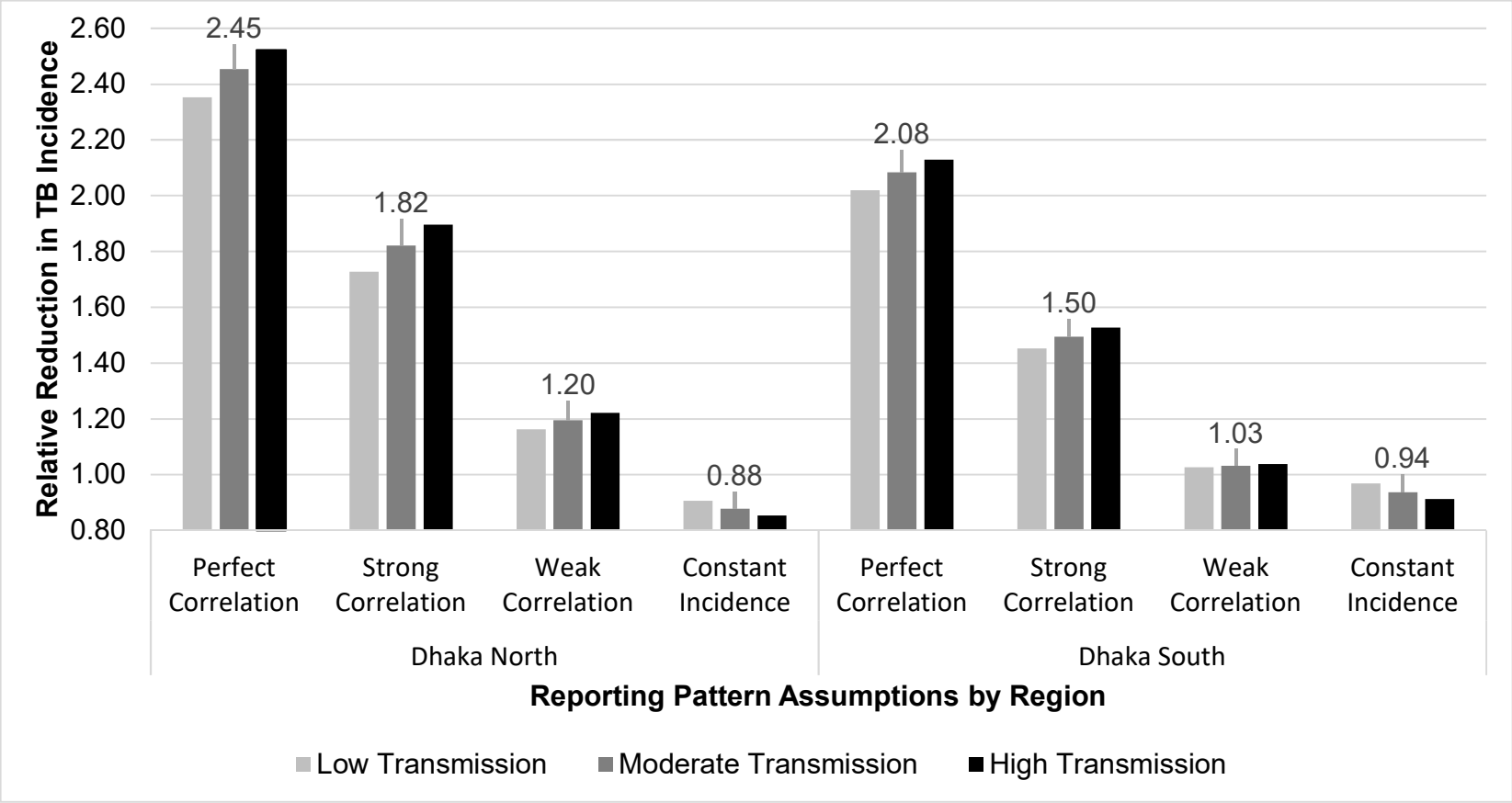
Figure 1. Relative reduction in TB incidence, comparing targeted to untargeted active case finding (ACF) in Dhaka North City Corporation (DNCC) and Dhaka South City Corporation (DSCC), under four different reporting pattern scenarios and three different levels of transmission (low, moderate, high). “Perfect Correlation” assumes 100% of patients report TB where they live. “Constant Incidence” assumes all wards in DNCC and DSCC, independently, have the same incidence rate. “Strong Correlation” assumes 50% of patients report TB in their ward of residence, 37% report in adjacent wards, and 13% report in distant wards. “Weak Correlation” assumes 18% of patients report TB in their ward of residence, 12% report in adjacent wards, and 70% report in distant wards. For example, assuming perfect correlation between reporting and residence and a moderate level of TB transmission, a relative reduction of 2.45 in DNCC indicates that an ACF intervention targeted to high-incidence wards would reduce TB incidence 2.45 times more than an untargeted strategy of equal intensity after 10 years of continuous implementation.



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Quantifying geographic heterogeneity in TB incidence and the potential impact of geographically targeted interventions in South and North City Corporations of Dhaka, Bangladesh: a model-based study

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Abstract

In rapidly growing and high-burden urban centres, identifying tuberculosis (TB) transmission hotspots and understanding the potential impact of interventions can inform future control and prevention strategies. Using data on local demography, TB reports and patient reporting patterns in Dhaka South City Corporation (DSCC) and Dhaka North City Corporation (DNCC), Bangladesh, between 2010 and 2017, we developed maps of TB reporting rates across wards in DSCC and DNCC and identified wards with high rates of reported TB (i.e. 'hotspots') in DSCC and DNCC. We developed ward-level transmission models and estimated the potential epidemiological impact of three TB interventions: active case finding (ACF), mass preventive therapy (PT) and a combination of ACF and PT, implemented either citywide or targeted to high-incidence hotspots. There was substantial geographic heterogeneity in the estimated TB incidence in both DSCC and DNCC: incidence in the highest-incidence wards was over ten times higher than in the lowest-incidence wards in each city corporation. ACF, PT and combined ACF plus PT delivered to 10% of the population reduced TB incidence by a projected 7%–9%, 13%–15% and 19%–23% over five years, respectively. Targeting TB hotspots increased the projected reduction in TB incidence achieved by each intervention 1.4- to 1.8-fold. The geographical pattern of TB notifications suggests high levels of ongoing TB transmission in DSCC and DNCC, with substantial heterogeneity at the ward level. Interventions that reduce transmission are likely to be highly effective and incorporating notification data at the local level can further improve intervention efficiency.

Introduction

Tuberculosis (TB) is the leading single-agent infectious cause of morbidity and mortality, with an estimated 10.0 million new TB cases and 1.4 million deaths worldwide in 2019 [1]. Despite the availability of effective treatment, TB incidence has not declined substantially in many high-burden countries, including Bangladesh, where an estimated 361 000 people developed new TB disease in 2019 [1, 2]. The End TB Strategy, launched by the World Health Organization as part of its post-2015 agenda, set goals to reduce TB incidence by 50% by 2025, and by 90% by 2035 [3]. Unfortunately, given the present slow decline in TB incidence of 1.5% per year, it is unlikely that these targets will be met unless concerted efforts are made to rapidly increase the rate of decline in TB incidence.

In high-burden settings, a substantial proportion of incident TB occurs as a result of recent transmission [4, 5]. This is particularly true in densely populated urban centres, such as Dhaka, which have higher social contact rates, facilitated by factors such as the use of mass public transportation, the presence of slums and markets, and high rates of internal migration [6–10]. Furthermore, it is known that TB, along with many of its common risk factors, such as low socio-economic status [11], poor living conditions (e.g. crowding, poor ventilation in housing) [12–14], migration status [8, 10], and Human Immunodeficiency Virus infection [15, 16], tends to cluster in hyperendemic 'hotspots.' These high-incidence areas can act as reservoirs of infection and drive secondary transmission within the larger community [12, 17, 18].

As such, interventions aimed at reducing transmission may be critical to bringing about a decline in TB incidence in these settings [19, 20]. Furthermore, targeting hotspots may be more effective in reducing TB incidence at the local (e.g. city) level compared with interventions that are delivered to the general population without any attempt to prioritise those at the highest risk. Empirical evidence for the effectiveness and feasibility of geographic targeting is currently lacking [21]. As such, by leveraging available surveillance data at the local level, models of geographically targeted interventions can inform evidence-based decision-making until data on specific interventions are collected. Models can also motivate this future empirical research by estimating the potential impact of targeted interventions in specific settings and by identifying important data gaps. Therefore, in this study, we aimed to understand the population-level impact of TB interventions, aimed at reducing TB transmission and the added value of targeting hotspots with these interventions. Using data on TB notification, patient reporting patterns and transmission models of TB, we estimate the impact of targeting potential TB interventions, namely active case finding (ACF, designed to reduce transmission by finding cases earlier) and preventive therapy (PT, designed to prevent reactivation of remote infection) to high-incidence geographical hotspots in Dhaka, Bangladesh.

Methods

Ward-level TB notification maps

We aggregated notification data from TB reporting centres within each ward of Dhaka South City Corporation (DSCC) and Dhaka North City Corporation (DNCC) between the years 2010 and 2017 – as of 2017, DSCC and DNCC consisted of 54 and 36 wards, respectively. Reporting centres provide TB treatment via Bangladesh's Directly Observed Therapy, Short-Course (DOTS) program. We generated annual estimates of ward-level TB notification rates, calculated as the number of reported TB cases within each ward divided by the population of the ward (estimated using the 2011 national census with 5% annual growth rates). Using GIS data of the administrative boundaries of DSCC and DNCC, we then generated maps of the distribution of estimated TB notification rates in each ward.

To account for discrepancies between ward of TB notification (where patients were diagnosed) and ward of residence (where patients lived), we used de-identified individual-level data on 2980 patients diagnosed with TB from selected reporting centres in five DSCC wards and 532 patients in a single DNCC ward between 2017 and 2018. Using these data as a guide, we adjusted previously generated ward-level TB notification rates to reflect the observed distribution of TB cases notified in a given ward that comprised patients living in the ward of notification, patients living in adjacent wards (distributed equally across all adjacent wards) and patients living in non-adjacent wards (distributed equally across all other wards in the corresponding city corporation).

Institutional review board

Johns Hopkins School of Public Health Institutional Review Board (IRB) policy does not require IRB oversight for studies involving data analysis of de-identified aggregated data. No informed consent was needed for this use of the data.

Transmission model

Drawing on our previous work [12, 17, 19], we constructed ward-specific epidemiological models to characterise transmission patterns and the natural history of TB in all wards of DSCC and DNCC. Following a deterministic, compartmental model structure (Fig. 1), each ward's population was stratified into three compartments: TB uninfected, latent TB infection (LTBI, including post-treatment), and active (infectious) TB disease. We assumed that uninfected individuals, upon being infected with TB, progress either to LTBI or to active TB disease (primary progression). Latently infected populations could develop active TB disease either via reactivation or via reinfection followed by primary progression. We assumed that prior TB infection provides partial protection against future TB infection. Finally, we modelled diagnosis and successful treatment of TB disease as a return to the LTBI compartment. The model did not consider age structure, drug resistance, or other risk factors that may affect TB natural history. A full description of the model, including differential equations describing the model, is included in the Supplementary materials (Appendix II).

We calibrated the models to ward-specific TB prevalence. Ward-specific TB prevalence was estimated based on the incidence maps generated (as described above). Following WHO estimates, we assumed that 67% of incident TB cases in Bangladesh are reported, and the average duration of TB disease is 1.5 years before individuals with active TB are successfully diagnosed and treated. Other model parameters were taken from the published literature (see Table A1, Appendix III for details) [19]. To enable a simple and transparent model calibration process, we assumed that there were no significant secular trends in TB prevalence or incidence at baseline. The Model calibration process is described in detail in Appendix II and implemented in excel spreadsheets included in the Supplementary materials.

Model scenarios

Genomic data (e.g. population-wide whole-genome sequencing) to inform the amount of ongoing TB transmission are not available for Dhaka or similar high-burden urban settings [22]. As such, we modelled three different scenarios, each reflecting different levels of TB transmission at the ward level and each independently calibrated to the estimated TB incidence in Dhaka. These scenarios were chosen to reflect reasonable levels of transmission that could each be consistent with the observed epidemiology of TB in Dhaka.

(1) *Low transmission*. In this scenario, an estimated 71% (interquartile range: 62%–79%) of incident cases in DSCC and 56% (interquartile range: 52%–61%) of incident cases in DNCC were due to recent transmission rather than reactivation of remote infection – a figure that is lower than estimated in models of Rio de Janeiro, Brazil [12], and other urban settings in countries where TB incidence is substantially lower than that of Bangladesh.
(2) *Moderate transmission*. In this scenario, we used our *best a priori* estimates of TB transmission, as described in our model of TB transmission in Karachi, Pakistan [19]. This resulted in 82% (interquartile range: 76%–87%) of incident cases in DSCC and 70% (interquartile range: 66%–75%) of incident cases in DNCC being due to recent transmission. This scenario is used as the reference for all results presented below.

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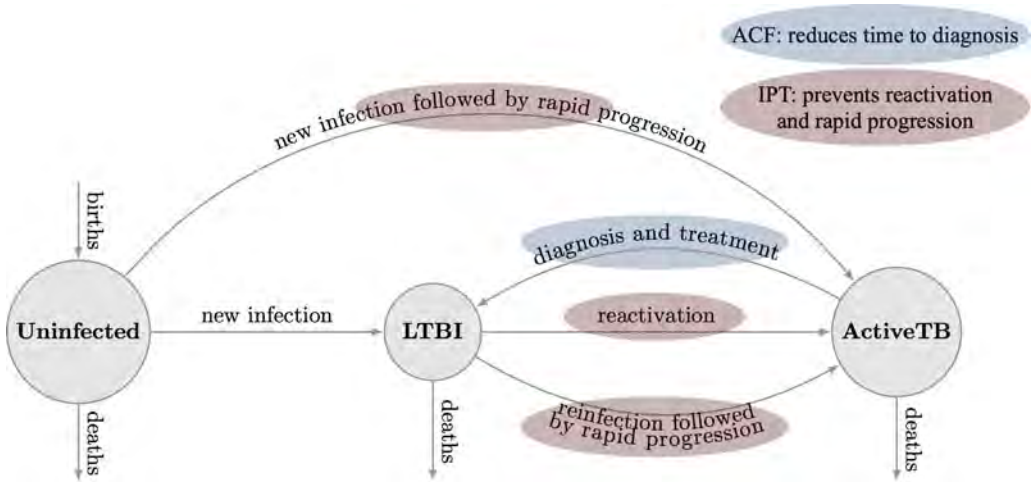

Fig. 1. Schematic representation of transmission model. In this ward-specific compartmental model, the population was divided into three compartments based on their TB status: uninfected (i.e. individuals who have not been exposed to TB), LTBI (i.e. individuals with LTBI) and active TB (i.e. individuals with infectious TB disease). We modelled two interventions: ACF, which was modelled to reduce the time for diagnosis and thus, resulting in an increase in the rate marked in blue; and PT, which was modelled to prevent reactivation and progression of the disease and thus, resulting in a reduction in the rates marked in red.

(3) *High transmission*. Here, we assumed higher transmission rates, similar to the 'high-transmission' scenario in our model of Karachi [19], such that the vast majority of TB is due to recent transmission. This resulted in 88% (interquartile range: 83%–91%) of incident cases in DSCC and 79% (interquartile range: 75%–83%) of incident cases in DNCC being due to recent transmission events.

Interventions

We modelled three different TB interventions; (i) ACF; (ii) mass PT and (iii) ACF and PT combined, with each intervention achieving the population-level coverage of 10% in DSCC and DNCC separately. For ACF, we assumed that implementation would reduce time to diagnosis by one-third (i.e. 33.3% reduction in the average time to diagnosis). For PT, we assumed adherence levels of 60% and efficacy of 80% in reducing reactivation and rapid progression of infections that existed at the time of the intervention. For the combined intervention, we assumed that both interventions, ACF and PT, would be implemented in the same population with independent effects. For simplicity, we assumed rapid scale-up of each intervention to the target level specified.

For all three interventions, we modelled two implementation strategies, either a citywide implementation (in which 10% of the entire population of DSCC and DNCC received the intervention, regardless of the ward of residence), or a targeted implementation (in which the interventions were targeted to high-incidence wards, but at a higher coverage such that the same number of people were covered as in the citywide implementation). For DSCC, we selected the 12 wards with the highest TB notification rates in 2017, which comprised ~20% of the total population of DSCC. Similarly for DNCC, we selected the six wards with the highest TB notification rates between 2015 and 2017; these wards comprised ~20% of the total population of DNCC. We assumed that 50% of the population in these wards would be covered by each intervention under targeted implementation, thereby achieving the population-level coverage of 10% in each city corporation.

Primary outcome

The primary outcome was the projected reduction in TB incidence in DSCC and DNCC, five and ten years after the implementation of each intervention, comparing the targeted implementation of the intervention in high incidence 'hotspots' *vs.* untargeted citywide implementation.

Sensitivity analyses

To explore the sensitivity of the model results to the changes in model parameters, we conducted multivariate uncertainty analyses. We generated 10 000 parameter sets for DSCC and DNCC separately using Latin Hypercube Sampling, carried out model simulations for each parameter set and estimated partial rank correlation coefficients, between the model parameters and key model outcomes, the relative reduction in 10-year TB incidence achieved through ACF, PT and a combination of both via targeted implementation compared to a citywide implementation [23] (see Appendix III for details).

Results

Spatiotemporal patterns of TB in DSCC and DNCC

TB notification data during the seven-year period between 2010 and 2017 suggests that while TB notification rates are generally higher in DSCC compared to DNCC, TB is highly heterogeneous at the ward level in both city corporations (Figs 2 and 3). Unadjusted ward-level notification rates in 2010 in both DSCC and DNCC ranged from 60.9 to 2822.6 per 100 000 per year, over 40-fold difference.

Using individual-level data from selected reporting centres, we estimated that 18%–50% of reported cases resided in the ward in which the reporting centre was housed, 12%–37% resided in neighbouring wards (wards within the city corporation sharing boundaries with the reporting centre) and the remaining resided elsewhere in Dhaka. For each ward, we, therefore, adjusted notification rates to more closely reflect potential patterns of patient residence by attributing 50% of the reported cases to the ward

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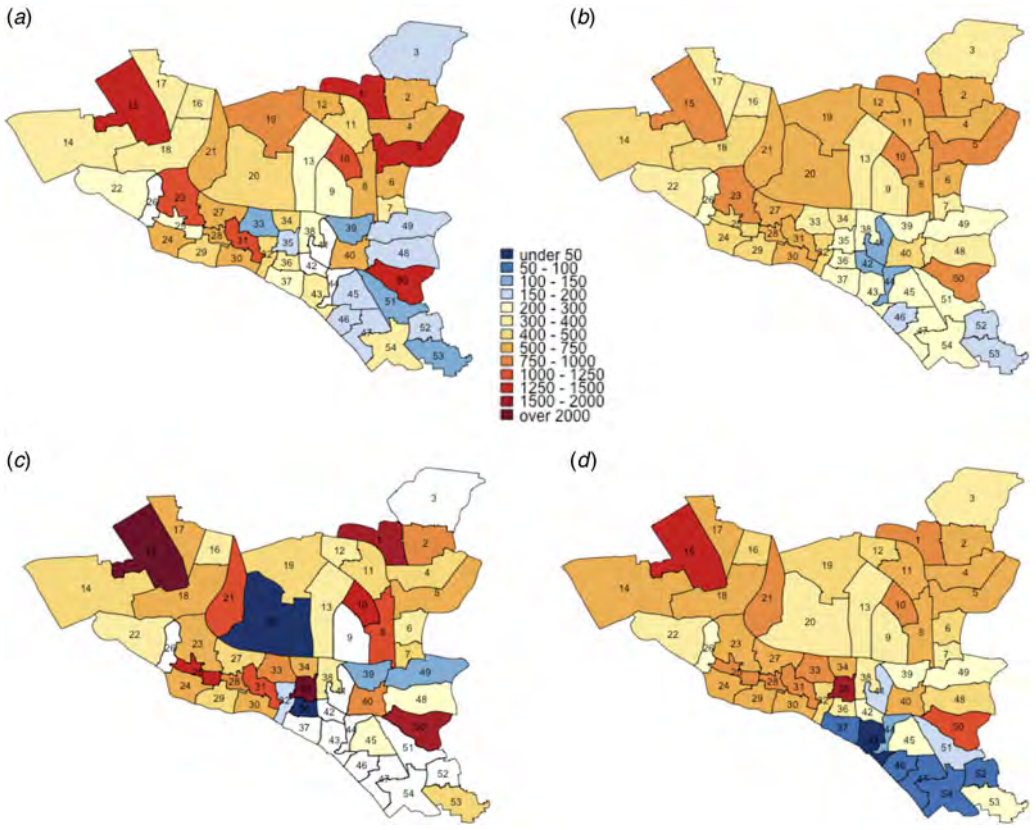

Fig. 2. Maps of DSCC with estimated TB notification rates in 2010 and 2017. Panels (*a*) and (*c*) show unadjusted notification rates (in units per 100 000 per year) in 2010 and 2017, respectively. Panels (*b*) and (*d*) show corresponding notification rates after adjustment for observed correlations between ward of residence and ward of reporting centre in 2010 and 2017, respectively.

housing the reporting centre, 40% to adjacent wards and 10% equally to all wards in the city corporation. Even after adjusting for potential clustering of reporting in this fashion, substantial geographic heterogeneity in TB incidence persisted in both DSCC and DNCC; distinct 'hotspots' with high TB notification rates and 'cold' patches with low TB notifications were still observed. This pattern of geographic heterogeneity persisted and intensified over time, as depicted by TB notification maps of DSCC and DNCC, which show darker shades of red and blue in 2017 (Figs. 2*c*, *d* and 3*c*, *d*) than in 2010 (Figs. 2*a*, *b* and 3*a*, *b*).

Changes in TB notification rates between 2010 and 2017 were also heterogeneous across wards. For example, in DSCC, the southern and northcentral sections had prominent declines in TB notification rates, whereas the central and northeastern parts experienced large increases (Fig. 4*a*; blue patches indicate a decline, and red and orange patches indicate increase). In DNCC, the central area had marked declines, whereas the eastern and southern areas experienced large increases (Fig. 4*b*).

Epidemiological impact of TB interventions

ACF implemented throughout DSCC over a five-year period and randomly targeting 10% of the population was projected to reduce TB incidence by 9.0%; when targeted to the 12 wards with the highest TB incidence, this impact grew to 14.6% projected reduction (Fig. 5). The corresponding impact of PT was a 15.2% (untargeted) and 22.3% (targeted) reduction in five-year incidence, and when ACF and PT were combined, the greatest reductions in five-year incidence were achieved: 22.6% if untargeted and 27.7% if targeted to the 12 highest-incidence wards (Fig. 5).

The impact of TB interventions in DNCC was slightly lower than in DSCC, reflecting the lower burden of TB incidence and TB transmission in DNCC relative to DSCC (Fig. 6). Projected reductions in five-year TB incidence in DNCC were: 7.0% from citywide ACF, 13.9% from hotspot-targeted ACF, 13.0% from citywide PT, 22.8% from targeted PT, 18.9% from citywide combined ACF and PT and 28.2% from targeted ACF and PT. Over a ten-year time horizon, the projected epidemiological impact of all citywide interventions grew by an additional 18%–41%; this grew to 19.8%–44.8% at 20 years. Notably, the relative added benefit of targeting was greatest at earlier timepoints. For example, ACF deployed in a targeted fashion in DSCC was 1.6 times more impactful compared to citywide ACF at year 5, but only 1.4-times at year 20, suggesting that the relative value of targeting can wane over time. The relative added benefit of the targeting diminished when both interventions, ACF and PT were implemented in a targeted fashion. For example, at year 5 in DSCC, ACF and PT when applied separately, was respectively, 1.6 and 1.5 times impactful when targeted. However, when combined, the relative impact of targeting was only 1.2 times more. The impact of interventions also increased with the intensity of transmission, with the high-transmission scenario leading to estimates of impact at least 20% greater than those in the low-transmission scenario for all interventions. However, the relative benefit of geographically targeted implementation also decreased with higher

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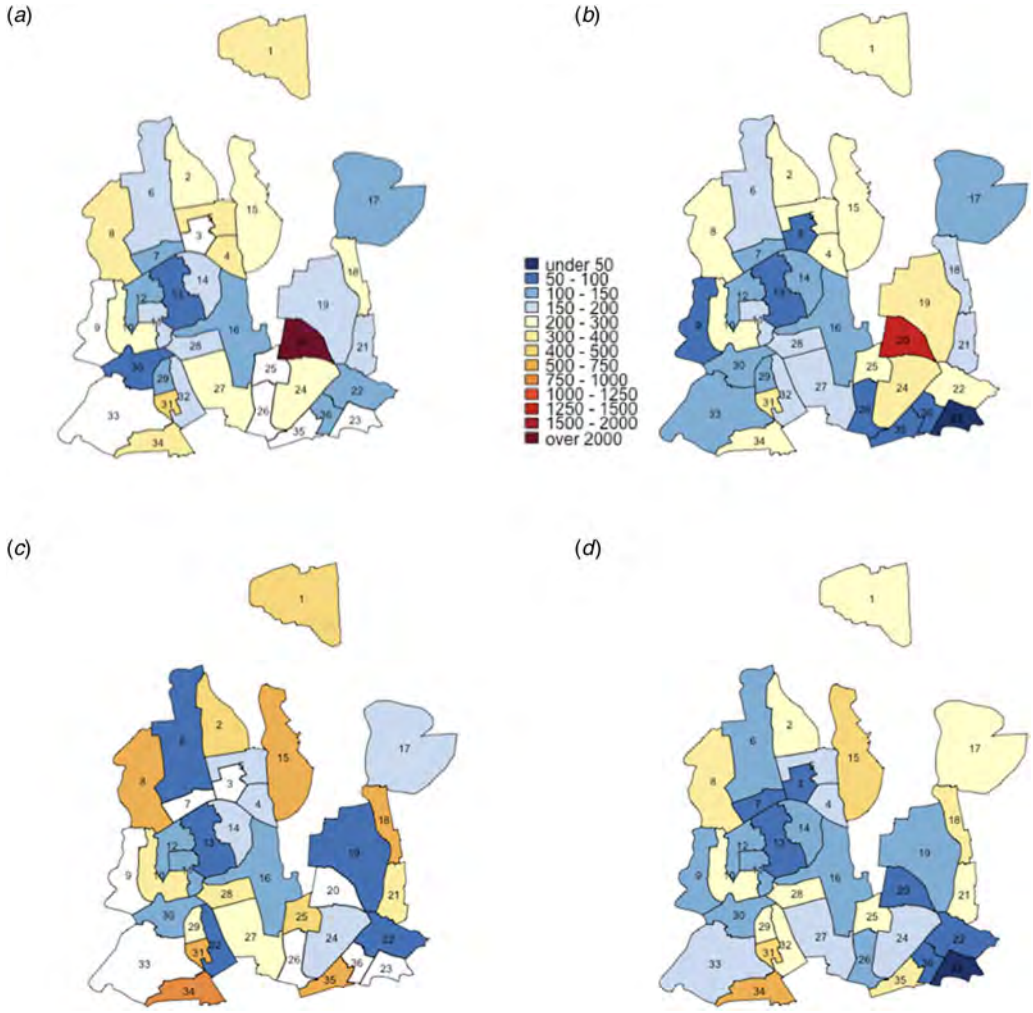

Fig. 3. Maps of DNCC with estimated TB notification rates in 2010 and 2017. Panels (*a*) and (*c*) show unadjusted notification rates (in units per 100 000 per year) in 2010 and 2017, respectively. Panels (*b*) and (*d*) show corresponding notification rates after adjustment for observed correlations between ward of residence and ward of reporting centre in 2010 and 2017, respectively.

levels of transmission; for example, targeted implementation of ACF in DNCC was estimated to generate a reduction in TB incidence that was 2.0 times greater than untargeted implementation in the low transmission scenario, compared to 1.7 times in the high transmission scenario (Figs. S5 and S6 in the Appendix I). Finally, the results from multivariate uncertainty analyses show that targeted interventions have greatest impact in settings where more incident TB is due to recent rather than remote infection. The model parameters that correlated most strongly with the relative value of targeting interventions were the level of protection against reinfection, the rate of TB diagnosis and the rate of rapid progression; an increase in any one of these increases the proportion of incident TB that is due to recent infection compared to remote (see Appendix III).

Discussion

In this study, we aimed to assess the benefits of potential TB interventions, specifically active case finding and mass preventive therapy, in Dhaka, Bangladesh – a high-incidence, densely urban South Asian city. We found that TB is geographically heterogeneous across wards, with ward-level notification rates varying by more than a factor of ten. Interventions in Dhaka to actively find TB cases and to prevent reactivation disease have the potential to affect substantial and rapid declines in TB incidence. For example, covering 10% of the population with ACF and PT could reduce TB incidence in Dhaka by about 20% within five years. Targeting these interventions to the wards with the highest TB notification rates could magnify the impact of these interventions still further, such that nearly 30% reductions in TB incidence could be achievable within five years. These results may help to motivate the implementation of interventions to reduce TB transmission in South Asian megacities and to collect data at the district level that could help inform evidence-based targeting of those interventions to high-incidence hotspots.

Geographic heterogeneity is a hallmark of most infectious diseases, including vector-borne diseases, such as malaria and dengue virus [24–26], and sexually transmitted diseases, such as gonorrhea, chlamydia and syphilis [27]. For many of these infections, it has been recommended that interventions be targeted to high-incidence hotspots. Nevertheless, TB differs from most other infectious diseases, particularly in terms of its airborne route of infection and lengthy/highly variable trajectory of latency and disease, which may mitigate the degree of geographic heterogeneity

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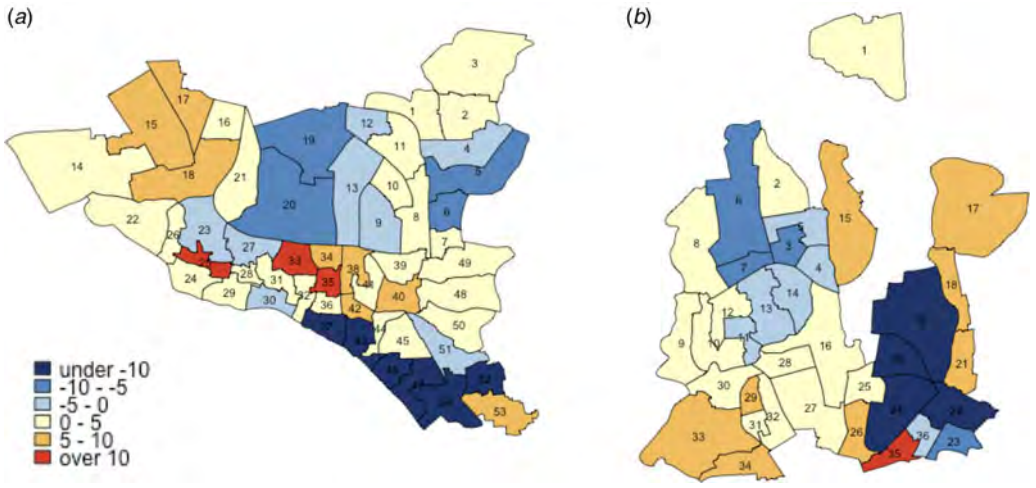

Fig. 4. Annual percentage change in TB incidence in DSCC and DNCC wards between 2010 and 2017. Panels (*a*) and (*b*) give the average annual changes (% per year) in estimated TB incidence at the ward level in DSCC and DNCC, respectively, between the years 2010 and 2017. Blue shading indicates a decline in TB incidence during the 7-year period (with darker shades representing steeper declines), whereas red shading indicates an increase (with darker shades representing greater increases).

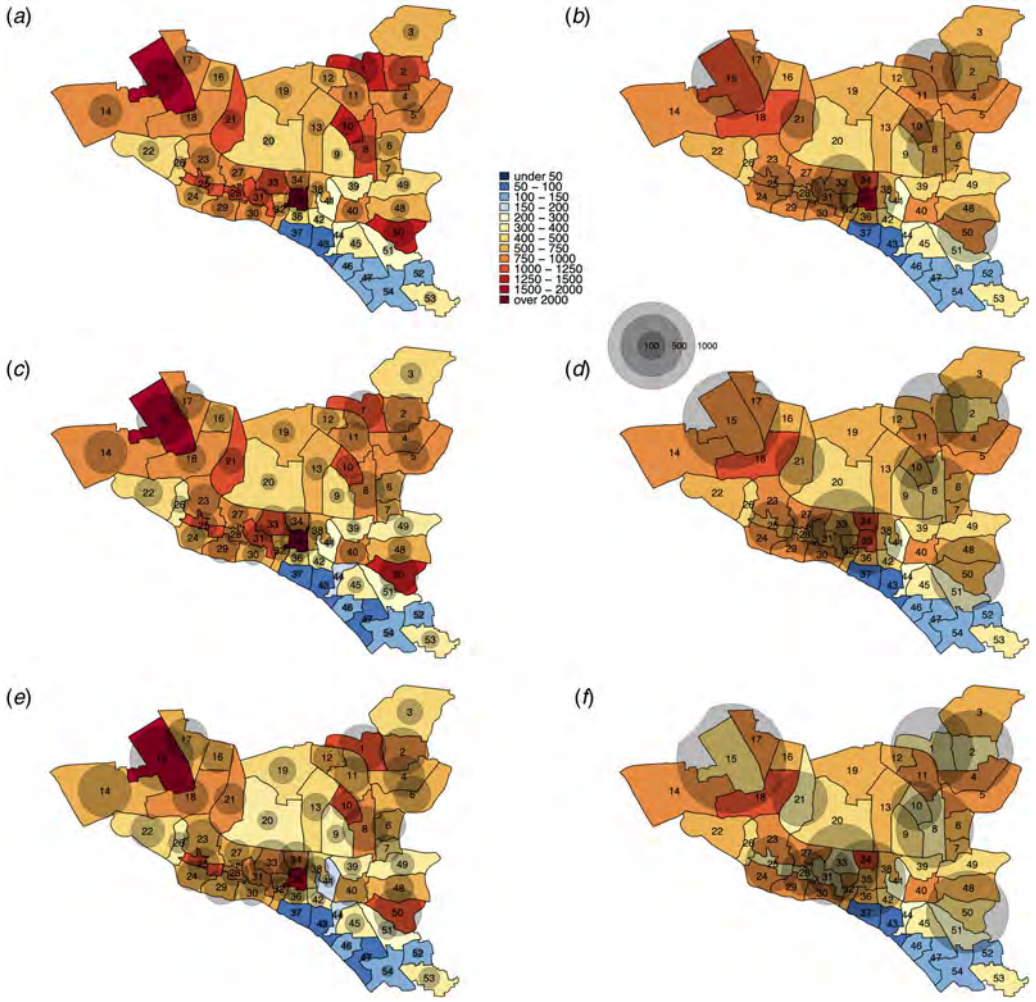

Fig. 5. Impact of TB interventions on ward-level TB incidence in DSCC after five years. The colours for each ward depict the projected TB incidence after five years of intervention and the bubbles indicate the absolute size of the reductions (the reduction in the number of incident TB cases achieved by the intervention in year 5). Panel (*a*) represents city-wide ACF, (*b*) represents the targeted case finding, (*c*) represents the city-wide PT, (*d*) represents the targeted PT, (*e*) represents the combination of citywide ACF and PT and (*f*) represents the combination of targeted ACF and PT.

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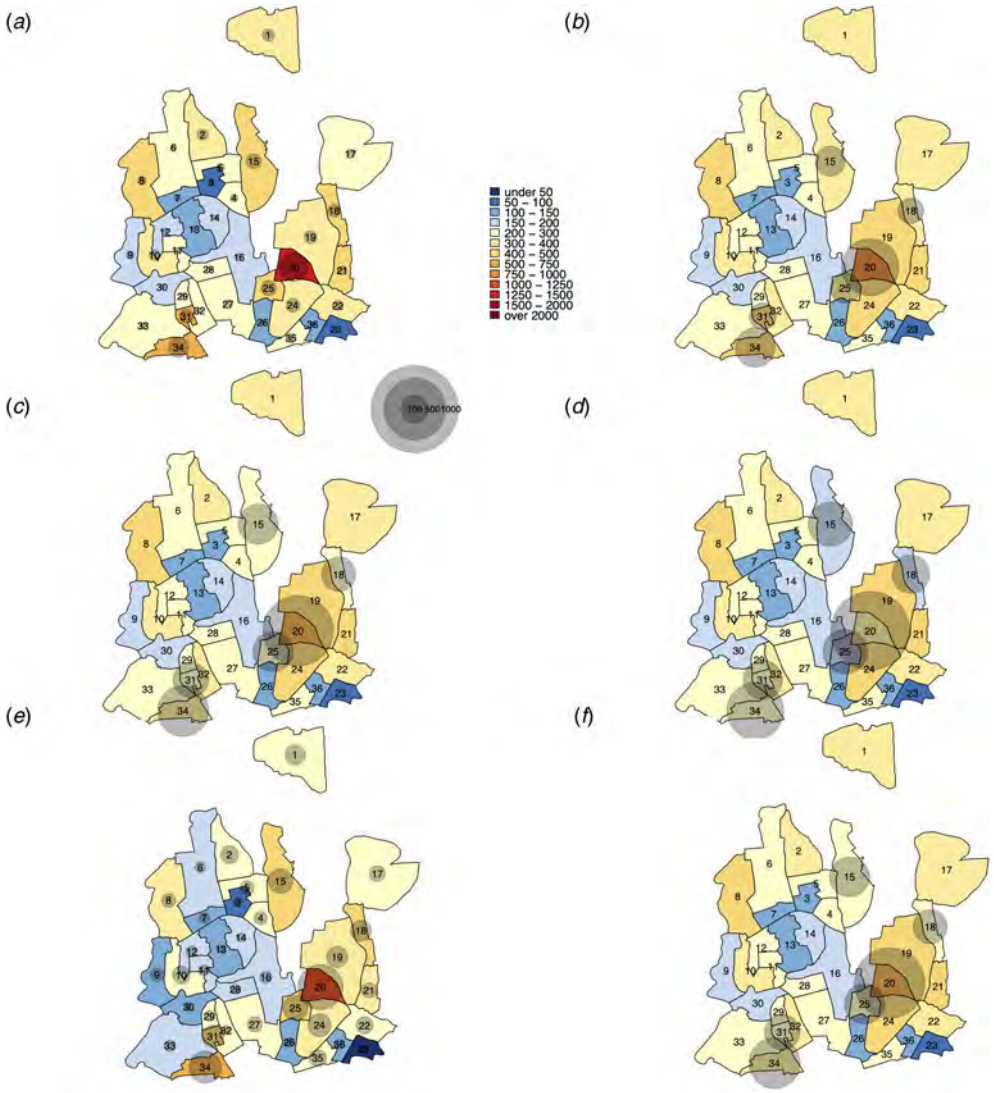

Fig. 6. Impact of TB interventions on ward-level TB incidence in DNCC after five years. The colours for each ward show the projected TB incidence after five years of intervention and the bubbles indicate the absolute size of the reductions (the reduction in the number of incident TB cases achieved by the intervention in year 5). Panel (*a*) represents city-wide ACF, (*b*) targeted case finding, (*c*) city-wide PT, (*d*) targeted PT, (*e*) combination of citywide ACF and PT, and (*f*) combination of targeted ACF and PT.

and the impact of such heterogeneity on disease transmission. Understanding the dynamics of geographic heterogeneity in TB incidence can therefore not only inform the prioritisation of existing TB interventions and resources but can also add insight into the natural history and transmission patterns of *M. tuberculosis*, the most deadly human pathogen. Such investigations may be particularly useful in urban settings such as Dhaka, where TB transmission is particularly intense and notification data are available at the scale of small administrative units.

In addition to informing city-level policy (in collaboration with partners such as the Bangladesh National Tuberculosis Program, which contributed to this work), our model findings can also help motivate the collection of finer-resolution data on TB notifications in Dhaka and other similar settings. Our results illustrate how the abilities to accurately identify high-incidence hotspots and assess reporting and mixing patterns, at an appropriate and actionable spatial scale (such as the ward level in Dhaka) can help to harness the full potential of geographically targeted TB interventions. In assessing the relative benefit of targeting actual interventions (rather than the stylised interventions presented here), the feasibility and cost-effectiveness of delivering interventions at the local scale must also be considered.

As with any modelling analysis, these findings should be interpreted in light of several data limitations and modelling assumptions. Empirical data were not available to inform certain important considerations such as the movement of individuals between wards and city corporations. This forced us to adopt a number of simplifying assumptions, which could affect our results in two distinct ways. First, discrepancies between patients' place of residence and place of notification could affect our ability to accurately assess the geographic distribution of TB risk and incidence from notification data alone. Because TB transmission largely occurs within households and communities, tracking patients by their place of residence may be a more accurate measure of capturing the spread of TB than the place of presentation [19]. In our study, we partially accounted for these discrepancies

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through adjustment based on patient-level data, which we collected from reporting centres in five DSCC wards and one DNCC ward. In this analysis, we found that nearly half of all cases were reported in the wards where patients did not live. These findings suggest that a systematic assessment of reporting patterns throughout DSCC and DNCC is necessary to more comprehensively address this concern.

Second, movement of individuals between wards can further drive the spread of TB within the city; for example, high-incidence hotspots can fuel TB in many other parts of the city if there is a large amount of movement between the hotspot and the other parts of the city [10, 12]. Although such mixing is generally difficult to quantify for an airborne disease, a lack of data on between-ward mobility may result in an underestimation of the impact of targeted interventions. Geographically targeted interventions have been shown to have higher relative benefit when there is more mixing between individuals in the hotspots and the general population [12, 17]. Given the importance of mixing, there is a need to better understand the mobility and migration of high-risk populations (e.g. commuting patterns), from the perspective of airborne transmission events.

Finally, we relied on ward-level case notification data to ascertain TB transmission risk within wards. Although we accounted for some of this discrepancy in the patient reporting patterns, some of the heterogeneity in case notifications could also reflect differences in access to TB care [28, 29] (e.g. lower case notification due to lower case notification ratios), demographics [30] (e.g. clustering of migrants from other high incidence areas) or socio-economic differences [31] (e.g. poverty). The relative impact of geographic targeting in such instances may not be as substantial or as sustained. Hence, a better understanding of the mechanisms driving geographic heterogeneity in TB reporting and incidence is needed to more comprehensively understand the incremental epidemiological value of geographic targeting. These considerations are particularly important, given that such targeting may increase programmatic costs and add logistical challenges, and inadvertently contribute to the stigmatisation of vulnerable communities [32, 33]. Ultimately, more detailed field studies are required to garner robust empirical evidence that geographically targeted case finding can be both impactful and successfully implemented [21].

These results lay the groundwork for future modelling analyses, including a more detailed characterisation of patient reporting patterns and mixing rates, as well as the integration of demographic, socio-economic and TB care-seeking factors. The incorporation of genomic data could also refine our interpretation of TB incidence [22]. Specifically, since the projected impact of TB interventions depends on the degree to which incident TB disease reflects recent transmission *vs.* reactivation, more accurate estimates of the proportion and geographic distribution of new cases due to the recent transmission can help refine estimates of intervention impact. Such additional analyses can also better quantify heterogeneity and help validate findings from simpler models such as the one presented here.

In summary, this mathematical model of TB transmission in DSCC and DNCC suggests that both ACF and PT can achieve important reductions in TB incidence over a five-year period. If these interventions are combined and targeted to those wards with the highest TB notification rates (as identified using ward-level data), the achievable reduction in incidence can approach 30% within five years. The success of these interventions is only possible if carried out in conjunction with strengthening existing diagnostic and treatment services, which would allow for appropriate diagnosis and treatment of an expanded number of individuals, without a loss in quality. These findings support efforts to intensify active TB case finding and PT in Dhaka, strengthen existing TB diagnostic and treatment services and collect additional supporting data to further tailor the implementation of these interventions to those populations that are most affected by high rates of TB transmission.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0950268821000832.

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Data availability. The data that support the findings of this study are openly available in Zenodo open access repository at 10.5281/zenodo.4681050.

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PLOS ONE

RESEARCH ARTICLE

Prevalence of latent tuberculosis infection among health workers in Afghanistan: A cross-sectional study

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Abstract

Background

About 26% of the world's population may have latent tuberculosis infection (LTBI). Health care workers are a high-risk category because of their professional exposure.

Methods

This cross-sectional study assessed the LTBI burden among health care workers in Afghanistan, a high-TB-burden country. We selected health facilities using a systematic sampling technique and invited all workers at the targeted health facilities to participate. Participants were interviewed about sociodemographic and exposure variables and received tuberculin skin tests for LTBI.

Results

Of the 4,648 health care workers invited to participate, 3,686 had tuberculin skin tests. The prevalence of LTBI was found to be 47.2% (1,738 workers). Multivariate analysis showed that a body mass index of $\geq$ 30 and marriage were associated with an increased risk of LTBI. Underweight (body mass index of $\leq$ 18 and below) and normal body mass index had no association with increased risk of LTBI.

Conclusion

LTBI is high among health care workers in Afghanistan. We recommend instituting infection control measures in health facilities and screening workers for timely TB diagnosis.

study through the Challenge TB project under cooperative agreement number AID-OAA-A-14-00029, and the Global Fund to Fight AIDS, Tuberculosis and Malaria provided funding for this study. The contents of the article are the responsibility of the authors alone and do not necessarily reflect the views of USAID or the US government, or the Global Fund . The publication fee is covered by the USAID funded Sustainable Technical and Analytic Resources (STAR) project, through Public Health Institute (PHI).

Competing interests: The authors have declared that no competing interests exist.

Background

In 2017, 10 million people developed tuberculosis (TB) and 1.3 million succumbed to the disease [1]. An estimated 2 billion people worldwide—26% of the global population—are believed to be infected with TB [1]. Of the 10 million estimated TB incident cases, about 4.4 million prevalent cases are found in the South-East Asia region [1]. Afghanistan has a prevalence rate of 340 and incidence rate of 189 per 100,000 population. In 2019, Afghanistan's National TB Program (NTP) diagnosed and reported 48,420 TB cases of all forms (73% of estimated incident cases) [1]. Although Afghanistan has a treatment success rate of 91%, the World Health Organization (WHO) estimates that 12,000 Afghans still die of TB annually, although in 2019 TB mortality declined to 9,800 [1, 2].

The only sign of TB infection is a positive reaction to the tuberculin skin test (TST) or a blood test. Persons with latent TB infection (LTBI) are not infectious, but having a TB infection is a precondition for having TB disease, and 5% to 10% of those infected could develop the disease in their lifetimes. The majority of those cases will develop within five years of infection [3]. Twenty-three percent of the world's population is estimated to have LTBI (based on TST), which represents a huge reservoir of potential TB disease and is therefore a challenge to TB control [4].

To control TB effectively, it is important to know the burden of TB infection among health care workers (HCWs), who are at higher risk of TB infection due to exposure to diagnosed and undiagnosed TB patients [5–8]. This risk is proportionally more alarming in low- and middle-income countries because of both increased exposure and lack of preventive measures, such as poor workplace ventilation and inadequate precautions during sputum collection and bronchoscopy [9]. Occupational risk factors associated with LTBI include duration of employment in a health care profession [5, 10–14]; being a nurse, diabetic, or smoker [11]; being over the age of 35 [15, 16]; employment in cleaning or housekeeping and in a health care setting with high patient turnover [17]; having been employed in an HIV clinic or ward [12]; and not having had a Bacille Calmette-Guérin vaccination or being immunocompromised [18].

In a systematic review of TB studies among HCWs in South Africa, most reflected a higher incidence and prevalence of active TB disease in HCWs, including drug-resistant TB, compared to the surrounding community or general population [19]. A review of HCWs in seven countries with high TB prevalence (> 100/100,000 population) reported an LTBI prevalence rate of 47% [20].

Through this study, we sought to address the lack of information on estimates of TB infection among HCWs in Afghanistan. The findings can assist the NTP and Ministry of Public Health to shape policy to ensure a safer working environment for HCWs.

Methods

Study design and population

This cross-sectional study among HCWs was conducted in 23 provinces of Afghanistan between September and December 2017. "Health care workers" for this study included any worker in the health facility: doctors, nurses, laboratory professionals, midwives, vaccinators, community health workers, cleaners, guards, administrative staff, and others. The sample size for the study was determined using a single proportion formula [21] assuming an LTBI prevalence (pone') of 47% among HCWs [20], type I error of 5%, and desired precision of 0.05, and a response rate of 60%. The resulting sample size was 1,281 HCWs. All 2,499 health facilities in Afghanistan—public, private, and prison—are listed in the national health information system register and a systematic random sampling technique to select study facilities. Assuming an

average number of five HCWs per health facilities, and no difference in LTBI between health facilities, the total number of health facilities required to obtain the sample of HCWs was 249. Health facilities were listed in alphabetical order and every 10th health facility was included in the study, the first one being picked by lottery method among those health facilities listed from 1–10. All HCWs in the randomized health facilities were then included as potential participants.

Training of data collectors

The data collection tool was developed in English first and translated into local languages (Dari and Pashto) and then retranslated into English by a third person who was not involved in the drafting of the first version to check the consistency of the questionnaires. The local language version was then administered to 50 health workers to check for clarity, consistency, and ease of understanding. Following this the actual data collectors, who were unemployed HCWs, were trained to pilot-test the questionnaires, which included sociodemographic and exposure variables, with study participants. Physicians with experience in administering TST were trained by the principal investigator (GQ) to follow study procedures under supervision to administer the test to 120 HCWs, as indicated in the study procedures below. The inter-observer agreement level for TST skin induration measurement was determined and the weighted Kappa value was 0.75. Twenty-two physicians with perfect skills were selected to conduct TSTs for the study.

Study procedures

Data collectors administered the questionnaires, which included HCWs' history of active TB and of TSTs, followed by screenings for active TB symptoms and signs, such as a cough lasting two weeks or more, night sweating, and weight loss. Those with signs of TB were asked to give a sputum sample for GeneXpert testing (Xpert MTB/RIF assay, Cepheid, Sunnyvale, USA). All HCWs with TB constitutional symptoms also received a chest X-ray.

HCWs without signs or symptoms of TB and with no history of active TB were administered 0.1 ml of 5 tuberculin units of purified protein derivative (BB-NCIPD Ltd., 1504 Sofia, Bulgaria) intradermally in the volar surface of the forearm [22]. Trained physicians read the TST induration within 48–72 hours of administration.

Exclusion criteria

HCWs with presumptive TB and those with a history of active TB were excluded, as were those who did not volunteer for the TST test.

Interpretation of TST results

Per the NTP's definition, the following cutoff points were used to interpret the skin test: CHWs with induration of $\geq$ 10 mm at 48–72 hours were considered to have LTBI, those with a reading of 0–9 mm and were HIV negative were considered negative for LTBI. If the CHW was HIV positive, 5–10 mm was also considered LTBI [22].

Data entry and analysis

The data were entered in Epi Info version 7.2.2.6 and transferred to SPSS version 23 for analysis. A univariate analysis was used to identify potential variables predicating positive TST with Pearson's chi-square test, and all variables with a P value of less than 5% in the bivariate analysis were further analyzed with multiple logistic regression analysis to determine any

associations. Adjusted odds ratios (AORs) and 95% confidence intervals (CIs) were used to determine the association with sociodemographic and exposure variables. In the calculation of the odds ratios, missed variables were excluded.

Ethical considerations

The study was approved by the Afghan Ministry of Public Health Institutional Review Board under approval number 43864, dated August 2, 2017. Study participants were properly instructed in local languages (Dari or Pashto) about the study purpose, the procedures to administer TST and possible side effects related to the injection site. After these explanations, all the study participants gave written consent in Dari or Pashto. Their information was kept confidential and not shared with anyone outside of the study team. The data set had no personal identifiers. Those who did not consent were excluded from the study. Those with signs of TB were provided a free diagnosis, and those diagnosed with TB were given free treatment, according to national guidelines.

Results

In total, the 249 health facilities sampled had 4,648 health workers, and, of these, 3,975 (85.5%) consented to participate; 154 (3.3%) refused to participate; 474 (10.1%) were excluded from the study because they were presumptive TB cases; and another 45 (0.9%) had a history of TB. We gave TSTs to 3,975 HCWs and read results for 3,686 (92.7%); 289 HCWs (7.3%) did not return for the reading and were excluded from the analysis (Fig 1).

In this study, male HCWs constituted 2,573 (69.8%) of participants. The mean age of study participants was 34.5, with a median age of 32. Of the participants, 2,923 (79.3%) were married, 2,152 (58.4%) were college or university graduates, and the average monthly income of 1,616 (43.8%) was less than US$130. In 1,966 (53.3%) of participants, body mass index (BMI) was normal (18–24.9); 1,195 (32.4%) were overweight (BMI = 25.0–29.9); 237 (7.4%) were obese (BMI = $\geq$ 30); 115 (3.1%) were underweight (BMI = $<$ 18); and in 134 HCWs (3.6%), measurements were not taken.

Of 3,686 test results, 1,738 were LTBI positive, for a prevalence of 47.1% (95% CI 45.4%-48.7%). Men had a higher TST positivity—a total of 1,237 (71.3%)—than women, of whom only 497 (28.5%) tested positive, but the difference was not statistically significant ($P > 0.05$). In the bivariate analysis, the only groups that showed significant associations with LTBI were married (OR = 2.13, 95% CI 1.77–2.57), aged between 35 and 44 (OR = 1.30, 95% CI 1.07–1.57), and illiterate (OR = 1.34, 95% CI 1.06–1.7) (Tables 1 and 2).

In the exposure variables, those who had worked in health care for less than 10 years had a higher prevalence of LTBI—1,115 (64.1%)—and the difference was significant ($P = 0.04$). The prevalence of LTBI was not associated with health facility type, cigarette smoking, or family history of TB ($P > 0.05$). There were only four reported cases of HIV-positive health workers; the majority (56.7%) of HCWs did not know their HIV status (Table 3).

In the multiple logistic regression analysis, only BMI values of 30+ (AOR 1.32, 95% CI 1.01–1.73) and being married (AOR 1.99, 95% CI 1.65–2.4) were associated with LTBI (Table 2). Years of service was not associated with LTBI (AOR 1.18, 95% CI 0.97–1.44)].

Discussion

The prevalence of LTBI among health workers in Afghanistan in this study was 47.1%, which is more than double the 23% reported among the global population [23]. There are no recent studies for Afghanistan, but two studies in 1958 and 1978 among children showed that the annual risk of infection was 3.5% [24]. In another survey among six- and seven-year-old

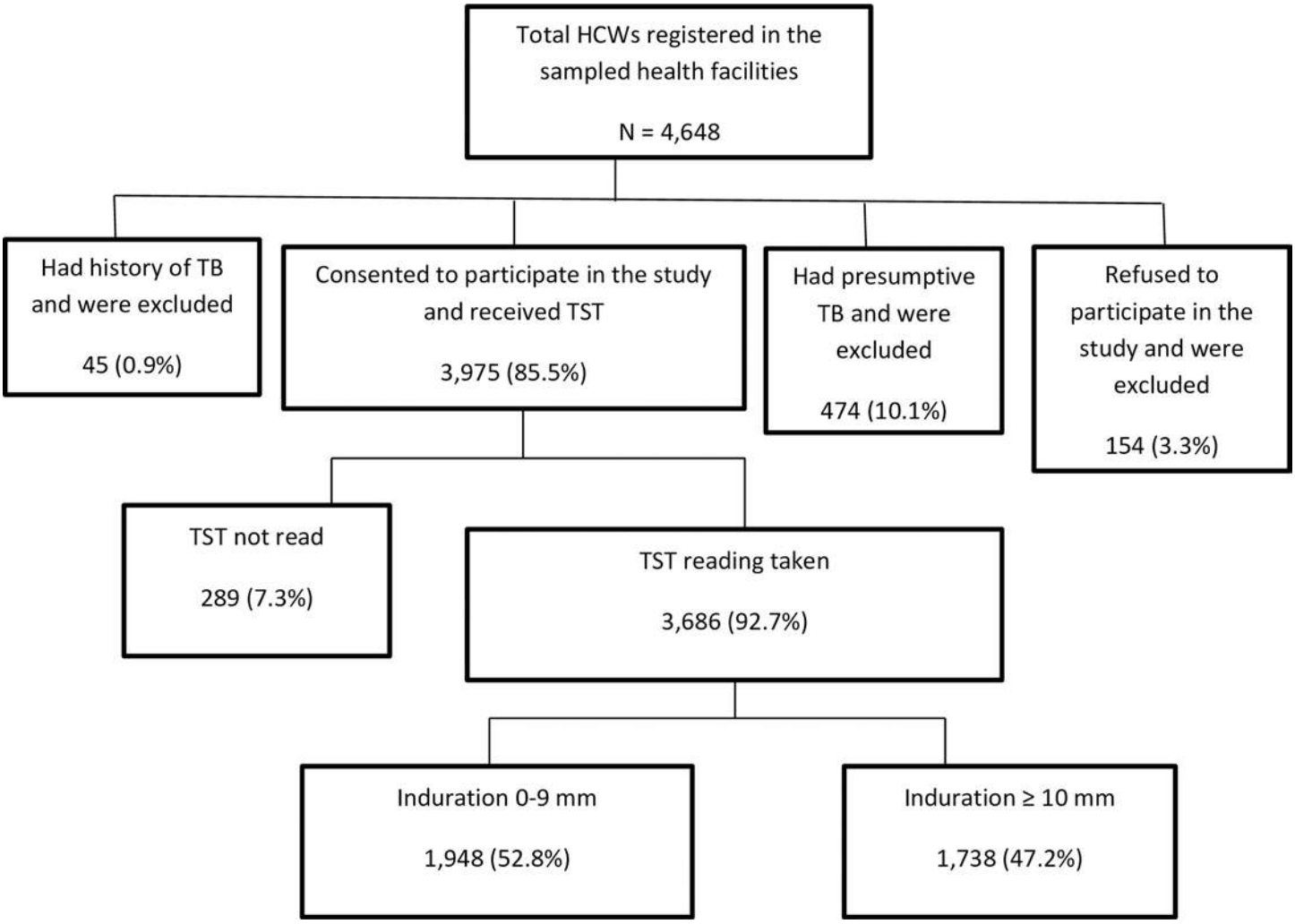

Fig 1. Flow chart showing health care workers who participated in the LTBI study in Afghanistan.

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children in Kabul, the prevalence of TB infection at a cutoff point of TST 8 mm and above was 4.3% [25].

Our findings are similar to those of studies of HCWs in other high-TB-burden countries. A systematic review of seven countries reported LTBI prevalence in HCWs ranging from 37% in Brazil to 64% in South Africa [21]. LTBI prevalence among HCWs was 36.8% in an Indian tertiary hospital [26]; in Côte d'Ivoire it was 79% [27]; 58.8% in Turkey [28]; 57% in Uganda [29]; and 39.4% in Brazil [30]. In neighboring Iran, however, the prevalence was 24.8% for high-risk workers such as laboratory professionals and 14.8% for low-risk HCWs [31]. Iran and Turkey, however, are low-TB-burden countries, with an incidence of 14 and 17/100,000 respectively [1].

In our study, administrative staff had a higher rate of LTBI, at 35%, followed by 19.3% for nurses, but the difference was not statistically significant (P = 0.2). Other studies reported that housekeeping staff, older health workers, and those working in areas of high patient turnover had higher rates of LTBI [6, 17, 32, 33]. The high LTBI in cleaners, guards, and other administrative staff is probably due to their exposure to patients at registration and in waiting areas as well as high exposure to sputum during cleaning and garbage disposal.

Table 1. Sociodemographic variables and association with LTBI among health care workers in Afghanistan (N = 3,686).

Variables		TST Positive (≥ 10 mm)	TST Negative (0–9 mm)	P Value
Sex	Male	1,237 (71.1%)	1,336 (68.8%)	P = 0.054
	Female	497 (28.6%)	601 (30.9%)	
	Missing data	4 (0.2%)	11 (0.6%)	
	Total	1,738 (47.1%)	1,948 (52.9%)	
Age	18–24	372 (21.4%)	441 (22.6%)	P = 0.025
	25–34	530 (30.5%)	601 (30.9%)	
	35–44	435 (25.1%)	398 (20.4%)	
	45–54	260 (15.0%)	336 (17.2%)	
	55–64	109 (6.3%)	128 (6.6%)	
	≥ 65	14 (0.8%)	20 (1.0%)	
	Missing data	15 (0.9%)	39 (1.2%)	
	Total	1,738 (47.1%)	1,948 (52.9%)	
Marital status	Married	1,490 (85.9%)	1,433 (73.6%)	P < 0.001
	Single	208 (12.0%)	481 (24.7%)	
	Separated	1 (0.1%)	3 (0.2%)	
	Not mentioned	27 (1.6%)	15 (0.8%)	
	Missing data	9 (0.5%)	16 (0.8%)	
	Total	1,735 (47.1%)	1,948 (52.9%)	
Highest level of education completed	Illiterate	192 (11.1%)	170 (8.7%)	P = 0.005
	Primary school	198 (11.4%)	199 (10.2%)	
	Secondary school	259 (14.9%)	289 (14.8%)	
	College or university graduate	962 (55.4%)	1,190 (61.1%)	
	Other	12 (0.7%)	5 (0.3%)	
	Missing data	115 (6.6%)	95 (4.9%)	
	Total	1,738 (47.1%)	1,948 (52.9%)	
Professional category	Doctor	224 (12.9%)	237 (12.2%)	P = 0.205
	Nurse	336 (19.3%)	334 (17.1%)	
	Midwife	151 (8.7%)	219 (11.2%)	
	Laboratory professional	95 (5.5%)	101 (5.2%)	
	Community health worker	67 (3.9%)	68 (3.5%)	
	Pharmacy professional	46 (2.7%)	55 (2.8%)	
	Vaccinator	123 (7.1%)	114 (5.9%)	
	Admin. and support staff	607 (35.0%)	715 (36.7%)	
	Other	70 (4.0%)	83 (4.3%)	
	Missing data	19 (1.0%)	22 (1.1%)	
	Total	1,738 (47.1%)	1,948 (52.9%)	
Monthly income (in Afghani)	< 10,000	777 (44.8%)	839 (43.1%)	P = 0.4
	10,000–20,000	664 (38.3%)	754 (38.7%)	
	20001–30,000	161 (9.3%)	168 (8.6%)	
	30001–50,000	43 (2.5%)	50 (2.6%)	
	> 50,000	18 (1.0%)	10 (0.5%)	
	Did not specify	57 (3.3%)	75 (3.9%)	
	Missing data	15 (0.9%	52 (2.7%)	
	Total	1,735 (47.1%)	1,948 (52.9%)	

(*Continued*)

Table 1. (Continued)

Variables		TST Positive (≥ 10 mm)	TST Negative (0–9 mm)	P Value
BMI (kg/m2)	< 18	43 (2.5%)	72 (3.7%)	P < 0.001
	18–24	882 (50.8%)	1,084 (55.6%)	
	25–29	603 (34.8%)	592 (30.4%)	
	30+	151 (8.7%)	122 (6.3%)	
	Missing data	56 (3.2%)	78 (4.0%)	
	Total	1,735	1,948	
History of TST	Yes	15 (0.9%)	15 (0.8%)	P = 0.448
	No	1,593 (91.6%)	1,787 (91.7%)	
	I do not know	130 (7.4%)	182 (9.3%)	
	Total	1,738	1,948	

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In the bivariate analysis, the factors associated with TB were age, years of professional experience, BMI, marital status, and education level. But in the multivariate analysis, the variables associated with LTBI were BMI and marital status. The AOR for obese participants (BMI ≥ 30) was 1.32 (95% CI 1.01–1.73), while the AOR for those with BMI between 18.0 and 24.9 was 0.83 (95% CI 0.72–0.97). There was no association in our study between LTBI and underweight, a finding which is in line with those of other studies; however, unlike LTBI, TB disease exhibits high prevalence among malnourished persons [34]. Another article reported that the risk of TB increased by 14% for each point reduction in BMI between 18.0 and 29.9,

Table 2. Multiple logistic regression analysis of factors associated with LTBI among health care workers in Afghanistan.

Variables		Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Years of professional service	< 10 years		1
	10–19 years	1.17 (0.99–1.39)	1.18 (0.97–1.44)
	20–39 years	0.97 (0.75–1.25)	1.04 (0.77–1.39)
	40+ years		*Insufficient number*
BMI (kg/m2)	<18		1
	18–24	1.28 (0.84–1.97)	1.20 (0.78–1.87)
	25–29	1.68 (1.09–2.60)	1.44 (0.93–2.25)
	30+	2.04 (1.26–3.34)	1.70 (1.04–2.80)
Marital status	Single		1
	Married	2.13 (1.77–2.57)	1.99 (1.65–2.40)
	Separated		*Insufficient number*
	Widowed		*Insufficient number*
	Not mentioned	1.60 (0.77–3.52)	1.41 (0.66–3.15)
Highest level of education completed	Illiterate		1
	Primary school	0.88 (0.64–1.19)	0.92 (0.67–1.27)
	Secondary school	0.77 (0.58–1.03)	0.87 (0.65–1.17)
	College or university graduate	0.72 (0.56–0.91)	0.85 (0.66–1.10)
Age	18–24		1
	25–34	1.05 (0.88–1.26)	1.02 (0.85–1.23)
	35–44	1.30 (1.07–1.57)	1.18 (0.95–1.46)
	45–54	0.93 (0.75–1.15)	0.88 (0.69–1.12)
	55–64	1.07 (0.80–1.44)	1.02 (0.74–1.40)
	≥ 65	0.85 (0.39–1.79)	0.74 (0.33–1.58)

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Table 3. Exposure variables and associated factors among health care workers in Afghanistan.

Variables		TST Positive (≥ 10 mm)	TST Negative (0–9 mm)	P Value
Years of professional service	< 10 years	1,115 (64.1%)	1,293 (66.3%)	P = 0.04
	10–19 years	405 (23.3%)	385 (19.7%)	
	20–39 years	130 (7.4%)	169 (8.6%)	
	40+ years	6 (0.3%)	10 (0.5%)	
	Missing data	82 (4.7%)	91 (4.6%)	
Type of health facility worked in	Public primary health care units	628 (36.1%)	668 (34.3%)	P > 0.05
	Public hospitals	676 (38.8%)	820 (42.1%)	
	Private health facility	326 (18.7%)	341 (17.5%)	
	Other health facilities	43 (2.4%)	53 (2.7%)	
	Not categorized	65 (3.7%)	66 (3.4%)	
HIV status	Positive	2 (0.001%)	2 (0.001%)	P > 0.05
	Negative	754 (43.3%)	835 (42.8%)	
	Unknown	982 (56.5%)	1,111 (57.0%)	
Cigarette smoking	Yes	91 (5.2%)	114 (5.8%)	P > 0.05
	No	1,475 (84.8%)	1,694 (86.9%)	
	Other	172 (9.8%)	140 (7.1%)	
Family TB history	Yes	78 (4.5%)	89 (4.6%)	P > .05
	No	1,624 (93.6%)	1,818 (93.3%)	
	Missing data	33 (1.9%)	41 (2.1%)	

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but it not clear whether that is true for those with body mass indexes of < 18 and ≥ 30 [35]. One possible reason for the low LTBI in underweight people could be that impaired immunity in malnourished people prevents reaction to the TST; instead, those with low BMI develop TB disease faster [36]. Cross-sectional studies also cannot show individuals' BMI histories, so creating an association for a chronic infection like LTBI by measuring BMI at a single point in time may not be appropriate and a longitudinal study would be preferable.

The other LTBI association we found is marital status: the AOR was 1.99 (95% CI 1.65–2.40) for married participants compared to 0.47 (95% CI 0.39–0.57) for single HCWs. Although the reason for the high association of LTBI with marriage is unknown, a similar finding has been reported in South Africa [37]. One reason could be linked to family size and therefore household overcrowding, which might facilitate disease transmission if one member of the household develops TB. Further studies are recommended because there is no plausible reason for married couples to have high LTBI.

In high-TB-burden countries like Afghanistan, where LTBI among HCWs is high, this study should spur action to prevent HCWs from developing TB. Although the benefits of preventive therapy are well established [38, 39]—the protection effectiveness of isoniazid (INH) alone was 90% in studies conducted in developing and developed countries [22]—recommendations for treating HCWs in high-TB-burden countries with ongoing transmission are different from those in low-incidence settings. There is no consensus on treating LTBI among HCWs or in communities in high-TB-burden countries [4]. The WHO's recently revised LTBI guidelines conditionally recommend that children, adolescents, and adults of all ages who are household contacts of bacteriologically confirmed pulmonary TB cases receive preventive treatment; however, treatment of HCWs is recommended only for low-TB-incidence countries, in part because the re-infection rate is high without a robust TB control program [3]. The lack of easy LTBI diagnostics is another factor for not treating HCWs in high-TB-burden countries.

There is a single experience of community-wide INH preventive therapy, in Alaska between 1958 and 1964, in which the TST prevalence in participating communities was above 80% and the annual risk of infection was 8% at baseline. In this community, daily INH was given for the intervention and placebo given in the control arm for 12 months. The incidence of the disease in the intervention group fell dramatically, and cumulative TB incidence was reduced by 60% [40].

Despite high re-infection rates in high-TB-burden countries, expanding preventive treatment beyond the current recommendation to include high-risk groups such as HCWs and contacts should be considered. The WHO LTBI guidelines conditionally recommend treating children over the age of five, adolescents, and adults in high-TB-burden countries, and Afghanistan can decide to treat HCWs, as they are a high-risk group [3]. Ample evidence shows that providing INH preventive therapy to HIV/AIDS patients and children under five has reduced TB disease, although re-infection is a possibility [5]. Studies in low-incidence settings have shown that INH prophylaxis reduced the development of active TB by 40% over two years or longer [39]. Another article reported that INH preventive therapy reduces the development of active disease by 60% to 90%, depending on treatment adherence levels [41]. All these data favor providing preventive therapy to high-risk groups like HCWs even in high-TB-burden countries like Afghanistan. Environmental, administrative, and personal protection measures to control TB infection that have been implemented in US health care settings associated with TB transmission among patients and HCWs have significantly reduced infections [42], but similar measures are usually poorly implemented in resource-poor countries.

Limitations

Our study has some limitations. We did not get complete information for most of the study subjects about Bacille Calmette-Guérin vaccination, which might affect TST results. Another drawback of this study is measuring BMI in a cross-sectional study and creating an association with LTBI. Cross-sectional studies cannot show individuals' BMI histories, so creating an association for a chronic infection such as LTBI by measuring the BMI at a single point in time may not be appropriate. We did not include other factors that affect LTBI, such as diabetes mellitus, malignancies, HIV, and other diseases, in our study.

Conclusion

LTBI in HCWs in Afghanistan is very high. Until evidence is generated globally on the effectiveness of targeted treatment of LTBI in high-TB-burden countries or on new sensitive and specific LTBI diagnostics or shorter treatments, we recommend regular screenings of HCWs for active TB and early treatment. Another recommendation is to strengthen the environmental, administrative, and personal protection measures against TB infection that are recommended by the WHO [43].

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SHORT COMMUNICATION

Experiences of introducing new drugs for drug-resistant TB at the ALERT Hospital, Addis Ababa, Ethiopia, 2017–2019

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BACKGROUND: Drug-resistant TB (DR-TB) remains a major public health concern. DR-TB patient data from ALERT (All Africa Leprosy, Tuberculosis and Rehabilitation Training Centre) Hospital, Addis Ababa, Ethiopia, who received bedaquiline (BDQ) and/or delamanid (DLM) containing regimens were analysed.

RESULTS: From 2017 to 2019, 51 DR-TB patients were enrolled. Of 33 patients, 31 (93.9%) had culture converted at 6 months. Of those with final outcomes, 77% (n = 10) were cured. Thirty (58.8%) developed adverse events, the most frequent of which were gastrointestinal disorders (70%), haematological disorders (16.7%) and QTc prolongation (16.7%). Twenty patients discontinued the offending drug permanently.

CONCLUSION: With close monitoring, introduction of new DR-TB regimens brought good early results, which encouraged wider programmatic implementation in Ethiopia.

Ethiopia is included in the WHO list of 30 high multidrug-resistant TB (MDR-TB) burden countries.[1] In 2017, 680 laboratory-confirmed cases of rifampicin-resistant TB (RR-TB)/MDR-TB patients were put on second-line drug treatment. Adults with RR-/MDR-TB were previously recommended at least 18 months of treatment, including a second-line injectable (SLI) agent.[2] In recent years, WHO recommendations for drug-resistant TB (DR-TB) treatment have included regimens containing bedaquiline (BDQ) or delamanid (DLM).[3,4] In 2016, the Ethiopian National TB Programme (NTP) developed guidelines for the introduction of BDQ and DLM. In April 2016, the first eligible patients were started on BDQ- and DLM-based individualised treatment regimens (BDQ-/DLM-ITRs).*

The Challenge TB Project (CTB), a USAID-supported global flagship TB project, supported the NTP to introduce and scale-up new drug-containing DR-TB regimens in Ethiopia. The CTB project also supported laboratory work and DR-TB patient management. In addition, it helped in supplying BDQ from the USAID BDQ donation program, and procurement of DLM.

*Eligibility criteria for BDQ-/DLM-ITR: pre-XDR (extensively drug-resistant) and XDR-TB cases, patients with previous exposure to SLIs, contacts of XDR or pre-XDR cases, patients unable to tolerate MDR-TB drugs, MDR-/RR-TB treatment failures, extensive or advanced MDR-TB disease, those with comorbidities or other conditions with increased likelihood of acquisition of additional resistance or treatment failure.

The All-African Leprosy Rehabilitation and Training Centre (ALERT) Hospital in Addis Ababa, Ethiopia, has been a DR-TB treatment centre for many years. In April 2017, BDQ- and DLM-ITR were introduced. We report here on early results and drug toxicity patterns among DR-TB patients enrolled on BDQ-/DLM-ITRs at the hospital from April 2017 to March 2019 and the lessons learnt. Data on patients on BDQ-/DLM-ITR and analysis were collected retrospectively. Data were collected from the hospital's DR-TB Department Register and patient charts. Ethical clearance was obtained from the Armauer Hansen Research Institute (AHRI)/ALERT Ethics Committee, Addis Ababa, Ethiopia.

ASPECTS OF INTEREST

Demographic and clinical characteristics

Of the 51 patients enrolled on BDQ-/DLM-ITRs, 29 (56.9%) were men, with a mean age of 32.3 ± 13.7 years. Mean body mass index was 16.3 ± 2.4 kg/m^2. Fifteen (30%) were HIV-positive and on antiretroviral therapy.

Thirty-six (70.6%) cases were tested using Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA), 10 (19.6%) using line-probe assays and 5 (9.8%) patients using conventional phenotypic drug susceptibility testing (DST). Respectively 26 (50.9 %) and 13 (25.4%) had been previously treated with first-line and second-line drugs. Respectively, 28 (54.9%), 10 (19.6%) and 13 (25.5%) patients were on BDQ-, DLM- and BDQ + DLM-ITR. By 6 months, 31/33 (93.9%) had culture converted; there were two deaths. Of 13 patients with final treatment outcomes, 10 (77%) patients were cured and 3 (23%) died.

Adverse drug events occurring during treatment

Thirty (58.8%) patients developed ⩾1 adverse event (AE) during treatment. Respectively 9.8%, 43.1% and 5.9% developed mild, moderate or severe AEs.[5] The most frequent AEs were as nausea, vomiting and gastritis (n = 21, 70%); haematological disorders (mainly anaemia, n = 5, 16.7%) and QTc prolongation (n = 5, 16.7%) (Figure). In respectively 40% and 14.3%, the offending drug(s) were either permanently removed or temporarily discontinued. Only one patient who received BDQ had electrocardiograph abnormalities resulting in permanent discontinuation of BDQ. At Week 5 of treatment, the patient developed QTcF > 450 ms but <500 ms, with premature ventricular complex bigeminy. This returned to normal after BDQ was discontinued.

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KEY WORDS
multidrug-resistant-TB; adverse event, treatment outcome; ALERT Hospital

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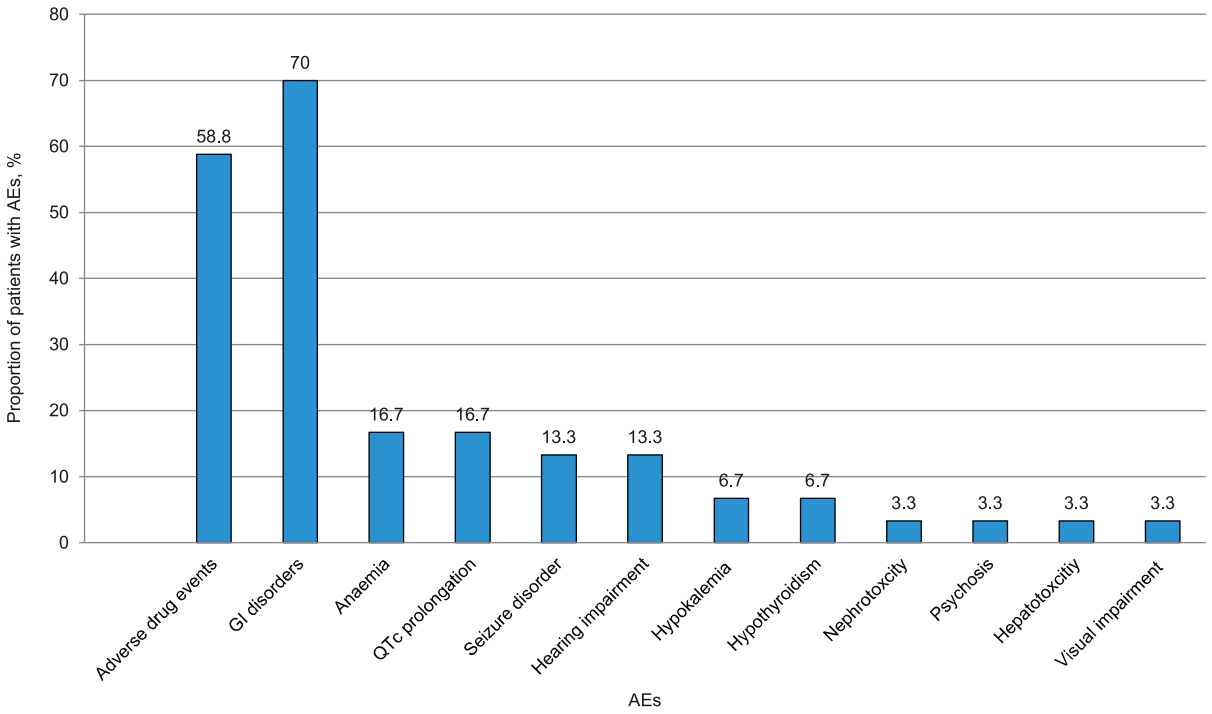

FIGURE Adverse events in patients on BDQ-/DLM-ITRs (*n* = 51). GI = gastro-intestinal; ITR = individualised treatment regimen.

Twelve (23.5%) patients developed serious adverse events (SAEs).[6] Six (11.7%) died, 1 (2%) developed severe pneumonia which treatment improved, and 5 (9.8%) developed medically significant conditions (seizure disorder in 4 patients and 1 patient had a psychotic episode – all improved with treatment). Of the 6 deaths, 4 were on BDQ-ITR and 2 on DLM-ITR; none were attributed to any specific drug (Table).

DISCUSSION

The management of DR-TB is challenging and needs thorough clinical evaluation of the patient, DST and meticulous patient monitoring. Six-month culture conversion was found to be >90% in the cohort – much better than a cohort study done in three countries in which 28 patients put on BDQ- and DLM-ITR showed a culture conversion rate of 74% by 6 months.[7]

TABLE Eligibility criteria, BDQ-/DLM-ITR, and possible cause of death (*n* = 51)

	n (%)
Indication for individualised treatment	
Hearing impairment	12 (23.5)
Pre-XDR-TB to SLI	3 (5.9)
Pre-XDR to FQ	7 (13.7)
Advanced and multiple cavitary lung lesions	16 (31.4)
Failed by standard MDR-TB treatment	5 (9.8)
Acute kidney injury	8 (15.7)
Chronic kidney disease	3 (5.9)
Treatment regimens	
Regimen containing BDQ	28 (54.9)
Regimen containing DLM	10 (19.6)
Regimen containing BDQ and DLM	13 (25.5)
Possible cause of death	
Severe respiratory failure secondary to severe pneumonia	1 (20 years old, male, HIV co-infected, C+)
Sudden death of unknown cause after overnight excess alcohol intake	1 (33 years old, male, HIV-infected, C–)
End-stage renal disease with uremic encephalopathy	1 (31 years old, male, chronic renal disease, C–)
Severe peripheral arterial disease with wet gangrene and severe sepsis	1 (42 years old, male, HIV co-infected, C–)
Respiratory failure secondary to severe pulmonary hypertension	1 (62 years old, male, Cardiac illness, C–)
Multi-organ failure secondary to disseminated TB	1 (19 years old, female, HIV co-infected, C+)

BDQ = bedaquiline; DLM = delamanid; ITR = individualised treatment regimen; XDR-TB = extensively drug-resistant TB; SLI = second-line injectable; FQ = fluoroquinolone; MDR-TB = multidrug-resistant TB; C = culture; + = positive; – = negative.

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The study was funded under the auspices of the United States Agency for International Development (USAID) supported Challenge TB project. Disclaimer: The findings and conclusions are those of the authors and Challenge TB, and do not necessarily reflect the views of USAID or the US Government. The funders had no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript.
Conflict of interests: none declared.

Adverse events are an almost inevitable occurrence during DR-TB treatment. Almost 60% in the cohort had ⩾1 AE, most commonly gastrointestinal disorders, QTcF prolongation and haematological disorders. Nausea, vomiting and dyspepsia were more prevalent, similar to an MDR-TB cohort treated in two other hospitals in Ethiopia.[8] In a large study conducted in 15 countries with patients receiving BDQ-ITR, including various other SLIs, 24/247 (9.7%) patients experienced a QTcF prolongation of >500 ms.[9] Haematological disorders were another important AE in patients on regimens containing linezolid, well known to potentially cause bone marrow suppression with severe anaemia.

Thirteen (25.5%) patients were on both BDQ and DLM because of the extremely limited drug options available to construct an effective regimen. However, just five (16.7%) developed moderate QTc prolongation (<500 msec) and of these, only two were on combined BDQ + DLM-ITR. This re-confirms the finding of others which show that the combined use of BDQ and DLM is a relatively safe therapeutic option.[10]

To manage the AEs in the study cohort, either the offending drug was permanently removed and replaced with a new drug (40%) or it was temporarily interrupted and additional ancillary drugs used (14.3%). The same practice has been implemented in different countries. SAEs occurred in 12 patients (6 deaths, 1 life threatening and 5 medically significant conditions), which is consistent with the findings of other studies. However, none of the deaths were attributed to any specific drug.

CONCLUSION

This hospital-based intervention showed that BDQ and/or DLM introduction is feasible and resulted in satisfactory 6-month culture conversion rates and final treatment outcomes. High levels of AEs led to drug discontinuation either permanently or temporarily. However with good monitoring and management practices, these were identified and managed appropriately in a timely manner. BDQ- and DLM-containing DR-TB regimens should be followed by rapid country-wide introduction in national policies of all-oral treatment regimens for a wide group of DR-TB patients to improve treatment outcomes and quality of life among DR-TB patients.

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CONTEXTE : La TB pharmacorésistante (DR-TB) reste une préoccupation de santé publique majeure. Les données des patients DR-TB de l'hôpital ALERT (All Africa Leprosy, Tuberculosis and Rehabilitation Training Centre, Addis Ababa, Ethiopie) qui ont reçu des protocoles contenant de la bédaquiline et/ou du délamanide ont été analysées.

RÉSULTATS : Des 51 patients DR-TB ont été enrôlés de 2017 à 2019, 90 ont eu une conversion de culture à 6 mois, 77% ont été guéris, 30 ont eu des effets secondaires, les plus fréquents étant des troubles gastro-intestinaux (70%), des troubles hématologique (16,7%) et un allongement de QTc (16,7%). Vingt patients ont définitivement arrêté le médicament incriminé.

CONCLUSION : Moyennant une surveillance étroite, l'introduction de nouveaux protocoles DR-TB a eu de bons résultats précoces qui encouragent une mise en œuvre programmatique plus large en Ethiopie.

Public Health Action (PHA) welcomes the submission of articles on all aspects of operational research, including quality improvements, cost-benefit analysis, ethics, equity, access to services and capacity building, with a focus on relevant areas of public health (e.g. infection control, nutrition, TB, HIV, vaccines, smoking, COVID-19, microbial resistance, outbreaks etc).

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JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Molecular Epidemiology of *Mycobacterium tuberculosis* strains isolated from pulmonary tuberculosis patients in south Ethiopia

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Abstract

Introduction: Understanding the epidemiology of tuberculosis is limited by lack of genotyping data. We sought to characterize the drug susceptibility testing patterns and genetic diversity of *M. tuberculosis* isolates in southern Ethiopia.

Methodology: A cross-sectional study was conducted among newly diagnosed sputum smear positive patients with tuberculosis visiting nine health facilities in southern Ethiopia from June 2015 to May 2016. Three consecutive sputum samples (spot-morning-spot) per patient were examined using acid-fast bacilli smear microscopy with all smear positive specimens having acid-fast bacilli cultures performed. *M. tuberculosis* isolates had drug susceptibility testing performed using indirect proportion method and were genotyped with RD9 deletion analysis and spoligotyping. Mapping of strain was made using geographic information system.

Results: Among 250 newly diagnosed patients with tuberculosis, 4% were HIV co-infected. All 230 isolates tested were *M. tuberculosis* strains belonging to three lineages: Euro-American, 187 (81%), East-African-Indian, 31 (14%), and Lineage 7 (Ethiopian lineage), 8 (4%); categorized into 63 different spoligotype patterns, of which 85% fell into 28 clusters. *M. tuberculosis* strains were clustered by geographic localities. The dominant spoligotypes were SIT149 (21%) and SIT53 (19%). Drug susceptibility testing found that 14% of isolates tested were resistant to $\geq$ 1 first line anti- tuberculosis drugs and 11% to INH. SIT 149 was dominant among drug resistant isolates.

Conclusions: The study revealed several clusters and drug resistant strains of *M. tuberculosis* in the study area, suggesting recent transmission including of drug resistant tuberculosis. Wider monitoring of drug susceptibility testing and geospatial analysis of transmission trends is required to control tuberculosis in southern Ethiopia.

Key words: Molecular epidemiology; Tuberculosis; drug susceptibility testing; geospatial cluster; Ethiopia.

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Introduction

Tuberculosis (TB) remains a major and urgent global public health problem, especially in low-income countries where the burden of disease is high. Globally, there were 10 million new cases and 1.2 million deaths among persons with TB in 2019. Drug-resistant TB is a major public health concern in many countries and continues to be a public health threat [1]. Ethiopia has a long history of TB [2] and is still hugely affected by the disease and it is one of fourteen countries appearing in all three WHO high burden country lists for TB, TB/HIV and MDR-TB [1]. According to the national anti-tuberculosis drug resistance survey in 2014, the prevalence of MDR-TB among new and previously treated TB cases was 2.3% and 17.8% respectively [3]. Additionally, data from different parts of the country show that drug-resistant TB is a major public health concern that demands attention [4,5].

Interruption of the transmission of *M. tuberculosis* is one of the primary goals of tuberculosis control programs. Tracking specific strains of *M.tuberculosis* circulating in the community informs public health authorities on patterns of spread and potential areas for action to curb the spread of TB in communities [6]. Spoligotyping is a PCR-based method commonly used to characterize *M. tuberculosis* strains circulating in a community [7] and strain differentiation is based on the polymorphism in the direct repeat (DR) locus, which is a distinct chromosomal region in *M. tuberculosis* genome [8]. Although the current trend is recommending the use of a combination of typing methods to provide a higher resolution and better characterize than spoligotype alone, the use of

spoligotype would still provide useful information relative to high burden settings with limited recourses. It has been extensively used for simultaneous detection and typing of *M. tuberculosis* [7].

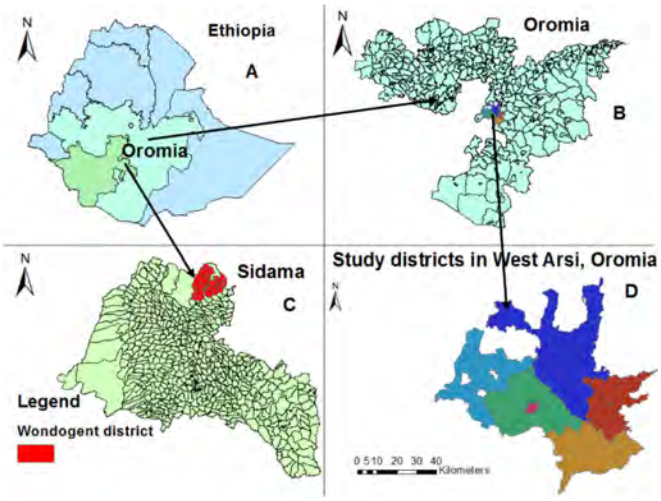
The lack of comprehensive molecular epidemiological data from most countries in Africa, such as Ethiopia, has limited the understanding of TB disease dynamics. While several molecular epidemiological studies have been conducted to describe the diversity and drug susceptibility profile of *M. tuberculosis* strains in various geographical areas of Ethiopia [9-11], data from the south, where population density is relatively higher, is limited. Moreover, there is no data on the spatial distribution of *M. tuberculosis* clustered strains in the country. In order to have a clear understanding of the ongoing transmission dynamics of *M. tuberculosis* in a community, GIS mapping supported cluster position studies are recommended [12]. The goal of our study was to characterize the drug susceptibility patterns and genetic diversity of *M. tuberculosis* isolates circulating in southern Ethiopia.

Methodology

Study design and area

This cross-sectional study was conducted at nine health facilities (two hospitals and seven health centers) in and around Shashemene area, in West Arisi Zone of Oromia Region, Ethiopia. Shashemene is a major urban center and commercial town, located 240 km south of the capital Addis Ababa. The estimated population of the study area was 3 million people. All nine health facilities included in the study area provided services for the diagnosis and treatment of TB through DOTS clinics. Patients enrolled at the nine health facilities from the West Arsi Zone and adjoining kebele of Wondogenet were mapped and fell into seven districts (Woredas) (Figure 1).

Figure 1. Map of the study area (East Arisi Zone districts, Oromia and Wondo Genet of Sidama Regional State)



A: Map of Ethiopia; B: Map of Oromia Regional State; C: Map of districts of Oromia Regional state and Wondogenet district from Sidama Regional State; D: Map of districts involved in the study.

Study population and variables

Among the persons suspected to have TB who were investigated at any one of the nine health facilities during the study period, all newly diagnosed sputum smear positive pulmonary TB patients who provided written informed consent for study participation were enrolled. Assent for the children and consent by parents or guardians for those under 18 yrs of age were also obtained. The study was conducted from June 2015 through May 2016. Three consecutive sputum samples (spot-morning-spot) were collected from each TB suspect. Socio-demographic and clinical information was obtained for all study participants by a TB clinic nurse at the respective health facilities using a pre-tested standard questionnaire. Data on HIV status was retrieved from health facility records.

Definition

Newly diagnosed patients with pulmonary TB refer to patients who had never been previously treated for TB or have only taken anti-TB drugs for less than 1 month. *M. tuberculosis* isolates (two or more) that share the same genotype based on spoligotyping were considered clustered.

Laboratory methods

Specimen collection

Sputum samples were collected at each respective health facilities using sterile sputum cups; sputum smears were prepared at the same day as the sputum collection and examined by an onsite health facility laboratory technologist. The remaining portion of the three sputum samples from AFB smear positive patients were pooled individually into 50 mL sterile screw capped universal test tubes and stored at the diagnostic centers at -20 ˚C for a maximum of one week until transported on cold chain to the Armauer Hansen Research Institute (AHRI) in Addis Ababa, Ethiopia for mycobacterial culture, RD9 deletion analysis and spoligotyping.

Mycobacterial culture

The pooled sputum samples were processed at AHRI within one day based on standard procedures as

previously described [13]. In brief, the sputum samples were digested and decontaminated using Petroff's method and the processed sample was inoculated into three tubes containing egg-based Löwenstein Jensen (LJ) media (two with glycerol and one with pyruvate). The inoculated media were incubated at 37 ˚C for at least 8 weeks, with weekly observation for the presence of mycobacterial colonies. Cultures with no growth after the eighth week were considered negative. Mycobacterial growth was confirmed by typical colony morphology and AFB staining.

Drug susceptibility test (DST)

The conventional indirect proportion method was employed to perform DST using 7H10 medium on 24-well tissue culture plates using a standard protocol [14]. In brief, four first line anti-TB drugs (isoniazid, rifampicin, ethambutol and streptomycin) were mixed with the agar media at recommended concentration and dispensed into 9 wells of the 24 well tissue culture plates and two wells were dispensed with drug free media. The agar plate was sealed with parafilm and incubated in an inverted position at 35 ˚C. The plates were checked on day 6, 12 and 19 for evidence of growth. Resistance was expressed as the percentage of colonies that grew on critical concentrations of the drugs, i.e. 0.2 µg/mL for isoniazid (INH), 1µg/mL for rifampicin (RPM), 5µg/mL for ethambutol (EMB) and 2µg/mL for streptomycin (STM). The interpretation of resistance was based on the standard criteria for resistance, i.e. 1% for all drugs [15].

DNA extraction

Mycobacterial genomic DNA was extracted by heating the isolates at 80 ˚C in a sonicator water bath for an hour [16].

RD9 deletion analysis

Region of difference 9 (RD9) deletion analyses was performed on heat-killed cells to confirm the presence or absence of RD9 for species identification of *M. tuberculosis* from the other members of MTBC as previously described [17]. It uses three primers (RD9flankF, RD9intR and RD9flankR) for PCR reaction. PCR amplification of the mixtures was done using a Thermal Cycler PCR machine. The PCR amplification product was run by electrophoresis in 1.5% agarose gel in 1× Trisacetate- ethylene diamine tetraacetic acid running buffer at 110volt for 35 minutes. Ethidium bromide at a ratio of 1:10, 100 base pair (bp) DNA ladder, and orange 6× loading dye was used in gel electrophoresis and the gel was visualized. The results were interpreted as *M. tuberculosis* when a band of 396 bp was observed (RD-9 positive). Detection of a band size of 575 bp was considered to be positive for the other members of *M. tuberculosis* complex species (*M. bovis* or *M. africanum).* DNA from *M. bovis* BCG and *M. tuberculosis* H37Rv were used as positive controls, whereas autoclaved ultrapure water was used as a negative control.

Spoligotyping

Isolates that were positive for *M. tuberculosis* by RD9 PCR were further characterized by spoligotyping following the procedure described earlier [7]. In brief, the direct repeat (DR) region of the isolate was amplified by PCR using oligonucleotide primers (DRa and DRb) derived from the DR sequence. Individual spoligotyping patterns were compared with the recent International Spoligotyping Database (SITVITWEB). Spoligotyping International Types (SIT) and sub-lineages (clades) were assigned according to signatures provided in SITVITWEB data base [18]. An isolate was defined as a shared type if the same spoligotype was found in the database. If no matching spoligotype was found in the database, the isolate was defined as orphan (new).

Data management

Data were double entered into an online REDCap database [19] and analyzed using STATA v1 (StataCorp, College Station, TX, USA).

Spatial analysis

Mapping of TB lineage and strain clusters was made using GIS. First, the proportion of different types of TB lineages was computed (stratified) by district to look for variations in geographic distribution of lineages. Second, clustered strains were mapped by geographic locations. ArcGIS software (10.2) was used for mapping the geographic distribution of lineages and clustered strains by district. The shape file of study districts were obtained from Central Statistics Agency of Ethiopia (CSA). A geographic projection of the World Geodetic System (WGS), Universal Transverse Mercator (UTM) Zone 37 N was used for analysis. The data of attributes (number and proportion of TB cases, lineages and TB strains) were geo-linked for each district with the geographic data (shape file) using feature identification.

Ethical consideration

The study was approved by the Institutional Review Boards of Addis Ababa University and the Armauer

Hansen Research Institute (AHRI) as well as the Ethiopian National Ethics Review committee. Study permission was also obtained from the Oromia Regional Health Bureau, Western Arisi zone Health Department, Southern Regional Health Bureau and Sidama Regional Health Bureau.

Results

Socio-demographic characteristics

Among 250 newly diagnosed sputum smear positive TB patients enrolled, 145 (58%) were male and 143 (57%) from urban areas (Table 1). The median age was 25 years (interquartile range [IQR] 20-30). One hundred twenty-nine (52%) were married, 195 (78%) had an educational level of at least primary school. Farmers, students and house wives altogether accounted for 70% (174) of the study participants. TB-HIV co-infection was present in 10 (4%).

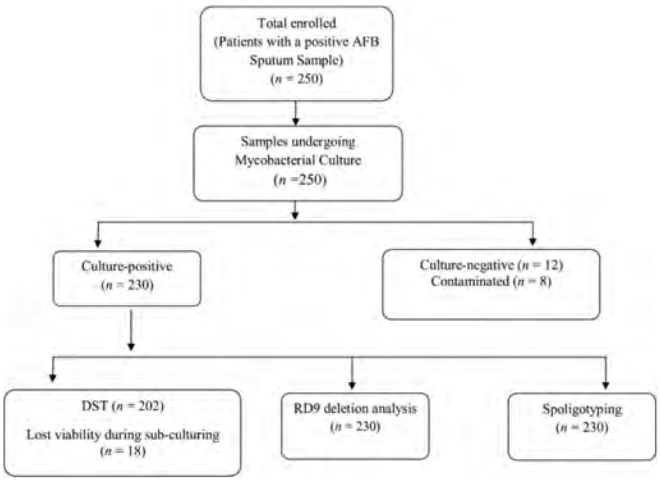
Genetic diversity of strains

All 250 AFB positive sputum samples had mycobacterial culture performed; 230 (92.0%) were positive, 8 (3.2%) were contaminated and 12 (4.8%) failed to grow on culture (Figure 2). The 230 isolates

Table 1. Sociodemographic characteristics and clinical variables of study participants, Southern Ethiopia (N = 250).

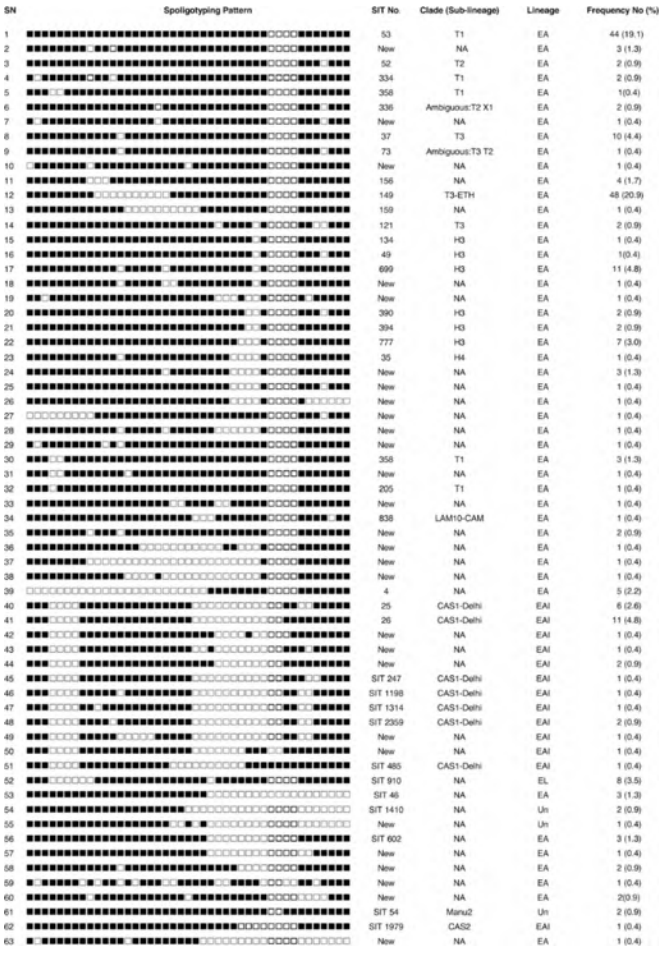
Characteristics	N (%)
Sex	
Male	145 (58.0)
Female	105 (42.0)
Age in years	
< 14	14 (5.6)
15-34	193 (77.2)
35-44	23 (9.2)
45-54	9 (3.6)
≥ 55	11 (4.4)
Location	
Urban	107 (42.8)
Rural	143 (57.2)
Marital status	
Single	109 (43.6)
Married	129 (51.6)
Other	12 (4.8)
Education	
Primary school and above	195 (78.0)
Illiterate	55 (22.0)
Occupation	
Farmer	79 (31.6)
Student	57 (22.8)
Housewife	38 (15.2)
Government employee	9 (3.6)
Other	67 (26.8)
HIV serostatus	
Positive	10 (4.0)
Negative	236 (96.0)
Not tested	4 (1.6)

Figure 2. Study Diagram.



DST: drug susceptibility testing; RD9: region of difference-9.

Figure 3. Spoligotype pattern of *M. tuberculosis* strains isolated from pulmonary tuberculosis patients in southern Ethiopia.



The black squares represent positive hybridization signals and white squares represent a lack of hybridization. EA: Euro-American; EAI: East-African-Indian; EL: Ethiopian lineage (L7); SIT: Spoligotype international type; NA: Not assigned; Un: unknown.

were all identified as *M. tuberculosis* by RD9 deletion analysis. Spoligotyping analysis identified 63 spoligotype patterns, of which 35 (56.0%) were already known in the international data base and 28 (44.0%) were new patterns (orphans).

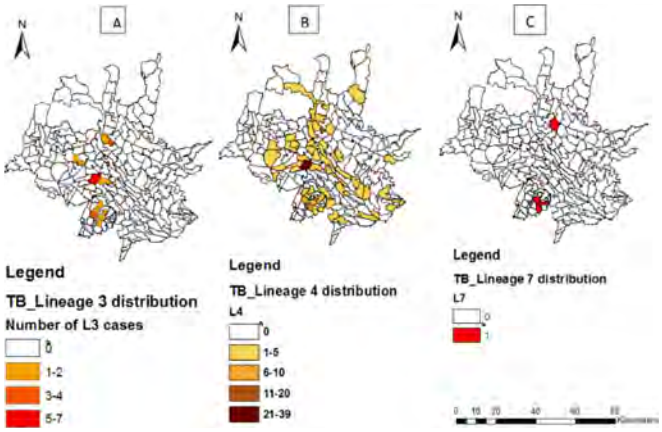
The lineage distribution showed that 187 (81%) isolates belonged to the Euro-American lineage (L4), 31 (14%) to East-African-Indian (L3) and 8 (4%) to Lineage 7 (Ethiopian lineage). Three strain types could not be assigned to any of the lineages. The predominant clade (sub-lineage) was T1 (51, 22%), followed by T3-ETH (48, 21%), H3 and CAS1-Delhi (23, 10%) each (Figure 3).

The most dominant shared types were SIT149 (48, 21%) and SIT53 (44, 19%) while (37, 16%) were orphan strains (of different spoligotype patterns). One hundred ninety-five (85%) of the isolates were clustered into 28 spoligotype patterns and the remaining (36, 16%) strains fell into single spoligotypes. Cluster size varied from 2 to 48 strains per cluster. Of the clustered 195 strains, 181(93%) were already registered in the international database and the other 14 (7%) were orphans. Sixty-two (27%) of the strains were not assigned for clade in the SITVITWEB database [18].

Mapping of TB lineage and strain clusters

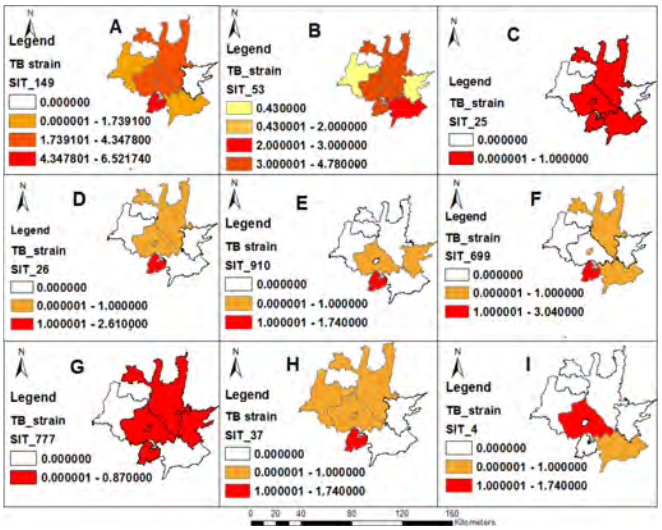
The spatial distribution of lineages identified in the study is presented in Figure 4. Mapping of the geographic location of clustered strains using GPS showed that the distribution of clustered strains varies within districtsand the highest proportions of clustered strains were observed in Wendogenet district of Sidama Region with SIT 149 (6.5%), SIT 699 (3.0%)and SIT 25 (2.6%). Shashemene town also had a higher proportion of clustered strains such as SIT 149 (4.4%), SIT 53 (4.8%) than other districts. The distribution of clustered strains varied across districts. Wondogenet had all types of TB clusters. (Figure 5).

Figure 4. Spatial distribution of TB lineages; West Arisi zone and Wondogenet district.



A: East-African-Indian (L3); B: Euro-American lineage (L4); C: Lineage 7 (Ethiopian lineage).

Figure 5. Spatial distribution of clustered strains by district; West Arisi zone and Wondogenet district.



SIT: Spoligotype international type. A: SIT 149; B: SIT 53; C:SIT 25; D:SIT 26; E: SIT 910; F:SIT 699; G:SIT 777; H: SIT 37; I: SIT 4.

Table 2. Resistance to first-line anti-TB drugs and to streptomycin among sputum positive TB in Southern Ethiopia.

Total tested	Number (n = 202)	Percentage (%)	95% CI
Pan sensitive	173	85.7	80.03 – 90.16
Any resistance	29	14.3	9.83 – 19.96
Monoresistance			
INH	22	10.9	6.92 – 16.02
RPM	1	0.5	0.01 – 2.72
STM	1	0.5	0.01 – 2.72
EMB	5	2.5	0.80 – 5.68
Combined drug resistance			
INH+RPM	0	0	
INH + EMB	1	0.5	0.01 – 2.72
INH + STM	3	1.4	0.30 – 4.27
INH+RPM+STM+EMB	0	0	

INH: Isoniazid; EMB: Ethambutol; RPM: Rifampicin; STM: Streptomycin.

Drug susceptibility profile

Drug susceptibility testing was carried out on 202 of 230 *M. tuberculosis* isolates for the first-line drugs: INH, RPM, EMB and for STM. A total of 29 (14.3%) isolates were resistant to any of the drugs tested. The highest monoresistance was observed for INH in 10.9% (22). No MDR-TB was detected in the current study (Table 2).

Genotyping of drug resistant strains

Genotyping of the drug-resistant strains showed SIT 149 (T3-ETH) to be dominant strain (9/43) among the drug resistant isolates followed by SIT 53 (3/43) and SIT 390 (2/43).

Discussion

The study revealed a heterogeneous pool of *M. tuberculosis* strains with several clusters including lineage 7 strains circulating in south Ethiopia. A high proportion of INH resistance was reported in the current study and SIT 149 (T3-ETH) was the most dominant circulating strain in the study area including among drug-resistant cases. The high clustering of strains by geographic location suggest the ongoing transmission of TB, including of drug-resistant TB in southern Ethiopia and calls for surveillance and wider monitoring of DST and improved control responses.

In the current study, the majority of the isolates (82%) belonged to the Euro-American lineage (L4) followed by East-Africa-Indian (L3), 14% and the Ethiopian lineage (L7), 4%. A recent study in southern Ethiopia (which was geographically close to our study) reported that 84% of the isolates were L4 [20]. Studies from other parts of the country reported variable proportion of lineage types in different geographic areas of Ethiopia [9, 21]. Overall, L4 is more predominant than all other lineages combined in Ethiopia [2,12] which is in line with our finding. Compared to other African countries, L4 was also predominantly found in Eritrea, Kenya and Uganda [2,22] while a higher proportion of L3 (25-35%) was reported from northern Ethiopia than elsewhere [9]. From African countries, L3 was predominantly reported from Sudan [2] which is geographically close to northern Ethiopia. Our finding showed lower prevalence of L3 in southern Ethiopia compared to northern Ethiopia.

Lineage 7 (Ethiopian lineage) accounted for 4% in the current study. One case of Lineage 7 was recently reported from the southern part of Ethiopia [20] and 6 cases (2%) from the southwest [23]. Lineage 7 was first reported from Woldia in Amhara region of Ethiopia with a prevalence rate 13% [9] and later 16% in the same region [24]. So far, lineage 7 has been prominently reported from the northern part of Ethiopia. The additional report of lineage 7 in the current study suggests its broader occurrence, including in the southern parts of the country. Considering the pre-modern split of this lineage in the phylogenetic tree of *M. tuberculosis* and its localization to Ethiopia only, further investigations into its epidemiology would be of much interest. This study indicated slight difference in the genetic diversity of *M. tuberculosis* in the southern Ethiopia compared to other parts of the country. The wider implication of this on the dynamics of the transmission of TB and drug resistance in the area has yet to be investigated well.

In the current study, SIT 149 was the most common spoligotype (21%) circulating in the study area. Previous studies in Ethiopia have indicated that SIT149, also known as T3-ETH (29), ETH-3 and more recently as L4.2.ETH1 [2], is the most common spoligotype widely distributed in the country [12]. It is also known to be more frequently associated with drug resistance than other spoligotype clusters [25]. It is important that the distribution of this spoligotype is closely monitored and its drivers identified to better tailor control efforts.

Clustering of strains is a marker for recent transmission [26] and indicates where to target interventions. Mapping of clustered strains using GIS has particular importance as it helps to locate cluster position of strains and thus describes the epidemiological links of *M. tuberculosis* strains to a specific geographic locality [12]. In this study, GPS mapping demonstrated the presence of *M. tuberculosis* strain clusters in different districts and identifying areas affected with possible recent transmission. To our knowledge, this is the first report in the country on mapping of *M. tuberculosis* clustered strains position in the community. Although spoligotyping may correctly identify *M. tuberculosis* complex in to various lineages and sub-lineages [7], it is known to overestimate clustering of isolates [27]. In our study, Shashemene town and Wendogenet district are areas with high proportion of clustered strains and this call for the need of strengthening TB control activities in the areas to curb the transmission of the disease.

In the current study, 14% of the newly diagnosed TB patients were resistant to ≥1 first-line anti-TB drugs which is lower than reports from other parts of the country, as high as 23% in Central [11] and 23% in Eastern [5], but relatively higher than the prevalence rate of 11% reported in Northern Ethiopia [4] and 9 % in Southern Ethiopia [28]. The difference in the

prevalence rates observed in different parts of the country could be due to differences in TB control program performance, population dynamics, methods or study periods. It is lower than reports from Nairobi which is as high as 30% [29].

INH monoresistance was 10.9% in the current study and it is comparable with reports from eastern Ethiopia, 9.5% [5], but lower than 13.2% from western [30] and higher than reports from central Ethiopia, 4.7% [11]. No MDR-TB was reported in the current study. However, in terms of ordering of drug resistance acquisition, study from South Africa [31] showed that isoniazid resistance was the initial resistance mutation to be acquired in drug resistant TB and is the common pathway for the development of MDR-TB. Therefore, the relatively high INH monoresistance that was observed in the current study should alert to the potential development of MDR TB in the study area and highlights the need for program based DST monitoring.

Linking strain typing data with data on drug resistance can be a useful way to monitor the spread of individual drug-resistant clones in communities [6].T3-ETH (SIT 149) was the most prevalent spoligotype (21%) among drug resistant strains in this series. Fifty percent (12/24) of the drug resistant *M. tuberculosis* isolates were SIT 149 in a collection dating from 2006-2010 [25] and T3-ETH (SIT 149) was associated with MDR-TB [10]. T3-ETH (SIT 149) is the predominant spoligotype cluster associated with drug resistance in Ethiopia [24]. However, the observed association between T3-ETH (SIT 149) and development of drug resistance may not necessarily indicate that these strains are more prone to be drug-resistant but could rather be a consequence of their high prevalence in the population [25]. The correlation between genotypes and TB drug resistance was still uncertain [32]. Further analysis on SIT149 identified genotype SIT149:A, a potential MDR-TB clone circulating in the Ethiopian highlands probably contributes to the spread of MDR-TB in the area that warrants further attention [25].

Limitations

The study had certain limitations. First, as our study participants were only newly diagnosed pulmonary TB cases, it was not possible to assess the magnitude of drug resistant TB in the previously treated TB and in extrapulmonary TB cases and the strain types between these groups. This has limited us from assessing the overall burden of drug resistant TB in the study area. Second, study participants were all patients seeking treatment at health facilities. Findings from such a selected population may overestimate the true burden of the problem at community level. Third, though Spoligotyping is a robust tool, in mixed TB infection; it is difficult to differentiate between *M.tuberculosis* strains; therefore, we did not asses mixed TB infection in our study.

Conclusions

The study identified heterogeneous pool of *M. tuberculosis* in different clusters, and high proportion of INH monoresistance. SIT 149 (T3-ETH) was the most dominant strain cluster circulating in the study area, including among drug resistant cases. The study highlights an ongoing transmission of TB, including of drug resistant TB, in southern Ethiopia and call for surveillance and wider monitoring of DST, supported by geospatial analysis to monitor transmission trends and improve control responses.

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Authors' contributions

YM: contributed to the conception and design of the study, acquisition of data and interpretation, and drafting and writing of the manuscript; MA, DD: contributed to the design of the study and supervision and revision of the manuscript; TH: contributed to data management and analysis; MH: contributed to geospatial analysis and revision of the manuscript; EH, MT and GH: contributed to laboratory work; AA, YW: contributed to the design of the study and supervision, interpretation of data and reviewing the manuscript and both had equal contribution as senior authors. All authors approved the final version of the manuscript.

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PERSPECTIVES

Coronavirus Disease 2019 Diagnosis in Low- and Middle-Income Countries

The Big New Bully Disrupting TB and HIV Diagnostic Services

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Coronavirus disease 2019 (COVID-19) undermines control of other infectious diseases. Diagnostics are critical in health care. This opinion paper explores approaches for leveraging diagnostics for COVID-19 while retaining diagnostics for other infectious diseases, including tuberculosis (TB) and HIV. The authors reflect on experiences with GeneXpert technology for TB detection and opportunities for integration with other diseases. They also reflect on benefits and risks of integration. Placement of diagnostics in laboratory networks is largely nonintegrated and designated for specific diseases. Restricting the use of diagnostics leaves gaps in detection of TB, HIV, malaria, and COVID-19. Integrated laboratory systems can lead to more efficient testing while increasing access to critical diagnostics. However, the authors have observed that HIV diagnosis within the TB diagnostic network displaced TB diagnosis. Subsequently, COVID-19 disrupted both TB and HIV diagnosis. The World Health Organization recommended rapid molecular diagnostic networks for infectious diseases and there is a need for more investment to achieve diagnostic capacity for TB, HIV, COVID-19, and other emerging infectious diseases. Integrated laboratory systems require mapping laboratory networks, assessing needs for each infectious disease, and identifying resources. Otherwise, diagnostic capacity for one infectious disease may displace another. Further, not all aspects of optimal diagnostic networks fit all infectious diseases, but many efficiencies can be gained where integration is possible. *(J Mol Diagn 2022, 24: 289—293; https://doi.org/10.1016/j.jmoldx.2021.12.008)*

The roll-out of new technologies and the substantial growth in political and financial commitment by countries, regions, and bilateral and international donors (such as the Global Fund to Fight AIDS, Tuberculosis and Malaria; President's Emergency Plan for AIDS Relief [PEPFAR]; and US Agency for International Development) and their global partners have facilitated a surge of global progress in health over the past 15 years.[1] Despite major progress in the global HIV and tuberculosis (TB) responses, these diseases continue to represent a public health burden in all regions, with inequitable coverage of diagnosis, prevention, and treatment.[2]

Globally, an estimated 10 million individuals fell ill with TB in 2019, a number that has been declining very slowly in recent years; although, in 2019, there was an estimated reduction of 1.2 million TB deaths among HIV-negative individuals.[3] Access to TB treatment has grown from 6 million in 2015 to 7.1 million in 2019, with increased access to TB preventive treatment as well, to 4.1 million.[4] New HIV infections among women aged 15 to 24 years fell by 25% between 2010 and 2018, and since 2010, AIDS-related mortality has declined by 33%.[5] Other diseases, such as hepatitis C and sexually transmitted diseases, have gained global prominence, with many low- and middle-income

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countries (LMICs) beginning to implement services to reduce morbidity and mortality.

The coronavirus disease 2019 (COVID-19) pandemic has significantly disrupted health services due to cases overburdening the health system or response measures that limit normal health program activities and care-seeking. As of October 14, 2021, there have been 239,007,759 confirmed cases of COVID-19, including 4,871,841 deaths, reported to the World Health Organization (WHO) globally, and 6,471,051,151 vaccine doses have been administered. The pandemic has undermined the progress made in the last decade in part because access to timely diagnostics for TB, HIV, and other opportunistic infections has been compromised; for example, to illustrate a few impacts of COVID-19, TB domestic resources have been diverted to COVID-19 response, affecting also staffing and facilities used to isolate COVID-19 cases. WHO has indicated that TB diagnosis has gone down 21% in 2020 compared with 2019 due to COVID, which translates into one-half million more deaths due to TB. If new strategies are not developed, implemented, and coordinated effectively at the global and national levels, long-term setbacks will result.[2–6] Effective interventions and services must be targeted to the most vulnerable individuals and populations—for example, pregnant women, young children, individuals living with HIV/AIDS or TB, the poor, and the elderly—while maintaining quality and efficiency in existing health programs.[6]

As countries make progress toward universal health care (UHC), diagnostics are a critical component of health benefits packages because most diseases or conditions cannot be managed without a clear diagnosis and laboratory tests for follow-up. COVID-19 exposes the need for a fundamental shift in service delivery models, including diagnostic integration and involvement of the private sector as highlighted in the last Lancet Commission report[7,8] (for a supplementary perspective, see *https://www.statnews.com/2019/05/20/diagnostics-universal-health-coverage-succeed*, last accessed December 8, 2020). The pandemic reveals that reality by exacerbating the gaps in detection of TB, HIV, and other opportunistic infections due, on one hand, to lack of laboratory capacity (eg, physical infrastructure and human resources) in some LMICs, even before the pandemic, and on the other hand, to mitigation strategies undertaken to respond to COVID-19.[7,8] These mitigation steps and shifting of resources have drastically reduced the capacity of health systems in LMICs to respond to other health issues because of overwhelmingly high demand for the care of patients with COVID-19 and interruptions within the supply chain.

Because the diagnostics have been built and funded specifically for certain diseases, the use of new advances that enable technology designed for one disease to detect other diseases is often not permitted. For example, GeneXpert, a technology that revolutionized TB molecular diagnostic testing and has a massive footprint in 145 LMICs, can now be used for HIV (viral load, early infant diagnosis) and COVID-19 testing through the recent release of the new Xpert Xpress SARS-CoV-2 cartridge (Cepheid, Sunnyvale, CA). However, financial and operational barriers generate concerns about how the utilization of this technology in weak laboratory systems and public health programs will undermine, for example, TB and HIV diagnostic capacity in some countries. Improper integration of technology may lead to suboptimal diagnosis and ultimately greater TB and HIV mortality. The newly introduced diagnostics need to be integrated in a phased, systematic manner, and optimized to meet program needs and targets for both existing diseases and new ones.[4–8]

Current Situation

Application of nucleic acid amplification tests (NAATs) has revolutionized rapid and accurate diagnostic testing for most pathogens for a decade. Automated batched or modular cartridge—based NAATs offer a combination of excellent sensitivity and specificity and reproducible, accurate test results, with minimal manipulation and decreased risk of cross-contamination, that has made PCR technology an appealing alternative to culture- or immunoassay-based testing for disease diagnosis. Although NAATs are more sensitive than most other tests for TB, culture remains the gold standard. However, culture can take months, whereas NAATs can be performed in less than 2 hours (*http://www.stoptb.org/assets/documents/resources/wd/ERPD%20approved%20TB%20diagnostics%20info%20note.pdf?*, last accessed January 25, 2022).[9–11] The opportunity for decentralization to lower levels of the health system makes NAATs an essential tool to implement the End TB Strategy and realize the UNAIDS 95-95-95 goals.[12]

For the past 10 years, the Xpert assay has represented the first major advance in TB diagnosis, allowing peripheral detection of rifampicin resistance, which enabled detection of drug-resistant TB and exponentially increased the numbers of cases treated. Additionally, the Xpert Ultra test increases the sensitivity of TB diagnosis in children, HIV-infected individuals, and paucibacillary and extrapulmonary TB; and since its endorsement by WHO, most countries have quickly started rolling out Xpert.[9–11] As of December 31, 2018, 10,562 GeneXpert machines (47,567 modules) had been procured across 136 of the 145 countries eligible for concessional prices (Cepheid, 2018; W. Van Gemert, unpublished data). However, existing GeneXpert technologies typically have low overall utilization, although this is site-dependent in several countries. Countries are not procuring enough cartridges to reach testing targets or fully utilize instruments due to algorithm constraints on implementation, weak specimen referral linkages to testing, and inadequate attention to maintenance and prompt repair.

High-throughput platforms, mostly at centralized levels, have been introduced on a massive scale for HIV early infant diagnosis, drug resistance detection, and viral load

monitoring for treatment response, with funding from the Global Fund, PEPFAR, and other agencies. The volume of viral load tests performed has increased significantly from the 15 million viral load tests conducted in 2017, and the number is projected to double to nearly 30 million by 2022. The UNAIDS 2020 report released during the COVID-19 pandemic showed that only 14 countries have achieved the 90-90-90 HIV treatment targets (90% of individuals living with HIV know their HIV status, of whom 90% are on antiretroviral treatment and of whom 90% are virally suppressed), including Eswatini, which has one of the highest HIV prevalence rates in the world. However, in many parts of the world, COVID-19 is colliding with the ongoing HIV epidemic.[6–8] A recent WHO HIV guideline recommends point-of-care diagnosis and monitoring as preferred over centralized laboratory testing because they significantly reduce turnaround time and result in saving lives.[10] Further, the WHO Health Assembly recommends integrated services; donors such as the Global Fund may reduce funding and expect further integration.

To control the spread of COVID-19, experts agree that an aggressive strategy of vaccination along with test, trace, and treatment is needed, combined with physical distancing measures and the use of masks. However, SARS-CoV-2 detection in some countries is limited by weak and uncoordinated laboratory systems, as well as insufficient laboratory equipment and test kits for PCR or access to rapid diagnostic tests. This insufficient capacity compels governments, for example, to restrict testing to individuals who meet specific narrow criteria.[13] Many efforts and partnerships to increase the response to COVID-19 in Africa and around the world have been launched, such as the Access to COVID-19 Tools Accelerator, which is coordinated by the Global Fund, WHO, UNICEF, and the Partnership to Accelerate COVID-19 Testing in Africa. However, after 19 months into the pandemic, lessons and progress in diagnostic pipelines are demonstrating the efficiency of antigen tests. The Global Fund is advocating for using antigen tests (3 USD, rather than GX for COVID-19 at 20 USD), and WHO is updating its antigen rapid diagnostic test guidance as well as preparing interim guidance on Recommendations for National SARS-CoV-2 Testing Strategies and Diagnostic Capacities.

Discussion

This paper aims to identify the best approach to using both existing and new technologies to address the COVID-19 pandemic and coexisting major public health challenges without jeopardizing the gains in diagnostic access for TB, HIV, and other opportunistic infections.

COVID-19 illustrates our common vulnerability to disease across borders, the public–private divide, and the limits of our fragmented approach to health.[2,11–13] A more coordinated, comprehensive, and integrated decentralization of services at the community level is urgently needed. In their paper, Pooran et al[11] make a case for value for money for point-of-care TB diagnostic services because such services reduce, not only death, but also economic loss in Africa. It also reduces transport costs to have testing performed more locally.

Governments and donors will need to revisit public health programs and systems in line with UHC in LMICs. Doing so will require a paradigm shift, with change management, task shifting, and bold policies. Centralized testing of patients for initial diagnosis should be shifted to the lowest administrative level possible (district), ideally at the point of care. Centralized laboratory staff will continue to have opportunities for leadership of the entire network, for example, quality assurance, introduction of new diagnostics, research, training, and mentoring.

The current diagnostic gaps in the HIV, TB, and COVID-19 response could be greatly mitigated by intensively investing in public health laboratory systems and optimizing use of existing technologies already introduced in many LMICs. However, many of the multiplex technologies are centralized in biosafety level 2 or 3 laboratories, due to high requirements for safety, human skills, resources, and alignment with vertical diagnostic programs.

The US Food and Drug Administration approved Xpert Xpress SARS-CoV-2 on March 21, 2020.[9,13] The test kit can deliver a COVID-19 diagnosis in 45 minutes. The machine can be placed in a biosafety level 1 or 2 laboratory or in mobile vehicles with similar safety requirements, making it ideal for community testing. This will reduce the costs of referral, from both the patient and health system perspectives. Other affordable point-of-care or near-patient multiplex platforms endorsed by WHO are available, such as TrueNat (Molbio Diagnostics, Goa, India) or TB loop-mediated isothermal amplification assay); and more platforms are in development or in clinical trials that can diagnose and monitor multiple diseases, including drug-resistant malaria [refer to: *https://www.devex.com/news/afterthe-pandemic-how-will-covid-19-transform-global-health-and-development-96936*, last accessed December 8, 2020; *http://www.stoptb.org/assets/documents/covid/Considerations%20for%20selection%20of%20SARS-CoV-2%20diagnostics.pdf*, last accessed December 8, 2020; *https://www.finddx.org/mal-fev/improved-malaria-rdts*, last accessed December 8, 2020].[14,15]

Multidisease molecular platforms [eg, Abbott's RealTime m2000sp and m-PIMA (Abbott, Abbott Park, IL); Cepheid's GeneXpert GX-4, -16, -48, and -80 modules; Hologic Panther, Roche COBAS AmpliPrep/COBAS TaqMan CAP/CTM 96; Roche cobas 4800/6800/8800 (Roche, Basel, Switzerland); Thermo Fisher's Applied Biosystems 7500 Fast Real-Time PCR system (Thermo Fisher, Waltham, MA); Becton Dickinson's BD MAX (Becton Dickinson, Franklin Lakes, NJ); and genesig Easy qPCR Detection Kit for nCoV-2019 (genesig, Chandler's Ford, UK)][6,7,10] have already been introduced for HIV, influenza,

hepatitis, and other diseases in many national reference laboratories and research institutes in LMICs. Additionally, the Food and Drug Administration has authorized—for emergency use—some of the test kits that can be accommodated by some of the platforms listed above for SARS-CoV-2.

Given these developments, the diagnostic pipeline for COVID-19 and other priority diseases is growing. Integrated technologies, such as next-generation sequencing, at peripheral levels might also be used for detection of drug resistance across diseases. Furthermore, treatment monitoring, such as viral load and bacterial load testing, might also be conducted using integrated platforms. Having well-functioning laboratory systems to detect multiple infectious diseases, their drug resistance patterns, and treatment responses at lower levels of the health system would enable a more equitable, human-centered approach, with increased access and decreased turn-around time, ultimately reducing morbidity and mortality from infectious disease, particularly TB and HIV.

Integration of diagnostic networks is at an early stage in LMICs. A few African, Asian, and Latin American countries have piloted diagnostic integration, mainly at selected central and intermediate laboratories; they include Cameroon (HIV and TB), Malawi (HIV and TB), Nigeria (hepatitis C and TB), Zimbabwe (HIV and TB), Brazil, the Caribbean countries, Democratic Republic of Congo, India, and Malaysia.[11] Best practices and lessons from these pilots are urgently needed to inform the development and scale-up of an integrated diagnostic laboratory network approach. This network will form the basis for a robust public health laboratory system in each country, with strong international and government collaboration, which will benefit all health programs, including reproductive health, maternal and child health, communicable diseases, emerging diseases, and cancer, in line with UHC.[7]

Several LMICs have already used GeneXpert technology to diagnose both TB and COVID-19,[8,14,16,17] but such integration has not been uniform across countries, revealing better approaches to follow in the future. The authors believe that no one size fits all, because countries vary in infrastructure, disease burden, and geographic peculiarities. Further, some countries have vector-borne diseases such as malaria and cholera that are relevant only in certain areas of the country. Nonetheless, many common links can be made across most LMICs to integrate their laboratory systems for infectious diseases and create a more resilient response on all tiers of their public health laboratory network, shifted closer and targeted to the communities that need them.

Recommendations

LMICs should take advantage of existing multiplex platforms, such as GeneXpert, high-throughput platform technologies, and laboratory networks, to introduce COVID-19 testing. These networks are already established and working well to make laboratory diagnostic services available in several countries. By integrating diagnostics for COVID-19 and other infectious diseases into a well-articulated laboratory system, we will gain efficiencies as well as move closer to UHC even during the COVID-19 pandemic. Introducing a vertical COVID-19 diagnostic service model would be expensive and inefficient in reaching the individuals who need the services—and it would not be sustainable.

Integrated, affordable multiplex technologies, particularly at the point of care, local and community levels, have the advantages of avoiding parallel diagnostic systems and duplication of activities such as referral and transport, equipment maintenance, human resource management, quality assurance, supply chain and quantification, and training—and duplication of the costs of those activities. In providing increased capacity and uptake for TB, HIV, COVID-19, and other existing or future opportunistic infections, integrated technologies offer better value for money and sustainability.

Innovative approaches to diagnostic integration can maximize investments while increasing access but require a strategic approach tailored to each country context based on mapping and optimizing the laboratory network, assessing the needs for detection capacity for each disease, and identifying the gaps so resources can be mobilized. Merely having the machines will not translate into great improvements. We must also strengthen:

- Political leadership to remove barriers to diagnostic integration, and roadmaps and strategic plans focused on increasing investment in diagnostic capacity in a holistic, coordinated way, with robust policies;
- Structures for supplies of consumables, maintenance, and sample transportation;
- Coordination and communication among disease control programs, including donors and the private sector;
- Technical assistance to ministries of health, local public health programs and institutions, and the private sector;
- Quality-assured, connected, and sustainable laboratory networks, led by a national public health laboratory or other governance body, to guarantee universal access to prevention, diagnostics, treatment, and care services; and
- Integrated laboratory information systems and dashboards to increase use of data and inform decision-making for patient management, program planning, and service delivery, while ensuring confidentiality.

Conclusion: Looking Ahead

Effective interventions and services will require transforming our way of diagnosing and treating individuals to enable countries to reach the End TB milestones and UNAIDS 95-95-95 goals, even while containing other diseases. If we do not act to mitigate the threat, COVID-19 will

lead to an upsurge in deaths from TB, HIV, and other opportunistic infections. If we take an integrated approach, leveraging the infrastructure and resources we have already invested in and moving swiftly to strengthen the health system as a whole, we can step up the fight against both COVID-19 and other diseases of major public health importance.

The authors call on all ministries of health, donors, implementers, partners, and supported countries to revisit their strategies by looking at all these opportunities. The authors recommend that donors focus investments in COVID-19 testing by taking advantage of existing platforms and infrastructures to maximize service coverage to save lives during the pandemic while serving as a benchmark to gauge progress toward implementing guidelines such as the WHO Essential Diagnostics List and investing in long-term UHC goals. This approach will cost far less than setting up parallel systems or centralizing testing in a few laboratories. This is a time to be bold and act fast.

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Author Contributions

A.U.N. wrote the manuscript; A.U.N., J.N.S., M.G. and P.G.S. wrote, reviewed, edited, and approved the final manuscript equally.

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Tuberculosis incidence in patients with chronic kidney disease: a systematic review and meta-analysis. ☆

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ABSTRACT

Objective: The aim of this study was to estimate global TB incidence in patients with CKD.
Methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method was followed to perform the study. Electronic and gray literature sources were investigated for studies published between 2000 and 2021. The Joanna Briggs Institute critical appraisal checklist was used to assess the quality of the studies, and STATA version 16 was used for analysis. The I^2 heterogeneity test was employed to assess heterogeneity. To examine publication bias, funnel plots and Egger's regression tests were performed.
Results: A total of 104 studies with a sample size of 1,548,774 were included. TB incidence in patients with CKD ranges from 60 per 100,000 in the UK to 19,270 per 100,000 in China. The pooled TB incidence was estimated as 3718 per 100,000 (95%CI; 3024, 4411). Higher pooled TB incidence was found in the African region (9952/100,000, 95%CI; 6854, 13,051), followed by the South-East Asian (7200/100,000, 95%CI; 4537, 9863) and Eastern Mediterranean (5508/100,000, 95%CI; 3470, 7547) regions. In particular, patients on hemodialysis (5611/100,000) and on peritoneal dialysis (3533/100,000) had higher incidence of TB than did renal transplantation patients (2700/100,000) and patients with predialysis CKD (913/100,000). Furthermore, extrapulmonary TB (2227/100,000) was more common than pulmonary TB (1786/100,000).
Conclusion: This study identifies high TB incidence in patients with CKD with regional disparities. Thus, the authors recommend active TB screening in this group of individuals.
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Introduction

TB is causing a major public health problem. After COVID-19, it is the leading cause of death from a single infectious disease worldwide (WHO, 2020). Currently, there are globally harmonized efforts to halt the effect of TB. The World Health Organization (WHO) has set an END-TB Strategy aimed to decrease TB incidence below ten per 100,000 of the population by 2035 (WHO, 2014). Early TB case detection and systematic screening of TB in high-risk groups are among the major strategic components recommended by the WHO (WHO, 2020). In this regard, those individuals with underlying chronic diseases such as CKD have a higher risk of acquiring TB. A pooled estimate conducted by Al-Efraij et al. (2015) revealed that dialysis populations showed an increased rate of 3.62 and transplant populations showed an increased risk of 11.35 compared with the general population (Al-Efraij et al., 2015). The increasing trend of CKD across the globe (GBD Chronic Kidney Disease Collaboration, 2020) may slow the effort to control and prevent TB. More importantly, the burden of CKD is increasing in low- and middle-income countries (Stanifer et al., 2016) where there is high TB prevalence.

It is well known that patients with CKD have higher TB risk, and numerous studies conducted in different countries have supported this fact (Abdelrahman et al., 2006; Atasever et al., 2005;

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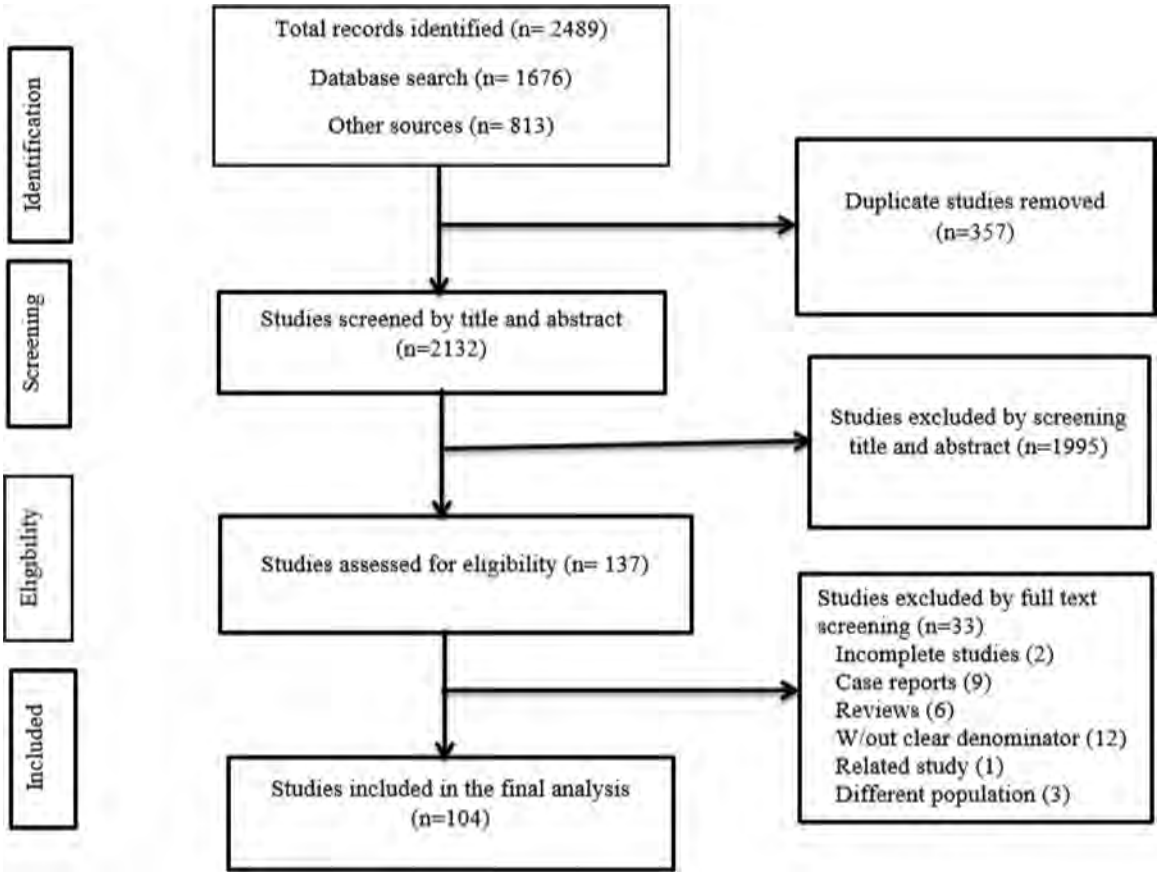

Figure 1. Flowchart describing the selection of studies for the systematic review and meta-analysis of tuberculosis incidence in patients with chronic kidney disease.

Banaga et al., 2016; Christopoulos et al., 2009; Guida et al., 2009; Hu et al., 2014; Kazancioglu et al., 2010; Klote et al., 2006; Lui et al., 2001; Min et al., 2018; Ram et al., 2007; Rao et al., 2013; Sen et al., 2008). However, there are limited data that describe the global and regional burden of TB in this group of the population. There are only a few pooled estimates conducted so far that are specific to certain groups of patients with CKD, such as those who undergo renal transplantation (Reis-Santos et al., 2013). However, global data that comprehensively assessed the burden of TB in this group of the population can be an important input for policy and guidance to strengthen the effort for TB prevention and control. Thus, this study aimed to assess the global, regional, and country-level incidence of TB among patients with CKD with any type of category (predialysis, on hemodialysis, on peritoneal dialysis, after kidney transplantation) using the available studies conducted so far across the globe.

Methods

Protocol and registration

The PRISMA reporting checklist (Liberati et al., 2009) was used to construct the methodology for this systematic review and meta-analysis investigation. The protocol is registered as CRD42021297074 in the International Prospective Register of Systematic Reviews (PROSPERO).

Article search strategy

Articles published from 2000 to 2021 in electronic databases PubMed, Global Health, CINAHL, Global Index Medicus, CABI Abstracts, and Environment Index that reported the incidence of TB in patients with CKD, regardless of study country, were searched until January 15, 2022. Additionally, we sought studies from gray literature sources Google Scholar and Google. Two investigators (A.A. and G.D.) conducted the article search, and the third investigator (Z.W.B.) resolved the inconsistencies. The keywords used during the article search included tuberculosis, *Mycobacterium tuberculosis*, chronic kidney disease, CKD, renal failure, renal disease, dialysis, hemodialysis, peritoneal dialysis, and kidney/renal transplantation. The Boolean operators AND and OR were used accordingly (Appendix).

Article selection procedure

All the 2489 articles identified from the whole search were exported to the EndNote X8 citation manager, by which 357 duplicates were removed. After screening the remaining 2132 articles by title and abstract, 137 articles were assessed for full-text review. Subsequently, 33 articles were excluded owing to being incomplete studies (two), case reports (19), reviews (six), without a clear denominator (12), different populations (three), and the related study (one). Finally, data were extracted from 104 articles (Figure 1).

Data items

Participants: Patients with chronic kidney disease.
Intervention: Not applicable.
Comparator: Not applicable.
Outcome: TB.
Study design: Observational studies.
Study setting: Any setting in any country across the globe.

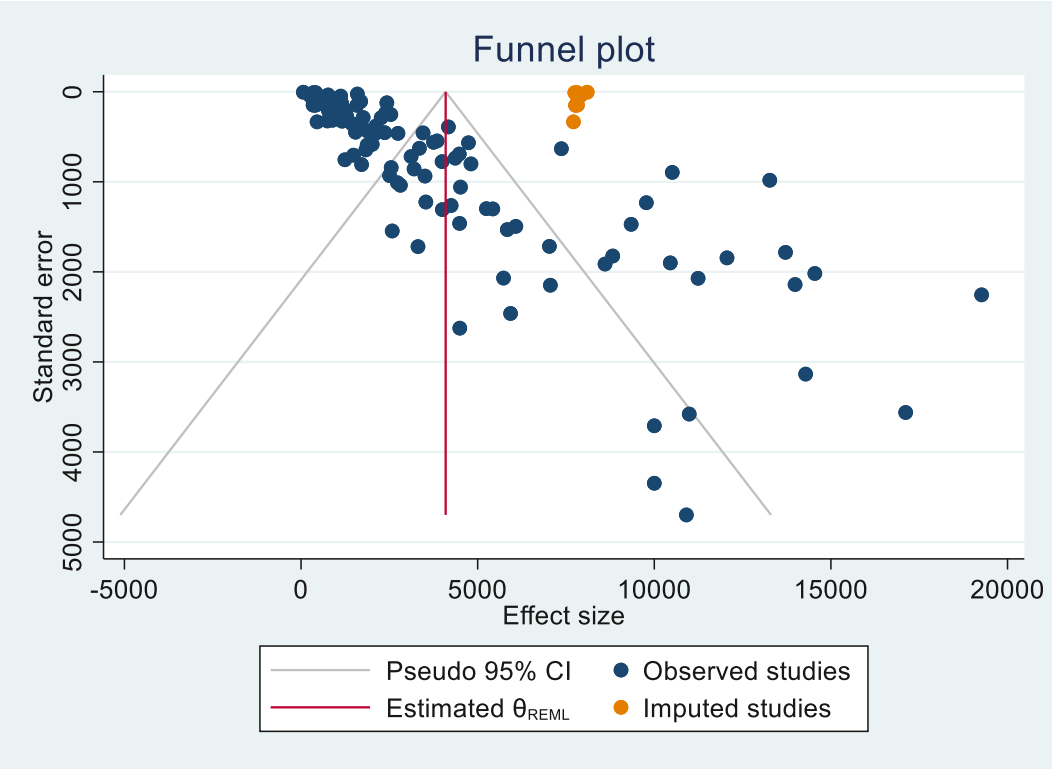

Figure 2. Funnel plot for the pooled incidence of tuberculosis in patients with chronic kidney disease per 100,000 population after trim-and-fill analysis.

Inclusion and exclusion

Studies that assessed TB incidence among patients with CKD with any stage (predialysis CKD, hemodialysis, peritoneal dialysis, or postrenal transplantation) were included in the study, whereas incomplete studies, case reports, reviews, studies without a clear denominator, and publications from a related study were excluded.

Data extraction

Data were extracted by two independent authors (A.A. and G.S.), and a third author (M.T.C.) resolved the inconsistencies. The extracted data include first author name, publication year, study country, study setting, study period, study design, diagnostic method, category of CKD, sample size, number of TB cases, number of pulmonary tuberculosis (PTB) cases, number of extrapulmonary tuberculosis (EPTB) cases, and TB burden category of the study country. The data were summarized using a Microsoft Excel 2016 spreadsheet (Appendix).

Quality and risk of bias assessment

The quality of the study was assessed using the Joanna Briggs Institute (JBI) critical appraisal tools (Porritt et al., 2014), and the result was graded as low, medium, and high if the quality score was < 60%, 60% to 80%, and > 80%, respectively. Two independent investigators (Ayinalem Alemu, Zebenay Workneh Bitew) assessed the quality of the study, and a third author (Getachew Seid) resolved the inconsistencies. We inspected the funnel plot and conducted Egger's regression tests to assess the publication bias (Lin and Chu, 2018). Trim-and-fill analysis was conducted to adjust publication bias (Shi and Lin, 2019) (Appendix).

Outcome

The primary outcome of this study was developing TB in patients with CKD. TB was defined based on the WHO definition such that bacteriologic confirmation (smear microscopy, culture, WHO-recommended rapid molecular diagnostic techniques) and/or clinical diagnosis with supportive investigations (imaging techniques, histopathology, or biochemical analysis of body parts/fluids), and placed on anti-TB treatment/response to anti-TB treatment.

Data synthesis and statistical analysis

The data were exported to STATA version 16 for statistical analysis. The pooled TB incidence in patients with CKD was estimated, along with 95%CI. The random-effect model was used, considering substantial heterogeneity among studies. Subgroup analysis was conducted among different categories. Heterogeneity among studies was assessed using the I2 heterogeneity test, and a value above 50% was considered as the presence of heterogeneity (Riley et al., 2011; Sterne and Egger, 2001). The asymmetry of the funnel plot and the statistical significance of Egger's regression test (P-value<0.05) were used to assess the presence of publication bias (Egger et al., 1997; Sterne et al., 2011).

Results

We extracted data from 104 studies conducted in 32 countries. Fifty, 27, and 27 studies were published from 2000 to 2009, 2010 to 2015, and 2016 to 2021, respectively. These studies were conducted in six continents: Asia (44), Europe (31), Africa (14), South America (eight), North America (five), and Australia and New Zealand (two). Based on the WHO regional category, six studies were conducted in countries grouped under the African Region (AFR), 17 in the Eastern Mediterranean Region (EMR), 31 in the European Region (EUR), 13 in the Region of the Americas (AMR),

13 in the South-East Asian Region (SEAR), and 24 in the West Pacific Region (WPR), respectively. Specifically, Turkey, Taiwan, India, Brazil, China, and Saudi Arabia were the countries with the most frequent studies, with 15, 11, nine, seven, seven, and five studies, respectively. Besides, 23 studies were reported from countries categorized as having high TB burden based on the 2021 Global TB Report. Regarding quality, 72 and 32 studies had high and medium quality, respectively (Appendix).

The sample size in individual studies ranges from 55 (Niang et al., 2005) to 408,873 (Park et al., 2019). Data were collected from 1,548,774 patients with CKD, and TB was detected in 12,189 patients. TB incidence ranges from 60 per 100,000 in the United Kingdom (Ruzangi et al., 2020) to 19,270 per 100,000 in China (Qianying et al., 2021). Based on the random-effects model, the pooled TB incidence in patients with CKD is estimated as 3718 per 100,000 (95%CI; 3024, 4411, I2; 99.98%). There was high heterogeneity among studies, and publication bias was detected (P<0.001). Based on the trim-and-fill analysis, the pooled estimate became 4095 per 100,000 (95%CI; 3414, 4776) (Figure 2, Table 1). We also estimated the pooled PTB and EPTB incidence. The PTB incidence was reported in 74 studies with an incidence ranging from 110 per 100,000 (Ahmed and Karter, 2004) to 12,610 per 100,000 (Ndamase et al., 2020), whereas in 73 studies, EPTB incidence was reported that ranged from 50 per 100,000 (Torre-Cisneros et al., 2009) to 10,990 per 100,000 (Tsevi et al., 2017). Among 534,883 patients with CKD, PTB was confirmed in 3257 patients, which yielded a pooled incidence estimate of 1786 per 100,000 (95%CI; 1430, 2141, I2; 98.99%). However, of 508,851 patients with CKD, EPTB was identified in 1417 patients, which gave a pooled incidence estimate of 2227 per 100,000 (95%CI; 1718, 2735, I2; 99.70%). High heterogeneity and publication bias were detected for both categories (P<0.001). After the trim-and-fill analysis, there was no change for PTB incidence, but the EPTB incidence became 1178 per 100,000 (95%CI; 487, 1869) (Table 1).

This study performed a subgroup analysis to estimate the pooled TB incidence among patients with CKD per country, continent, WHO regional category, CKD category (predialysis, hemodialysis, peritoneal dialysis, and postrenal transplantation), publication year, and the country's TB burden category.

In Africa, we extracted data from 14 studies conducted in eight countries with an incidence that ranged from 1430 per 100,000 in Sudan (Banaga et al., 2016) to 17,120 per 100,000 in South Africa (Ndamase et al., 2020). Among 5080 patients with CKD, 258 patients developed TB, which gave a pooled TB incidence of 7460 per 100,000 (95%CI; 4936, 9984, I2; 93.52%). There was high heterogeneity, and publication bias was detected (P<0.001). After the trim-and-fill analysis, the pooled estimate became 4117 per 100,000 (95%CI; 937, 7297). Specific to the study country, the pooled TB incidence estimate/individual study ranges from 3230 per 100,000 in Sudan to 12,060 per 100,000 in Morocco. In the Asian continent, we extracted data from 44 studies conducted in nine countries. TB incidence ranges from 35 per 100,000 (Shu et al., 2020) in Taiwan to 19,270 per 100,000 in China (Qianying et al., 2021). Among 941,107 patients with CKD, 6372 developed TB, which yielded the pooled TB incidence estimate of 4363/100,000 (95%CI; 3057, 5669, I2; 99.98%). The pooled incidence ranges from 1170 per 100,000 in South Korea to 9050 per 100,000 in Nepal. High heterogeneity was detected, and publication bias was detected (P<0.001). After the trim-and-fill analysis, the pooled estimate did not change. In Europe, 31 studies were conducted in ten countries with TB incidence ranging from 60 per 100,000 (Ruzangi et al., 2020) in the United Kingdom to 10,450 per 100,000 (Erkoc et al., 2004) in Turkey. Of 290,760 patients with CKD, 811 patients developed TB, which gave a pooled incidence of 2590 per 100,000 (95%CI; 1857, 3324, I^2; 99.39%). The pooled incidence was as low as 360 per 100,000 in Belgium to as high as 8820 per 100,000 in Greece. There was high heterogeneity, and publication bias was detected (P<0.001). However, after the trim-and-fill analysis, the pooled TB incidence became 1515 per 100,000 (95%CI; 560, 2470). In South America, eight studies were undertaken in two countries, with both the lowest (1150/100,000) (Rocha et al., 2013) and the highest (4480/100,000) (Matuck et al., 2004) incidences from Brazil. Of 16,248 patients with CKD, 306 developed TB, resulting in a pooled estimate of 2249 per 100,000 (95%CI; 1540, 2959, I^2; 86.60%). There was high heterogeneity with publication bias (P=0.008). However, after the trim-and-fill analysis, the pooled estimate did not change. The highest pooled incidence was from Brazil (2310/100,000), whereas the lowest was from Colombia (1870/100,000). We also extracted data from five studies conducted in North America, with four studies from the United States of America (USA) and one study from Mexico. In USA, the incidence ranges from 460 per 100,000 (Jie et al., 2005; Tsevi et al., 2017) to 1880 per 100,000 (Bardenheier et al., 2019). In this region, 4402 patients with CKD developed TB among 280,413 patients, which resulted in a pooled estimate of 1146 per 100,000 (95% CI; 502, 1790, I^2; 96.51%). There was high heterogeneity, with no publication bias (P=0.301). Lastly, two studies were found in Australia and New Zealand. Forty patients with CKD developed TB among 15,166 patients, which gave a pooled incidence estimate of 258 per 100,000 (95% CI; 174, 343, I2; 0.00%). There were no heterogeneity and no publication bias (Table 1, Appendix).

Per the WHO regional categories, the highest pooled TB incidence estimate was detected in the AFR (9952/100,000, 95%CI; 6854, 13,051, I2; 45.62%) (Table 1, Figure 3), followed by the SEAR (7200/100,000, 95%CI; 4537, 9863, I2; 98.87%) (Table 1, Figure 4), and the EMR (5508/100,000, 95%CI; 3470, 7547, I2; 97.98%) (Table 1, Figure 5). The pooled TB incidence estimates among patients with CKD who reside in the EUR, WPR, and AMR regions were 2590 per 100,000 (95%CI; 1857, 3324, I2; 99.39%), 2065 per 100,000 (95%CI; 1133, 2997, I2; 99.97%) and 1820 per 100,000 (95%CI; 1258, 2382, I2; 96.94%), respectively (Table 1, Figures 6–8). Publication bias was detected in all regions except the AFR. After the trim-and-fill analysis, changes in the pooled estimates were observed for the AFR, EMR, EUR, and WPR regions that gave an incidence of 7206 per 100,000 (95%CI; 3538, 10874), 3480 per 100,000 (95%CI; 968, 5992), 1515 per 100,000 (95%CI; 560, 2470), and 3027 per 100,000 (95%CI; 2072, 3982), respectively (Table 1).

Per publication year, the pooled TB incidence estimates were 4052 per 100,000 (95% CI; 3073, 5031, I2; 99.75%), 3402 per 100,000 (95%CI; 2228, 4576, I2; 99.71%), and 3508 per 100,000 (95% CI; 1840, 5176, I2; 1,00.05%) in studies published from 2000 to 2009, 2010 to 2015, and 2016 to 2021, respectively. There was high heterogeneity, and publication bias was detected in all categories (P<0.001). After the trim-and-fill analysis, the pooled TB incidence estimates became 4142 per 100,000 (95%CI; 3168, 5117), 4007 per 100,000 (95%CI; 2841, 5172), and 4116 per 100,000 (95%CI; 2554, 5678) in studies published from 2000 to 2009, 2010 to 2015, and 2016 to 2021, respectively (Table 1, Appendix). Based on the country's TB burden category, the pooled TB incidence in the HBCs and the remaining countries was estimated as 3283 per 100,000 (95% CI; 1865, 4700, I2; 99.90%), and 3846 per 100,000 (95%CI; 3050, 4642, I2; 99.97%), respectively. There was high heterogeneity, and publication bias was detected in both groups (P<0.001). After the trim-and-fill analysis, the pooled TB incidence estimates in HBCs and not HBCs were estimated as 4315 per 100,000 (95%CI; 2946, 5688), and 4009 per 100,000 (95%CI; 3221, 4798), respectively (Table 1).

In the present study, we were also able to assess TB incidence per the CKD categories predialysis, hemodialysis, peritoneal dialysis, and postrenal transplantation. In patients with predialysis CKD, data were extracted from six studies with a sample size rang-

Table 1
Summary of pooled estimates of tuberculosis incidence among patients with CKD across different categories.

Category			Number of studies	Sample size	Number of TB cases	Pooled TB incidence			Egger's regression test, P-value	Pooled estimate after trim-and-fill analysis		
						Estimate*, 95%CI	Heterogeneity			Estimate*, 95%CI	Observed studies	Imputed studies
							I^2	P-value				
Tuberculosis incidence			104	1,548,774	12,189	3718(3024, 4411)	99.98%	<0.001	<0.001	4095 (3414, 4776)	104	9
Pulmonary tuberculosis incidence			74	534,883	3257	1786 (1430, 2141)	98.99%	<0.001	<0.001	1786 (1430, 2141)	74	-
Extrapulmonary tuberculosis incidence			73	508,851	1417	2227(1718, 2735)	99.70%	<0.001	<0.001	1178 (487, 1869)	73	21
TB incidence per continent	Africa	***Overall***	***14***	***5080***	***258***	***7460 (4936, 9984)***	***93.52%***	***<0.001***	<0.001	***4117 (937, 7297)***	***14***	***6***
		Coted'ivoire	1	118	7	5930 (1110, 10760)	-	-				
		Egypt	2	1340	65	8570 (-1720, 18850)	90.86%	<0.001				
		Morocco	1	340	41	12060 (8440, 15670)	-	-				
		Senegal	2	313	35	11190 (7470, 14900)	0.00%	0.95				
		South Africa	2	281	31	11690(1860, 21510)	82.90%	0.02				
		Sudan	2	1678	38	3230 (-670, 7130)	88.63%	<0.001				
		Togo	1	91	10	10990 (3970, 18000)	-	-				
		Tunisia	3	919	31	3030 (1810, 4250)	0.00%	0.23				
	Asia	***Overall***	***44***	***941,107***	***6372***	***4363(3057, 5669)***	***99.98%***	***<0.001***	<0.001	***4363(3057, 5669)***	***44***	***-***
		China	7	14,422	365	5120 (830, 9410)	99.60%	<0.001				
		India	9	9.909	611	8020 (5020, 11030)	97.62%	<0.001				
		Nepal	2	646	66	9050 (10, 18090)	93.75%	<0.001				
		Pakistan	1	350	6	1710 130, 3300)	-	-				
		Saudi Arabia	5	2546	210	8600 (5280, 11910)	76.92%	0.01				
		South Korea	4	484,478	2436	1170 (440, 1900)	99.64%	<0.001				
		Taiwan	11	411,470	2554	1400 (880, 1910)	99.37%	<0.001				
		Thailand	2	2421	14	1350 (-1330, 4030)	64.94%	0.09				
		Iran	3	14,865	110	2010 (-10, 4040)	94.88%	<0.001				
	Australia	***Overall***	***2***	***15,166***	***40***	***258 (174, 343)***	***0.00%***	***0.55***	***-***	***258 (174, 343)***	***2***	***-***
	Europe	***Overall***	***31***	***290,760***	***811***	***2590 (1857, 3324)***	***99.39%***	***<0.001***	<0.001	***1515 (560, 2470)***	***31***	***10***
		Belgium	1	2502	9	360 (90, 620)	-	-				
		Czech Republic	1	1305	11	4000 (1440, 6570)	-	-				
		Denmark	1	275	11	840 (290, 1400)	-	-				
		France	2	20,120	106	600 (270, 940)	78.56%	0.03				
		Greece	1	272	24	8820 (5350, 12400)	-	-				
		Poland	1	1289	15	1160 (520, 1800)	-	-				
		Spain	4	6445	53	830 (360, 1300)	74.43%	0.01				
		Turkey	15	7469	293	3900 (3080, 4720)	65.575	<0.001				
		United Kingdom	4	250,627	273	920 (130, 1710)	97.98%	<0.001				
		Yugoslavia	1	456	16	3510 (1670, 5340)	-	-				
	North America	***Overall***	***5***	***280,413***	***4402***	***1146 (502, 1790)***	***96.51%***	***<0.001***	***0.301***	***1146 (502, 1790)***	***5***	***-***
		United States of America	4	***279,868***	***4392***	1050 (340, 1760)	97.47%	<0.001				
		Mexico	1	***545***	***10***	1830 (570, 3100)	-	-				
	South America	**Overall**	*8*	***16,248***	***306***	***2249 (1540, 2959)***	***86.60%***	***<0.001***	***0.008***	***2249 (1540, 2959)***	***8***	***-***
		Brazil	7	15,607	294	2310 (1500, 3120)	89.23%	<0.001				
		Colombia	1	641	12	1870 (710, 3030)	-	-				
TB incidence based on WHO regions		African Region	6	803	83	9952 (6854, 13051)	45.62%	0.11	0.262	7206/ (3538, 10874)	6	3
		Eastern Mediterranean Region	17	22,038	501	5508 (3470, 7547)	97.98%	<0.001	<0.001	3480 (968, 5992)	17	5
		European Region	31	290,760	811	2590 (1857, 3324)	99.39%	<0.001	<0.001	1515 (560, 2470)	31	10
		Region of the Americas	13	296,661	4708	1820(1258, 2382)	96.94%	<0.001	<0.001	1820(1258, 2382)	13	-
		South-East Asian Region	13	12,976	691	7200(4537, 9863)	98.87%	<0.001	0.029	7200(4537, 9863)	13	-
		West Pacific region	24	925,536	5395	2065(1133, 2997)	99.97%	<0.001	<0.001	3027 (2072, 3982)	24	8
TB incidence per publication year	2000-2009		50	354,028	5784	4052 (3073, 5031)	99.75%	<0.001	<0.001	4142 (3168, 5117)	50	1
	2010-2015		27	112,532	1526	3402 (2228, 4576)	99.71%	<0.001	<0.001	4007 (2841, 5172)	27	4
	2016-2021		27	1,082,214	4879	3508 (1840, 5176)	100.00%	<0.001	<0.001	4116 (2554, 5678)	27	4
TB incidence per CKD category	Pre-dialysis		6	734,868	3104	913 (407, 1418)	99.92%	<0.001	0.46	778 (279, 1276)	6	1
	Hemodialysis		35	329,796	5145	5611 (4186, 7035)	99.87%	<0.001	<0.001	4329 (2690, 5969)	35	7
	Peritoneal dialysis		18	35,086	509	3533 (2220, 4846)	86.29%	<0.001	<0.001	2746 (1391, 4100)	18	5
	Post-transplantation		43	154,438	2050	2700(1878, 3522)	99.58%	<0.001	<0.001	3324 (2523, 4125)	43	8
TB incidence per TB burden	HBC		23	517,559	3146	3283 (1865, 4700)	99.90%	<0.001	<0.001	4315 (2946, 5688)	23	6
	Not HBC		81	1,031,215	9043	3846 (3050, 4642)	99.97%	<0.001	<0.001	4009 (3221, 4798)	81	3

WHO; world health organization, CKD; chronic kidney disease, TB; tuberculosis, HBC; high burden country, "*"; tuberculosis incidence per 100,000 population. "-" Not applicable

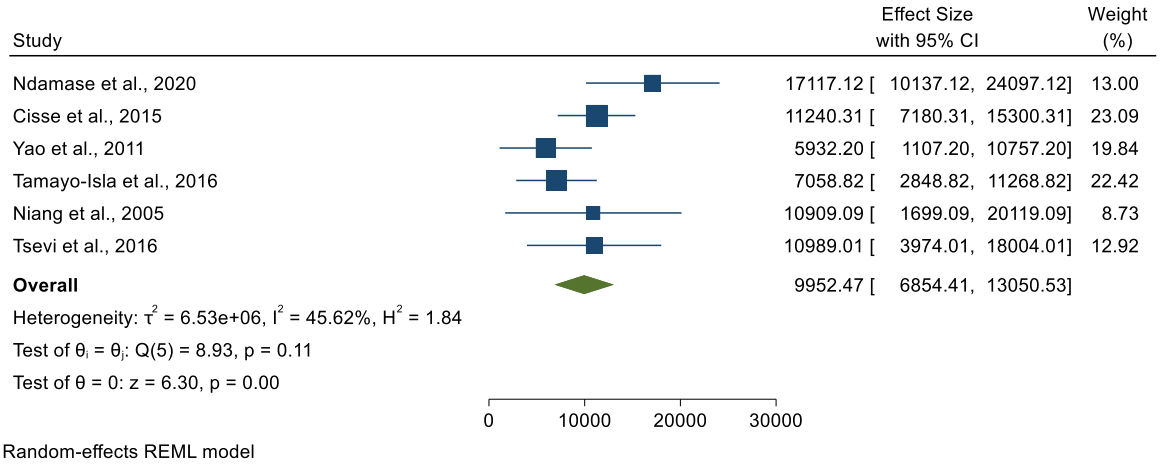

Figure 3. Forest plot for the pooled incidence of tuberculosis in patients with chronic kidney disease in the African Region per 100,000 population.

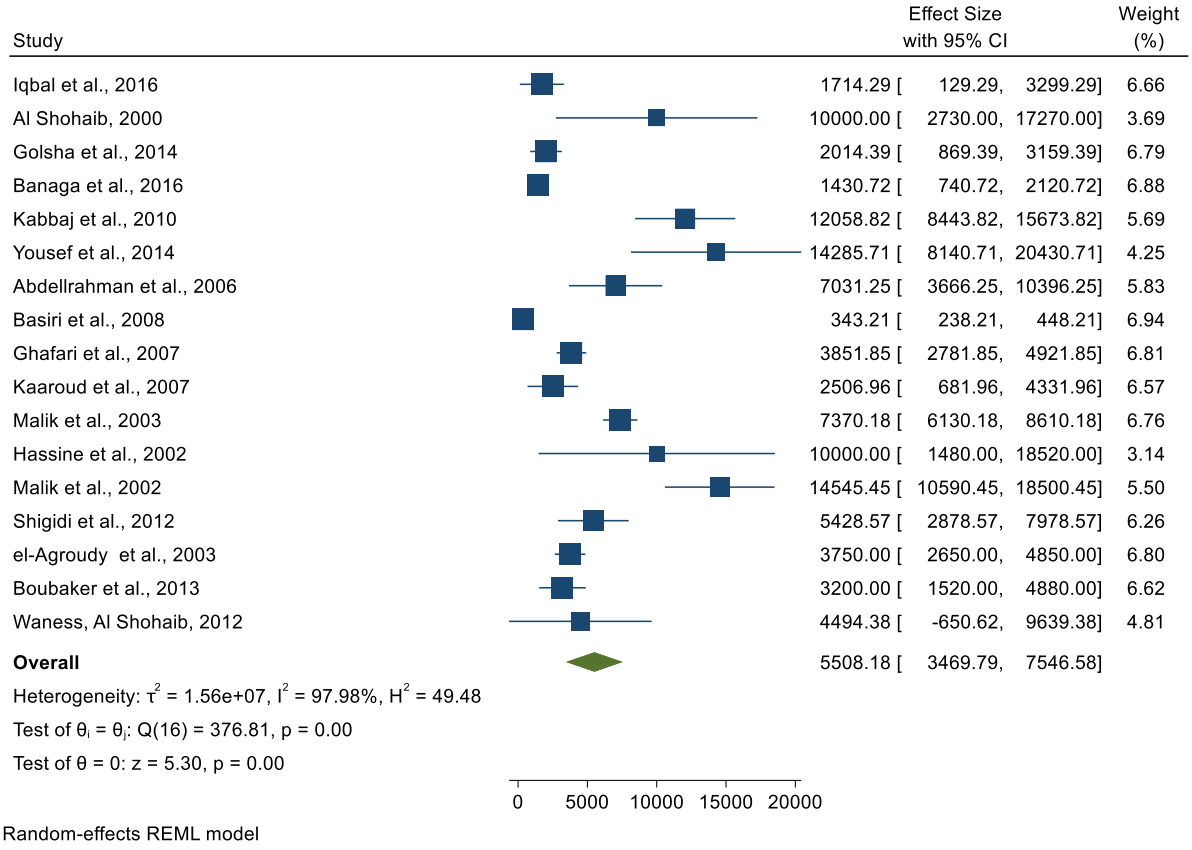

Figure 4. Forest plot for the pooled incidence of tuberculosis in patients with chronic kidney disease in the Eastern Mediterranean Region per 100,000 population.

ing from 707 (Li et al., 2021) to 408,873 (Park et al., 2019). In this group, TB incidence ranges from 60 per 100,000 (Li et al., 2021) to 1580 per 100,000 (Ruzangi et al., 2020). Among 734,868 patients with predialysis CKD, 3104 developed TB, which gave a pooled estimate of 913 per 100,000 (95% CI; 407, 1418, I2; 99.92%) (Table 1, Figure 9). In the hemodialysis group, TB incidence was determined in 35 studies, with a sample size ranging from 55 (Niang et al., 2005) to 233,543 (Klote et al., 2006) and with TB incidence ranging from 500 per 100,000 (Chou et al., 2001) to 18,420 per 100,000 (Pradhan and Sigdel, 2020). Of 329,796 patients with CKD on hemodialysis, 5145 developed TB, which resulted in a pooled incidence of 5611 per 100,000 (95%CI; 4186, 7035, I2; 99.87%) (Table 1, Figure 10). Furthermore, TB incidence among patients on peritoneal dialysis was reported in 18 studies, with a sample size ranging from 18 (Sen et al., 2008) to 25,704 (Klote et al., 2006). TB incidence in this group ranges from 310 per 100,00033 (Ahmed and Karter, 2004) to 22,220 per 100,000 (Sen et al., 2008). Among 35,086 patients on peritoneal dialysis, 509 developed TB, which gave a pooled estimate of 3533 per 100,000 (95%CI; 2220, 4846, I2; 86.29%) (Table 1, Figure 11). Besides, we were also able to assess postrenal transplantation TB incidence using data extracted from 43 studies that utilized a sample size ranging from 38 (Erkoc et al., 2004) to 49,983 (Li et al., 2011). The incidence ranges from 340 per 100,000 (Basiri et al., 2008; Torre-Cisneros et al., 2009) to 14,680 per 100,000 (Vachharajani.et al., 2000). Among 154,438 patients with CKD who un-

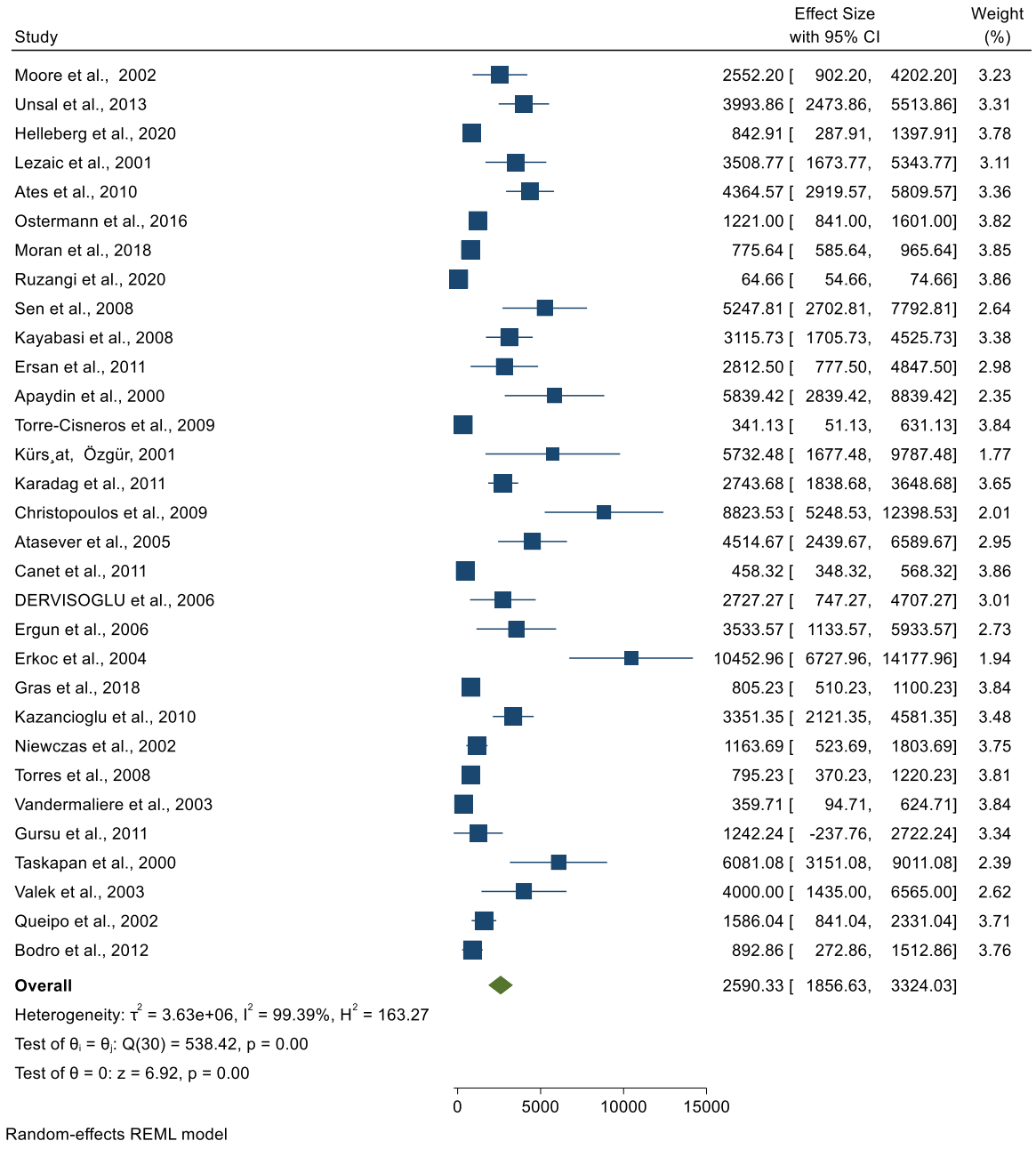

Figure 5. Forest plot for the pooled incidence of tuberculosis in patients with chronic kidney disease in the European Region per 100,000 population.

derwent renal transplantation, 2050 developed TB, which yielded a pooled estimate of 2700 per 100,000 (95%CI; 1878, 3522, I2; 99.58%) (Table 1, Figure 12). In all four categories, there is high heterogeneity among studies, whereas publication bias was detected for hemodialysis, peritoneal dialysis, and postrenal transplantation (P<0.001), but not for the predialysis group (p=0.46). After the trim-and-fill analysis, the pooled TB incidence was changed to 778 per 100,000 (95%CI; 279, 1276), 4329 per 100,000 (95%CI; 2690, 5969), 2746 per 100,000 (95%CI; 1391, 4100), and 3324 per 100,000 (95%CI; 2523, 4125) among predialysis, hemodialysis, peritoneal dialysis, and renal transplanted patients, respectively (Table 1).

We conducted a meta-regression analysis to assess the effect of sample size and publication year on the heterogeneity among studies. The multivariate meta-regression model revealed that sample size significantly predicted heterogeneity among studies (P=0.048), but not publication year (P=0.386). However, this model only explains 4.55% of the heterogeneity (Table 2).

Discussion

We conducted this study to estimate the pooled incidence of TB in patients with CKD, based on data generated at the global level. To our knowledge, this study is the first detailed systematic review and meta-analysis that assessed TB incidence using data generated from 1,548,774 patients with CKD, reported in 104 studies conducted in 32 countries. The pooled estimate revealed that 3718 patients with CKD per 100,000 patients developed TB. This study revealed regional and country-level disparities, where patients with CKD who resided in the African and Asian continents had the highest TB incidence.

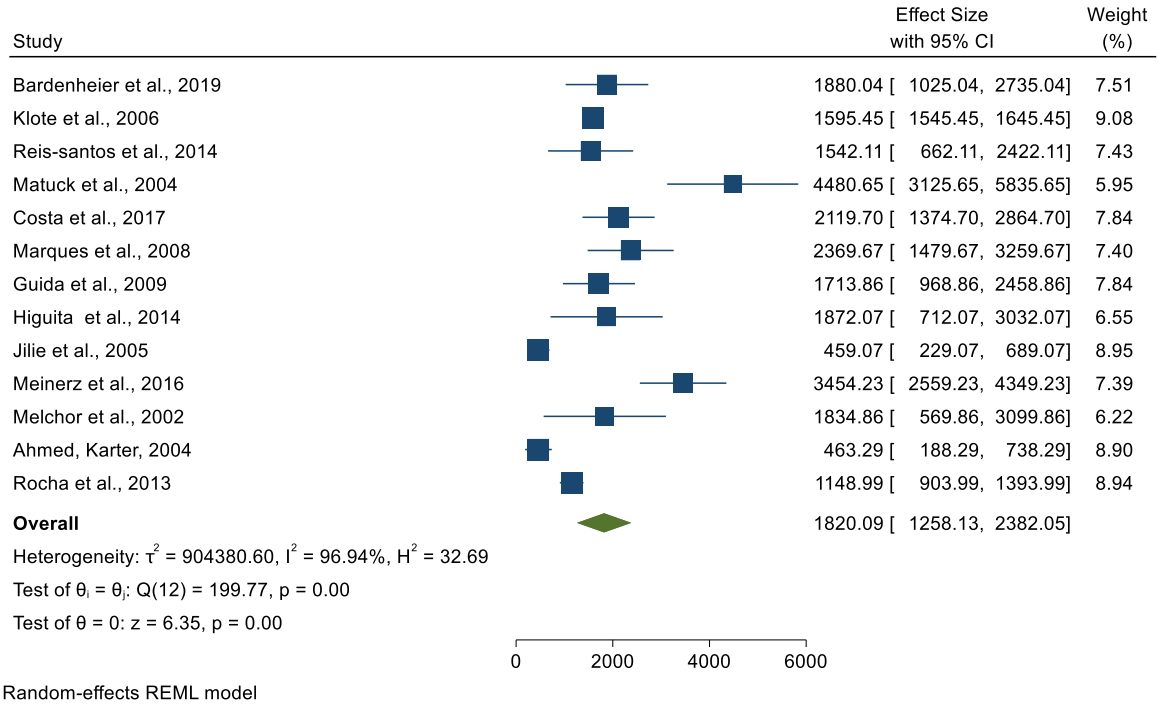

Figure 6. Forest plot for the pooled incidence of tuberculosis in patients with chronic kidney disease in the Region of the Americas per 100,000 population.

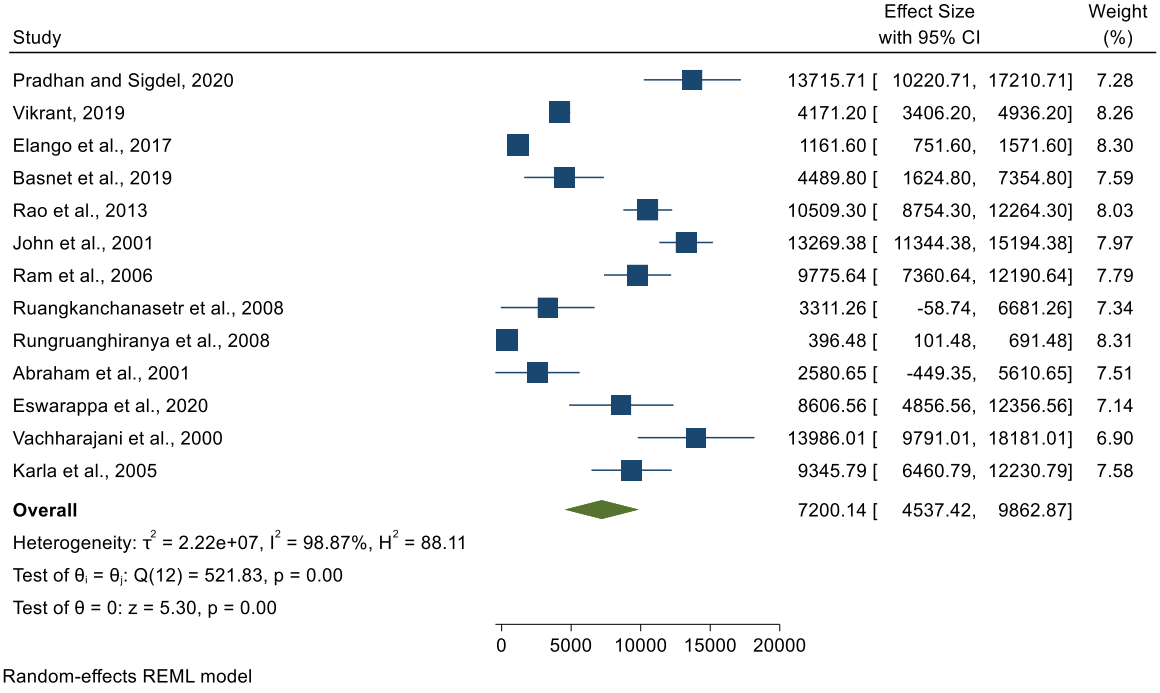

Figure 7. Forest plot for the pooled incidence of tuberculosis in patients with chronic kidney disease in the South-East Asian Region per 100, 000 population.

Table 2
Meta-regression analysis of heterogeneity using sample size and publication year.

Variable	Unadjusted model		Adjusted model	
	Coefficient (95%CI)	P-value	Coefficient (95%CI)	P-value
Sample size	-.0124174 (-.0232985, -.0015363)	0.025	-.0112559 (-.0224295, -.0000822)	0.048
Publication year	-75.73045 (-186.0649, 34.60397)	0.179	-49.63406 (-161.7534, 62.48531)	0.386

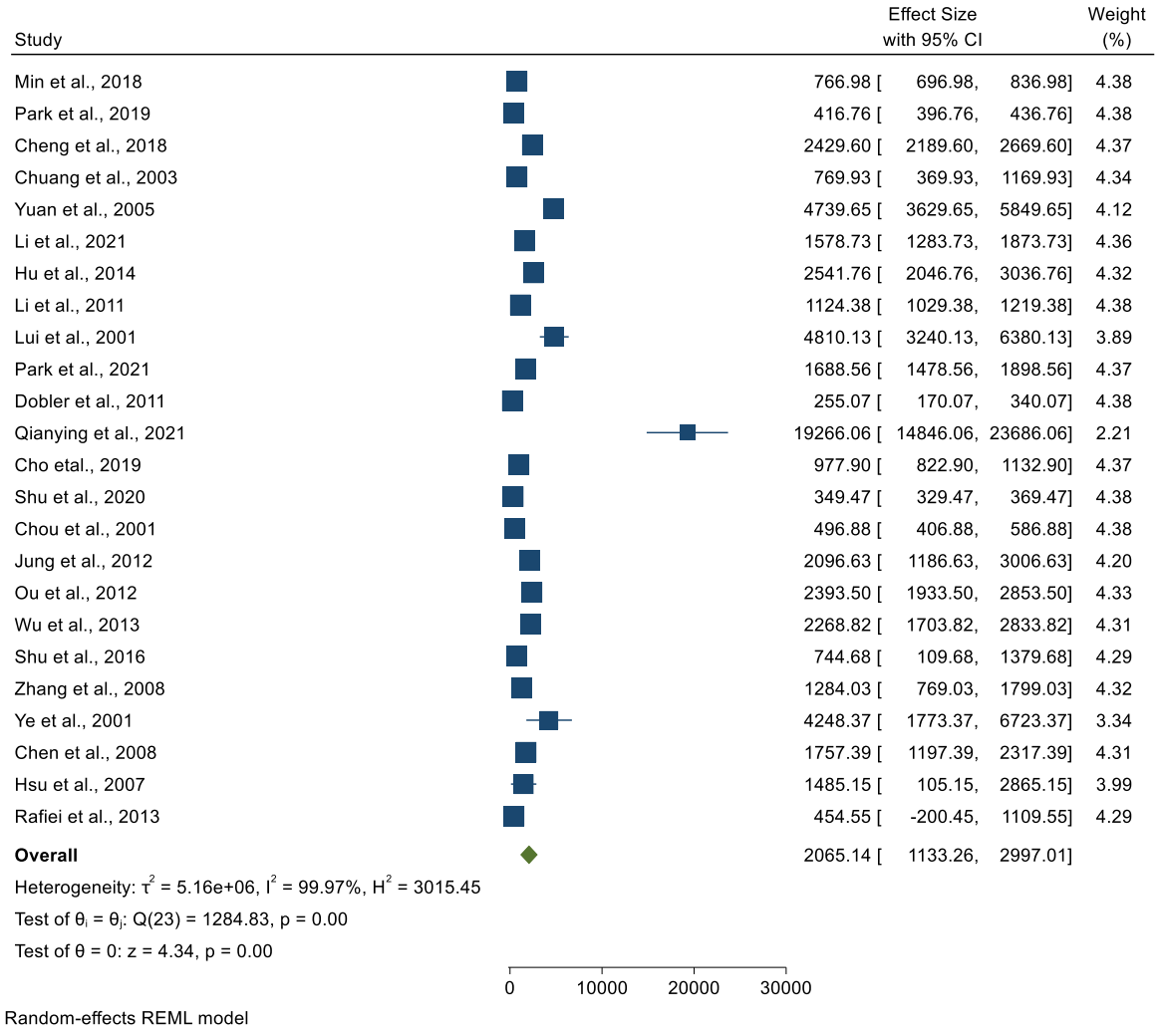

Figure 8. Forest plot for the pooled incidence of tuberculosis in patients with chronic kidney disease in the West Pacific Region per 100,000 population.

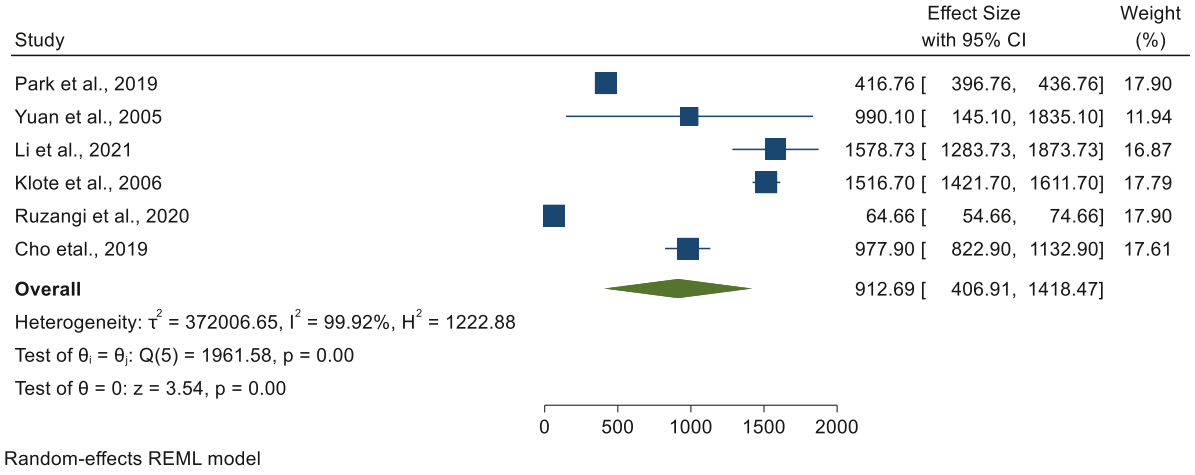

Figure 9. Forest plot for the pooled incidence of tuberculosis in patients with predialysis chronic kidney disease per 100,000 population.

The present study revealed that patients with CKD have a high TB risk. The incidence rate is far higher than the global TB incidence among the general population. This underlined the importance of systematic and active TB case detection in this group of individuals, as already recommended by the WHO consolidated guideline on TB. The guideline recommends systematic screening for TB among people attending health care services who have clinical risk factors for TB, and it includes people with immune, compromising conditions (organ transplant, renal failure, dialysis) (WHO, 2021). Thus, collaborative and integrative approaches are necessary to achieve the targets of the END-TB strategy.

The findings also revealed a higher incidence of EPTB than PTB in patients with CKD that might be due to late diagnosis; however, it should be investigated further. This study also revealed regional

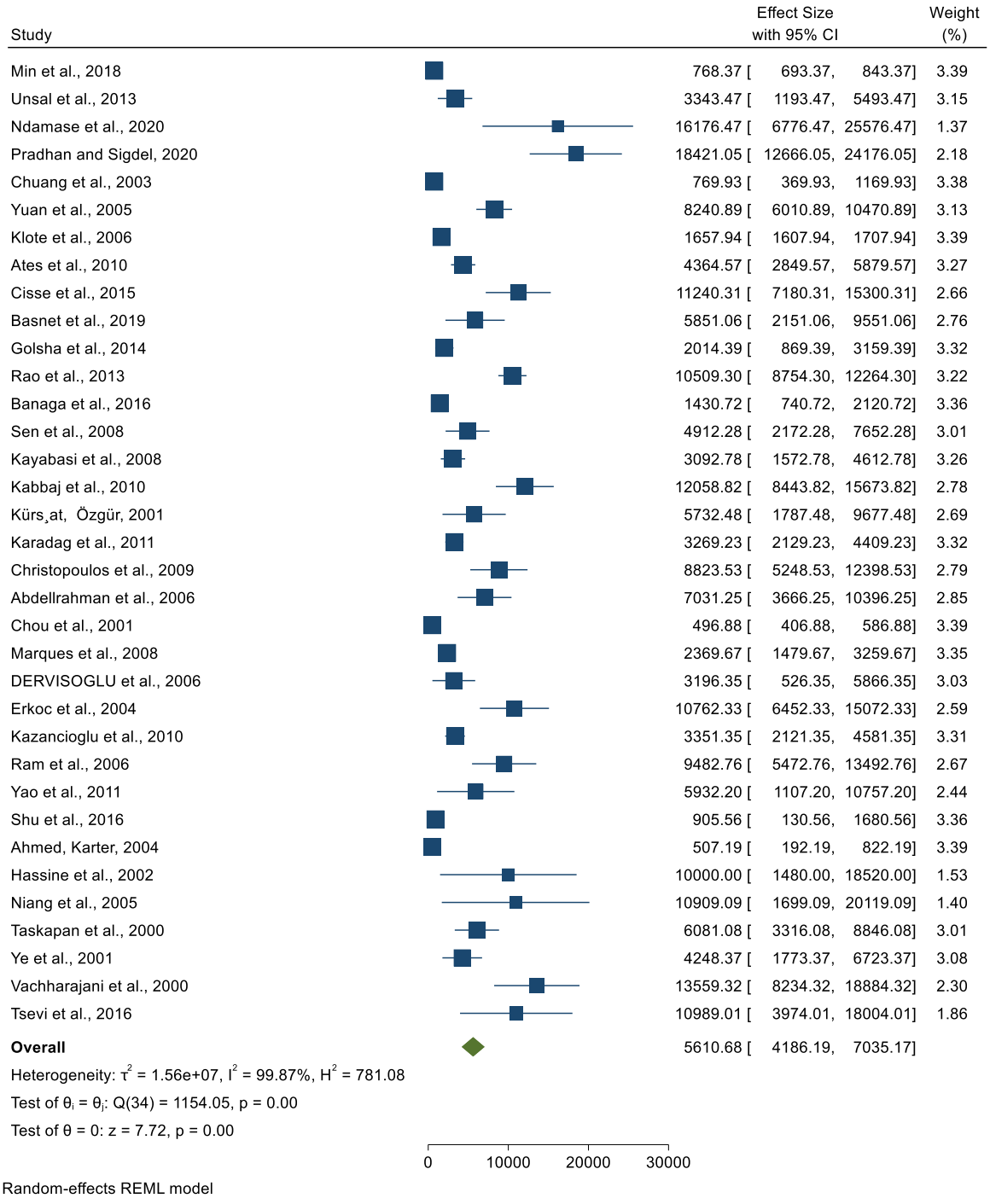

Figure 10. Forest plot for the pooled incidence of tuberculosis in patients with chronic kidney disease on hemodialysis per 100,000 population.

disparities of TB incidence among patients with CKD, where the highest incidence was detected in the African continent, followed by Asia and Europe, whereas the lowest pooled TB incidence was found in Australia and North America. Active TB transmission due to the presence of high TB prevalence among the general population in Africa and Asia might be the main reason. However, the TB pooled incidence among patients with CKD who reside in high TB burden countries (HBCs) and in other countries is comparable. This might be due to the lower number of studies in the HBCs (23/104) than in the counterparts (81/103) included in this study.

In the present study, the pooled estimates revealed that TB incidence among patients with CKD in all six WHO regions was far higher than the incidence in the general population based on the 2020 Global TB Report. The pooled TB incidence found in the African Region (9952/100,000) was very high compared with the incidence among the general population (226/100,000). The SEAR becomes the second region, with a higher pooled TB incidence being 7200 per 100,000, which is higher than the 217 per 100,000 TB incidence among the general population. Similarly, the EMR becomes the third region in terms of TB incidence (5508/100,000), which was higher than the 114 per 100,000 TB incidence among the general population in this region. The list of the top three WHO regions with higher pooled TB incidence among patients with CKD that were identified by our study is concurrent with the top lists

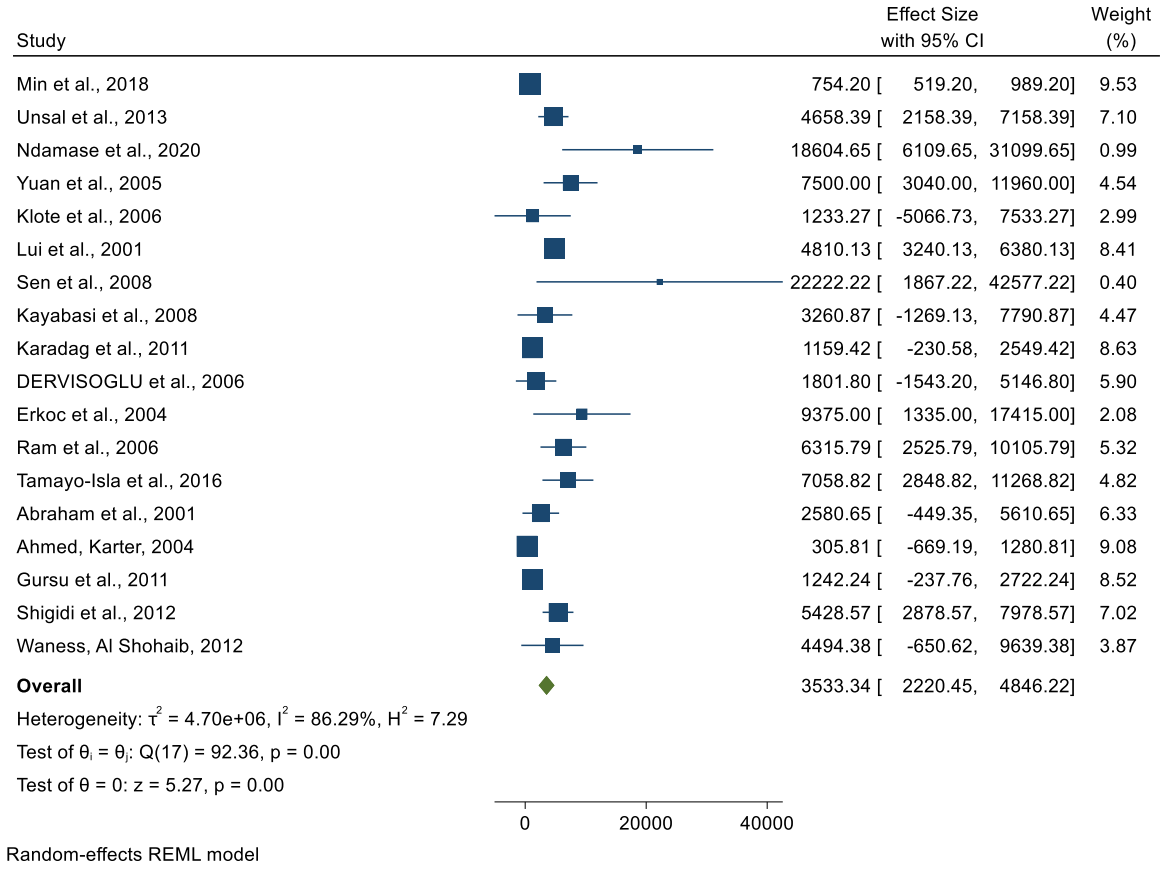

Figure 11. Forest plot for the pooled incidence of tuberculosis in patients with chronic kidney disease on peritoneal dialysis per 100,000 population.

based on the 2020 Global TB Report. Our study also revealed that patients with CKD who lived in the EUR, WPR, and AMR regions had higher TB incidence than did the general population. Thus, all the above findings revealed the need to adhere to the WHO guideline that recommends active TB screening in this group of individuals. Besides, the WHO recommends that patients who are initiating anti-TNF treatment, receiving dialysis, and preparing for an organ or hematological transplant and patients with silicosis should be systematically tested and treated for latent TB infection (LTBI) (WHO, 2018). Finally, the national TB and noncommunicable disease programs should collaborate to halt the dual burden of CKD and TB.

This study also assessed the pooled TB incidence among patients with CKD based on the year of publication. The findings revealed that there is a comparable TB incidence based on the publication year. Even though the TB incidence has been decreasing for the last decades at the global, regional, and country level, its incidence in patients with CKD has remained stagnant; this might have resulted from lower attention being given to this group of individuals. To achieve the END-TB targets, giving priority to high TB risk groups, including patients with CKD, is mandatory.

In this study, data were analyzed in detail to assess the pooled TB incidence based on the CKD categories, i.e., predialysis CKD, hemodialysis, peritoneal dialysis, and postrenal transplantation. The findings revealed that comparably higher TB incidence was found in hemodialysis patients (5611/100,000), followed by the peritoneal dialysis patients (3533/100,000). Patients on dialysis are at high risk of TB, which needs considerable attention to decrease TB transmission. This study also revealed a higher pooled postrenal transplantation TB incidence (2700/100,000). Higher TB risk in this group of individuals is due to taking immune suppressants that resulted in the reactivation of LTBI (Sundaram et al., 2008). Thus, LTBI screening and treatment in renal-transplanted individuals is key to reducing TB incidence. This study found the lowest pooled TB incidence among patients with predialysis CKD (913/100,000). However, this is far higher than the global TB incidence among the general population. Thus, all these findings revealed a higher TB incidence in patients with CKD at any stage. One important factor for this high TB incidence in patients with CKD at any classification or at any stage might be due to the immunosuppression that might reactivate the LTBI, with which people might already have been infected in childhood or adolescence, to active TB (WHO, 2018). Continuous TB screening of patients with CKD is important. There is a high percentage of people with subclinical TB, and it means that the entry point to TB screening cannot be based on symptoms because up to 80% of people with TB do not have symptoms (Frascella et al., 2021). Thus, the pooled TB incidence among patients with CKD that we found in this study might be underestimated, and the real incidence may be much higher; this needs continuous and active TB screening as per the WHO guideline recommendations.

Finally, this study should be interpreted considering the important limitations. Primarily, the study was based on individual studies published in the English language, which might affect the true estimates. The higher heterogeneity observed among the studies might also affect the estimates. There is clinical heterogeneity among the studies; i.e., the TB diagnostic method is not uniform. Furthermore, in three studies, the TB diagnostic method was taking two or more anti-TB drugs, which might include the treatment for LTBI and TB. In 18 studies, the TB diagnostic methods are not even described. Given the TB diagnostic methods are not uniform, it became difficult to perform a subgroup analysis. In the

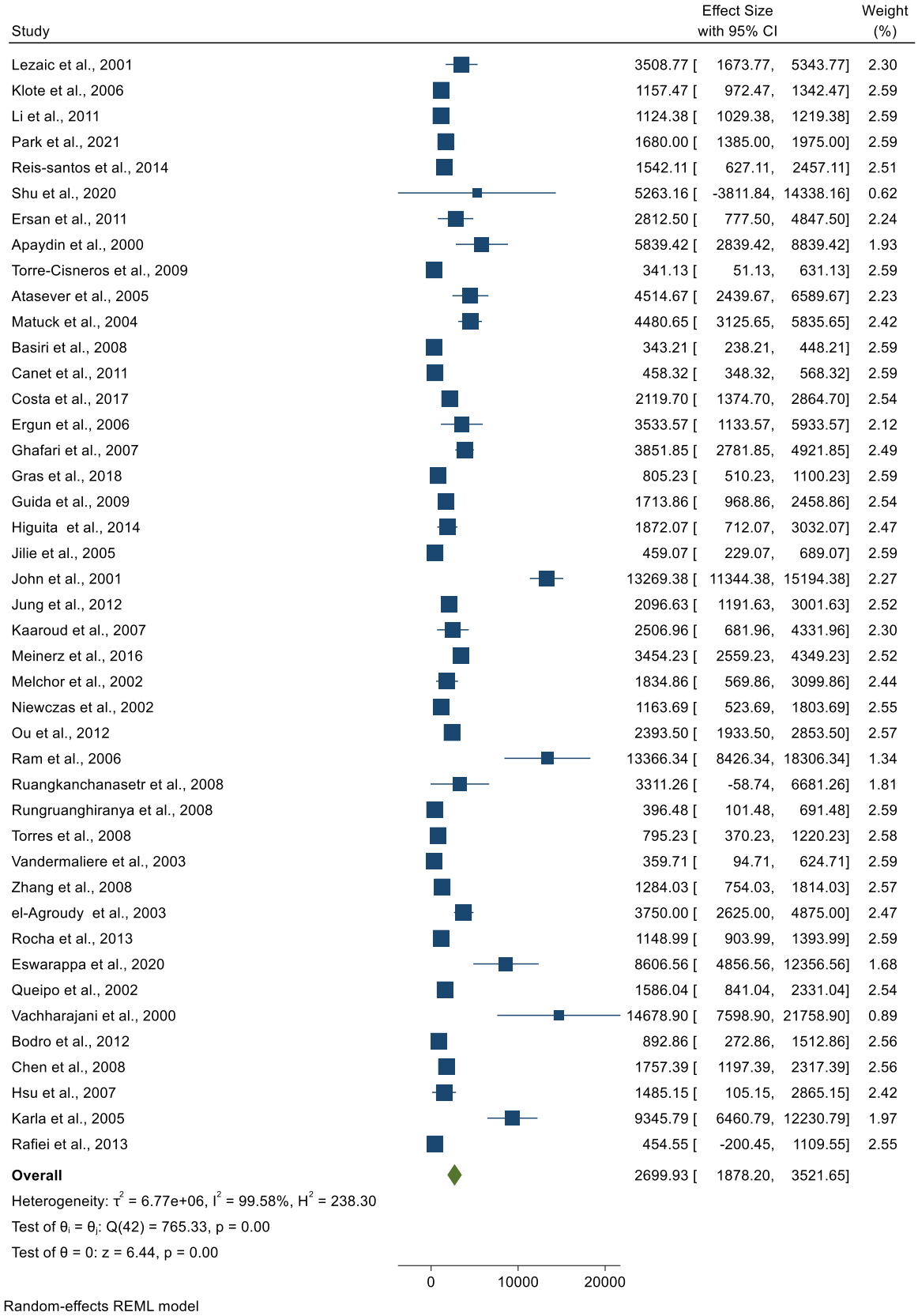

Figure 12. Forest plot for the pooled incidence of postrenal transplantation tuberculosis per 100,000 population.

current study, there was high publication bias that might have affected the true estimates, and we tried to adjust it using the trim-and-fill analysis; however, we are not sure whether the publication bias was due to the presence of high heterogeneity among studies or to unsearched/unpublished studies. Besides, most of the studies were conducted using retrospective data that might have affected the true estimates. Finally, most of the studies (75/104) were from Asian and European countries, which might affect the global pooled estimate.

In the end, this study revealed that 3718 per 100,000 patients with CKD develop TB with regional and country-level disparities, where patients with CKD residing in the African and Asian countries had the highest incidence. Based on the WHO regional category, higher TB pooled incidence was found in the AFR, followed by the SEAR and EMR. The incidence of TB among patients with CKD is stagnant. The findings also revealed that patients with CKD at any stage had a higher risk of TB, with a comparably higher incidence in dialysis patients. Besides, unlike the general population, patients with CKD had a higher EPTB incidence than PTB. Thus, the authors recommend that the national TB prevention and control programs prioritize attention to this group of individuals and approach them in a strategic manner. Furthermore, they shall consider such findings during a periodic review of the national guidelines, including active TB screening.

Competing interests

The authors have no competing interests to declare.

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Ethical approval and consent to participate

Not applicable.

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Author contributions

A.A. conceptualized, designed, and drafted the manuscript. A.A., G.D., G.S., M.T.C., and Z.W.B. performed article searching, data extraction, and quality assessment. A.A. and Z.W.B. conducted data analysis and wrote the manuscript. K.E., N.B., and B.G. reviewed the final manuscript. All authors read, reviewed, and approved the final manuscript.

Availability of data and materials

All data generated or analyzed during this study are included in this article and its supplementary information files.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.05.046.

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BMJ Open

How many of persistent coughers have pulmonary tuberculosis? Population-based cohort study in Ethiopia

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ABSTRACT

Objective Many individuals with persistent cough and smear microscopy-negative sputum test for tuberculosis (TB) remain at risk of developing the disease. This study estimates the incidence of pulmonary TB (PTB) among initially smear-negative persistent coughers and its risk factors.

Design A prospective population-based follow-up study.

Setting Health extension workers visited all households in Dale *woreda* three times at 4-month intervals in 2016–2017 to identify individuals with symptoms compatible with TB (presumptive TB) using pretested and semistructured questionnaires.

Participants We followed 3484 presumptive TB cases (≥15 years) with an initial smear-negative TB (PTB) test.

Outcome measures Bacteriologically confirmed PTB (PTB b+) and clinically diagnosed PTB (PTB c+).

Results 3484 persons with initially smear-negative presumptive PTB were followed for 2155 person-years (median 0.8 years); 90 individuals had PTB b+ and 90 had PTB c+. The incidence rates for PTB b+ and PTB c+ were both 4176 (95% CI 3378 to 5109) per 100 000 person-years. We used penalised (lasso) and non-penalised proportional hazards Cox regression models containing all exposures and outcomes to explore associations between exposures and outcomes. In lasso regression, the risk of development of PTB b+ was 63% (HR 0.37) lower for people aged 35–64 years and 77% (HR 0.23) lower for those aged ≥65 years compared with 15–34 year-olds. Men had a 62% (HR 1.62) greater risk of PTB b+ development than women. The risk of PTB c+ was 39% (HR 0.61) lower for people aged 35–54 years than for those aged 15–34 years. Men had a 56% (HR 1.56) greater risk of PTB c+ development than women.

Conclusions PTB incidence rate among persistent coughers was high, especially among men and young adults, the latter signifying sustained transmission. Awareness about this among healthcare workers may improve identification of more new TB cases.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study was population based with a large sample size.
⇒ By embedding the study in the health system, community health workers who knew the area well were involved in identifying individuals with presumptive tuberculosis (TB) for further follow-up.
⇒ A previous smaller study conducted in the same area made it possible to explore changes over time.
⇒ Acid-fast bacilli smear microscopy was used as the principal test as this is used routinely by the TB programme in rural areas and has a very high specificity, but the sensitivity is relatively low.
⇒ We used HIV testing within the last year as a proxy for infection since information on HIV status was not available.

BACKGROUND

Sub-Saharan Africa is the region with the highest estimated tuberculosis (TB) incidence rate worldwide (226/100 000 population in 2020), and almost one-third of cases in Africa involve coinfection with HIV.[1] Ethiopia has a high burden of TB and TB/HIV coinfection, and TB ranks number 4 among causes of death in the country. Still, the estimated incidence rate of TB in Ethiopia has decreased slowly since 2007.[2 3] Over the last decades, the strategy for TB control (directly observed treatment, short course) has been implemented in the country, with varying degrees of success. The population appreciates active case finding in the communities,[4] and this expansion of care has improved case notification.[5] Approximately 10% of individuals with persistent cough in Ethiopia show bacteriological evidence of TB, but even those who test negative still may have TB.[6 7] In this large high-risk group for TB, the symptoms of the disease may be non-specific. One study showed that half of the symptomatic infectious TB cases in Ethiopia were undiagnosed in communities and concluded that more intensified ways of case finding were needed.[8] Other factors contributing to underdiagnoses are the low sensitivity of smear microscopy[9 10] and the population not seeking healthcare when they should.[11] Undiagnosed TB leads

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to increased morbidity and mortality, economic hardship and sustained transmission.

Individuals with positive smear results are treated with a standard TB regimen. National guidelines recommend that persistent coughers with two negative sputum smears return for re-examination if their symptoms persist for >14 days. At re-examination, the patient may prove to not have TB, have TB in the sputum or may be diagnosed clinically, the latter two followed by TB treatment.[12] The risk of TB among persistent coughers was investigated in a study in parts of the same *woreda* 5 years earlier and in a smaller sample.[13]

The number of individuals with smear-negative presumptive TB needing follow-up visits is high and the mechanisms for follow-up are currently weak.[12 14 15] Leaving this high-risk group behind is not acceptable practice and assessment of the implications for the TB control programme has not been done. Therefore, our objectives were to: (1) estimate the incidence rate of TB among persistent coughers; and (2) assess potential determinants of TB.

METHODS

Design and setting

This study uses data from a population-based prospective cohort study conducted between October 2016 and November 2017 in Dale.[16] The population includes 3746 persons who were identified with presumptive TB based on symptoms from the household screening rounds. Among them, 262 (7%) had TB disease at enrolment, leaving 3484 persons for follow-up in the current study. Dale is located in the previous Sidama Zone, current Sidama Region, of Ethiopia, and is a densely populated agrarian community with an estimated total population of 267 000 individuals living in 36 rural *kebeles* (the smallest administrative units). The study area has 10 health centres, 2 clinics (which provide healthcare comparable to that provided at the health centres) and 36 health posts (which provide drugs under direct observed treatment short-course (DOTS) services at each *kebele*). Microscopy, but not GeneXpert nor X-ray examination, is available at the health centres. Health extension workers (HEWs) and community health workers are the main health service providers at the community level. The primary test for pulmonary TB (PTB) diagnosis is sputum smear microscopy.[17] The only GeneXpert equipment in the area is located outside of Dale in the town administration of Yirgalem.[18 19] We used the Strengthening the Reporting of Observational Studies in Epidemiology cohort reporting guidelines (online supplemental file S1).[20]

Patient and public involvement

No patients were involved in setting the research question or the outcomes, the conduct, interpretation, writing or dissemination of the results. The study was conducted in close collaboration with the *woreda* TB and leprosy programme in Dale. They were informed about the study in advance and were actively involved throughout the design and implementation phases and in dissemination of the results. The project team organised consultative meetings with participants from regional, zonal and *woreda*-level offices, non-governmental organisations and religious organisations throughout the full study period. Village women were included as representatives for the population in Dale.

Data collection and participants

Data collectors were trained for 2 days with a local and experienced project supervisor supporting the study implementation. HEWs systematically visited every household in Dale in three consecutive rounds (October 2016 to January 2017, February to May 2017 and June to September 2017) to sensitise household members to TB and ask them about the presence of symptoms compatible with TB. A symptom-screening questionnaire (online supplemental file S2) was used to identify individuals with presumptive PTB defined as cough for≥14 days, with or without related symptoms such as fever, haemoptysis, night sweats, poor appetite, weight loss, difficulty in breathing and chest pain. These individuals were referred to local services at public health posts for sputum (expectorate) collection and follow-up.

A persistent cougher was defined as a person with presumptive TB who were initially negative on sputum smear microscopy (ie, negative on the first test and any other test taken within 30 days apart). The study population included persistent coughers aged 15 years or older. The observation time was measured from the date of enrolment to the date of treatment initiation or end of study (November 2017).

Clinical samples and diagnosis

Each participant provided two spot sputum samples at the health post, which were sent to the health centre for smear microscopy. Sputum samples from smear-positive cases and those from smear-negative cases with symptom persistence after 2–4 weeks of follow-up with antibiotic treatment were sent to Yirgalem Hospital for GeneXpert-based test. Smear and/or GeneXpert-positive samples were sent to Armauer Hansen Research Institute in Addis Ababa for culture. As part of the study, quality assurance of smear microscopy results was done through rechecking of 50% random samples at the regional external quality assurance site.

Study variables

Sociodemographic, economic and clinical risk factors served as the exposure variables. We included catchment area and marital status as exposure variables in the models, as they serve as indicators of non-random differences in access to healthcare facilities and diagnosis in this setting. The outcome was a case of PTB: bacteriologically confirmed (PTB b+), clinically diagnosed (PTB c+) or both combined. PTB b+ was defined as any TB diagnosed based on smear microscopy, culture or GeneXpert

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laboratory results. Clinical PTB (PTB c+) was defined by a clinical decision to start TB treatment in those with persistent cough, usually supported by radiological findings and evidence from other tests according to the National tuberculosis and leprosy (NTLP) guidelines. All-type PTB was the combination of PTB b+ and PTB c+.

Statistical analyses

Data were entered into Excel database and the quality was assessed by frequency distributions, cross-tabulations and by duplicate entry of a random sample constituting 10% of the data set. The difference between the first and second data entries was 0.1%; errors were not systematic and were corrected before further analyses with OpenEpi[21] and Stata V.14 software.[22] The incidence rate of TB was calculated by dividing the number of PTB cases by time of observation which is the number of person-years (PY). Basic descriptive analysis included median, range, mean and SD.

The R statistical software was used for regression analyses and modelling.[23] We ran separate Cox proportional hazards regression models for each exposure and exposure group, and constructed a fully adjusted model. This approach allowed us to explore confounding variables by comparing crude HR and adjusted HR (aHR) per exposure group and overall aHR; all estimated with 95% CIs. Associations were deemed significant when p values were <0.05.

For the main analyses, we ran complete-case multivariable Cox proportional hazards lasso (penalised) regression models containing all exposures for PTB, PTB b+ and PTB c+, with 1000 cross-validations. Lasso regression involves automated variable selection and yields penalised HRs; it gives no CIs nor p values (online supplemental file S3); HRs that differed from 1 were considered to be significant. It is the preferred method when adjustment for many exposure variables is required and the number of cases is limited.

RESULTS

Description of the study population

We screened 45 384 households with 136 181 adults in Dale *woreda* and identified 3746 individuals with presumptive PTB during the study period. Of them, 262 individuals had TB on initial examination and were excluded from follow-up. The remaining 3484 individuals (58% female) met the inclusion criteria for the current study of persistent coughers and were thus included for further analysis. The mean age of the study subjects was 42.7 (SD 17.4) years for men and 40.0 (SD 14.6) years for women. Seventeen presumptive PTB cases were diagnosed as extra-PTB and were excluded from further analysis. The total observation time for the participants was 786 581 person-days/2155 PY, and the median number of days under observation for participants was 301 days/0.8 years.

Incidence rates of PTB

There were 180 individuals diagnosed with PTB. PTB b+ was detected in 90 patients; 40 of them were smear and GeneXpert positive, 13 were only smear positive, 34 were only GeneXpert positive and 3 were only culture positive. There were 90 individuals diagnosed with PTB c+; GeneXpert was negative in 71 cases, invalid in 1 case and 18 were not offered this test. None of these were cultured. Chest X-rays were taken of 142 persistent coughers who could not produce sputum and/or required further investigation; 86 had findings suggestive of TB, 55 had no abnormal findings and 1 yielded a non-specific result. Only four cases did not have an X-ray as part of the PTB c+ diagnosis. The incidence rates of PTB b+ and PTB c+ were both 4176 (95% CI 3378 to 5109) per 100 000 PY. The overall incidence rate of PTB among persistent coughers was 8353 (95% CI 7197 to 9642) per 100 000 PY.

PTB risk factors

The risks of developing PTB b+ and PTB c+ among individuals with persistent cough are presented in tables 1 and 2, respectively. All-type PTB is presented in online supplemental table S1. The risks of PTB b+ and PTB c+ differed according to age (crude and adjusted p=0.001) (tables 1 and 2). The risk of developing PTB b+ and PTB c+ was significantly lower among individuals aged 35–64 years (PTB b+: lasso HR 0.37; PTB c+: lasso HR 0.61). For PTB b+, this risk was also lower among individuals aged ≥65 years (lasso HR 0.23). Men had had significantly higher risk of developing PTB b+ compared with women (lasso HR 1.62) and PTB c+ (lasso HR 1.56). Four out of nine catchment areas had significantly higher risk of PTB b+ than the reference. Increasing years of education were significantly associated with decreasing risk of developing PTB b+ (lasso HR 0.85) and PTB c+ (lasso HR 0.79, per year). Increasing middle-upper arm circumference (MUAC) was significantly associated with decreasing risk of PTB (per centimetre increase in MUAC; PTB b+: lasso HR 0.85; PTB c+: lasso HR 0.81).

Furthermore, individuals living in houses with separate kitchens had lower risk of developing PTB (PTB b+: lasso 0.85; PTB c+: lasso HR 0.46). HIV testing in the past year was associated with development of PTB (PTB b+: lasso HR 1.51; PTB c+: lasso HR 1.23). Individuals living with persistent coughers had lower risk of developing PTB c+ (lasso HR 0.43), but not PTB b+.

DISCUSSION

This study revealed a high incidence rate of PTB among persistent coughers with negative initial smear microscopy results, which was eight PTB cases per 100 PY of observation. Young adults, men, individuals with little education and those with low MUAC had increased risk of developing PTB. These results were consistent across crude, adjusted and penalised analyses for PTB b+ and PTB c+. The TB control programme should consider systematic follow-up of persistent coughers as a strategy to improve case finding.

Strengths of this study include the large sample and data collection via systematic and repeated population-based

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Table 1 Risk factors for bacteriologically confirmed pulmonary tuberculosis in Dale, Ethiopia, 2016–2017

Covariates		n=3377	TB=90	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value	Lasso HR
Sociodemographic data								
Age group (years)		3377	90		0.001*		0.001*	
15–34		1180	60	1		1		
35–64		1902	29	0.29 (0.19 to 0.46)	0.001	0.24 (0.14 to 0.39)	0.001	0.37
65 and more		295	1	0.06 (0.01 to 0.45)	0.006	0.04 (0.01 to 0.33)	0.002	0.23
Catchment area		3377	90		0.052*		0.046*	
S Mesenkala		397	10	1		1		
Magara		215	7	1.37 (0.52 to 3.60)	0.523	1.93 (0.70 to 5.32)	0.203	–
Hida Kaliti		73	5	2.66 (0.91 to 7.79)	0.074	4.09 (1.27 to 13.1)	0.018	1.71
Bera Tadicho		423	12	1.17 (0.50 to 2.70)	0.72	3.01 (1.24 to 7.30)	0.015	1.19
Goida		254	5	0.83 (0.28 to 2.43)	0.737	1.77 (0.58 to 5.37)	0.316	–
Boa Badagalo		654	14	0.88 (0.39 to 1.99)	0.767	1.40 (0.59 to 3.32)	0.447	–
Dagyia		380	5	0.58 (0.20 to 1.69)	0.315	1.48 (0.48 to 4.52)	0.496	–
Gidamo		201	11	2.11 (0.90 to 4.97)	0.087	5.90 (2.34 to 14.8)	0.001	2.37
Moto		451	7	0.63 (0.24 to 1.65)	0.345	1.07 (0.39 to 2.90)	0.897	–
Semen Kege		329	14	1.84 (0.82 to 4.15)	0.14	3.88 (1.60 to 9.42)	0.003	1.67
Occupation		3377	90		0.283*		0.684*	
Farmer		2252	62	1		1		
Housewife		865	17	0.75 (0.44 to 1.28)	0.295	0.99 (0.54 to 1.80)	0.964	–
Merchant		68	1	0.53 (0.07 to 3.82)	0.528	0.43 (0.06 to 3.20)	0.408	–
Student		159	9	2.08 (1.04 to 4.19)	0.039	1.82 (0.81 to 4.07)	0.146	1.17
GO		15	1	2.34 (0.32 to 16.8)	0.4	1.97 (0.26 to 15.1)	0.516	–
Daily labourer		10	–	–	0.995	–	0.998	–
Other		8	–	–	0.995	–	0.998	–
Male gender		1390	50	1.81 (1.19 to 2.74)	0.005	2.31 (1.43 to 3.72)	0.001	1.62
Marital status—not married†		944	27	1.50 (0.94 to 2.39)	0.09	0.77 (0.43 to 1.36)	0.365	–
Number in household		3377	90	1.11 (0.95 to 1.29)	0.194	1.11 (0.94 to 1.31)	0.217	1.03
Years of education		3005	60	0.86 (0.80 to 0.92)	0.001	0.78 (0.72 to 0.85)	0.001	0.85
Clinical information								
MUAC (cm)		3346	90	0.83 (0.76 to 0.90)	0.001	0.80 (0.72 to 0.88)	0.001	0.85
BMI <18.5 kg/m^2‡	No	1362	20	1		1		
	Yes	2002	61	1.48 (0.95 to 2.30)	0.083	1.27 (0.80 to 2.02)	0.312	–
Risk factors for TB								
Previous TB	No	2851	73		1			
	Yes	524	17	1.17 (0.69 to 1.98)	0.563	1.38 (0.73 to 2.60)	0.32	–
TB history in the household (5 years)	No	2883	76		1			
	Yes	492	14	1.03 (0.58 to 1.82)	0.924	1.26 (0.61 to 2.59)	0.534	–
Lived with a persistent cougher	No	2443	70	1		1		
	Yes	934	20	1.17 (0.69 to 1.98)	0.563	0.57 (0.31 to 1.05)	0.07	0.88
HIV test in the past year	No	2682	63	1				
	Yes	694	27	1.42 (1.02 to 1.97)	0.037	2.18 (1.35 to 3.53)	0.002	1.51
Ever alcohol drinker§	No	3192	86	1		1		
	Yes	185	4	0.77 (0.28 to 2.09)	0.602	0.63 (0.18 to 2.15)	0.457	0.96
Ever chewed chat¶	No	3166	86	1		1		
	Yes	211	4	0.67 (0.33 to 1.36)	0.263	0.62 (0.15 to 2.66)	0.524	0.93

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Table 1 Continued

Covariates		n=3377	TB=90	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value	Lasso HR
Ever smoker**	No	3251	87	1		1		
	Yes	126	3	0.72 (0.29 to 1.74)	0.461	1.13 (0.21 to 6.06)	0.889	–
Smoker currently in the household	No	3132	86	1		1		
	Yes	243	4	0.60 (0.22 to 1.62)	0.311	0.58 (0.16 to 2.09)	0.408	0.87
Smoker previously in the household	No	3082	82	1		1		
	Yes	294	8	1.02 (0.49 to 2.11)	0.954	1.03 (0.41 to 2.59)	0.942	–
Economic indicators								
Rooms in house (n)		3377	90	0.84 (0.65 to 1.09)	0.185	0.99 (0.73 to 1.33)	0.924	
Light source, electricity	No	2770	74	1		1		
	Yes	607	16	1.00 (0.58 to 1.72)	1	1.68 (0.92 to 3.06)	0.093	1.06
Fuel for cooking, electricity††	No	3350	90	1		1		
	Yes	27	0	–	0.995	–	0.997	
Separate kitchen	No	2643	80	1		1		
	Yes	734	10	0.43 (0.23 to 0.84)	0.013	0.38 (0.15 to 0.95)	0.038	0.85
Cooking room ventilation	No	2996	10	1		1		
	Yes	381	10	0.94 (0.48 to 1.81)	0.843	3.37 (1.41 to 8.03)	0.006	–
Heating in house	No	3287	89	1		1		
	Yes	90	1	0.43 (0.06 to 3.07)	0.398	0.26 (0.03 to 2.18)	0.213	0.86
Bank account	No	3245	88	1		1		
	Yes	130	1	0.27 (0.04 to 1.91)	0.188	0.48 (0.06 to 3.93)	0.495	0.92
Land agriculture	No	409	12	1		1		
	Yes	2968	78	0.87 (0.47 to 1.60)	0.658	1.27 (0.65 to 2.47)	0.482	–
Mobile phone	No	608	16					
	Yes	2769	74	0.93 (0.54 to 1.59)	0.777	0.72 (0.40 to 1.32)	0.291	–
TV	No	3309	89	1		1		
	Yes	68	1	0.55 (0.08 to 3.93)	0.549	1.84 (0.23 to 15.0)	0.568	–
Radio	No	2899	79	1		1		
	Yes	478	11	0.79 (0.42 to 1.49)	0.473	1.20 (0.57 to 2.52)	0.636	–
Refrigerator	No	3345	90	1		1		
	Yes	32	0	–	0.994	–	0.997	–
Walls—wood with other‡‡	No	1760	54	1		1		
	Yes	1617	36	0.70 (0.46 to 1.07)	0.102	0.93 (0.57 to 1.51)	0.758	
Roof—corrugated iron§§	No	2175	71	1		1		
	Yes	1202	19	0.47 (0.28 to 0.78)	0.003	0.53 (0.28 to 1.01)	0.054	0.69

*P value for the variable as a whole for variables with more than one value.
†Single, divorced, widowed or unknown marital status versus married (reference).
‡BMI <18.5 kg/m^2 versus BMI ≥18.5 kg/m^2 (reference).
§Ever alcohol drinker is a person who drinks alcoholic beverages to a notable level at present or in the past versus not.
¶Ever chewed chat is a person who chews chat at present or in the past versus not.
**Ever smoker is a person who smokes cigarette at present or in the past versus not.
††Use of electricity for cooking versus use of kerosene, charcoal, wood, cow dung or agricultural by-products, or no cooking in household (reference).
‡‡House walls made of brick, cement or wood with mud versus house with walls of wood only (reference).
§§Corrugated iron sheet roof versus thatched, leaf or unspecified roof (reference).
BMI, body mass index; GO, government employee; MUAC, middle-upper arm circumference; TB, tuberculosis; TV, television.

symptom screening during home visits. The bacteriological examinations were done according to the routines of TB programme with important elaboration in sputum examination (GeneXpert and culture) and quality assurance of tests. Furthermore, incidence rates were also estimated for clinically diagnosed TB cases, which is a challenge for clinicians. HEWs and community health workers were involved in the study at the grass-roots level throughout its implementation and referred symptomatic individuals immediately for further examination.

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Table 2 Risk factors for clinically diagnosed pulmonary tuberculosis in Dale, Ethiopia, 2016–2017

Covariates		n=3377	TB=90	Crude HR (95% CI)		Adjusted HR (95% CI)		Lasso HR
Sociodemographic data								
Age group (years)		3377	90		0.001*		0.001*	
15–34		1168	48	1		1		
35–64		1909	36	0.45 (0.29 to 0.70)	0.001	0.46 (0.28 to 0.77)	0.003	0.61
65 and more		300	6	0.46 (0.20 to 1.07)	0.072	0.41 (0.16 to 1.01)	0.053	0.72
Catchment area		3377	90		0.001*		0.001*	
S Mesenkala		406	19	1		1		
Magara		213	5	0.53 (0.20 to 1.43)	0.21	0.59 (0.21 to 1.63)	0.309	0.92
Hida Kaliti		72	4	1.09 (0.37 to 3.19)	0.882	1.19 (0.36 to 3.89)	0.779	–
Bera Tadicho		430	19	0.97 (0.51 to 1.83)	0.923	2.68 (1.30 to 5.54)	0.008	1.99
Goida		260	11	0.97 (0.46 to 2.04)	0.934	1.62 (0.72 to 3.66)	0.246	1.54
Boa Badagalo		651	11	0.37 (0.18 to 0.79)	0.009	0.60 (0.27 to 1.30)	0.193	0.87
Dagyia		375	0	–	0.995	–	0.995	0.44
Gidamo		190	0	–	0.996	–	0.997	0.56
Moto		458	14	0.67 (0.33 to 1.33)	0.25	1.04 (0.50 to 2.19)	0.914	–
Semen Kege		322	7	0.51 (0.22 to 1.22)	0.13	0.86 (0.34 to 2.20)	0.753	–
Occupation		3377	90		0.362*		0.761*	
Farmer		2251	61	1		1		
Housewife		865	17	0.77 (0.45 to 1.31)	0.335	0.82 (0.44 to 1.52)	0.522	–
Merchant		69	2	1.05 (0.26 to 4.28)	0.95	0.63 (0.12 to 3.31)	0.582	–
Student		159	9	2.06 (1.02 to 4.15)	0.043	2.24 (0.99 to 5.06)	0.053	1.72
GO		15	1	2.29 (0.32 to 16.5)	0.41	2.22 (0.29 to 16.9)	0.444	–
Daily labourer		10	0	–	0.995	–	0.999	–
Other		8	0	–	0.995	–	0.999	–
Male gender		1388	48	1.66 (1.10 to 2.51)	0.016	2.01 (1.26 to 3.21)	0.003	1.56
Marital status—not married†		948	31	1.48 (0.93 to 2.36)	0.1	0.98 (0.55 to 1.76)	0.957	–
Number in household		3377	90	1.12 (0.96 to 1.30)	0.163	1.08 (0.92 to 1.28)	0.336	1.03
Years of education		3005	60	0.77 (0.71 to 0.83)	0.001	0.73 (0.67 to 0.80)	0.001	0.79
Clinical information								
MUAC (cm)		3346	90	0.79 (0.72 to 0.85)	0.001	0.78 (0.70 to 0.85)	0.001	0.81
BMI <18.5 kg/m^2‡	No	1374	28	1		1		
	Yes	2003	62	1.56 (1.00 to 2.44)	0.051	1.41 (0.88 to 2.27)	0.154	1.09
Risk factors for TB								
Previous TB	No	2855	77	1		1		
	Yes	520	13	0.84 (0.47 to 1.52)	0.568	1.20 (0.60 to 2.39)	0.612	–
TB history in the household (5 years)	No	2884	77	1		1		
	Yes	491	13	0.94 (0.52 to 1.69)	0.829	1.46 (0.70 to 3.04)	0.313	–
Lived with a persistent cougher	No	2453	80	1		1		
	Yes	924	10	0.32 (0.16 to 0.61)	0.001	0.22 (0.10 to 0.48)	0.001	0.43
HIV test in the past year	No	2687	68	1		1		
	Yes	689	22	1.24 (0.76 to 2.00)	0.387	1.61 (0.97 to 2.66)	0.063	1.23
Ever alcohol drinker§	No	3193	87	1		1		
	Yes	184	3	0.56 (0.18 to 1.78)	0.327	0.58 (0.14 to 2.47)	0.462	0.92
Ever chewed chat¶	No	3166	86	1		1		
	Yes	211	4	0.66 (0.24 to 1.80)	0.42	0.94 (0.23 to 3.80)	0.936	–
Ever smoker**	No	3252	88	1		1		
	Yes	125	2	0.57 (0.14 to 2.31)	0.43	0.50 (0.07 to 3.59)	0.494	0.87

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Table 2 Continued

Covariates		n=3377	TB=90	Crude HR (95% CI)		Adjusted HR (95% CI)		Lasso HR
Smoker currently in the household	No	3133	87	1		1		
	Yes	242	3	0.44 (0.14 to 1.39)	0.163	1.01 (0.18 to 5.57)	0.991	0.93
Smoker previously in the household	No	3085	85	1		1		
	Yes	290	4	0.50 (0.18 to 1.35)	0.169	0.67 (0.16 to 2.86)	0.592	–
Economic indicator								
Rooms in house (n)		3377	90	0.85 (0.66 to 1.10)	0.222	0.94 (0.69 to 1.26)	0.663	–
Light source, electricity	No	290	4	1		1		
	Yes	3085	85	0.78 (0.44 to 1.41)	0.416	0.98 (0.50 to 1.93)	0.949	–
Fuel for cooking, electricity††	No	3350	90	1		1		
	Yes	27	0	–	0.995	–	0.999	
Separate kitchen	No	2643	80	1		1		
	Yes	734	10	0.16 (0.06 to 0.44)	0.001	0.20 (0.06 to 0.68)	0.01	0.46
Cooking room ventilation	No	3001	85	1		1		
	Yes	376	5	0.44 (0.18 to 1.08)	0.072	1.55 (0.52 to 4.63)	0.433	–
Heating in house	No	3288	90	1		1		
	Yes	89	0	–	0.994	–	0.997	0.97
Bank account	No	3245	88	1		1		
	Yes	132	2	0.53 (0.13 to 2.14)	0.369	0.93 (0.14 to 6.20)	0.941	–
Land agriculture	No	397	24	1		1		
	Yes	2956	66	0.37 (0.23 to 0.59)	0	0.51 (0.30 to 0.86)	0.012	0.55
Mobile phone	No	2771	76	1		1		
	Yes	606	14	0.78 (0.44 to 1.38)	0.391	1.23 (0.65 to 2.31)	0.524	–
TV	No	3309	89	1		1		
	Yes	68	1	0.55 (0.08 to 3.92)	0.548	0.29 (0.01 to 6.97)	0.444	–
Radio	No	2901	81	1		1		
	Yes	476	9	0.63 (0.31 to 1.25)	0.183	1.20 (0.55 to 2.61)	0.651	–
Refrigerator	No	3343	88	1		1		
	Yes	34	2	2.29 (0.56 to 9.31)	0.246	6.52 (0.95 to 44.4)	0.056	1.29
Walls—wood with other‡‡	No	1773	67	1		1		
	Yes	1604	23	0.36 (0.23 to 0.58)	0.001	0.43 (0.25 to 0.74)	0.002	0.52
Roof—corrugated iron§§	No	2176	72	1		1		
	Yes	1201	18	0.44 (0.26 to 0.73)	0.002	0.98 (0.52 to 1.85)	0.944	–

*P value for the variable as a whole for variables with more than one value.
†Single, divorced, widowed or unknown marital status versus married (reference).
‡BMI <18.5 kg/m^2 versus BMI ≥18.5 kg/m^2 (reference).
§Ever alcohol drinker is a person who drinks alcoholic beverages to a notable level at present or in the past versus not.
¶Ever chewed chat is a person who chews chat at present or in the past versus not.
**Ever smoker is a person who smokes cigarette at present or in the past versus not.
††Use of electricity for cooking versus use of kerosene, charcoal, wood, cow dung or agricultural by-products, or no cooking in household (reference).
‡‡House walls made of brick, cement or wood with mud versus house with walls of wood only (reference).
§§Corrugated iron sheet roof versus thatched, leaf or unspecified roof (reference).
BMI, body mass index; GO, government employee; MUAC, middle-upper arm circumference; TB, tuberculosis; TV, television.

This strong collaboration strengthened the quality of the field study. Since we included clear and reproducible exposures in the analyses, the results may be included in meta-analyses and further validated by other studies. The study also had some weaknesses. Information on HIV status was not available and information on HIV testing within the last year was used as a proxy for infection. As smear microscopy was used as the principal test, case numbers could have been underestimated due to the suboptimal sensitivity of this test. GeneXpert expansion to the primary healthcare level in the rural setting could improve case detection. Furthermore, symptom-based screening can miss up to half of PTB b+ cases who present with no or very few symptoms.[13 24] The repeated screening in this study might have helped to reduce the risk of missed cases.

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Compared with a study conducted among persistent coughers 5 years ago (2011–2012) which covered six of the 36 kebeles included in the current study (online supplemental table S2), we found a lower incidence rate for smear-positive TB at 1502/100 000 PY compared with the previous 3912/100 000 PY.[13] The decline is similar to the overall decline in case notification in Dale (10% vs 9%) in this period. During the same period, the regional case notification increased but nationally declined slowly by 3% per year.[5] The expansion and decentralisation of the DOTS strategy to the health posts over this period may have improved service delivery. There were also methodological differences between the previous study and ours, such as participant selection, design and analysis, which restrict the comparison.

We found no other reports of estimation of incidence rates of PTB c+ among persistent coughers in the literature; thus, comparison is limited to the incidence rates of PTB b+. The proportion of PTB b+ among persistent coughers was higher than routine TB control in this study as expected. This may be partly due to more elaborate testing of risk groups; GeneXpert and culture are not routinely available in rural areas. In most low-income countries, GeneXpert testing is limited to larger centres. TB diagnosis at peripheral sites was based mainly on smear microscopy at the time of the study.[13]

Male persistent coughers had greater risks of developing PTB b+ and PTB c+ compared with their female counterparts in this study. Consistent with this finding, gender disparities in TB notification are common in many countries, with more men than women affected, and with longer delay in diagnosis for men.[25] However, a recent study showed a male to female ratio of TB cases close to 1 in a setting similar to that of Dale.[26] Furthermore, other studies have revealed more TB cases among females than among males in Ethiopia,[11 27] the reason could be better access due to community screening. Since 2010, HEWs have implemented community-based active case finding in the study area, increasing the awareness of TB in this population.[4] Thus, previous community care interventions to raise awareness of TB in the population may have contributed to the identification of persistent coughers. A previous study showed varying numbers of PTB in different locations in the study area.[28] The study conducted in the northern and southern parts of Ethiopia suggests that clustering (ie, geographical distribution) is common.[29] Variable programme performances, including reporting completeness, access to diagnosis and population density, are well-known factors contributing to clustering.[30] The national poverty line has been declining since 2004 in the country, but the reduction in rural areas where the poorest segments of the populations are concentrated has been slower. Around 67% of adults in this population group have not completed primary education.[31] In one study conducted in Ethiopia, the risk of developing TB was almost three times greater among individuals with low educational levels as compared with well-educated individuals.[32] Similarly, in our study, individuals with little education had higher rates of PTB b+ and PTB c+ in both crude and adjusted analyses. Access to a separate kitchen reduced the risks of PTB b+ and PTB c+. These findings are consistent with those of a study conducted in India, in which improved housing wall types and separate kitchens were associated with a reduced risk of TB.[33] Poorly built housing is strongly related to poverty[34] and poverty is related to the TB risk.[4] A low MUAC was associated with higher risk of developing PTB, which is no surprise as wasting is a key symptom of TB. However, undernutrition is a known factor for development of TB.[35] HIV is one of the strongest known risk factors for developing TB.[5] The prevalence of HIV in southern region was low at 0.4% among 15–49 year-olds,[36] and HIV coinfection among patients with TB in the study area is much lower than the national level at 0.7%.[37] The region of this study has the lowest prevalence of HIV in the country at 0.4%[36] among 15–49 year-olds. HIV testing was not included in the study as blood sampling was not feasible at community level at that time. Only individuals identified with TB were tested and the remaining participants reported whether they had been HIV tested within the last year or not. We do not know the reason for HIV testing, nor the result, but still found that reporting an HIV test was associated with PTB. Living with a known patient with TB (under treatment) in the household was not associated with PTB. However, living with a persistent cougher (with no proven TB at the baseline) was associated with developing PTB c+ (but not PTB b+) compared with living without coughers in the house. Persistent cough is a non-specific indicator with various underlying aetiologies. It is prevalent among older people regardless of the TB prevalence in this age group. One study showed that almost 12% of older adults in Ethiopia had cough of >2 weeks' duration, but they had a lower risk of TB than young people.[38]

Penalised regression models reduce the variability (inconsistency) of the results but may have bias. In contrast, multivariable regression results tend to have less bias, but greater variability. We analysed both with proportional Cox regression models and lasso regression, with many adjustments the latter may give more reliable results.

CONCLUSIONS

This study showed a high incidence rate of PTB among persistent coughers in Ethiopia. The rate was highest among men and young adults suggesting sustained community transmission. Awareness among healthcare workers about the importance of follow-up of persistent coughers may improve early detection of PTB and reduce transmission in the community. HEWs and community health workers have the capacity to provide TB care where access to diagnostic services, referral, and recording and reporting are in place. Thus, through their training they may be reminded to be particularly aware of symptoms among young adults.

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Contributors BAW, DGD and EH conceived the study. ABB, DGD and GAM implemented the study in the community and collected the data. ABB, DGD, BAW and EH supervised the fieldwork. ABB, BAW and RAW analysed the data and drafted the manuscript. RAW was responsible for the statistical analyses. ABB, MHD, SGH, DGD, EH, RAW and BAW finalised the write-up. All authors reviewed and approved the final version of the manuscript. BAW acts as guarantor of the publication.

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Multidrug-resistant tuberculosis control in Rwanda overcomes a successful clone that causes most disease over a quarter century

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ABSTRACT

Summary background: Multidrug-resistant (MDR) tuberculosis (TB) poses an important challenge in TB management and control. Rifampicin resistance (RR) is a solid surrogate marker of MDR-TB. We investigated the RR-TB clustering rates, bacterial population dynamics to infer transmission dynamics, and the impact of changes to patient management on these dynamics over 27 years in Rwanda.

Methods: We analysed whole genome sequences of a longitudinal collection of nationwide RR-TB isolates. The collection covered three important periods: before programmatic management of MDR-TB (PMDT; 1991–2005), the early PMDT phase (2006–2013), in which rifampicin drug-susceptibility testing (DST) was offered to retreatment patients only, and the consolidated phase (2014–2018), in which all bacteriologically confirmed TB patients had rifampicin DST done mostly via Xpert MTB/RIF assay. We constructed clusters based on a 5 SNP cut-off and resistance conferring SNPs. We used Bayesian modelling for dating and population size estimations, TransPhylo to estimate the number of secondary cases infected by each patient, and multivariable logistic regression to assess predictors of being infected by the dominant clone.

Results: Of 308 baseline RR-TB isolates considered for transmission analysis, the clustering analysis grouped 259 (84.1%) isolates into 13 clusters. Within these clusters, a single dominant clone was discovered containing 213 isolates (82.2% of clustered and 69.1% of all RR-TB), which we named the "Rwanda Rifampicin-Resistant clone" (R3clone). R3clone isolates belonged to Ugandan sub-lineage 4.6.1.2 and its rifampicin and isoniazid resistance were conferred by the Ser450Leu mutation in *rpoB* and Ser315Thr in *katG* genes, respectively. All R3clone isolates had Pro481Thr, a putative compensatory mutation in the *rpoC* gene that likely restored its fitness. The R3clone was estimated to first arise in 1987 and its population size increased exponentially through the 1990s', reaching maximum size (~84%) in early 2000 s', with a declining trend since 2014. Indeed, the highest

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proportion of R3clone (129/157; 82·2%, 95%CI: 75·3–87·8%) occurred between 2000 and 13, declining to 64·4% (95%CI: 55·1-73·0%) from 2014 onward. We showed that patients with R3clone detected after an unsuccessful category 2 treatment were more likely to generate secondary cases than patients with R3clone detected after an unsuccessful category 1 treatment regimen.

Conclusions: RR-TB in Rwanda is largely transmitted. Xpert MTB/RIF assay as first diagnostic test avoids unnecessary rounds of rifampicin-based TB treatment, thus preventing ongoing transmission of the dominant R3clone. As PMDT was intensified and all TB patients accessed rifampicin-resistance testing, the nationwide R3clone burden declined. To our knowledge, our findings provide the first evidence supporting the impact of universal DST on the transmission of RR-TB.

1. Introduction

Multidrug-resistant tuberculosis (MDR-TB; i.e. TB resistant to at least rifampicin and isoniazid) is among the top global challenges in TB control and management [1]. Rifampicin resistance (RR) is a solid surrogate marker of MDR-TB [2]. The direct transmission of resistant strains, also known as primary resistance, is postulated to be the main driver of the MDR-TB epidemic [3,4]. The majority of RR-TB patients remain undiagnosed and untreated, leaving a large number spreading resistant *Mycobacterium tuberculosis* complex (MTBC) strains [5]. Moreover, despite recent advances in treatment, the global average of RR-TB treatment success has stagnated around 57% [6].

Besides direct transmission, acquisition of RR occurs through selection of mutant strains during anti-TB treatment, usually due to inappropriate prescription, stock-outs, inadequate adherence or penetration of drugs [4,7]. The overall higher prevalence of resistance among previously treated TB patients often results from missed primary resistance in combination with acquisition of resistance during the previous treatment episode [8].

To better direct setting-specific programmatic control efforts, understanding the key determinants of RR-TB trends is important given the differences in strategic responses. While acquired resistance can be controlled by supporting adherence to appropriate and optimised therapy [9], the control of primary resistance requires suitable interventions, such as early diagnosis combined with prompt effective therapy [3,10,11], and an appropriate contact tracing strategy. However, RR-TB transmission studies and strain population dynamics in endemic countries are scarce, including in the African Great Lakes Region [12,13].

In Rwanda, the first cases of RR-TB were identified in 1989 [14]. A baseline drug-resistance survey conducted in the early 1990′s showed a low rate of RR-TB: only 1·3% in new and 6·5% among previously treated TB patients [15]. Massive disruptions to the health system and a lack of RR-TB treatment during the 1990′s [14] resulted in increased RR-TB cases. A second drug-resistance survey conducted in 2005 showed a statistically significant increase in RR-TB prevalence: 3·9% in newly diagnosed and 9·4% in previously treated TB patients [16]. Consequently, the programmatic management of RR-TB (PMDT) was initiated in 2005 and integrated as a core component in the national TB control program [14]. The PMDT introduced the standardized long multidrug-resistant (MDR-)TB regimen and the countrywide surveillance of drug-resistant TB. Diagnostic improvements led to shortened delays in initiating MDR-TB treatment and significantly decreased its mortality in Rwanda [17]. Moreover, the prevalence of RR-TB among new TB patients decreased to 1·4% in 2015 [18], likely due to shortened diagnostic and therapeutic delays [17], while no change was observed in previously treated TB patients (10·7%) [18]. However, the contribution of primary versus acquired resistance to these fluctuations in RR-TB prevalence is unknown, making it difficult to evaluate how to further reduce the number of RR-TB cases.

Whole genome sequencing (WGS) has been adopted as the molecular gold standard for outbreak and transmission analysis [19–21] primarily using SNP-based transmission clustering of closely related MTBC strains, allowing for the level of transmission to be measured by assessing the clustering rate. Through a unique longitudinal collection of nationwide RR-TB isolates spanning a quarter century (1991–2018), we used WGS-based molecular epidemiology to estimate the actual contribution of primary resistance in the RR-TB epidemic in Rwanda.

2. Methods

2.1. Study design and population

This longitudinal genome analysis included baseline RR-TB isolates from nationwide patients, collected for diagnostic purposes. Before inception of the PMDT (1991–2005), when drug resistance testing was not yet possible in Rwanda, sputum specimens were sent to the Institute of Tropical Medicine (ITM), Antwerp, Belgium. Afterwards, isolates were sent to ITM for distinct drug-resistance surveys (ie, 1993, 2005, and 2015) [15,16,22], and for quality control. During the early phase of the PMDT, 2006–13, the diagnosis of RR-TB mainly relied on phenotypic drug-susceptibility testing (pDST) on Löwenstein-Jensen medium (LJ), and the GenoType MTBDR*plus* line probe assay (Hain Lifescience, Nehren, Germany) performed in Rwanda, while molecular RR-TB diagnostic assays, mainly Xpert MTB/RIF, were further expanded in the 2014–18 period [17] (Fig. 1).

The sampling fraction and composition for our study depended on available isolates and varied per period (Table 1).

Before 2013, testing for RR-TB was merely undertaken for previously treated patients, thus the majority of isolates during this period were from patients with treatment failure or relapse, sometimes after multiple first-line treatment episodes. Our previous analysis showed that from 2013 onwards, after revising the drug-resistance diagnostic approach particularly the universal DST, most RR-TB was diagnosed among new TB patients, although previously treated patients were still being prioritized for RR-TB testing [17].

2.2. Retrieval of isolates for WGS and data collection

All available isolates registered as RR-TB patients were retrieved from −80 °C freezers and regrown on multiple LJ slants appropriate for genomic DNA extraction. Patients' clinical and demographic data were collected from the national RR-TB databases and/or patients' files and were linked to their specific isolates based on patients' and samples' unique identifiers assigned during diagnosis.

2.3. Whole genome sequencing, assembly and resistance prediction

Regrown cultures were scraped and heat-killed in 150 μL of 0·5 M Tris-EDTA buffer (pH 8.5) followed by genomic DNA extraction using an in-house optimised protocol [23]. WGS was outsourced to FISABIO (Valencia, Spain) and KU Leuven (Leuven, Belgium) sequencing facilities. Genomic libraries were built using the Nextera XT kit and sequenced on an Illumina MiSeq or NextSeq platform with paired end, 150-bp read lengths (California, USA).

For sequence analysis, non-MTBC reads were filtered out from Fastq datasets using Centrifuge v1.0.3 [24]. Reads mapping to any variant in the MTBC were retained. Samples with<95% reads mapped to the MTBC

were excluded from further analysis. Reads were next mapped to the inferred ancestral *M. tuberculosis* genome [25] with MTBseq [24] using default values (filter for variants was set at 5%). TB-Profiler v2.6 [26] was used to define WGS-based resistance profiles with the tbdb mutation database [26] accessed on 13/07/2020. All isolates without a known RR-conferring mutation, and sequence results showing polyclonal TB infection (i.e. multiple strains in one sample) or heteroresistance (i.e. mixed population of drug-resistant mutants and wildtype, when the mutants population is still < 95%) were excluded from analysis.

2.4. Phylogeny and transmission analysis

A SNP alignment was created using MTBseq after which constant site counts for the remainder of the genome was created using a custom Python script. This data was then input to RAxML-NG v0.9.0 [24] to create a Maximum Likelihood phylogeny with a GTR + G + asc substitution model [26], site-repeat optimisation [26], 10 starting trees and 200 bootstrap replicates.

For transmission analysis, custom Python scripts were used to construct clusters from the SNP alignment based on a 5 SNPs cut-off [20,27] using a loose cluster definition (ie, isolates in a cluster differed at most 5 SNPs from at least 1 other isolate in the cluster) [27,28]. MDR-TB transmission clusters were further confirmed by assessing whether the SNPs conferring resistance to rifampicin and isoniazid were the same for all members of a cluster. Moreover, a measurement based on a 12 SNPs cut-off was used to assess the steadiness of the 5 SNPs predefined clusters. All custom python scripts are available at https://github.com/conmeehan/pathophy.

Table 1
Sampling fraction versus transmission cluster (5 SNPs cut-off, same MDR-resistance SNPs).

Year	WHO RR-TB notification, corrected*	Included in analysis (%)	unclustered isolates n (%)	Isolates in cluster n (%)	Isolates in the R3clone n (%)
1991–2005	–	96	21 (21·9)	75 (78·1)	59 (61·5)
2006–2013	479	93 (19·4)	5 (5·4)	88 (94·6)	78 (83·9)
2014	73	12 (16·4)	4 (33·3)	8 (66·7)	6 (50·0)
2015	88	31 (35·2)	6 (19·3)	25 (80·7)	19 (61·3)
2016	69	26 (37·7)	4 (15·4)	22 (84·6)	22 (84·6)
2017/ 2018[#]	58	50 (86·2%)	9 (18·0)	41 (82·0)	29 (59·2)
Total[¥]	767	212 (27.6)	28 (13.2)	184 (86.8)	154 (72.6)

*Based on a recent finding, only 14·3% of RR on Xpert with a very low bacterial load was confirmed as rifampicin-resistant (RR); [#]including Jan-March (2018/03) with only 9 confirmed RR patients being registered in this period; [¥]Exclude 96 isolates collected between 1991 and 2005 as no notification data for that period. MDR = multidrug resistant; SNPs = single nucleotide polymorphisms.

2.5. Estimation of epidemiological parameters using Bayesian phylogenetics

Dating and population size estimations (i.e. an independent measurement of the bacterial population burden which is less affected by sampling fraction differences) were undertaken using BEAST v1.10.4 [29]. The SNP alignment was imported into BEAUti and tips were dated based on the date of isolation. Where only the year of isolation was known, the date was set to January 1st and the uncertainty was set to 1

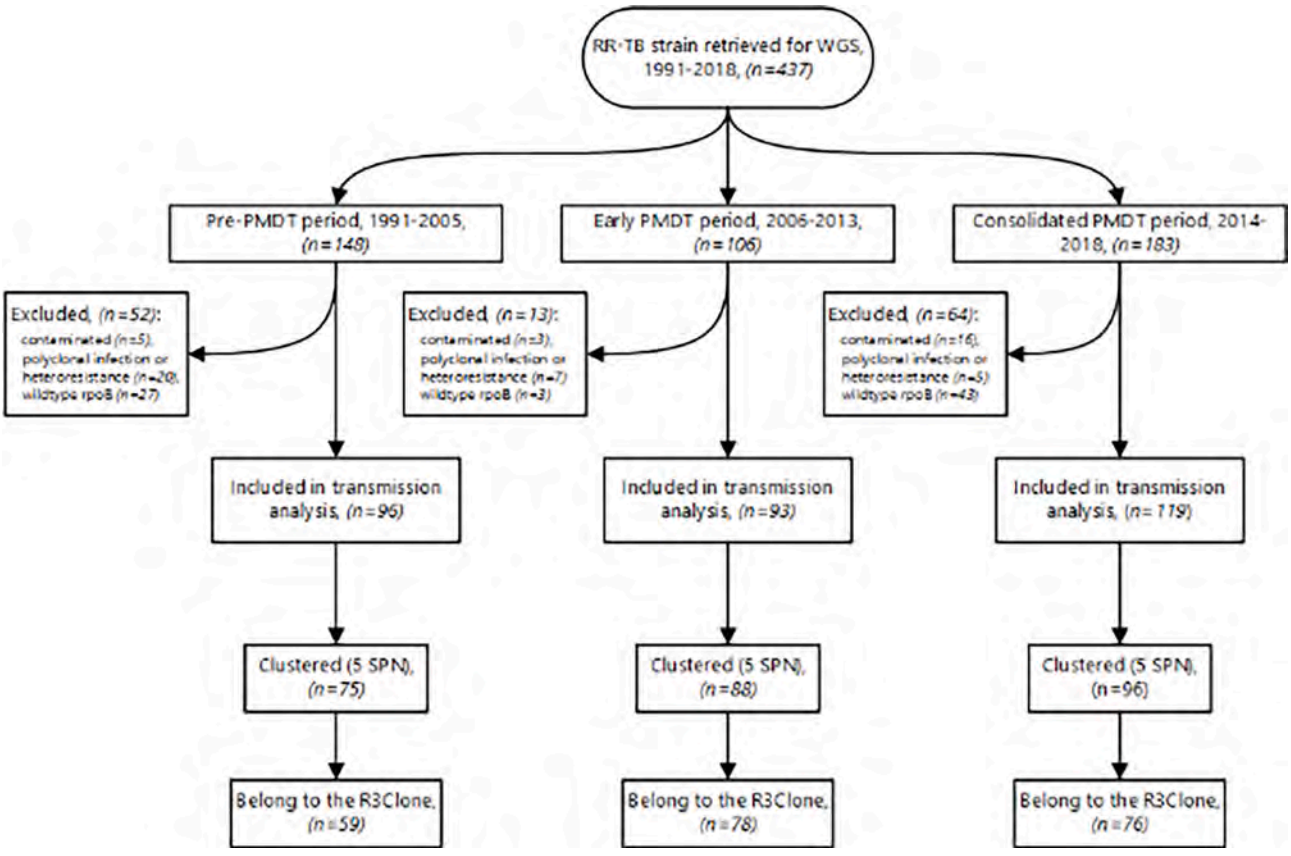

Fig. 1. Study population and clustering results.

to allow the Markov chain Monte Carlo (MCMC) process to better incorporate this uncertainty in the final dating estimates. A GTR + G site model was used in conjunction with an uncorrelated relaxed clock [20] with lognormal distribution and a Skyride [20] with time-aware smoothing tree prior. The ucld.mean was set to lognormal with a mean in real space and a starting value of 0·0005 as has been shown to be appropriate for Lineage 4 isolates [27]. The XML document was then manually edited to add the constant site count for each base as an ascertainment bias correction.

BEAST was run in four separate times with an MCMC chain length of 100 M sampling every 10,000 steps. Trees were combined between runs using LogCombiner with a 50% burn-in per run. TreeAnnotator was used to create a maximum clade credibility tree with mean node heights. The Skyride plot was created using the Tracer v1.7.1 [20] demographic reconstruction analysis with default options with the age set to 2018.

2.6. Estimation of secondary cases

To estimate the secondary cases generated from a single isolate, we used a subset of 93 strains from the dominant clone which had detailed data on previous TB treatment history. We used a Bayesian approach to model the influence of previous treatment history on transmission dynamics, specifically the number of secondary cases infected by a primary case. The TreeAnnotator maximum clade credibility tree was input to the R package TransPhylo v1.4.4 [30] to estimate secondary case contact rates for each isolate. All zero length branches were set to $1*10^{-11}$ and the last sampled date set to 2018 based on the sampling dates of the isolates. The following parameters were then used for the TransPhylo run, based on those used by Didelot *et al.* on their MTBC outbreak dataset [30]: w.shape = 1.3; w.scale = 1/0.3; ws/shape = 1.1; ws.scale = 1/0.4; mcmcIterations = 20 M; thinning = 2000; Convergence was confirmed using coda v0.19.4 [31]. After a burn-in of 50%, an approximate per-individual average number of transmissions (offspring) was calculated from the remaining 50% of MCMC samples. Isolates were then grouped by patient's previous TB treatment history such as new TB (New), failure or relapse to anti-TB category 1 (Cat1), and failure or relapse to anti-TB category 2 (Cat2, i.e. first-line re-treatment regimen for previously treated TB patients). To test for significance in secondary case numbers between previous history on TB treatment groups (New, Cat 1, Cat 2), the corresponding per-individual average number of transmissions were compared using a three-way ANOVA with a Tukey's Honest Significant Differences post-hoc test to determine which groups differed in secondary case contact rates. The Cohen's d effect size was then calculated pairwise between the groups (New, Cat1 and Cat2) using the effsize package [32]. Boxplots of the secondary case counts were created using ggplot2 [33].

2.7. Metadata statistical analysis

The Pearson's chi-square and Fisher's exact tests were used to test for associations between the predominant clone (R3clone, see Results section) and potential predictors. Multivariable logistic regression was used to assess predictors of being infected by the R3clone. STATA version 14·2 (College Station, TX: STATA Corp) was used for metadata analysis.

2.8. Ethics

The study protocol was approved by the Rwanda National Ethical committee, Kigali, Rwanda (IRB 00001497 of IORG0001100; Ref No·0069/RNEC/2017), the Institutional Review Board of the Institute of Tropical Medicine, Antwerp, Belgium (IRB/AB/AC/062; Ref No.1208/17; 19/03/2018), and the Ethics Committee of the Antwerp University Hospital, Universitair Ziekenhuis Antwerpen Ethische Commissie, Antwerp, Belgium (REG No.B300201836458; 14/05/2018).

3. Results

3.1. MTBC isolates and patient characteristics

Overall, 437 individual patients' MTBC isolates registered as RR-TB were retrieved and sequenced. Of the 437 isolates, 56 were excluded from analysis, either due to poor sequence quality (n = 24) or sequence results demonstrating mixed populations (polyclonal TB infection or heteroresistance) (n = 32) (Fig. 1). In addition, 73 were excluded as no known RR-conferring mutation was identified by WGS. Most of these isolates had a wildtype *rpoB* gene sequence, and were initially diagnosed via Xpert MTB/RIF assay, thus likely explained by false RR associated with low bacterial load samples tested on Xpert MTB/RIF [34]. Of 308 isolates considered for the transmission analysis, 96 (31·2%) were isolated between 1991 and 2005 (before starting the PMDT), 93 (30·2%) were isolated between 2006 and 2013 (in the early PMDT phase, prior to expanding utilization of rapid molecular RR-TB diagnostic assays), and 119 (38·6%) were isolated between 2014 and 2018 (after expanding MDR/RR-TB molecular diagnostic assays) [17] (Fig. 1).

The sex was documented for 251 of 308 patients. Most were male (151, 60·2%). The median age was 34 years (interquartile range (IQR): 27–44 years). HIV-coinfection status was documented for 164 (53·3%), of whom 77 (47·0%) were HIV-coinfected. Of 181 with data on TB treatment history, 101 (55·8%) were previously treated TB patients, while 80 (44·2%) were new TB patients. All new patients were diagnosed since 2013, after implementing universal DST, the majority (59; 73.8%) using the Xpert MTB/RIF assay.

SNP-based lineage assignment [35] classified strains as Ugandan sub-lineage 4.6.1.2 (240, 79·5%), Ugandan sub-lineage 4.6.1.1 (18, 6·0%), and lineages 4.3 (22, 7·2%), 4.7 (20, 6·5%), 4.4 (1, 0·3%), and 4.8 (1, 0·3%), while four (1·3%) were lineage 3.1.1 (Delhi-CAS), one (0·3%) was lineage 2.2.1 (Beijing strain), and for the first time a single L8 strain was documented from this dataset [36] (S1 Table).

Of the 308 RR isolates, 292 (94·8%) had concomitant resistance to isoniazid, thus were MDR-TB. The majority (274, 89·0%) of RR was due to the Ser450Leu *rpoB* mutation. Three isolates (all diagnosed before 2005) harboured the *rpoB* gene Val170Phe mutation, a RR-conferring mutation outside the rifampicin-resistance determining region (RRDR).

The majority (259, 88·7%) of resistance to isoniazid was due to the Ser315Thr *katG* mutation, while only two isolates had Ser94Ala *inhA*, a rare isoniazid resistance conferring mutation (Supplementary Table 1). No double mutants (*katG* and *inhA*), conferring the highest levels of isoniazid resistance, were seen. Two isolates had fluoroquinolone resistance-conferring mutations in the *gyrA* gene (Asp94Gly and Asp94Ala), but neither showed genotypic or phenotypic resistance to second-line injectables. There was no mutation known to be associated with novel or repurposed second-line MDR-TB drugs, such as bedaquiline, linezolid, delamanid and clofazimine [37].

3.2. Transmission clusters

Using a 5 SNP cut-off and loose cluster definition, also considering rifampicin and isoniazid resistance-conferring SNPs, grouped 259 (84·1%) isolates into 13 clusters (Table 1; Fig. 2).

Among 49 unclustered isolates (i.e., unclustered), the majority (37; 75·5%) were from previously treated TB patients, while 12 (24.5%) were from new TB patients. Of the 259 isolates in clusters, 213 (82·2%) belonged to a single dominant clone within Ugandan sub-lineage 4.6.1.2 that we named the "Rwanda rifampicin-resistant clone (R3clone)" (Fig. 2). The remaining 12 clusters had between 2 and 11 isolates each. By increasing the clustering cut-off to 12 SNPs, the R3clone cluster increased by only 17 isolates (S2 Table). Subsequent analyses are based on the 5 SNP cut-off defined clusters.

In the R3clone, resistance to rifampicin and isoniazid was conferred by Ser450Leu *rpoB* and Ser315Thr *katG* respectively. Moreover, all isolates of the R3clone, as early as 1991, harboured a putative

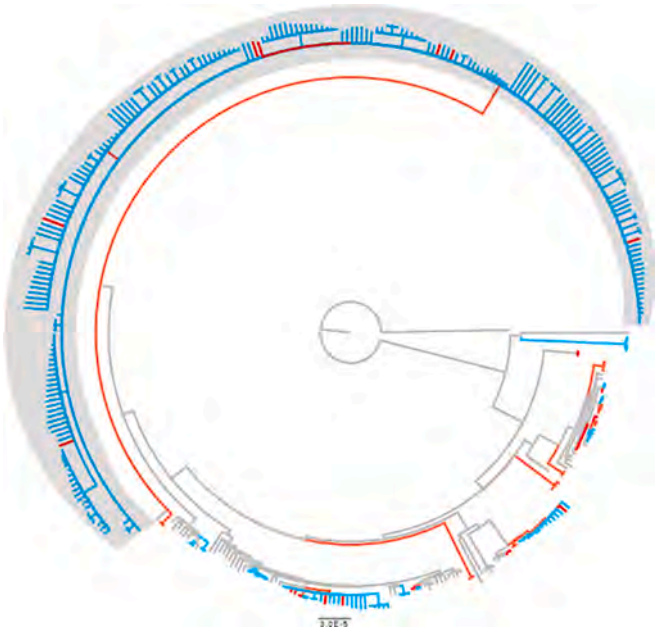

Fig. 2. Phylogenetic tree of RR-TB strains in Rwanda. The red leaves show clusters by 12SNP and blue by 5 SNP cut-off. The R3clone is shown in grey box. All branches with bootstrap support below 70% were collapsed into polytomies.

compensatory mutation Pro481Thr in the *rpoC* gene. The R3clone is resistant to ethambutol (EmbB Met 306Val or His1002Arg) and all except five were resistant to pyrazinamide (*pncA* Met175Ile, His43Pro, Gln141pro or Gln10Arg). Thus, most R3clone isolates were resistant to all first-line TB drugs. The mutation at position 80 in *gyrA* (Thr80Ala) was present in all R3clone isolates.

3.3. R3clone population dynamics

Of the 96 RR-TB isolates from the pre-PMDT period, 59 (61·5%, 95% CI: 51.0–71.2) belonged to the R3clone, increasing to 78 of 93 isolates (83·9%, 95%CI: 74.8–90.7) during the early PMDT phase, followed by a decline to 76/119 (63·9%, 95%CI: 54.6–72.5) in the consolidated PMDT period.

In a multivariable analysis, the odds of being affected by R3clone was significantly higher in the early PMDT phase (adjusted odds ratio [aOR] 2.5, 95%CI 1.1–5.6). Female patients had a significantly higher odds of being affected by the R3clone (aOR 2·6, 95%CI 1·2-5·9), while the odds of having R3clone TB was not significantly different between age groups, Kigali city versus other provinces in Rwanda or HIV-positive versus HIV-negative(Table 2).

The Bayesian phylogeny of the R3clone estimated that the strain first arose in 1987 (95% HDP: 1981–1991) (Fig. 3), with a steady exponential increase in population size through the 1990 s', turning into a constant population size in the early 2000 s', followed by a declining trend starting in 2014 (Fig. 3).

The estimation of secondary case contact rates grouped by previous TB treatment history, revealed that isolates from unsuccessful treatment on Cat2 treatment were more likely to have linked offspring (i.e. more transmissions) than those isolated from unsuccessful treatment Cat1 or new patients (p-value < 0·0001; Cohen's d effect size: large; Fig. 4). There was no significant difference observed between isolates from new versus Cat1 patients and Cohen's d effect size was negligible.

4. Discussion

Our data showed that RR-TB disease in Rwanda is largely driven by a single dominant "R3clone", estimated to have arisen in 1987, only four years after the introduction of rifampicin into the African Great Lakes region [36]. The estimated bacterial population size of the R3clone increased until 'universal DST' became implemented. To the best of our knowledge, this is the first molecular evidence to demonstrate a clear association between RR-TB transmission and delays in starting appropriate treatment. We showed that patients in Cat 2 with the R3clone were more likely to generate secondary cases. Such patients likely with primary RR-TB, received multiple rounds of ineffective first-line anti-TB treatment before being diagnosed correctly, while they continued to spread RR-TB strains. The specific genetic features of the R3clone, such as full resistance to first-line drugs, the combination of the Ser450Leu *rpoB* gene mutation, which has the smallest associated fitness cost of all RR-conferring *rpoB* mutants [38], - and the Pro481Thr *rpoC* putative fitness compensating mutation [39,40], present since the emergence of the clone, enabled the ongoing propagation of the R3clone over more

Table 2
Factors associated with R3clone (5 SNP cut-off, same MDR-resistance SNP).

		Total n	R3 clone n (%)	Univariate analyses OR (95% CI)	Multivariable analyses aOR (95% CI)
Total	n	308	213 (69·2)		
Sex n = 251	Male	151	90 (59·6)	reference	reference
	Female	100	78 (78·0)	2·4 (1·4-4·2)	2·6(1.2-5·9)
	Unknown	57	57 (18·5)		
Age[years]	<30	62	46 (74·2)	2·3 (0·8-6·8)	1·6 (0·5-5·4)
	[30–44]	75	54 (72·0)	2·1 (0·7-5·9)	1·6 (0·5-5·0)
	[45–54]	25	18 (72·0)	2·1 (0·6-7·4)	1·5 (0·4-6·0)
	>54	19	10 (52·6)	reference	reference
	Unknown	127	85 (66·9)		–
TB treatment history*	New	80	46 (57·5)	reference	
	Previously treated	101	74 (73·3)	1·5 (0·8-3·0)	
	Unknown	127	93 (73·2)		
HIV	Negative	86	65 (76·5)	reference	
	Positive	78	50 (64·9)	0·6(0·3-1·2)	
	Unknown	144	98 (68·1)		
Resident in Kigali city	Yes	83	66 (79·5)	2·1 (1·1-4·2)	1·8 (0·9-3·6)
	No	93	60 (64·5)	reference	reference
	Unknown	132	87 (65·9)		
Period of RR diagnosis	Period1 (1991–2005)	96	59 (61·5)	reference	reference
	Period 2 (2006–2013)	93	78 (83·9)	3·3 (1·6-6·5)	2·5 (1·1-5·6)
	Period 3 (2014–2018)	119	76 (63·9)	1·1 (0·6-1·9)	1

RR = rifampicin-resistant; MDR = multidrug resistant; SNP = single nucleotide polymorphism, *TB treatment history had collinearity with the period of rifampicin-resistant tuberculosis diagnosis, as before 2013, testing for RR-TB was merely undertaken for previously treated patients.

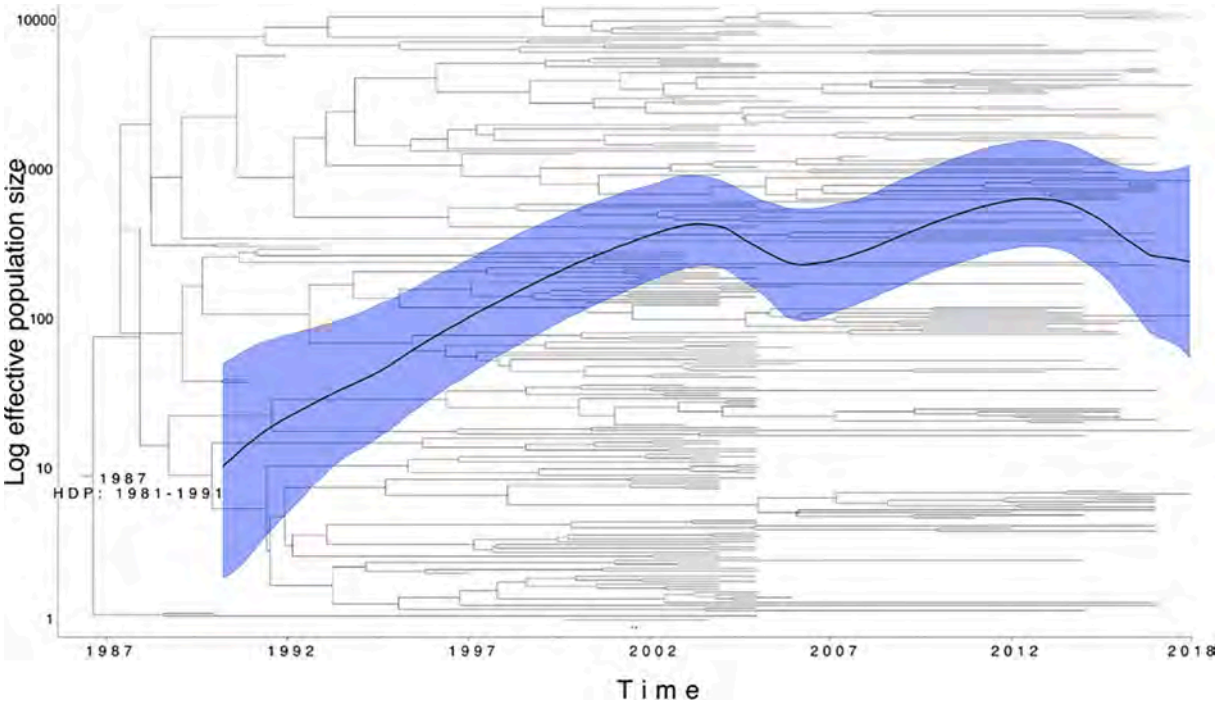

Fig. 3. Bayesian phylogenetic tree of R3clone and associated Skyride plot. Date of emergence of the clone is indicated at the root node. The mean estimate of population size changes is indicated by the solid black line with the High Posterior Density Interval of this estimate in the shaded blue area. The bush-like topology suggests continuous spread as opposed to consecutive single transmission events.

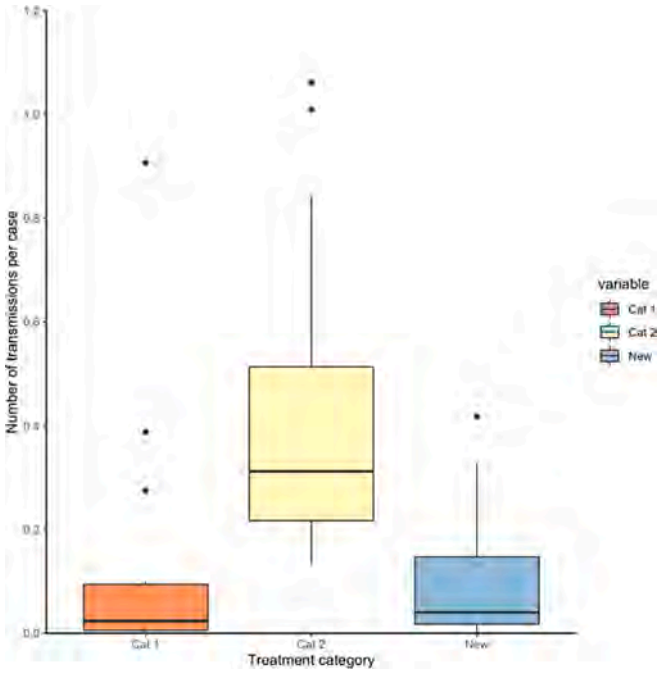

Fig. 4. Number of secondary transmissions per case for 93 selected R3clone isolates grouped by tuberculosis (TB) treatment history. Cat 1: patients diagnosed with rifampicin-resistant TB after failure or relapse to category 1 anti-TB treatment; Cat 2: patients diagnosed with rifampicin-resistant TB after failure or relapse to category 2 anti-TB treatment.

than a quarter century, especially during the early years when rifampicin DST was only offered to retreatment patients. This finding corroborates the recent global genomic analysis that showed decades old resistance likely associated with ongoing transmission by fit clones in most countries [41].

We showed that the nationwide R3clone bacterial population increased in the 1990 s' through the 2000 s', explaining much of the increased prevalence of RR-TB among new TB patients observed in the 2005 drug-resistance survey [15,16]. This was driven by the weak health system during the genocide period [14]. The programmatic efforts that resulted in a drastically shortened diagnostic and treatment delay [17] interrupted the active propagation of this R3clone pathogen population growth. Although it seems logical that RR-TB transmission could be interrupted by swift diagnosis and appropriate treatment, so far there was no such public health evidence to support this aspect of universal DST. Similar to a recent analysis that showed association of health-care delays with an increased rate of secondary TB among dependents [42], Cat 2 patients had several years likely with primary RR-TB before being diagnosed and switched to appropriate MDR-TB treatment, while expected that many died before being diagnosed. This finding underscores that rapid universal DST may interrupt RR-TB transmission, as observed in Rwanda where new patients became eligible for rapid molecular rifampicin DST since 2013 [14].

Our findings confirm what a previous modelling study posited: transmission accounts for a median of 96% of all incident MDR-TB [3], including 61% in previously-treated patients [3]. It is also consistent with the findings in high MDR-TB endemic settings, such as the former Soviet Union, where the most frequent and fit clones harbour compensatory mutations in the *rpoA* and/or *rpoC* genes [43,44]. Novel approaches that identify the main RR-TB transmission hotspots, followed by well-designed targeted active case finding, can further help to decrease RR-TB in Rwanda and be an example of such programmes for other TB endemic countries.

The predominance of the R3clone population as the driver of the RR-TB epidemic might not be unique for Rwanda, and rather reflect a regional problem. However, limited WGS data from the Great Lakes region is available, and no R3clone was identified among 32 RR-TB genomes from the Ugandan isolates collected during a drug-resistance survey conducted between 2008 and 2011 [13].

Consistent with the routine pDST-based drug-resistance surveillance [45], as well as the 2015 drug-resistance survey [17], only two isolates

among successfully sequenced RR-TB isolates had a mutation conferring resistance to fluoroquinolones. Overall, the very low rate of fluoroquinolone resistance could partly explain the high treatment success in Rwanda observed with the two WHO-endorsed long and short MDR-TB regimens [17,46]. While a combination of Thr80Ala and Ala90Gly mutations in the *gyrA* gene was shown to induce hyper-susceptibility to fluoroquinolones [47], the R3clone isolates only had theThr80Ala mutation, typical for the lineage 4.6.2, which has been associated with a slightly increased minimal inhibitory concentration compared to wild-type *gyrA* strains [47].

Our study has important strengths. This analysis included strains isolated over 27 years, including the first RR-TB diagnosed in Rwanda, thus representing the reality of the RR-TB population dynamics in Rwanda. Moreover, this is the first study analysing RR-TB transmission using WGS within the Great Lakes region. The finding of transmission driving the RR-TB epidemic in Rwanda is important to neighbouring countries to conduct similar molecular epidemiological analyses to guide regional RR-TB control efforts.

This analysis also had limitations. Some selection bias may have occurred, as the RR-TB detection rate increased over time as better diagnostic tools became available and accessible. Moreover, the sampling fraction depended on availability of isolates (e.g. in 2016, the proportion of R3clone represented almost 85%, as the analysis included only 26 out of 69 RR-TB notified). <50% of all RR-TB cases notified to the WHO were included for 1991–2013, while 86% of isolates were included for 2014–2018. However, the Bayesian analysis used to estimate the size of the entire circulating bacterial population is robust to low sampling fractions due to the use of a coalescent process. To assess occurrence of secondary cases, we used only 93 (43.7%) R3clone strains which had detailed patient information. A larger dataset would allow for differentiation between new and Cat 1 patients. The samples were collected from different timepoints with improved conditions of life in later years when most new cases were diagnosed. Moreover, the time between sampling and occurrence of potential secondary cases might be shorter for recent cases. Finally, this analysis did not include rifampicin-susceptible TB isolates. While the large contribution of primary resistance can be inferred based on the 5-SNPs clustering and the fact of having R3clone in new TB patients, the exact contribution of acquired resistance cannot be fully determined. Data on socio-economic factors were not collected, while living conditions may have changed in the study period.

In conclusion, transmission mostly driven by R3clone has been the determinant of the RR-TB epidemic in Rwanda. Improved RR-TB patient management, resulting in shortened diagnostic and treatment delays, resulted in a reduction of RR-TB transmission. For further enhanced control, in addition to rapid identification of RR-TB patients followed by effective treatment, well-designed and targeted interventions will be important.

CRediT authorship contribution statement

Jean Claude S. Ngabonziza: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Visualization, Funding acquisition. **Leen Rigouts:** Conceptualization, Methodology, Investigation, Data curation, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Gabriela Torrea:** Conceptualization, Investigation, Writing – review & editing. **Tom Decroo:** Methodology, Investigation, Writing – review & editing. **Eliane Kamanzi:** Investigation, Resources, Data curation. **Pauline Lempens:** Investigation. **Aniceth Rucogoza:** Investigation, Resources, Data curation. **Yves M. Habimana:** Investigation, Resources, Data curation. **Lies Laenen:** Investigation, Data curation. **Belamo E. Niyigena:** Investigation, Resources, Data curation. **Cécile Uwizeye:** Investigation, Data curation. **Bertin Ushizimpumu:** Investigation, Resources, Data curation. **Wim Mulders:** Formal analysis, Investigation, Data curation. **Emil Ivan:** Investigation, Resources, Data curation, Writing – review & editing. **Oren Tzfadia:** Investigation. **Claude Mambo Muvunyi:** Investigation, Data curation. **Patrick Migambi:** Investigation, Resources, Data curation. **Emmanuel Andre:** Investigation, Data curation. **Jean Baptiste Mazarati:** Investigation, Resources. **Dissou Affolabi:** Investigation, Funding acquisition. **Alaine N. Umubyeyi:** Investigation, Resources, Data curation. **Sabin Nsanzimana:** Investigation, Resources, Data curation. **Françoise Portaels:** Investigation, Data curation. **Michel Gasana:** Investigation, Resources, Data curation. **Bouke C. de Jong:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Conor J. Meehan:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data sharing

Raw read data for all WGS samples can be retrieved from the ENA using the accession code PRJEB43270.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jctube.2022.100299.

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Title page

Pre-extensively drug-resistant tuberculosis among multidrug-resistant tuberculosis patients in Ethiopia: a laboratory-based surveillance study

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ABSTRACT

Background: The rise of drug-resistant tuberculosis (DR-TB) has presented a substantial challenge to the national tuberculosis (TB) control program. Understanding the epidemiology of pre-extensively drug-resistant tuberculosis (pre-XDR-TB) could help clinicians to adapt MDR-TB treatment regimens at an earlier stage. This study aimed to assess second-line anti-TB drug resistance among MDR-TB patients in Ethiopia using routine laboratory-based data.

Methods: Laboratory-based cross-sectional data were collected from the national TB reference laboratory and seven regional tuberculosis culture laboratories in Ethiopia from July 2019 to March 2022. The required data, such as drug-susceptibility testing (DST) results and sociodemographics, were collected on a structured checklist from laboratory registration books and electronic databases. Data were entered into a Microsoft Excel spreadsheet and analyzed using SPSS version 23. Descriptive statistics were performed to show the distribution and magnitude of drug resistance.

Results: Second-line drugs (SLDs) susceptibility testing was performed for 644 MDR isolates, of which 19 (3%) were found to be pre-XDR-TB cases. Of the total MDR-TB isolates, 19 (3%) were resistant to at least one fluoroquinolone drug, while 11 (1.7%) were resistant to at least one injectable second-line drug. Of the 644 MDR-TB isolates, 1.9% (5/261) pre-XDR were from new MDR-TB cases, while 3.7% (14/383) were from previously treated MDR-TB patients. The most frequently identified mutations, based on MTBDR*sl* results, were in codon *A90V* of the *gyrA* gene (77.3%) and *A1401G* of the *rrs* gene (45.5%).

Conclusion: The overall prevalence of pre-XDR-TB in Ethiopia is considerable. The majority of SLD resistance mutations were in the *gyrA* gene at position *A90V*. Modern, rapid DST is necessary to enable identification of pre-XDR-TB and XDR-TB in supporting proper regimen administration for patients.

Introduction

Multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) are a global public health problem. MDR-TB is a mycobacterial strain that is resistant to at least two first-line antibiotics, such as rifampicin (RIF) and isoniazid (INH) (WHO, 2019a). Pre-extensively drug-resistant tuberculosis (Pre-XDR TB) also refers to the *Mycobacterium tuberculosis* (MTB) strain that meets the criteria for multidrug-resistant or rifampicin-resistant (RR) tuberculosis and resistance to fluoroquinolones (Shibabaw et al., 2020). XDR-TB is defined as a MTB strain that is MDR/RR and resistant to one fluoroquinolone (levofloxacin, moxifloxacin) and at least one additional group-A medication (bedaquiline, linezolid) (WHO, 2021a; Yao et al., 2021).

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A recent estimation indicated that 3.3% of MDR/RR-TB cases worldwide occurred among new TB cases and 17.7% among previously treated cases in 2019 (WHO, 2020). Twenty per cent of MDR-TB patients developed resistance to one of the fluoroquinolones in 2020 (WHO, 2021). In 2018, a considerable proportion (6.2%) of MDR-TB cases worldwide developed XDR-TB (WHO, 2019b).

Ethiopia is one of the 30 high MDR/RR-TB and TB/HIV burden countries (WHO, 2021b). In 2019, the incidence of MDR/RR-TB in Ethiopia was 0.71% among new TB cases and 12% among previously treated cases (WHO, 2020). Moreover, four XDR-TB cases were reported in Ethiopia in 2017 and 2018 (WHO, 2018; WHO, 2019b).

Routine laboratory-based drug-resistance surveillance is important and cost-effective in providing up-to-date information on the prevalence and distribution of drug-resistant tuberculosis. It is also useful in showing the effectiveness of current TB control programs and in designing a targeted response to the emerging threat of new DR-TB, which could limit drug options (WHO, 2015). Therefore, our study aimed to assess second-line anti-TB drug resistance among MDR-TB patients in Ethiopia using routine laboratory-based data.

Materials and methods

Study design and area

A laboratory-based cross-sectional study was conducted in eight TB culture and drug-susceptibility testing (DST) laboratories in Ethiopia from July 2019 to March 2022. Data were collected retrospectively from the Ethiopian Public Health Institute National TB Reference Laboratory (NTRL) and seven regional TB culture and DST laboratories.

There are 10 TB culture and DST laboratories in Ethiopia (nine regional and one national referral). Molecular diagnostic approaches (first-line and second-line line-probe assays) are used in all TB culture and DST laboratories (Dagne et al., 2021). For both RR and MDR TB cases, a second-line line-probe assay was performed before or within 1 week of treatment initiation with the DR-TB regimen (WHO, 2019b). All verified MDR/RR-TB isolates from patients with pulmonary TB (PTB) or extrapulmonary TB (EPTB) were included in the study. SLD resistance data were obtained using a second-line LPA (MTBDR*sl*) genotypic DST method.

Sampling technique

All consecutive MDR/RR-TB isolates in the selected TB culture and DST laboratories and second-line probe assay (MTBDR*sl*) tests conducted during the study period were included in the study.

Laboratory testing

All laboratory procedures were completed in TB laboratories with quality assurance based on WHO guidelines and the national TB laboratory algorithm (WHO, 2019a; FMoH, 2018). One national TB reference laboratory and seven regional laboratories used solid media (Lowenstein-Jensen) and a fluorometric BACTEC MGIT 960 to detect MTB. Additionally, GenoType MTBDR*sl* (Hain Lifescience GmbH, Nehren, Germany) testing was performed as per the WHO recommendations to identify SLD-resistant TB. Quality assurance for culture and DST was performed regularly by the National TB Reference Laboratory for all regional TB culture laboratories, and demonstrated consistent proficiency.

Data analysis

The data were entered into a Microsoft Excel spreadsheet and exported to the SPSS version 23 statistical package for analysis. The distributions of second-line anti-tuberculosis resistance profiles among patients with different demographic and clinical profiles were compared, and the prevalence of anti-TB drug resistance among MDR-TB patients was analyzed.

Table 1
Baseline demographic and clinical characteristics of MDR/RR-TB patients

Characteristics	Category	Frequency	Percentage
Sex	Male	400	62.1%
	Female	244	38.9%
Age group, years	< 15	43	6.7%
	≥ 15	601	93.3%
HIV status	Positive	60	9.3%
	Negative	233	36.2%
	Unknown	351	54.5%
Patient category	New case	261	40.5%
	Previously treated case	383	59.5%

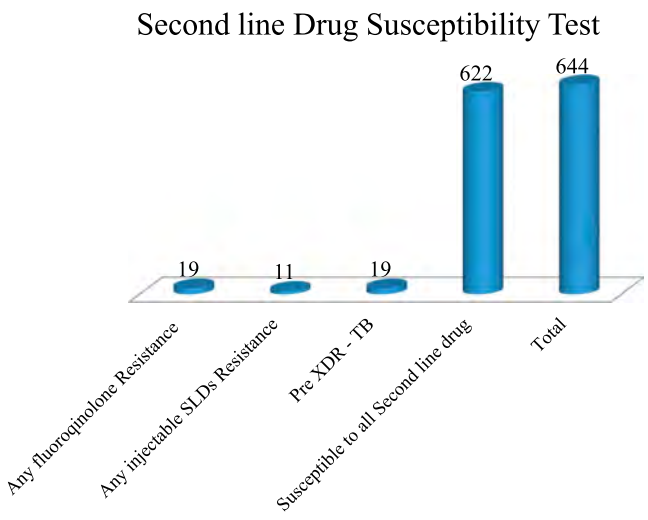

Figure 1. Second-line anti-TB drug resistance among MDR-TB isolates tested.

Results

Patient characteristics

Table 1 shows the participants' basic characteristics. Of the 644 MDR-TB isolates that underwent second-line DST, 261 (40.5%) were new, while 383 (59.5%) were previously treated for MDR-TB. Most of the patients (601; 93.3%) were older than 15 years. Male sex was predominant (400; 62.1%), and HIV coinfections occurred in 60 (9.3%) cases. The mean (± SD) age of the participants was 29 ± 11.8 years.

Second-line anti-tuberculosis resistance profiles

Of the 644 MDR-TB isolates for which SLD susceptibility testing was performed, 622 (96.6%) MTB strains were susceptible to all SLDs, whereas 19 (3%) were resistant to at least one fluoroquinolone (i.e. pre-XDR-TB) and 11 (1.7%) were resistant to at least one injectable SLD (Figure 1).

Table 2 shows the distribution of pre-XDR-TB according to the participants' characteristics. Among 261 new MDR-TB cases, five (1.9%) had pre-XDR-TB, while of the 383 previously treated MDR-TB cases, 3.7% had pre-XDR-TB.

Mutational profiling by MTBDRsl assay

Of the total 22 isolates that were resistant to SLD, 17 had mutations in the *gyrA* gene and 11 had mutations in the *rrs* gene. Of the 22 isolates that had *gyrA* gene mutation, 17 (77.3%) had a mutation at codon *A90V*,

Table 2
Distribution of pre-XDR-TB patients

Characteristics	Category	Frequency	Percentage	χ^2	*p*-value	Total
Sex	Male	14	3.5%	0.341	0.559	400
	Female	5	2.1%			244
Age group	< 15	–	–	0.755	0.385	43
	≥ 15	19	3.2%			601
Treatment history	New	5	1.9%	1.133	0.287	261
	Previously treated	14	3.7%			383
HIV status	Positive	5	8.3%	19.01	< 0.01	60
	Negative	11	4.7%			233
	Unknown	3	0.8%			351

Table 3
Mutation characteristics for second-line drug-resistant TB cases

Gene	Resistance-associated probes	Codon mutation	SLD-resistance pattern	Number of isolates (n = 22)	Proportion (%)
gyrA	Δ*WT2* + *MUT1*	*A90V*	OFL; LFX	9	40.9
gyrA	Δ*WT3* + *MUT1*	*A90V*	OFL; LFX	2	9.1
gyrA	Δ*WT1*	*D94N/D94Y*	OFL; LFX	1	4.5
gyrA and *rrs*	Δ*WT3* and Δ*WT1* + *MUT1*	*S91P* and *A1401G*	OFL; LFX; KAN; AM; CAP	1	4.5
gyrA and *rrs*	Δ*WT2* + *MUT1* and Δ*WT1* + *MUT1*	*A90V*, *A1401G*	OFL; LFX; KAN; AM; CAP	6	27.3
rrs	Δ*WT1* + *MUT1*	*A1401G*	KAN; AM; CAP	3	13.6
rrs	Δ*WT2* + *MUT2*	*G1484T*	KAN; AM; CAP	1	4.5

AM— amikacin, CAP — capromycin, KAN — kanamycin, LFX — levofloxacin, MUT — mutant, OFL — ofloxacin, WT — wild type

one (4.5%) at codon *D94N/D94Y*, and one (4.5%) at codon *S91P*. Of those isolates with *rrs* gene mutations, 10 (45.5%) had a mutation at codon *A1401G* and 1 (4.5%) at codon *G1484T* (Table 3).

Discussion

The present study aimed to analyze second-line DST data for 644 MDR/RR-TB patients tested during the study period in one NTRL and seven regional TB culture laboratories in Ethiopia. Of 644 MDR/RR-TB isolates 19 (3%) were resistant at least to one FQ and thus considered as pre-XDR-TB. Eleven isolates (1.7%) were also resistant to at least one injectable drug. Among 261 new MDR-TB cases, 1.9% were shown to be pre-XDR-TB, and of 383 previously treated MDR-TB cases, 3.7% had pre-XDR-TB. According to the MTBDR*sl* results, the most frequently observed mutations were in codon *A90V* of the *gyrA* gene (77.3%) and in codon *A1401G* of the *rrs* gene (45.5%).

Our results showed a 3% prevalence of pre-XDR-TB. Compared with our findings, pre-XDR-TB has been found to be more common in India (56%), China (34%), Bangladesh (16%), Pakistan (24%), South Africa (17%), and Nigeria (17%), according to many studies (Adwani et al., 2016; Daniel et al., 2013; Mlambo et al., 2008; Tasnim et al., 2018; Yuan et al., 2012). Additionally, a study from India showed higher prevalences of pre-XDR-TB (49.4%) and XDR-TB (11.4%) than our findings (Singhal et al., 2016). A study published in France showed higher prevalences of pre-XDR-TB (20.0%) and XDR-TB (7%) than our findings (Guglielmetti et al., 2018). Our study found a lower prevalence of pre-XDR-TB among MDR-TB cases.

Out of 644 MDR-TB patient isolates, 19 (3%) cases were found to have pre-XDR-TB. The study found that 1.9% of the pre-XDR-TB isolates were new TB cases, while 3.7% of the pre-XDR-TB isolates had previously been treated with first-line drugs for active TB disease. The results of our study were comparable to those of an earlier investigation conducted in Ethiopia, which looked at newly diagnosed and previously treated pre-XDR-TB cases in MDR-TB patients (Shibabaw et al., 2020).

The percentage of pre-XDR-TB among MDR-TB isolates was slightly lower than reported in a previous study in Bangladesh (Tasnim et al., 2018). Drug-resistance patterns in MDR-TB isolates may differ due to mutational variability in mycobacterial genes linked with anti-TB drug resistance (Lan et al., 2019). It is also possible that resistance is initiated as a result of transmission from person to person. In areas where SLDs are not available, WHO recommends that treatment decisions be guided by the patient's clinical history and recent surveillance data (WHO, 2016).

Our results also revealed a higher prevalence of FQ-resistant pre-XDR-TB cases (3%) than injectable SLD-resistant pre-XDR-TB cases (1.7%). According to data from previous studies, the prevalence of FQ-resistant MDR-TB (pre-XDR-TB) has increased (Singhal et al., 2016). In Ethiopia, fluoroquinolones are used indiscriminately in most common infections, including pneumonia and pyrexia of unknown origin, in addition to MTB infection, which may explain the higher prevalence of FQ-resistant pre-XDR-TB cases observed in our study (Tasnim et al., 2018; Shibabaw et al., 2020). FQs present two disadvantages when used as antibiotics: first, their anti-mycobacterial action can delay the diagnosis of TB; second, when used for previous infections, they can lead to the selection of FQ-resistant MTB mutants (Tasnim et al., 2018). Since FQ antibiotics are oral medications and easily accessed in Ethiopian pharmacies without a prescription, FQ exposure is more frequent than injectable SLD exposure (Shibabaw et al., 2020). Injectable SLDs comprise aminoglycosides (amikacin, kanamycin, and capreomycin). They are also available in Ethiopia without a prescription for bacterial diseases other than tuberculosis. Injectable SLD resistance may have evolved as a result of the indiscriminate use of these antibiotics (Dijkstra et al., 2018).

Our study revealed mutations in the *gyrA* and *rrs* genes. A *gyrA* gene mutation was identified as conferring FQ resistance, while an *rrs* gene mutation induced injectable SLD resistance. The most frequently observed mutations were in codons *A90V, D94N/D94Y*, and *S91P* (77.3%, 4.5%, and 4.5%, respectively). According to several studies, the majority of mutations linked with FQ resistance occurred in codons *A90V* and *D94N/D94Y* in the *gyrA* gene (Brossier et al., 2016; Chen et al., 2012; Cheng et al., 2021; Jian et al., 2018). According to our analysis, the most common *rrs* gene mutation was in *A1401G* (45.5%). Similar studies have reported high frequencies of mutation in codon *A1401G* (Cheng et al., 2021; Jian et al., 2018; Rufai et al., 2020). The *gyrB* and *eis* genes were found to be mutation free in the MDR strains in

our study. This could be attributed to the low number of SLD-resistant isolates.

Our study had some limitations. First, some data relating to patient characteristics were unavailable. Second, due to a lack of phenotypic DST data, we did not compare it with the molecular testing. Third, our results did not determine the factors associated with drug resistance. However, our findings provide important evidence of additional drug resistance among MDR-TB.

Conclusions

The majority of SLD resistance mutations were found in the *gyrA* gene at position *A90V*. Our results highlight the role of *gyrA* mutations in the development of FQ resistance, and provides an estimate of the proportion of MDR-TB cases in Ethiopia that are pre-XDR-TB. As a result, MDR-TB strains must be regularly screened for *gyrA* mutations in order to detect second-line TB drug resistance promptly, which is critical for developing effective treatment regimens and controlling the spread of drug-resistant TB. The overall prevalence of pre-XDR-TB was determined to be 3%. However, the prevalence of XDR-TB was unclear, due to recent changes to the XDR-TB definition.

Our study strongly indicates the need for modern, rapid DST in order to identify pre-XDR-TB and XDR-TB and thus support proper regimen administration for patients. Conducting DST at the baseline is recommended to prevent the development of additional drug resistance and for better patient management. Early diagnosis and treatment initiation for drug-resistant TB is important in inhibiting the transmission of resistant strains. Furthermore, comprehensive recording of routine laboratory surveillance data is required to track the progress of the TB control program and help meet the sustainable development goal of eliminating tuberculosis.

Abbreviations

DST: drug sensitivity testing; EPHI: Ethiopian Public Health Institute; EPTB: extrapulmonary tuberculosis; FQ: fluoroquinolone; INH: isoniazid; LPA: line probe assay; MDR: multidrug resistance; MTB: *Mycobacterium tuberculosis*; MTBC: *Mycobacterium tuberculosis* complex; NTRL: National Tuberculosis Reference Laboratory; PTB: pulmonary tuberculosis; pre-XDR-TB: pre-extensively drug-resistant tuberculosis; RIF: rifampicin; RR-TB: rifampicin-resistant tuberculosis; SPSS: Statistical Package for Social Sciences; TFC: treatment follow-up center; TIC: treatment initiating center; TB: tuberculosis; WHO: World Health Organization

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Authors' contributions

GD conceptualized and developed the protocol, conducted the study, and drafted the manuscript. AA, HHT, KE, and AK reviewed and edited the draft manuscript. Supervision, investigation, and data analysis, were performed by GD, HHT, AM, AK, AA, BY, BZ, BD, GS, HM, MG, MA, SM, WS, YA, DFG, MT, BB, NW, EA, AS, MH, ZT, AW, TB, DFG, and SA. The final paper was read, evaluated, and approved by all authors.

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Conflicts of interest

There are no conflicts of interest.

Availability of data and material

All data analyzed in this study can be obtained from the corresponding author.

Ethical approval and consent to participate

This study received ethical approval from the Institutional Review Board of the Ethiopian Public Health Institute. Participant consent was not required because it was a retrospective review. No patients' names or IDs were used at any point during the procedure.

Consent for publication

Not applicable.

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Detection of *Mycobacterium tuberculosis* and rifampicin resistance by Xpert® MTB/RIF assay among presumptive tuberculosis patients in Addis Ababa, Ethiopia from 2014 to 2021

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ABSTRACT

Objective: This study aimed to determine the frequencies and trends of *Mycobacterium tuberculosis* and rifampicin resistance among presumptive tuberculosis patients in Ethiopia, who were tested using the Xpert MTB/RIF assay between 2014 and 2021.

Methods: Data were collected retrospectively from patient registries. Laboratory-based data were extracted from the national tuberculosis (TB) referral laboratory database. All patients referred to the National Tuberculosis Reference Laboratory (NTRL) for TB diagnosis from all over the country between March 1, 2014 and September 30, 2021, and tested using the Xpert MTB/RIF assay, were included. The extracted data were entered into a Microsoft Excel sheet and analyzed by Statistical Package for Social Sciences (SPSS) version 23.

Results: Among a total of 13 772 individuals tested using the Xpert MTB/RIF assay, the majority (8223; 59.7%) were males, and 48.5% (6678) of the individuals were aged between 15 and 39 years. *Mycobacterium tuberculosis* (MTB) was detected in 17.0% (2347) of the examined individuals. Of the detected MTB cases, nearly 9.9% (233) were rifampicin resistant (RR-TB), while 24 (1.0%) were RR-intermediate. Among all RR-TB cases, more than half (125; 53.6%) were detected in males, and 105 were new TB cases. Extrapulmonary (EPTB) patients had a greater rate of rifampicin resistance (11.0%) than pulmonary (PTB) patients (9.6%).

Conclusion: The frequency of TB and RR-TB remains high in the study setting. RR-TB was found to have a statistically significant association with previous anti-TB medication treatment. As a result, improving treatment adherence in recognized instances could assist in preventing MTB and RR-TB cases.

Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* complex organisms, also known as tubercle bacilli. The bacillus spreads slowly and widely in the lungs producing hard nodules (tubercles) or cheese-like masses that produce cavities (WHO, 2020). It is a contagious illness that primarily affects the lungs, but can infect any organ in the body (Adhikari et al., 2021). TB has existed for millennia

Abbreviations: EPHI, Ethiopian Public Health Institute; EPTB, extrapulmonary tuberculosis; MDR, multidrug resistance; MTB, *Mycobacterium tuberculosis*; MTBC, *Mycobacterium tuberculosis* complex; NTRL, National Tuberculosis Reference Laboratory; PTB, pulmonary tuberculosis; RIF, rifampicin; RR-TB, rifampicin-resistant tuberculosis; SPSS, Statistical Package for Social Sciences; TB, tuberculosis; WHO, World Health Organization.

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and remains a major global health problem. It causes ill-health for approximately 10 million people each year, and is one of the top ten causes of death worldwide (WHO, 2020).

The prevalence of multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) was estimated to be 3.3% in new cases and 18% in previously treated cases globally in 2020. Overall, an estimated 465 000 incident cases of MDR/RR-TB were reported and the global proportion of RR-TB cases estimated to have MDR-TB was 78% (WHO, 2020). The establishment and spread of MDR-TB has become a major TB control issue, which cannot be addressed with currently available anti-TB medications. Multidrug-resistant tuberculosis treatment involves time-consuming and costly chemotherapy, using second-line medicines that are both toxic and ineffective (El Hamdouni et al., 2019). Drug resistance is mostly a man-made problem that arises through the misuse and mismanagement of medications, either alone or in combination (Demissie et al., 2021).

For timely management of the disease, rapid detection and identification of *Mycobacterium tuberculosis* (MTB) in infected individuals is critical. Rapid molecular tests like Xpert have been approved by WHO and are used as the initial diagnostic test for the detection of TB and rifampicin resistance in adults and children (WHO, 2016). The test simultaneously detects *Mycobacterium tuberculosis* complex (MTBC) and resistance to rifampicin (RIF) in less than 2 hours. Xpert MTB/RIF can detect mutations in the *rpoB* gene and present the results (Boehme, 2010). In the diagnosis of PTB and EPTB, the Xpert MTB/RIF assay is rapid, as well as being highly sensitive and specific (Tessema et al., 2012; Blakemore et al., 2010; Rahman et al., 2018). Rifampicin resistance can be diagnosed quickly, allowing TB patients to begin treatment sooner rather than waiting for results from other classic methods of drug susceptibility testing.

Rapid diagnosis, continuous surveillance, and regular monitoring of drug-resistant TB are critical for disease management and earlier treatment initiation in countries with a high TB prevalence. However, only a few studies have aimed to determine the prevalence of tuberculosis and rifampicin-resistance in presumptive TB cases in Ethiopia (Demissie et al., 2021; Gebretsadik et al., 2020; Derbie et al., 2016; Araya et al., 2020; Mulu et al., 2017; Arega, et al., 2019; Worku et al., 2019). Therefore, our study aimed to determine the frequency of *Mycobacterium tuberculosis* and rifampicin-resistant TB among presumptive TB individuals.

Methods and materials

Study design and study pried

A laboratory-based retrospective cross-sectional study was carried out using presumptive TB patient records that were referred for Xpert MTB/RIF assay testing to the National Tuberculosis Reference Laboratory (NTRL) of the Ethiopian Public Health Institute (EPHI) between March 1, 2014 and September 30, 2021. The NTRL is an accredited national reference laboratory in Addis Ababa, Ethiopia, and provides a range of services: surveillance; technology evaluation; operational research; support for TB laboratory networking; training; mentoring and supervision; external quality assurance; and diagnostic services, such as GeneXpert MTB/RIF testing. The NTRL has one GeneXpert machine that can analyze 16 samples at a time. The laboratory receives samples from variety of healthcare facilities for GeneXpert testing, culture, and drug susceptibility testing; approximately 6000–8500 presumptive TB patients are tested annually. During the study period, 102 public and 175 private health facilities referred samples to the NTRL.

Study population

All presumptive PTB and EPTB patients who were referred to NTRL at the EPHI and tested with the Xpert MTB/RIF assay between March 2014 and September 2021 became the study population.

Data collection

The data were collected using a standardized extraction sheet. Epidemiological, clinical, and laboratory data were collected from the archived database and registration books. The patient's demographics, including age, sex, HIV status, TB treatment history, and MTB and RR results were collected. Microsoft Excel 2016 was used to keep track of all demographic and laboratory test findings.

Laboratory methods

The Cepheid Xpert MTB/RIF system was used to test the specimens. For identification purposes, each sample was given a unique laboratory number. The sputum samples were mixed with the sample reagent in a 2:1 dilution (sample reagent:sputum) using a 50 ml falcon tube. EPTB samples with a volume of < 10 mL were used unconcentrated, whereas samples with a volume > 10 mL were concentrated by centrifugation (3800 × g for 15 min) and decanted to remove the supernatant before resuspension of the sediment in saline. A transfer pipette was used to add a double volume of the sample reagent to a minimum of 0.7 ml of concentrated sample. Next, the falcon tubes were tightly screw-capped and forcefully shaken before being incubated for 10 minutes. After the first incubation, each tube was shaken once more before being incubated at room temperature for 5 minutes. Using of a disposable transfer pipette, 2 mL of liquefied material was transferred to the sample chamber of the Xpert MTB/RIF cartridge. The cartridge was then inserted into one of the Xpert MTB/RIF system's modules, which ran the test automatically. Results were automatically generated within 2 hours and reported as MTB not detected or MTB detected (with semiquantification), and as RIF resistance not detected or RIF resistance detected.

Data analysis

All participants' information and laboratory data were entered onto a Microsoft Excel 2016 spreadsheet, which was then exported and analyzed using the Statistical Package for Social Sciences (SPSS) version 23 (IBM Corp, Armonk, NY). Descriptive analysis was used to describe the demographic and clinical profiles of the study participants. A chi-squared test was performed to describe the presence of association. Statistical significance was determined at a p-value < 0.05, with a 95% confidence interval.

Results

Demographic and clinical characteristics

In total, 13 772 specimens were collected during the study period, including 9762 (70.9%) presumptive PTB cases and 4010 (29.1%) presumptive EPTB cases. The age of the study participants ranged from 2 months to 98 years old, with 48.5% being between the ages of 15 and 39 years. More than half of the study participants were male (8223; 59.7%). Of all the 13 772 study participants, the majority (71.1%) did not have a TB history. The HIV status of the study participants was not recorded for 81.1% of the study participants, while 12.5% were HIV seronegative and 6.5% were HIV seropositive (Table 1).

Frequency of Mycobacterium tuberculosis

Mycobacterium tuberculosis was detected in 17.0% (2343/13 772) of the study participants. The frequency of PTB among presumptive PTB patients was 18.5% (1805/9762), while the frequency of EPTB among presumptive EPTB patients was 13.4% (538/4010). Among the identified EPTB cases, lymph node TB (lymphadenitis) was the most common form, accounting for 57.2% (115/201), followed by abscess TB at 37.9% (61/161). MTB was detected in 18.1% (1486/8223) of male patients and

Table 1
Study participants' demographic and clinical characteristics.

Variables	Category	Frequency	Percentage
Sex	Male	8223	59.7
	Female	5549	40.3
Age in years	< 15	1054	7.6
	15–39	6678	48.5
	40–59	3659	26.6
	> 60	2381	17.3
TB classification	New	9767	71.0
	Relapse	2104	15.3
	Failure	740	5.8
	Defaulter	101	0.7
	Unknown	1060	7.7
HIV status	Positive	889	6.5
	Negative	1716	12.5
	Not recorded	11167	81.1
Type of presumptive TB	PTB	9762	70.9
	EPTB	4010	29.1
Year of GeneXpert test	2014	377	2.7
	2015	1934	14.0
	2016	2703	19.6
	2017	4167	30.3
	2018	2528	18.4
	2019	1497	10.9
	2020	323	2.3
	2021	243	1.8
Total		13772	100

EPTB – extrapulmonary tuberculosis, PTB – pulmonary tuberculosis

15.4% (857/5549) of females. Among HIV-positive patients, TB was detected in 15.0% (133/889), while among HIV-negative patients the frequency was 16.1% (277/1716). TB was detected in 16.1% (1576/9767) of new cases, 20.8% (438/2104) of relapse cases, and 22.6% (167/740) of treatment failure cases (Table 2).

Frequency of rifampicin resistance among Mycobacterium tuberculosis

Among 2343 MTB detected cases, RR-TB was found in 233 individuals (9.9%), while 1.0% (24/2343) of the cases were indeterminate. The proportions of RR-TB among new TB cases and previously treated TB cases were 6.7% (105/1576) and 18% (112/633), respectively. Female patients had a slightly higher rate of RR at 12.6% (108/857) compared with male patients at 8.4% (125/1486). The frequency of RR-TB among children under 15 years confirmed to have TB was 10.9% (8/73). The frequencies of RR-TB among new treatment, relapse, treatment after failure of the initial treatment, and defaulter cases with TB were 6.7% (105/1576), 16.9% (74/438), 19.2% (32/167), and 21.4% (6/28), respectively. The difference in rifampicin resistance between PTB and EPTB cases was not statistically significant ($p = 0.31$) (Table 3).

Trends for Mycobacterium tuberculosis and RR-TB by years

One aim of this study was to assess the frequency of TB and RR-TB based on the year when the specimens are examined. The frequency of MTB was 20.4% (77/377) in 2014, 17.4% (336/1934) in 2015, 15.1% (409/2703) in 2016, 16.4% (684/4167) in 2017, 17.9% (454/2528) in 2018, 20.3% (304/1497) in 2019, 13.3% (43/323) in 2020, and 16.1% (39/243) in 2021. The frequency of RR among these confirmed MTB cases was 35.1% (27/77) in 2014, 14.3% (48/336) in 2015, 11.3% (46/409) in 2016, 8.5% (58/684) in 2017, 4.9% (22/454) in 2018, 6.9% (21/304) in 2019, 16.3% (7/43) in 2020, and 7.6% (3/39) in 2021. Thus, MTB frequency decreased from 20.4% in 2014 to 16.1% in 2021, but increased slightly to 17.9% in 2018 and 20.3% in 2019. The frequency of RR-MTB showed a significant decline from 35.1% in 2014 to 6.9% in 2019 but increased to 16.3 in 2020 before falling back to 7.6% in 2021 (Figure 1).

Discussion

A retrospective study was carried out using the records of presumptive TB patients to determine the frequencies of MTB and RR-TB using the Xpert MTB/RIF diagnostic tool. The overall frequency of MTB (17.0%) among presumptive TB patients was comparable to reports from San Diego County in the USA (17.8%) (Rice et al., 2017), the Republic of Democratic Congo (16.3%) (Lupande et al., 2017), and northwest Ethiopia (14.6%) (Derbie et al., 2016). In contrast, studies conducted in northern parts of Ethiopia (23.2%) (Mulu et al., 2017), northwest Iran (40.5%) (Atashi et al., 2017), Taiwan (33.6%) (Chiang et al., 2018), Dubai in UAE (30.9%) (Habous et al., 2019), Pakistan (28.8%) (Rasool et al., 2019), China (36.6%) (Tang et al., 2017), and Bangui (79.1%) (Farra et al., 2019) showed higher frequencies of MTB than our finding. On the other hand, some studies carried out in north Ethiopia reported lower MTB frequencies — (8.9%) (Gebretsadik et al., 2020), (11.0%) (Wasihun et al., 2021), and (5.7%) (Ayalew et al., 2020), as did studies from southern Ethiopia (11.9%) (Worku et al., 2019), Nepal (13.8%) (Sah et al., 2020), and South Africa (11.4%) (Velen et al., 2021). These differences could be related to variations in the clinical characteristics of study participants, community TB control practices, and localized variations in TB epidemiology and frequencies.

In our study, the 15–39 years age group had the highest frequency of MTB, accounting for (24.4%) of the total. This observation was in agreement with previously reported studies from different countries — (18.7%) (Araya, 2020), (15.6%) (Wasihun et al., 2021), and (14.16 %) (Sah et al., 2020). This could be related to the fact that those in this age group are more likely to be exposed to the external environment, and have a wider range of travelling.

In this study, the rate of MTB detection was highest among patients with EPTB suspected of having TB lymphadenitis (57.2%), followed by abscess tuberculosis (37.9%). This finding was consistent with a previous study conducted in Ethiopia that showed tuberculosis lymphadenitis to be the predominant type of EPTB infection (78.4%), followed by abscess TB (10.7%) (Fanosie et al., 2016). According to recent research from Iran, TB lymphadenitis (36.4%) is the most common form of EPTB, followed by abscess TB (24.7%) (Baghbanbashi et al., 2021). In northeast Ethiopia, investigations revealed that TB lymphadenitis (33.3%) was the most frequent form of EPTB, followed by pleural forms (11.9%) (Metaferia et al., 2018). In contrast, other studies have found genitourinary TB (27.2%) to be the most common type of EPTB, followed by meningeal TB (19.4%) (Gunal et al., 2011). These variations could be attributable to the dynamics of EPTB epidemiology, which are unique to each geographical area, and the genetic variation among the population.

In our study, rifampicin resistance was detected in 9.9% of confirmed TB cases. This was comparable to the results of other studies conducted in Ethiopia — 9.3%, 10.3%, and 11.9% (Derbie et al., 2016; Mulu et al., 2017; Worku et al., 2019), and in Nepal (10.2%) (Sah et al., 2020). However, our figure was lower than that found in a study in the Democratic Republic of Congo (20.8%) (Lupande et al., 2017). On the other hand, it was higher than in studies conducted in northwest Ethiopia (4.3% and 0.5%) (Demissie et al., 2021; Liyew et al., 2020), northeast Ethiopia (5.3%) (Gebretsadik et al., 2020), Nepal (3.36%) (Adhikari et al., 2021), northwest Iran (4.3%) (Atashi et al., 2017), and Nigeria (7.3%) (Ukwamedua et al., 2019). The reasons for these differences may be due to differences in the clinical characteristics of study participants, study periods, and TB control practices.

In our study, the frequencies of RR-TB among previously treated and new TB patients were 18.0%, and 6.7%, respectively. Similar findings were reported in studies in Ethiopia with previously treated TB patients (17.1%) and in treatment-naive patients (6.7%) (Mulu et al., 2017). In contrast, another study in Ethiopia indicated a higher frequency (27.4%) of RR-TB in previously treated TB patients than our finding, while drug resistance among new TB cases (7.6%) was similar to our result (Arega et al., 2019). A high rate of RR-TB in previously treated patients might be due to the development of drug-resistant strains, pos-

Table 2
Prevalence of positive *Mycobacterium tuberculosis* results among the study participants.

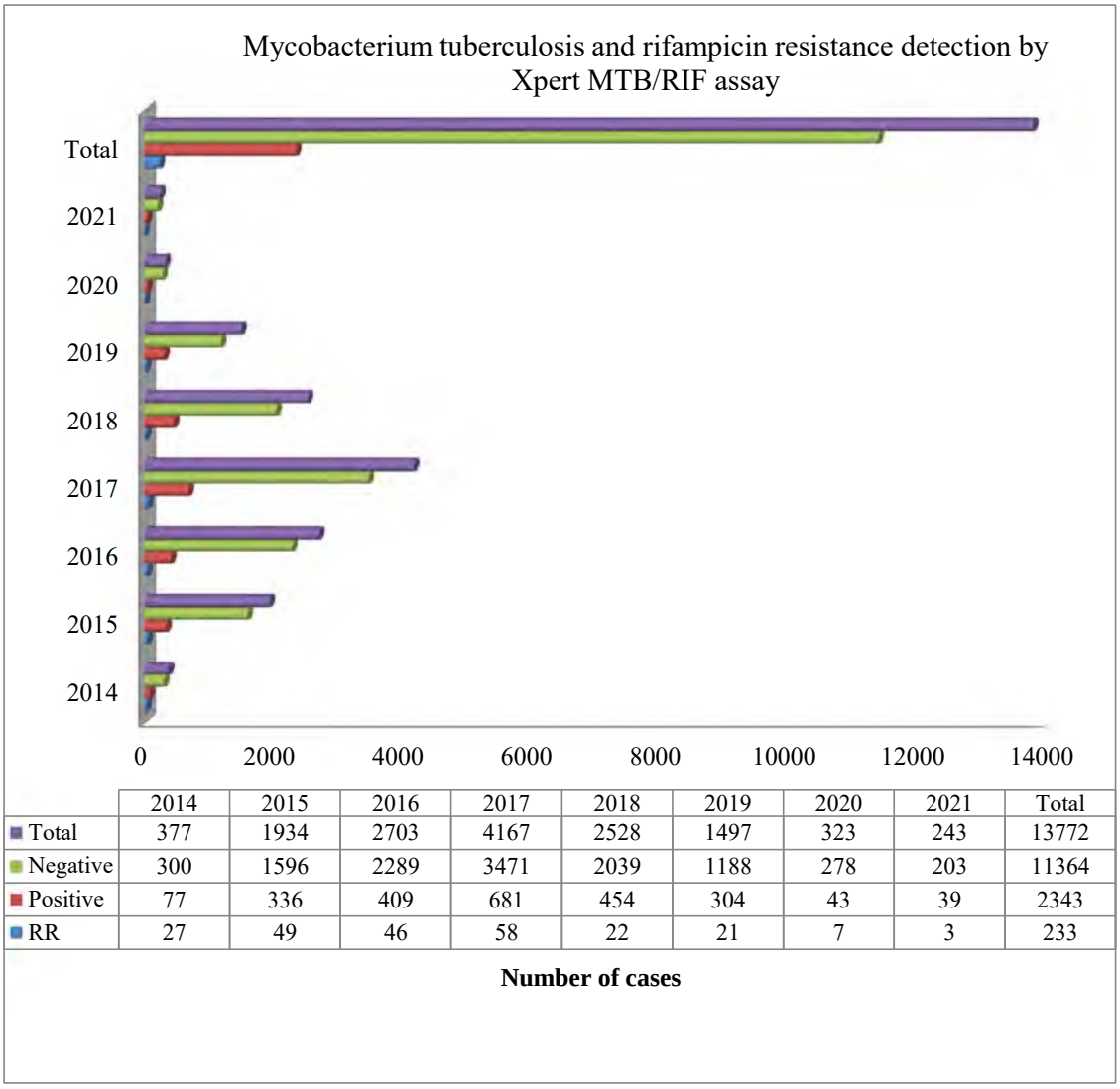
Variables	Category	GeneXpert for *Mycobacterium tuberculosis*			χ^2	*p*-value	Total
		Positive *N* (%)	Negative *N* (%)	Unsuccessful result (error or invalid)*N* (%)			
Sex	Male	1486 (18.1)	6686 (81.3)	51 (0.6)	23.524	< 0.001	8223 (59.7)
	Female	857 (15.4)	4675 (84.5)	17 (0.3)			5549 (40.3)
Age in years	< 15	73 0 (6.9)	971 (92.1)	10 (0.9)	443.232	< 0.001	1054 (7.6)
	15–39	1629 (24.4)	5015 (75.1)	34 (0.5)			6678 (48.5)
	40–59	487 (13.3)	3157 (86.3)	15 (0.4)			3659 (26.6)
	> 60	154 (6.5)	2218 (93.2)	9 (0.4)			2381 (17.3)
TB category	New	1576 (16.1)	8148 (83.4)	41 (0.4)	69.316	< 0.001	9767 (71.0)
	Relapse	438 (20.8)	1652 (78.5)	12 (0.6)			2104 (15.3)
	Failure	167 (22.6)	570 (77.0)	3 (0..4)			740 (5.8)
	Defaulter	28 (27.7)	73 (72.3)	–			101 (0.7)
	Unknown	134 (12.6)	918 (86.6)	8 (0.8)			1060 (7.8)
HIV status	Positive	133 (15.0)	753 (84.5)	3 (0.3)	5.246	0.263	889 (6.5)
	Negative	277 (16.1)	1433 (83.5)	6 (0.4)			1716 (12.)
	Not reported	1933 (17.3)	9175 (82.2)	57 (0.5)			11167 (81.1)
Sample site	PTB	1805 (18.5)	7900 (80.9)	57 (0.6)	58.510	< 0.001	9762 (70.9)
	EPTB	538 (13.4)	3461 (86.3)	11 (0.27)			4010 (29.1)
Specimen type	Sputum	1805 (18.5)	7900 (80.9)	57 (0.6)	497.867	< 0.001	9762 (70.9)
	Pleural fluid	178 (9.1)	1766 (90.6)	5 (0.3)			1949 (14.1)
	Lymph node aspirate	115 (57.2)	85 (42.3)	1 (0.5)			201 (1.5)
	CSF	25 (6.6)	351 (93.4)	–			376 (2.7)
	BAL	56 (13.1)	367 (86.2)	3 (0.7)			426 (3.1)
	Ascitic fluid	15 (5.3)	265 (94.3)	1 (0.4)			281 (2.0)
	Pus	49 (30.5)	111 (68.9)	1 (0.6)			161 (1.2)
	Urine	8 (6.4)	116 (93.6)	–			124 (0.9)
	Abscess	61 (37.9)	100 (62.1)	–			161 (1.2)
	Peritoneal fluid	23 (8.3)	252 (91.7)	–			275 (2.0)
	Other	8 (14.3)	48 (85.7)				56 (0.4)
Total		2343 (17.0)	11361 (82.5)	68 (0.5)			13772 (100)

EPTB – extrapulmonary tuberculosis, PTB – pulmonary tuberculosis, *N* – number, CSF –cerebrospinal fluid, BAL – broncho-alveolar lavage, χ^2 – chi-squared

Table 3
Rifampicin resistance profiles detected among 2343 confirmed *Mycobacterium tuberculosis* patients.

Variables	Category	Rifampicin resistance status			χ^2	*p*-value	Total
		Resistant *N* (%)	Not resistant *N* (%)	Indeterminate *N* (%)			
Sex	Male	125 (8.4)	1346 (90.6)	15 (1.0)	10.698	0.005	1486 (63.4)
	Female	108 (12.6)	740 (86.4)	9 (1.1)			857 (36.6)
Age in years	< 15	8 (10.9)	65 (89.1)	–	8.246	0.221	73 (3.1)
	15–39	175 (10.7)	1438 (88.3)	16 (0.1)			1629 (69.5)
	40–59	38 (7.8)	441 (90.6)	8 (1.6)			487 (20.8)
	> 60	12 (7.8)	142 (92.2)	–			154 (6.6)
TB category	New	105 (6.7)	1458 (92.5)	13 (0.8)	81.582	< 0.001	1576 (67.3)
	Relapse	74 (16.9)	359 (81.9)	5 (1.2)			438 (18.7)
	Failure	32 (19.2)	135 (80.8)	–			167 (7.1)
	Defaulter	6 (21.4)	22 (78.6)	2 (7.1)			28 (1.2)
	Unknown	16 (11.9)	114 (85.1)	4 (3.0)			134 (5.8)
HIV status	Positive	15 (11.3)	118 (88.7)	–	2.101	0.717	133 (5.7)
	Negative	27 (9.7)	246 (88.8)	4 (1.5)			277 (11.8)
	Unknown	191 (9.9)	1722 (89.1)	20 (1.0)			1933 (82.5)
Sample site	PTB	174 (9.6)	1615 (89.5)	16 (0.9)	2.336	0.306	1805 (77.0)
	EPTB	59 (11.0)	471 (87.5)	8 (1.5)			538 (23.0)
Specimen type	Sputum	174 (9.6)	1615 (89.5)	16 (0.9)	31.170	0.093	1805 (77.0)
	Pleural fluid	19 (10.7)	158 (32.6)	2 (1.1)			178 (6.7)
	Lymph node aspirate	20 (17.4)	94 (81.7)	1 (0.9)			115 (4.9)
	CSF	–	25 (100)	–			25 (1.1)
	BAL	2 (3.6)	53 (94.6)	1 (1.8)			56 (2.4)
	Ascitic fluid	1 (6.7)	14 (93.3)	–			15 (0.7)
	Pus	5 (10.2)	43 (87.6)	1 (2.0)			49 (2.1)
	Urine	1 (12.5)	7 (87.5)	–			8 (0.3)
	Abscess	9 (14.7)	50 (81.9)	2 (3.3)			61 (2.6)
	Peritoneal fluid	–	22 (95.7)	1 (4.3)			23 (1.0)
	Other	3 (37.5)	5 (63.5)	–			8 (0.3)
Total		233 (9.9)	2086 (89.1)	24 (1.0)			2343 (100)

EPTB – extrapulmonary tuberculosis, PTB – pulmonary tuberculosis, *N* – number, CSF –cerebrospinal fluid, BAL – broncho-alveolar lavage, χ^2 – chi-squared.



	2014	2015	2016	2017	2018	2019	2020	2021	Total
Total	377	1934	2703	4167	2528	1497	323	243	13772
Negative	300	1596	2289	3471	2039	1188	278	203	11364
Positive	77	336	409	681	454	304	43	39	2343
RR	27	49	46	58	22	21	7	3	233

RR- rifampicin resistance

Figure 1. Graph of Xpert MTB/RIF assay tests, 2014–2021.

sibly exacerbated by poor treatment adherence during the first-line anti-TB treatment.

In our study, the proportion of RR-TB cases among EPTB cases (11.0%) was higher compared with that for PTB cases (9.6%). This was in agreement with a study in Ethiopia that reported an RR-TB frequencies of 9.8% among PTB cases and 11.3% among EPTB cases (Mulu et al., 2017). Increases in RR-EPTB infection may be due to the fact that most EPTB patients are immunocompromised.

The frequency of RR-TB among children under 15 years was 11.3% in our study. This finding was higher than those of previous studies carried out in Ethiopia (7.9%) and China (0.52%) (Arega et al., 2019; Liyew et al., 2020). On the other hand, our result was lower than figures reported in South Africa (22%) (Dodd et al., 2014) and China (30%) (Jiao et al., 2015). An explanation for these differences could be related to differences in tuberculosis frequency in the general population, sputum sample collecting methods, the study environment, sociocultural practices, and diagnosis.

In our study, the frequency of RR-TB was higher in females compared with males. This finding was comparable with that of previous studies in Addis Ababa and Bangui, where rifampicin resistance was higher in females than in males (Araya et al., 2020; Farra et al., 2019). In contrast, other studies have found the proportion of RR-TB to be higher among male patients, for example in northwest Ethiopia (Demissie et al., 2021; Mulu et al., 2017; Wasihun et al., 2020) and southern Nigeria (Ukwamedua et al., 2019). This disparity in RR-TB incidence between genders could be attributed to differences in social roles, risk behaviors, and activities.

Our research also assessed the frequencies of MTB and RR-MTB by year across the study period. The frequency of MTB was shown to have decreased from 20.4% in 2014 to 16.1% in 2021, following a slight rise to 20.3% in 2021. RR-MTB frequency also decreased significantly — from 35.1% in 2014 to 6.9% in 2019, increasing again to 16.3% in 2020 before falling to 7.6% in 2021. Other investigations in central Ethiopia (Araya et al., 2020), northwest Ethiopia (Demissie et al., 2021), and northern Ethiopia (Wasihun et al., 2020) all showed generally decreasing MTB/RR patterns, in agreement with our findings.

The decreasing MTB/RR patterns from 2014 to 2019 due to previous GeneXpert diagnoses in the country were for selective patients, such as HIV-positive patients, children, and suspected RR cases, and not for all presumptive TB cases. The increasing MTB and RR-TB prevalences in 2020 and 2021 in our study might have been due to the unprecedented COVID-19 pandemic, which could have had a variety of conse-

quences for TB prevention and control systems. Staying at home to avoid the spread of COVID-19 may have made TB transmission easier within households. In addition, the interruptions to healthcare services caused by the COVID-19 workload and resource transfer could have affected TB treatment and diagnosis. Furthermore, the pandemic's considerable economic damage will have a long-term influence on TB prevention and control systems, particularly in resource-scarce, high-TB-burden developing countries such as Ethiopia.

There were a few limitations to this research. First, retrospective data were used for this research, with inherent drawbacks such as incomplete clinical data. Second, no alternative diagnostic approach was used as a comparison in this study, such as culture or phenotypic DST —for eligible cases, the Xpert MTB/RIF test was the only technique used to diagnose TB and RIF resistance. Despite these limitations, this study provides relevant information on the use of the Xpert MTB/RIF assay for detecting MTB and RR-TB cases in the studied area.

Conclusions

Our study showed that there was a significant frequency of tuberculosis and RR-TB in Ethiopia, with RR-MTB prevalence high in both PTB and EPTB patients. Previous anti-TB treatment had resulted in a high RR-TB prevalence. Therefore, efforts to prevent DR/RR-TB should focus on effective drug resistance surveillance, preventing the emergence of new cases of DR/RR-TB, and treating existing patients. Strengthening TB infection control activities should be the focus of future interventions.

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Ethical approval and consent to participate

Permission for this study was obtained from the National Tuberculosis Reference Laboratory of the Ethiopian Public Health Institute. Participants were not approached for consent forms because the study was based on a retrospective record review. Throughout the process, no patient names or identifiers were used.

Author contributions

GD: study concept, data analysis, and writing of the manuscript. GD, AA, KE, AK, and HHT: study design, manuscript drafting. AM, AK, AA, BY, BZ, BD, MG, GS, HMJ, MT, MA, SM, WS, DFG, YA, AW, MH, BB, MG, and ZT: data analysis, interpretation, and quality control. The final paper was read, evaluated, and approved by all authors.

Availability of data and material

The data sets used or analyzed during this study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable, because details such as videos or images relating to study subjects were not recorded for this study.

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There are no competing interests stated by the authors.

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Article

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Narrative Review

Prospects for tuberculosis elimination in Ethiopia: feasibility, challenges, and opportunities

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Prospects for tuberculosis elimination in Ethiopia: feasibility, challenges, and opportunities

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Abstract

To end the global tuberculosis (TB) epidemic and eliminate TB, countries around the world committed to significantly expanding the scope of their efforts, including rapid uptake of new tools, interventions, and strategies, and envisioned a world free of TB. Between 2010 and 2020, Ethiopia experienced a 5% average annual decline in TB incidence. However, at that current rate, ending the TB epidemic (<10 TB cases/100,000 population) may not be possible soon. As a high TB and TB/HIV burden country, Ethiopia's TB epidemic is characterized by a high rate of transmission in the general population and hard-to-reach areas and progression of latent TB infection (LTBI) rather than cross-border migration. Studies suggest that a combination of interventions, such as intensive household screening with TB preventive therapy, has the potential to significantly decrease the incidence of TB. The feasibility of reducing the population-level TB incidence by a combination of interventions in Ethiopia is unknown. Based on the World Health Organization's TB elimination framework and the END TB strategic documents and previously published reviews in TB elimination we conducted a narrative review to summarize and estimated the effect of a combined intervention package (community-based TB screening for active case finding and TB and LTBI prevention and treatment among high-risk groups like household and close contacts). The projected annual decline of TB incidence was above 16%. With this level of impact and nationwide scale-up of the interventions, Ethiopia aligns well with ending the TB epidemic before 2035 and shifting toward TB elimination in the foreseeable future. In the Ethiopia setting, we recommend future studies generating evidence on the impact of the combination intervention package to reduce TB incidence in Ethiopia, which is aiming to shift from control to TB elimination.

Introduction

Despite the curable and preventable nature of tuberculosis (TB), the disease continues to be a public health problem globally, affecting an estimated 10 million people annually and causing 1.3 million deaths among HIV-negative people and an additional 214,000 deaths among HIV-positive people [1]. The African region accounts for nearly one-third of the estimated global burden of TB [2]. The global TB incidence is declining at 2% per year [1], and without further intervention, it is estimated to continue at the same rate. With the unprecedented impact of COVID-19, the annual rate of decline in TB incidence reversed to the level seen eight years ago [1].

In the recent past, African countries experienced a progressive decline in TB incidence [1,2]. However, further advancements in ending the epidemic and ultimately achieving TB elimination have slowed [3]. To end the global TB epidemic, countries around the world committed to significantly expanding the scope of their efforts in the areas of early and universal access to diagnosis and treatment, strengthening government leadership in multisectoral actions against TB, and research and innovations [3]. The long-term vision is a world free of TB, and the strategic goal is to end the global TB epidemic by 2035, defined as a global incidence of fewer than 100 cases/million populations. This will require a 95% reduction in the number of deaths due to TB and a 90% reduction in the incidence of TB [4].

In 2014, the World Health Organization (WHO) introduced a framework to eliminate TB in low-incidence countries [3]. The WHO highlighted eight priority action areas to reach TB elimination.

Addressing key affected populations, active TB screening and latent TB infection (LTBI) identification in high-risk groups, optimizing multidrug-resistant (MDR)-TB prevention and care, and investing in research and new tools were among the key intervention areas. This framework aimed to achieve pre-elimination of TB (<10 TB cases/million) in 2035 and elimination (<1 TB case/million) in 2050 in countries that are approaching the low TB incidence level [5]. In high-resourced countries such as the United States [6] and European countries [7], the comprehensive strategies designed to eliminate TB have achieved significant results, although they have been challenged by TB outbreaks among cross-border migrants, emerging immune-compromising conditions, and inadequate TB infection control [8].

Although TB elimination strategic frameworks had been prepared by WHO for low TB incidence countries, they should also be considered by countries with an intermediate and steadily decreasing TB incidence (i.e. <50 cases/100,000 population) [9]. The 2020 WHO *Consolidated Guidelines on TB: TB Preventive Therapy* recommend implementing all interventions at maximum potential and are now applicable to any country, including high TB incidence countries [10]. For example, in high TB burden countries such as India, Pakistan, Vietnam, and Bangladesh, a ZERO TB Initiative was launched to support cities, districts, and islands that are committed to achieving a rapid reduction in the number of people suffering from TB. This initiative calls for coalitions among local governments, businesses, and civil society; uses the comprehensive Search-Treat-Prevent approach; and focuses TB prevention and care on households (HHs), the places where people seek care, and where people work [11].

Tuberculosis elimination introduced in an integrated manner, including in rural and urban settings in resource-constrained and high TB burden countries, may accelerate the decline in TB incidence. However, an intensified and accelerated TB case reduction strategic framework has never been used or studied in a low-income and high TB burden country like Ethiopia. There is a need to develop a context-based intervention package that can lead to a significant decline in TB incidence [12-14], which will later help achieve the TB elimination goal while passing through the pre-elimination phase, where TB elimination is conceivable and could be reached [15]. National TB programs (NTPs) also need to start making changes to their thinking, organization, and design of interventions, from control to elimination [16,17].

This review aims to present evidence to support the combination intervention package to reduce TB incidence in Ethiopia-country aiming to shift from control to TB elimination in the near future. The article will address critical gaps in much-needed country-specific plans and strategies for TB elimination programs, which other countries with similar settings may learn from.

Methods

The basis for this narrative review is WHO´s TB elimination framework [1]; the END TB strategic documents beyond 2015 [18]; previously published reviews assessing progress of TB elimination at the regional or national levels [7,14-16,18-22]; and the NTP and national strategic plan in Ethiopia [23,24]. A writing group comprising the Ethiopian Federal Ministry of Health (FMoH); NTP; Regional Health Bureaus; and several US Agency for International Development (USAID)-funded projects´ lead organizations, such as Management Sciences for Health (MSH) and *Koninklijke Nederlandse Centrale Vereniging* (KNCV) TB Foundation, drafted the review.

Based on progress made in the last 10 years and literature estimates of the effect of combined intervention (community-based TB screening for active case finding (ACF), TB and latent TB infection (LTBI) prevention and treatment among high-risk groups), the annual decline of TB incidence was projected through 2035 and

beyond. The main factors included in the projection and estimates were: 1) the routine program performance as a baseline, e.g. annual TB incidence taken from the annual WHO report; 2) the number of contacts per index TB case; 3) risk of TB among contacts; 4) proportion of potentially preventable TB among household contacts; 5) tuberculosis preventive therapy (TPT) coverage among household contacts and PLHIV; and 6) estimated TB prevention with efficacy of TPT.

The draft review was also presented as a panel discussion at the 15thTB Research Annual Conference in Addis Ababa March 22-23, 2021, and feedback was solicited on the prospects for TB elimination and potential combination of approaches that we present in this review.

Results

Tuberculosis and TB/HIV trend in Ethiopia: despite significant strides made in controlling TB, Ethiopia remains among the top 30 high TB burden countries. According to the WHO Global TB Report 2021, the rates of national TB incidence, TB in HIV, TB/HIV co-infection, and MDR-TB were 132/100,000; 8.6/100,000; 6.5%; and 1.4/100,000, respectively [1]. Approximately 29% of the estimated TB cases were reported to be missing (Table 1). Of those notified to the NTP [1], cases predominated in the younger population, and 70% of notified cases were in the age group of 15-54 years [25]. TB prevalence at the sub-national level was reported to vary from 90-256/100,000 population [25]. Nevertheless, Ethiopia is among a few high TB burden countries that demonstrated a consistent decline in the TB incidence rate, from 369/100,000 population in 1990 to 132/100,000 population in 2020. Similarly, the TB-related mortality rate declined from 89/100,000 in 1990 to 17/100,000 in 2020 [1].

In the last six years, through concerted efforts of key stakeholders, the TB incidence rate declined from 192/100,000 population to 132/100,000 population, which is a 5% decline on average annually (Figure 1) [1,26]. Although Ethiopia met one of the end TB milestones (at least 20% TB incidence reduction compared to 2015) [18], with this current rate of decline, ending the TB epidemic (<10 TB cases/100,000 population) and reaching the targets for ending TB (to reduce TB deaths by 95% and to cut new cases by 90% between 2015 and 2035) may not be possible in the near future, as there are considerable gaps between the expected target and the current status (Table 1). Therefore, scale-up of working interventions such as HH contact tracing, ACF, and TB preventive strategies on a larger and more sustainable scale is essential.

Eliminate tuberculosis components in Ethiopia: the cornerstones of the WHO-recommended end TB strategies are universal health coverage with innovative approaches that combine diagnostic, treatment, and preventive interventions [4]. Recent surveys conducted in Europe demonstrated that the majority of countries evaluated do not have all of the interventions in place to reach elimination [7]. Furthermore, the studies in Europe emphasized the importance of studying countries that are able to demonstrate that TB elimination can be reached [7,19,20]. This, however, remains to be seen as there are limited data demonstrating the impact of combination TB elimination interventions.

To reduce the population-level incidence of TB in Ethiopia, it is essential to have context-based large-scale interventions aimed at interrupting further transmission and averting future cases. Households contact screening, intensive (mass) community-based TB screening for ACF in geographic areas with poor access to diagnostics in high TB burden settings, and identifying individuals with LTBI on a large scale are key to eliminating TB in Ethiopia. According to our estimates and projections, ending the TB epidemic before or by 2035 Ethiopia is possible if TB incidence declines by an annual factor of 15% or more from the current incidence of 132/100,000 population (Figure 2). This requires highly effective strategies to reduce TB transmission among populations at risk of developing TB, such as HH

contacts and people living with HIV (PLHIV). Moreover, to halt the TB epidemic, ACF and prompt initiation of the correct treatment are essential components of TB elimination strategies [27]. Details on the potential effects of intensive community-based TB screening, HH contact investigation, and tuberculosis preventive therapy (TPT) among HH contacts and PLHIV within the Ethiopian context are described below.

Community-based screening and active case finding: intensive (mass) community-based screening is only recommended among subpopulations with poor access to health care; those living in poor areas and remote areas; and those associated with other risk factors (e.g. prisoner, migrant, refugee, homeless) [28] (Table 2). Otherwise, indiscriminate mass screening is not the WHO-recommended strategy for case finding due to its low benefit (the yield ranges from 0.1% to 0.7% [28]). Data from 18 prevalence surveys demonstrated that in many settings, more than half of the prevalent TB cases in a community were undiagnosed [28]. For similar reasons, the TB prevalence survey in Ethiopia suggested the need to strengthen community-based screening for early detection and treatment of cases to reduce TB transmission in the community [25]. Therefore, targeting entire communities (i.e. subpopulations with poor access to health care) through mass screening is critical in a high TB burden country such as Ethiopia. The feasibility and impact of community-based screening have been studied in the recent past in Southern Ethiopia, where Yassin *et al.* demonstrated a close to doubling of the TB incidence rate, from 102 cases/100,000 population (95% confidence interval, CI: 99.1-105.8) before implementation to 177 TB cases/100,000 population (95% CI: 172.6-181.0) after community intervention, and improved treatment outcomes for bacteriologically confirmed TB (77% [95% CI: 75.0-78.8] to 93% [95% CI: 91.8-94.2]) before and after community intervention (the package included advocacy, training, engaging stakeholder and community member, and ACF using house-to-house visits and TB screening by female extension health workers) [29]. A randomized controlled trial by Datiko *et al.* found higher mean TB case-detection rates in the intervention communities (122.2% versus 69.4% control, p=0.001), which included increasing awareness of TB and TB symptoms, facilitating sputum collection, and supporting treatment in the community [30]. In Ethiopia, because close to one-third of TB cases are estimated to be missed [1], a focused community-based screening in geographic areas with a high TB burden may help find missed TB cases early, thereby reducing TB transmission, and early treatment may improve treatment outcomes. To guide the targeted intervention, Ethiopia may prioritize regions, zones, and districts with TB incidence above the current WHO estimates, which is 132,000/100,000 [1], those with poor access to health facilities. In addition, symptom screening with chest X-ray regardless of symptom should be extended to high-risk groups such as PLHIV, health care workers, prisoners, migrants, patients with Diabetes Mellitus, children < 5 years of age and HH, and close contacts [10].

Tuberculosis preventive therapy in Ethiopia: in Ethiopia, TPT has been recommended for high-risk groups, particularly PLHIV and children under the age of 15 who are HH contacts of infectious TB cases, to reduce the risk of progression to active TB disease. Although the recommendations have been in national TB and HIV guidelines for more than a decade, the implementation of TPT for either of the eligible priority risk groups has been low (42-49%) [1,2]. Several challenges and barriers related to the capacity of health care providers, consistency in quality of TB screening, passive contact tracing, issues of adherence with increased pill burden, and concerns about potential drug resistance with isoniazid monotherapy have been attributed to the protracted progress of TPT implementation in the country. In 2020, 15,635 PLHIV newly enrolled in HIV care and 42% were on TPT, and among children under 5 years of age who were contacts of bacteriologically confirmed pulmonary TB cases only 31% were initiated on TPT (Table 1). This is far from what the country intends to achieve [1].

Tuberculosis preventive therapy among high-risk groups

Tuberculosis preventive therapy among households contacts with index tuberculosis cases: on average, among the estimated 10 contacts identified for each person with infectious TB, 30% to 51.4% are found to have LTBI, and 4% to 5% of contacts develop active TB [31,32]. Of the contacts who will ultimately have TB disease, approximately 75%, 81%, and 92% develop TB disease in the first three months, six months, and one year after exposure, respectively [31,32]. From the Sidama region in Southern Ethiopia, Yassin *et al.* in 2020 reported that from 1,517 HH contacts of 344 index cases who were visited and screened for TB and followed up for a median of 37 months, 5% (77/1,517) developed TB during 4,713 person-years of follow-up with an estimated TB incidence of 1,634 (95% CI: 1,370-2,043) per 100,000 person-years of follow-up, which is much higher than the estimated TB incidence for the general population in Ethiopia of 210/100,000 [33].

In the context of Ethiopia, among the 132,000 notified TB cases in 2020, 29,568 new TB cases were estimated in 2021 to come from the pool of close contacts, representing 22.4% of the notified TB cases. In this estimate, the assumptions included 20% extrapulmonary TB, 30% bacteriologically unconfirmed TB (smear negative), the remaining bacteriologically confirmed TB infecting 10 other people, and 4% of contacts developing active TB (Figure 3) [32]. To avert the active TB cases coming from households and close contacts, if the resource allows the programmatic approach for Ethiopia might be bi-annual or annual screening among households and other high-risk groups. Asymptomatic individuals after screening might be offered TPT.

In earlier trials conducted among HH contacts, a 74% to 77% reduction in TB cases was achieved after one year of treatment with isoniazid preventive therapy [34,35]. Tuberculosis preventive therapy, especially with higher coverage when combined with other prevention and treatment strategies, will contribute to TB elimination [36-39]. With the implementation of TPT among HH contacts, there is great potential to avert a substantial number of incident TB cases in Ethiopia. With TPT implementation among HH contacts and an assumption of 50% efficacy of TPT (i.e. prevent the development of TB by 50%), more than 18,000 TB cases are estimated to be averted in one year, which translates to a reduction of 16 TB incidence/100,000 population, which is twice the current annual average decline of eight TB incidence/100,000 population.

Tuberculosis preventive therapy among people living with HIV: in a recent systematic review, the effectiveness of TPT in risk reduction for TB among PLHIV was well demonstrated, with 33% overall and 64% among those who were tuberculin skin test positive [10]. In 2019 and 2020, there was suboptimal uptake of TPT (42 and 49%) among HIV-positive newly enrolled cases, and 10,000 HIV-positive cases were reported as incident TB [1,2,40] in Ethiopia. To achieve an optimal reduction of incident TB among HIV-positive people, TPT coverage needs to be scaled up. With the scale-up of TPT to more than 90% and 50% efficacy of TPT, close to 5,000 HIV-positive TB cases are estimated to be averted, which translates to 4.5 TB incidence per 100,000 populations in one year.

Tuberculosis preventive therapy among other high-risk groups: because of an increased risk for progression to active TB, healthcare workers, prisoners, homeless people, and immigrants are considered to be high-risk groups and are prioritized for systematic TB screening, testing, and treatment of LTBI [10]. Because evidence of the benefit in people with diabetes is limited, systematic testing and treatment is not recommended by WHO. However, depending on the settings (i.e. with an increased risk for progression to active TB), countries may consider offering TPT among people with diabetes [10]. In Ethiopia, the prevalence of diabetes among people 18 years of age and above is increasing [2].

Multidrug-resistant tuberculosis (MDR-TB) prevention and care: for many years, Ethiopia was one of the 30 high MDR/RR-TB burden countries, but in 2021 it was removed from the list [41]. The country cites political commitments; expansion of laboratory, clinical, and community-level services; and significant in-country and global collaborative efforts for this achievement. During the implementation period of the just-ending tuberculosis and leprosy national strategic plan (TBL-NSP), services have expanded, effectively allowing decentralized access to diagnostics, including for TB culture and drug susceptibility and testing, and treatment of drug-resistant tuberculosis (DR TB) in peripheral settings [24].

Nonetheless, MDR-TB in Ethiopia remains a significant challenge and needs to be a focus to work toward ending the TB epidemic and elimination. A significant proportion of MDR-TB cases who continuously transmit the disease are not caught by routine care. In 2019, only 47% of the estimated MDR/Rifampicin-Resistant TB cases were enrolled in treatment. The same report stated a 75% treatment success rate [2]. Highly sensitive case-finding strategies and high-quality patient management is one priority area to improve DR-TB care. The long treatment duration with highly toxic drugs imposes significant challenges on adherence to treatment. To improve our case finding, we must conduct contact screening for all bacteriologically confirmed TB/DR-TB cases and enroll all patients in treatment. Optimal DR-TB case management and improvement of treatment outcomes need universal implementation of active drug safety monitoring and patient-centered support. Both first- and second-line drug susceptibility testing coverage should be scaled up for appropriate regimen design and prompt assignment of patients to effective treatment to halt continuous transmission.

Discussion

From our assessment and projection reaching TB elimination by 2050 in Ethiopia is too ambitious, given the efficacy of the current tools and health service delivery [38]. Globally, notwithstanding the progress made toward meeting Millennium Development Goals (MDGs) and the post-MDG WHO TB elimination framework, only four countries, Antigua and Barbuda, Barbados, Montserrat, and Niue and San Marino, has ever reached TB elimination. In 2019, 54 countries had achieved ending the TB epidemic (<10 cases/100 000 population/year). Morocco is the only country in Africa reaching such a low incidence of TB; the rest are mostly in the Americas and European region [2].

Unlike most countries in the WHO African region, Ethiopia has achieved the 2020 milestone toward ending the TB epidemic targets, which is at least 20% reduction in the absolute number of TB cases between 2015 and 2020 [1]. However, with the current rate, ending the TB epidemic in Ethiopia may not be possible soon. Thus, the rate needs to decline rapidly, with a 15% average annual decline to end the epidemic and a 20% average annual decline to eliminate TB before or in 2050, which requires a considerable commitment.

Intensified research and innovation in line with TB elimination is one of WHO´s eight priority action areas [4]. The global strategy emphasizes that countries need to study their TB epidemic and design customized combination interventions if TB control is to shift to elimination [12-14,42]. To that effect, many countries, particularly in Europe, are working on a context-based TB elimination framework [7,42,43]. In this review, end TB strategies tailored for Ethiopia for a potential accelerated TB incidence decline using a high-impact combination intervention are presented.

The experience from low TB incidence countries [15] shows that the combined TB interventions recommended by WHO in 2014 have been implemented. These countries, however, were challenged by TB transmission in high-risk groups, such as migrants from high TB burden countries [15]. For example, 41% of Oman´s population were migrants from high-incidence

countries and accounted for 60% of the annual TB cases [13]. The ZERO TB initiative in the cities and islands of Asia-Pacific countries applied a Search-Test-Treat approach, putting in place a set of TB prevention and control interventions [11]. Data from previous experience suggest that a remarkable reduction in TB incidence may not be possible with a single intervention unless a combination of preventive, diagnostics, treatment, and follow-up interventions are in place. Although Suárez *et al.* reported that the widespread application of directly observed treatment, short course (DOTS) in Peru in the 1990s was associated with a marked and sustained decline in TB incidence [44], subsequent evidence from Brazil and New York City, however, suggests that multiple interventions, rather than DOTS alone, are likely to be associated with an accelerated decline in TB incidence [45,46]. Hence, a combined approach of case finding, active contact racing, identifying high-risk and treatment of LTBI, and improved surveillance are essential.

For Ethiopia, there are a number of opportunities to assist in accelerating the decline in TB incidence: (1) using local evidence, we know the working interventions to end the TB epidemics; (2) together with the stakeholders and partners the NTP is launching a quasi-experimental study aiming to demonstrate accelerated TB decline with a combination intervention, the result of which may help define a pathway toward TB elimination that may be scaled up nationally; (3) Ethiopia has a solid TB control program, although an elimination plan has not been formalized, the NTP is committed to TB elimination and is actively participating in the experimental study; (4) to increase access to diagnosis, Xpert MTB/RIF systems are decentralized at the woreda (district) level, and line probe assays are available at central and regional laboratories; (5) TPT, including the shorter three-month isoniazid and rifapentine (3HP) regimen, is included in the national guidelines; and (6) the shorter oral regimes for DR-TB are also adopted in the country and are being implemented.

A lot of uncertainty remains in the following areas, which are considered major challenges in the context of Ethiopia: (1) High-level commitment. There is a need for a national TB elimination plan, supported by high-level ministerial commitment. India is a good example of this, whereby TB elimination is given ministerial attention with regular follow-up [2]. (2) Funding and sustainability. The government expenditure on health is not optimal. The 2021 evaluation report indicated that about half of the resources available to implement the national TB strategic plan were from donor contributions, and the rest were from the government budget [47]. Per the WHO 2020 global report, the TB-specific funding gap remains at more than 50% (USD 47 million) [2]. To achieve end TB strategies, a TB-specific budget needs to be allocated, particularly for maintaining quality health service that should be free for TB patients. (3) Sub-optimally operating infrastructure and health systems. Ethiopia has major human resource challenges, including a shortage of health care workers, urban/rural and regional disparities, poor motivation and retention, and suboptimal performance [48]. The shortage of laboratory professionals, particularly in rural health facilities, is a challenge. Further, the number of radiologists is small [24]. Staff improvement both in quality with adequate training and rational coverage of health facilities with enough staff to deliver TB services is of paramount importance, and this is also dependent on a well-funded environment. (4) Intersectoral collaboration for poverty alleviation and improvement of undernutrition and poor housing condition; and (5) impact of COVID-19. Ethiopia is not exempt from the effect of the pandemic, which is even more challenging with ongoing instability in some part of the country. Globally, the success of TB incidence reduction has been reversed by eight years (to 2012). Tuberculosis screening strategies need to be coordinated with COVID-19 activities.

Our review has some limitations. First, as a narrative review there was not a strict protocol or inclusion and exclusion criteria followed and the methods used for the literature review was

dependent of the objective of the review focus area set by the authors. Second, the design of the studies included varies from clinical trial to programmatic and operational studies that brings a difference in designs in study settings, selection of population studies, data quality. Notwithstanding that there were limited body of knowledge around TB elimination, particularly in African settings, the authors attempted to include all available relevant published data focused on TB elimination globally, and those conducted in African region, including Ethiopia. We presented evidence to support the combination intervention package to reduce TB incidence in Ethiopia, which is aiming to shift from control to TB elimination in the near future. This article attempted to address critical gaps in much-needed country-specific plans and strategies for TB elimination programs, which other countries with similar settings may learn from.

Conclusion

Although there is a lot of global experience with TB elimination trials, most evidence is concentrated in developed countries with low TB incidence. However, evidence from low-income countries like Ethiopia is also worth generating. Therefore, enhancing research in countries with a substantial TB burden is important for TB epidemic reduction or elimination. In Ethiopia, the planned study may assist in developing and implementing a novel TB elimination framework for the TB program, building on the current success of the NTP. With the current rate of TB incidence reduction in Ethiopia, the milestones of end TB - pre-elimination and elimination - would not be achieved. However, if the defined TB elimination packages are introduced and enhanced, it is possible to achieve the elimination rate with the annual TB reduction rate of 16%. Hence, it is recommended to introduce the combination intervention packages in Ethiopia to develop the national TB elimination framework so that the country might shift from a control to an elimination TB program.

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What is known about this topic

- *The 2020 WHO Consolidated Guidelines on TB: TB Preventive Therapy recommend implementing all interventions at maximum potential and are now applicable to any country, including high TB incidence countries;*
- *Multiple interventions, rather than DOTS alone, are likely to be associated with an accelerated decline in TB incidence;*
- *Between 2010 and 2020, Ethiopia experienced a 5% average annual decline in TB incidence; however, at that current rate, ending the TB epidemic (<10 TB cases/100,000 population) may not be possible soon.*

What this study adds

- *This review showed the evidence for effect of a combined intervention package of community-based TB screening for active case finding and TB and LTBI prevention and treatment among high-risk groups (e.g. household [HH] and close contacts, health care workers);*
- *With the combination intervention the projected annual decline of TB incidence was above 16%, and with this level of impact and nationwide scale-up of the interventions, Ethiopia aligns well with*

ending the TB epidemic before 2035 and shifting toward TB elimination in the foreseeable future;

- *This review sets a stage for other low- and middle-income countries to consider combination intervention if they are to achieve TB elimination.*

Competing interests

The authors declare no competing interests.

Authors' contributions

Tefera Belachew Agizew, Zewdu Gashu Dememew conceptualized, designed the review, collected data, analyzed, wrote the first manuscript. Nebiyu Hiruy designed the review, wrote, and reviewed the manuscript. Emawayish Tesema and Eshetu Abdissa Abelti analyzed data and participated in writing the results section. Taye Leta, Eshetu Abdissa Abelti, Asfawesen Gebreyohannes, Yohannes Molla Alemayehu, Ahmed Bedru Omer, Pedro Guillermo Suarez, Yewulsew Kassie, Anteneh Kassa, Daniel Gemechu supervised the review and reviewed the manuscript. Degu Jerene conceptualized, designed the review, collected data, reviewed the data, and participated in writing the Results section. All co-authors contributed to the writing of the manuscript. They have also read and agreed to the final manuscript.

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Figure 3: estimated TB among contacts of potential bacteriologically confirmed index TB cases in 2021

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Table 1: the current gaps between global priority indicators and targets for monitoring the implementation of the end TB strategy by 2025

Priority indicators	**Status in 2020**	**Targets by 2025**	**Gap to target**
Treatment coverage	71.0%	≥90%	19%
TB treatment success rate	90.0%	≥90%	0%
Preventive treatment coverage			
Children under 5 years of age	31%	≥90%	59%
People living with HIV	42%	≥90%	48%
Tuberculosis affected households facing catastrophic costs	Not available	0%	Not available
Uptake of new diagnostics	36%	≥90%	54%
Uptake of new drugs	Not available	≥90%	Not available

Table 2: key intervention areas for accelerated TB incidence reduction in Ethiopia			
Type of intervention	**Standards of care**	**Key action area**	**Effect on TB incidence**
1.0 Community-based TB screening and active case finding	- Health extension workers ask for TB symptoms during routine home visits.	- Annual mass screening among subpopulations with poor access to health care, such as those living in poor and remote areas.	- Minimize the missed TB cases (29%).
	- Symptom-guided TB screening, Xpert MTB/RIF for all presumptive TB patients.	- Symptom-guided TB screening, chest X-ray, and Xpert MTB/RIF for all presumptive TB patients.	
		- Simultaneous symptom screening and digital X-ray with artificial intelligence (X-ray for all high-risk groups, such as PLHIV, HCWs, prisoners, DM, and household and close contacts) regardless of TB symptoms.	- Maximize TB case finding and narrow the gap between the reported and estimated incident TB cases.
			- Maximize opportunities for TB preventive therapy among those who screened negative for TB.
2.0 Tuberculosis preventive therapy	- Eligible PLHIV offered TPT in a routine setting.	- Eligible PLHIV offered TPT in a routine setting; mobilize indigenous community structures (e.g., Iddirs) to increase TPT-seeking behavior.	- Maximize coverage to 90% from the current 42%.
	- Under 5 years of age HH contacts followed passively.	- Under 5 years of age HH contacts actively followed up by mobilizing indigenous community structures (e.g., Iddirs) to increase TPT-seeking behavior.	- Maximize coverage to 90% from the current 31%.
		- Active follow-up of HH and close contacts, health care workers, prisoners, and DM by mobilizing indigenous community structures (e.g., Iddirs) to increase TPT-seeking behavior.	- Maximize coverage to 90%; the current status not known.
3.0 Contact investigation	- Routine, passive, and prospective contact investigation.	- Active, prospective, reverse, and retrospective or follow-up contact investigations.	- Minimize the missed TB cases or narrow the gap between the reported and estimated incident TB cases.

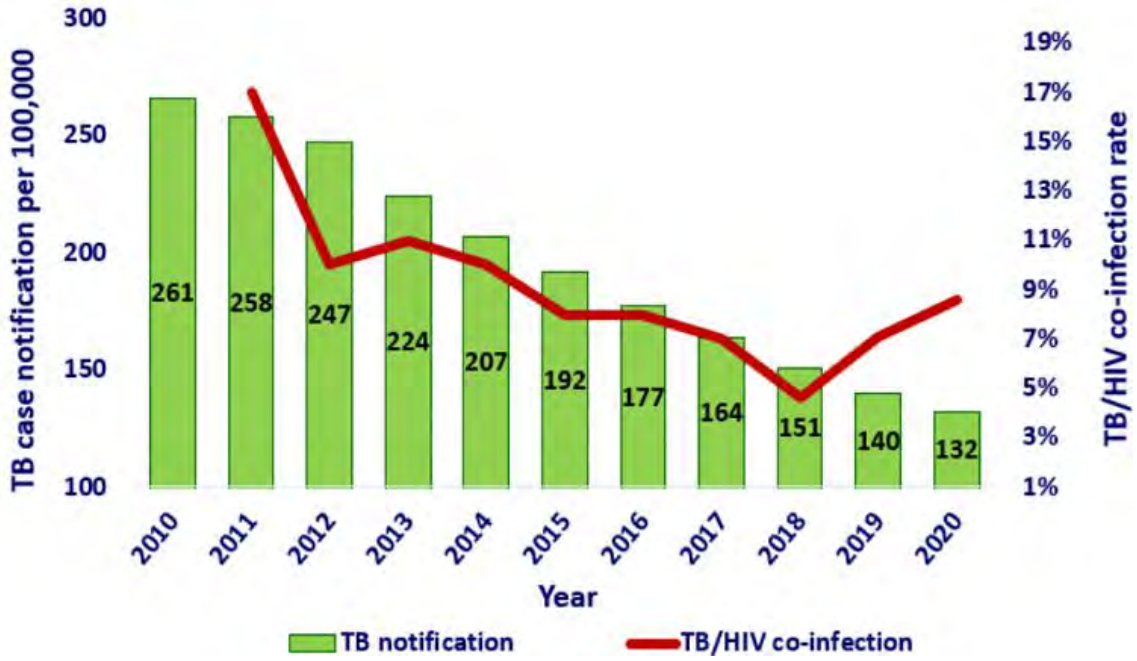

Figure 1: tuberculosis and TB HIV trends in Ethiopia (2010-2020)

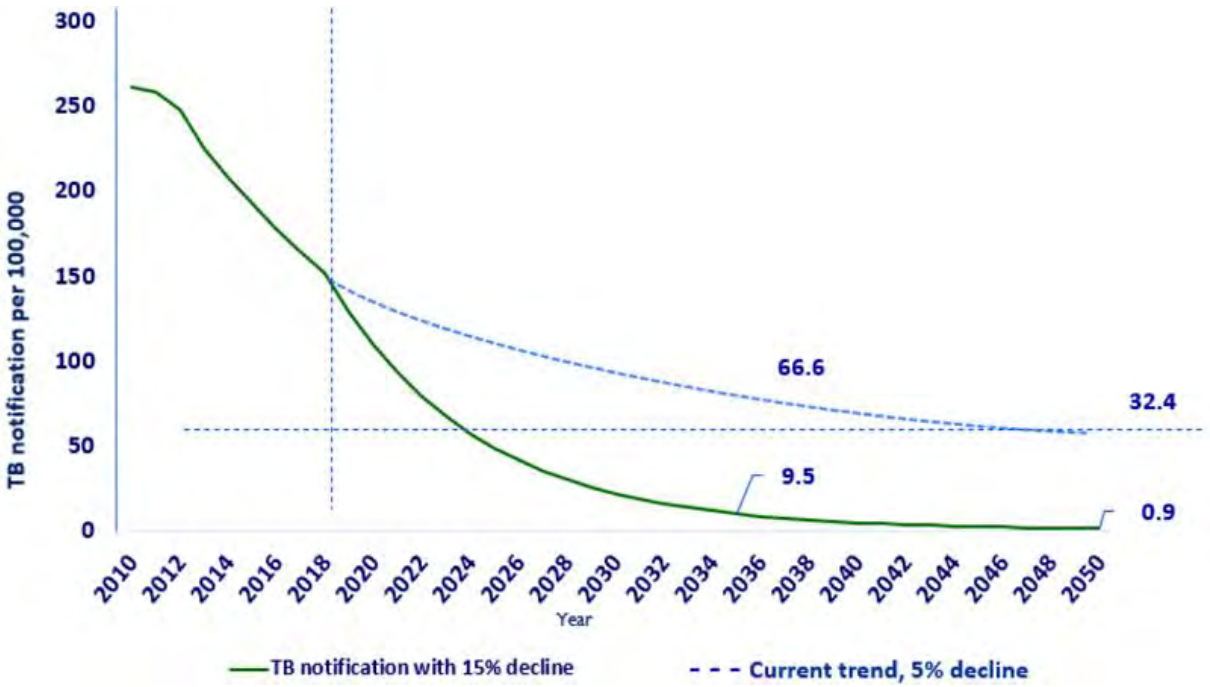

Figure 2: tuberculosis notification trend in Ethiopia, current 5% versus estimated 15% annual decline

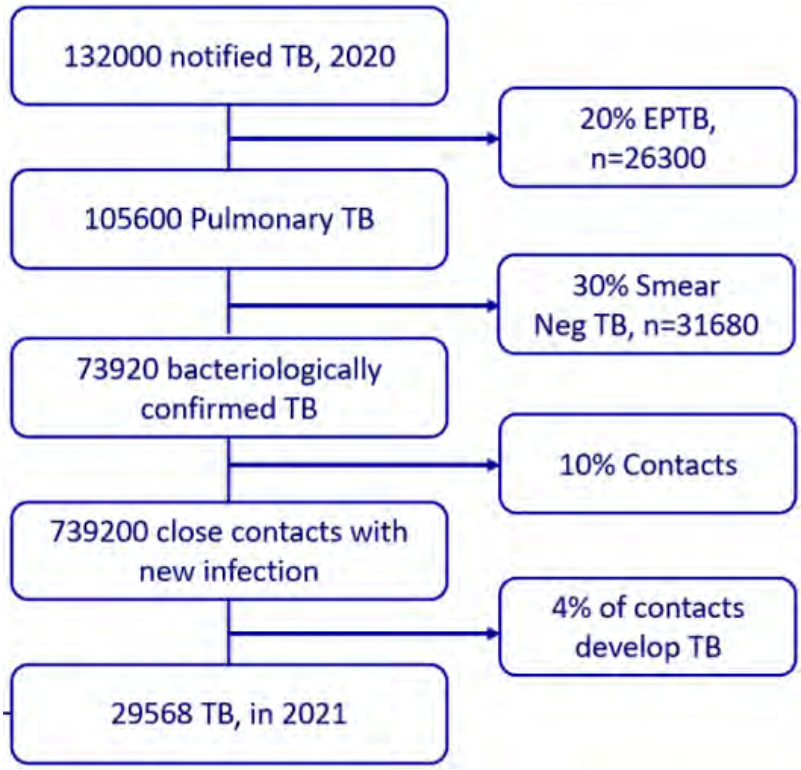

Figure 3: estimated TB among contacts of potential bacteriologically confirmed index TB cases in 2021

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RESEARCH ARTICLE

Bacteriologically confirmed extrapulmonary tuberculosis and the associated risk factors among extrapulmonary tuberculosis suspected patients in Ethiopia: A systematic review and meta-analysis

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Abstract

Background

The actual burden of bacteriologically confirmed extrapulmonary tuberculosis (EPTB) and risk factors in Ethiopia is not well known due to the lack of a strong surveillance system in Ethiopia. Thus, this study was conducted to estimate the pooled prevalence of bacteriologically confirmed EPTB and the associated risk factors among persons suspected to have non-respiratory tuberculosis in Ethiopia.

Methods

A systematic review and meta-analysis of published studies reporting the prevalence of EPTB from searched electronic databases; Science Direct, PubMed, and Google Scholar was estimated spread across the research periods, nationally, and in different areas, using a fixed-effects model. We used I^2 to analyze heterogeneity in the reported prevalence of bacteriologically confirmed extrapulmonary tuberculosis.

Results

After reviewing 938 research articles, 20 studies (19 cross-sectional and 1 retrospective) from 2003 to 2021 were included in the final analyses. The pooled prevalence of bacteriologically confirmed EPTB was 43% (95%CI; 0.34–0.52, I^2 = 98.45%). The asymmetry of the funnel plot revealed the presence of publication bias. Specifically the pooled prevalence of bacteriologically confirmed EPTB based on smear microscopy, Xpert MTB/RIF assay, and culture were 22% (95%CI; 0.13–0.30, I^2 = 98.56%), 39% (95%CI; 0.23–0.54, I^2 = 98.73%) and 49% (95%CI; 0.41–0.57, I^2 = 96.43%) respectively. In this study, a history of pulmonary tuberculosis (PTB) contact with PTB patients, contact with live animals, consumption of raw

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milk, HIV-positive, male, and lower monthly income, were found to be independently associated with bacteriologically confirmed EPTB.

Conclusion

Ethiopia has a high rate of bacteriologically confirmed EPTB. A history of previous PTB, being HIV-positive and having contact with PTB patients were the most reported risk factors for EPTB in the majority of studies. Strengthening laboratory services for EPTB diagnosis should be given priority to diagnose EPTB cases as early as possible.

Introduction

Pulmonary tuberculosis (PTB), which affects the lungs, accounts for 85% of all reported tuberculosis cases globally [1]. However, extrapulmonary tuberculosis (EPTB), which affects parts of the body other than the lung is becoming a major concern in TB prevention and control efforts [2]. The prevalence of EPTB among notified TB cases in the African region in the 2018 global report was 16%, which is the second-highest next to the Eastern Mediterranean region (24%), which is more than the global prevalence of EPTB (15%). The lowest prevalence was reported in the Western Pacific region (8%) [3]. EPTB is assumed to be produced by the spread of bacteria through the bloodstream from a primary focus in the lung, and hence represents a disseminated form of tuberculosis. EPTB most commonly affects the lymph nodes, abdomen, pleura, bones, and meninges, but the prevalence varies with age, sex, and geographic location [4].

Extrapulmonary TB remains a critical concern both in developing and developed countries. EPTB accounts for 15% to 30% of all tuberculosis cases [5,6]. In persons with HIV/AIDS and other immunocompromised states, it is a prevalent opportunistic infection [7]. In Ethiopia, there is a scarcity of evidence on bacteriological diagnosis and evaluation of EPTB.

Extrapulmonary tuberculosis is difficult to diagnose for a variety of reasons. Many types of EPTB necessitate invasive diagnostic sampling, which can be dangerous to the patient and expensive. Because most types of EPTB are paucibacillary (TB disease caused by a limited number of bacteria), detection by smear microscopy is less sensitive. This particularly affects resource-limited settings, where the more sensitive methods of mycobacterial culture examination are not widely available. Culture has its own set of drawbacks such as a very long turnaround time and necessitating a well-equipped biosafety laboratory [8]. Molecular methods are a quick and sensitive procedure that only requires a small amount of sample and may be used on killed bacteria; however, they require highly trained technologists and can be expensive [9]. As a result of these challenges, EPTB is frequently diagnosed solely based on clinical suspicion, and many people are given the incorrect diagnosis, resulting in needless TB treatment or poor outcomes from untreated EPTB. Even in tertiary health care facilities, the majority of patients had started anti-tuberculosis therapy without bacteriological evidence. These people were misdiagnosed or received therapy too late, and they overestimated the scale of the problem at the community level [10]. In Ethiopia, there are few data on bacteriologically confirmed EPTB among suspected EPTB cases. There is no comprehensive review and meta-analysis of the current research to determine the prevalence of bacteriologically confirmed EPTB among EPTB suspects and its risk factors are poorly understood. s. As a result, this study aimed to investigate the prevalence of bacteriologically confirmed EPTB and the associated risk factors amongst persons suspected to have non-respiratory TB in Ethiopia.

Materials and methods

Search strategy

We systematically searched electronic databases such as MEDLINE (PubMed), Science Direct, and grey literature sources such as Google Scholar and Google for articles published in the English language. We used key terms such as "Tuberculosis lymph node", "Tuberculosis cardiovascular", "Tuberculosis central nervous system", "Tuberculosis cutaneous", "Tuberculosis endocrine", "Tuberculosis gastrointestinal", "Tuberculosis hepatic", "Tuberculosis ocular", "Tuberculosis osteoarticular", "Tuberculosis pleura", "Tuberculosis splenic", "Tuberculosis urogenital", and "Ethiopia" both in MeSH and free text.

Eligibility criteria

We included studies that reported the prevalence of EPTB in Ethiopia. Observational studies, such as cohort (prospective or retrospective) and cross-sectional studies, were included. Studies that were written in English and published before October 26, 2021 (the last date of the searching date), were considered. The studies were included regardless of the diagnostic methods used. The articles without a journal name and/or authors, conference proceedings or presentations, and reviews were excluded from the final analysis.

Data extraction

We created a data extraction sheet using a Microsoft Excel® 2010 worksheet. Two independent authors (GD, AA) extracted data including study period, study setting (community or facility-based), study site, test method, sample size, and the number of positive patients. The third author (DF) resolved the inconsistencies that arose between the two authors. To ensure consistency, another co-author (HHT) independently examined the extracted data.

Operational definition

In this meta-analysis, the WHO definition of a positive test result was applied. This states that a positive diagnostic test result using smear microscopy, culture, and Xpert MTM/RIF tests are bacteriological confirmation of EPTB [11].

Risk of bias assessment and study quality

Two authors (GD and DF) independently assessed the quality of the studies using the Newcastle-Ottawa quality assessment scale adapted for cross-sectional studies [12]. The tool has three components: selection, comparability, and outcome/exposure. The selection part is scored from zero to five stars, and the comparability is scored from zero to two stars. The outcome is scored from zero to three stars. To minimize the subjective interpretation of bias from scoring two reviewers (GD and DF) assessed the quality of individual studies. Furthermore, when the disagreements that occurred throughout the quality grading process were settled by consulting a third author (AA) [12]. We used I^2 to analyze heterogeneity in reported prevalence [13,14]. A funnel plot was also used to investigate the presence of publication bias. The presence of publication bias was determined using a funnel plot. By showing funnel plots with the logarithms of effect size and their standard errors, we were able to quantify publication bias.

Statistical analysis

For statistical analysis, STATA® 14 Stata Corp LLC, Texas, USA software was employed. We estimated the pooled prevalence of bacteriologically confirmed EPTB and a 95% confidence

interval using a fixed-effect meta-analysis model. The 'metaprop' command in STATA 14 was used to determine the pooled prevalence of bacteriologically confirmed EPTB in all patients with EPTB. The distributional information of EPTB was displayed using a forest plot. The pooled effect estimate on the prevalence of bacteriologically confirmed EPTB cases was based on a subgroup analysis of publications comparing culture, smear microscopy, and Xpert MTB/RIF assay methods.

Ethical consideration and consent

Since this study is based on previously published articles ethical approval is not applicable.

Result

Study selection

The three electronic databases yielded a total of 938 articles, which were then imported into an Endnote X8 citation manager, and 173 duplicates were removed. Next, 722 articles were screened by title and abstract. Around 43 articles that passed the first stage were assessed through a full-text review. During this review, the study subjects, study design, study quality, and outcome were considered. Because of this reason 23 articles were removed. Finally, 20 articles became eligible for data extraction The recommended reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram were used to complete the overall screening (Fig 1).

Characteristics of the studies included in the review

Of the total of 20 articles reviewed, eight studies were undertaken in the Amhara region [15–22], four studies in Addis Ababa [23–26], four in Oromia [27–30], one study in the Southern Nations Nationalities and People Region [31], and the remaining three studies were based on data collected from different regions of the country [32–34]. The data collection period ranges from 1998 [31] to 2020 [26]. The sample size investigated ranged from 90 [18] to 1,198 participants [34]. The majority of the studies were cross-sectional studies, with one retrospective study. Fourteen studies only examined one type of sample, while the remaining six studies reported evaluating various sample types. Regarding diagnostic methods, five studies used smear microscopy and culture methods [26,29,32–34], three studies used smear microscopy, culture, and Xpert MTB/RIF assay [15,25,28], two studies applied smear microscopy [16,31], two studies used the Xpert MTB/RIF assay [20,22], two studies used the culture and Xpert MTB/RIF assay [19,30], one study used the Xpert MTB/RIF and microscopy [21], and the remaining five studies used the culture [17,18,23,24,27] (Table 1).

The pooled prevalence of bacteriologically confirmed EPTB

The frequency of EPTB varied widely over the 20 studies. The prevalence ranged from 9% [21] to 78% [32]. The pooled prevalence of bacteriologically confirmed EPTB was 43% (95%CI; 0.34–0.52, I^2; 98.45%) according to the random-effects methodology. The highest EPTB prevalence was reported from Addis Ababa, Bar Dar, and Dire Dawa [32], with a rate of 78%, while the lowest was reported from Dessie [21], with a rate of 9% (Fig 2). The pooled proportion of bacteriologically confirmed EPTB studies is represented by a funnel plot (Fig 3). The graph depicted studies with fewer participants and events scattered throughout the pooled horizontal estimate, implying a greater influence due to chance.

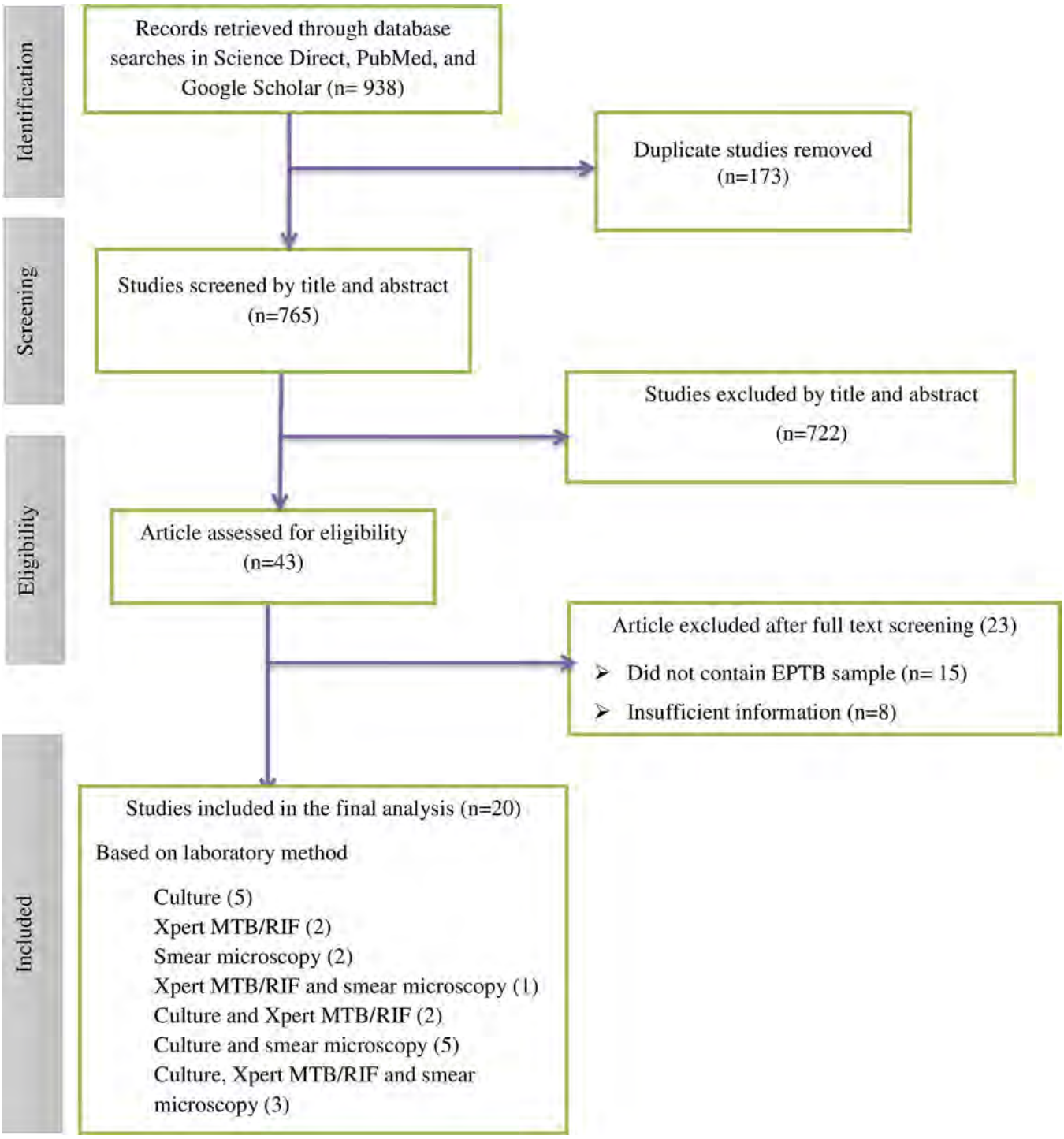

Fig 1. A PRISMA flow diagram depicting the screening and selection process to identify literature describing extra-pulmonary TB cases in Ethiopia.

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Subgroup analysis by diagnostic testing methods

There was no heterogeneity among studies conducted in culture, smear microscopy, and Xpert MTB/RIF assay, according to the subgroup analysis diagnostic test. There is heterogeneity among studies that look at multiple diagnostic tests. For culture, smear microscopy, and

Table 1. General characteristics of studies describing extrapulmonary tuberculosis in Ethiopia.

First Author [ref.]	Publication Year	Study Design	Study area	Study Setting	Study time	Sample size (N)	Number of cases with bacteriological confirmation (n/N, %)	Type of EPTB	Diagnostic Method	Risk factors for bacteriologically confirmed TB
Yassin et al [31]	2003	cross-sectional	Butajira	Facility-based	1998–2000	147	107 (72.8)	Lymph node	Microscopy	not stated
Iwnetu et al [32]	2009	cross-sectional	Addis Ababa, Bar Dar, Diredawa	Facility-based	2004–2005	150	117 (78)	Lymph node	Microscopy Culture	not stated
Derese et al [33]	2012	Retrospective	Woldia, Butajira, Gonder	Facility-based	2011	134	50 (37.3)	Lymph node	Microscopy Culture	not stated
Biadglegne et al [15]	2013	cross-sectional	Bahirdar, Gondar & Dessie	Facility-based	2012	437	226 (51.7)	Lymph node	Microscopy Culture Xpert MTB/RIF	Retreated, Male, Age < 14, Urban
Zenebe et al [16]	2013	cross-sectional	Gonder	Facility-based	2012	344	34 (9.9)	Lymph node	Microscopy	history of PTB, raw milk, monthly less income, TB contact
Garedew et al [17]	2013	cross-sectional	Debre Birhan	Facility-based	2010–2011	98	36 (36.7)	Lymph node	Culture	not stated
Abdissa et el [27]	2014	cross-sectional	Jimma	Facility-based	2012	200	147 (73.5)	Lymph node	Culture	not stated
Birhanu et al [18]	2014	cross-sectional	Dessie	Facility-based	2012–2013	90	32 (35.6)	Lymph node	Culture	not stated
Berg et al [34]	2015	cross-sectional	Gondar, Woldiya, Ghimbi, Fiche, and Butajira, Jinka and Filtu, AA	Facility-based	2006–2010	1198	456 (38.1)	Lymph node	Microscopy Culture	having regular and direct contact with live animals, low education level
Tadesse et al [28]	2015	cross-sectional	Jimma	Facility-based		143	88 (61.5)	Lymph node	Microscopy Culture Xpert MTB/RIF	not stated
Korma et al [23]	2015	cross-sectional	Addis Ababa	Facility-based	2012 to 2013	200	116 (58)	pleural, peritoneal and synovial fluids	Culture	not stated
Abdissa et al [29]	2015	cross-sectional	Jimma	Facility-based	2013	144	96 (66.7)	Lymph node	Microscopy Culture	not stated
Fanosie et al [19]	2016	cross-sectional	Gonder	Facility-based	2015	141	37 (26.3)	Peritoneal fluid, CSF, Pleural fluid, lymph node	Culture Xpert MTB/RIF	Adult patients, history of contact with known pulmonary TB, HIV positive
Zewdie et al [24]	2016	cross-sectional	Addis Ababa,	Facility-based	2013	206	74 (35.9)	Lymph node	Culture	not stated
Mulu et al [20]	2017	cross-sectional	Debre Markos	Facility-based	2014 to 2015	182	53 (29.1)	Peritoneal, Pus, lymph node, pleural fluid	Xpert MTB/RIF	Retreated, Male, HIV positive, Age 41–50
Metaferia et al [21]	2018	cross-sectional	Dessie	Facility-based	2017	353	31 (8.8)	Peritoneal fluid, CSF, Pleural fluid, lymph node	Microscopy Xpert MTB/RIF	history of PTB, contact with PTB patients

(*Continued*)

Table 1. (Continued)

First Author [ref.]	Publication Year	Study Design	Study area	Study Setting	Study time	Sample size (N)	Number of cases with bacteriological confirmation (n/N, %)	Type of EPTB	Diagnostic Method	Risk factors for bacteriologically confirmed TB
Tadesse et al [30]	2018	cross-sectional	Jimma	Facility-based	2015–2017	572	242 (42.3)	Lymph node, CSF, pleural, peritoneal, and pericardial fluids.	Culture Xpert MTB/RIF	not stated
Fantahun et al [25]	2019	cross-sectional	Addis Ababa	Facility-based	2015–2016	152	75 (49.3)	Lymph node	Microscopy Culture Xpert MTB/RIF	not stated
Tedla et al [22]	2019	cross-sectional	Dessie	Facility-based	2018	337	92 (27.3)	Peritoneal fluid, CSF, Pleural fluid, lymph node synovial fluid	Xpert MTB/RIF	HIV-positive, history of PTB
Assefa et al [26]	2021	cross-sectional	Addis Ababa	Facility-based	2020	211	50 (23.7)	Lymph node	Microscopy Culture	not stated

HIV-human immunodeficiency virus; MTB/RIF-Mycobacterium tuberculosis/ Rifampicin; PTB-pulmonary tuberculosis; TB-Tuberculosis.

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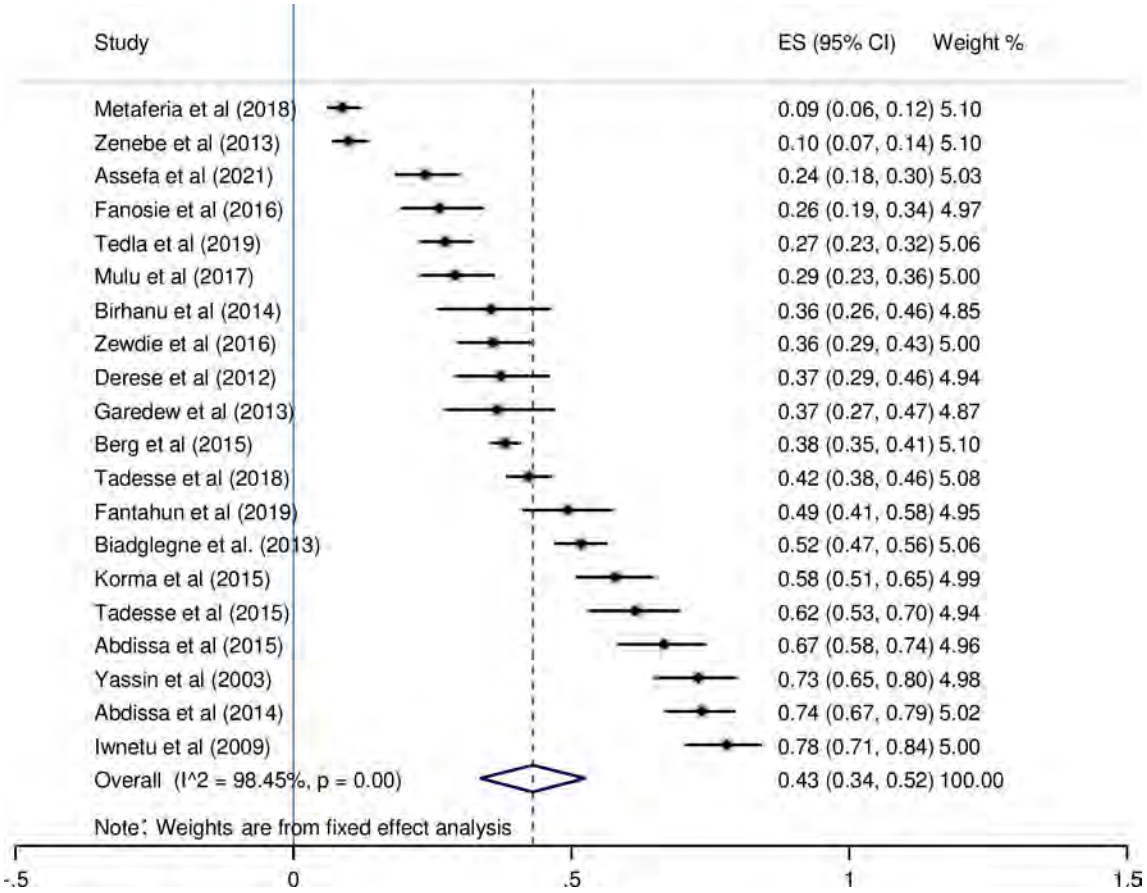

Fig 2. The pooled proportion of bacteriologically-confirmed EPTB cases amongst all studies identified for review.

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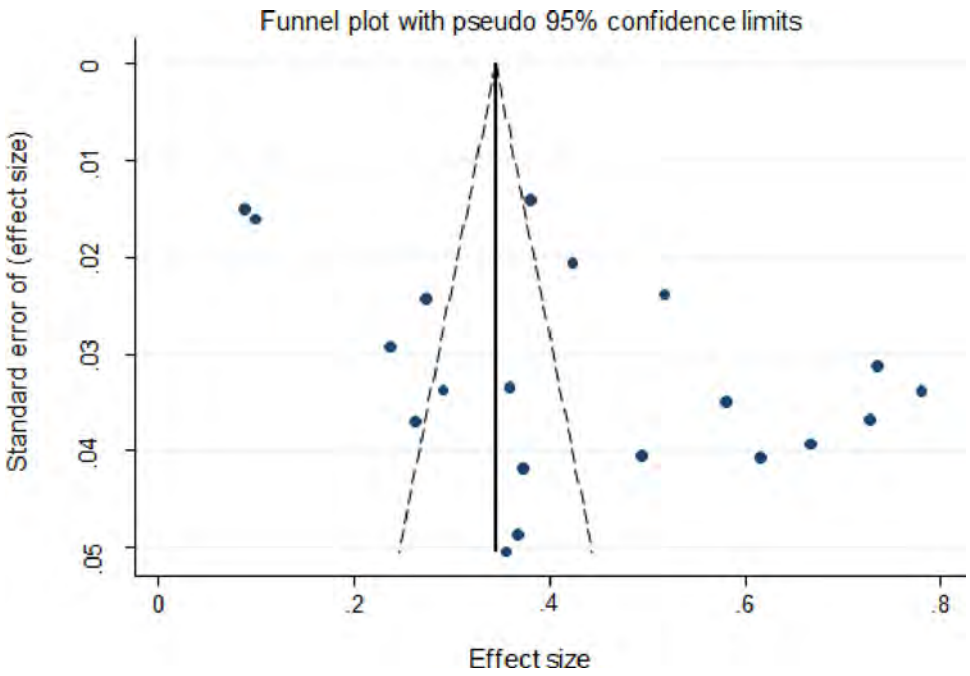

Fig 3. Funnel plot for the pooled proportion of bacteriologically-confirmed EPTB cases amongst all studies identified for review.

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Xpert MTB/RIF assay diagnostic methods, the prevalence of pooled effect estimates was 49% (95%CI; 0.41–0.57, I^2 = 96.43%) (see Fig 4), 22% (95%CI; 0.13–0.30, I^2 = 98.56%) (see Fig 5), 39% (95%CI; 0.23–0.54, I^2 = 98.73%) (see Fig 6), respectively.

Risk of bias across studies publication

Visual inspection revealed indications of publication bias for the majority of the culture diagnostic method estimates, with most studies clustered at the funnel's apex and a few spread to the extreme right and left corners (Fig 7). The funnel plots for Xpert MTB/RIF assay and smear microscopy methods were most studies clustered at the funnel's bottom and a few spread to the extreme right corners (Figs 8 and 9).

Associated risk factors of bacteriologically confirmed EPTB

The impact of each study on the overall meta-analysis summary estimate was investigated. A history of PTB infection and contact with PTB patients was found to be significant risk factors for EPTB incidence in the majority of investigations [15,16,19–22]. Furthermore, having regular and direct contact with live animals, as well as the consumption of raw milk, were found to be strongly related to the incidence of EPTB [16,34]. Additionally, being HIV-positive [19,20,22], ages <14 [15], age 41–50 [20], being male [15,20], monthly less income [16], urban [15] were all linked to the most common EPTB.

Discussion

This systematic review and meta-analysis estimated the pooled prevalence of bacteriologically confirmed EPTB and the associated risk factors among persons suspected to have non-respiratory tuberculosis in Ethiopia using published studies over the last two decades. This meta-analysis included a total of 5439 EPTB suspects from 20 studies published between 2003 and 2021.

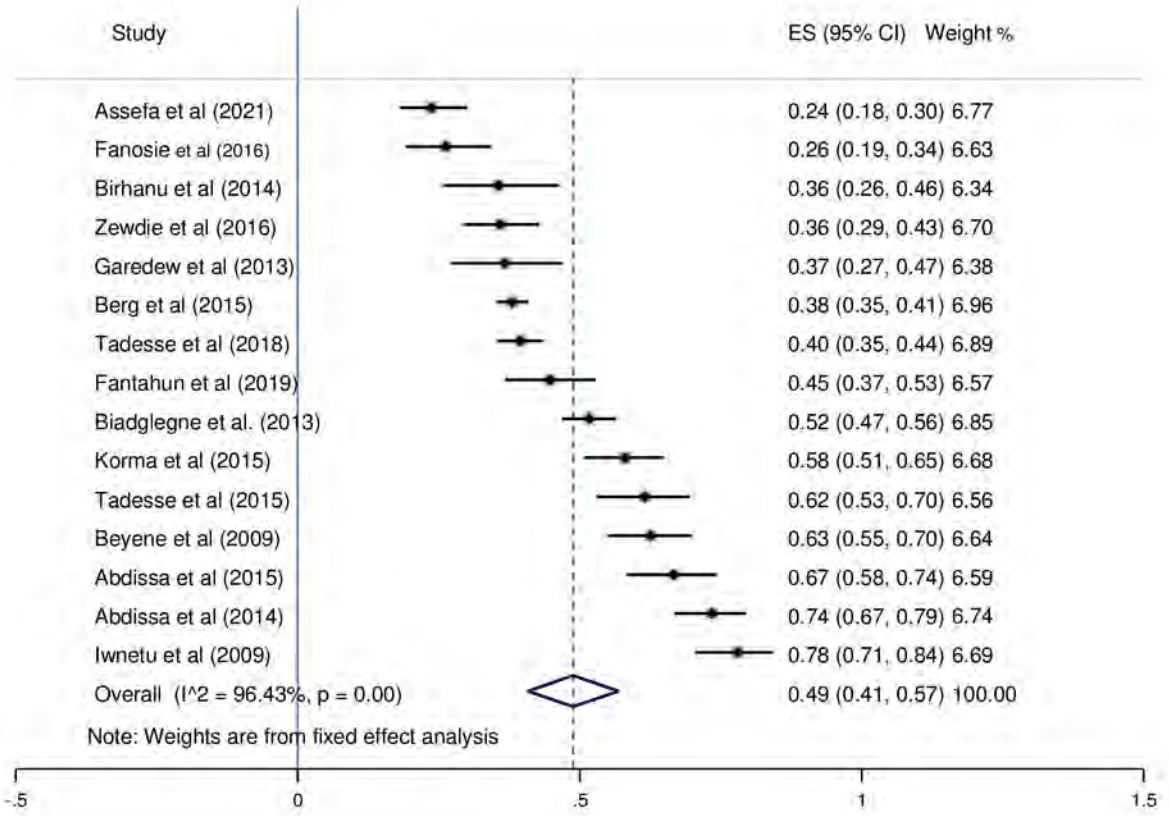

Fig 4. Pooled proportion of culture-positive EPTB using a fixed-effects model.

https://doi.org/10.1371/journal.pone.0276701.g004

The pooled estimated prevalence of samples with any bacteriological evidence in the studies was 43% (95%CI; 0.34–0.52, I^2; 98.45%). A history of PTB infection and contact with PTB patients, contact with live animals, raw milk, HIV, male, less income, and urban, contact with EPTB patients were all found to be independently associated with EPTB in this study.

The overall pooled prevalence of bacteriologically confirmed EPTB in this systematic review and meta-analysis data was 43%. This finding is approximately similar to that previously reported from Cameroon [35]. In contrast, when compared to the estimated prevalence of bacteriologically-confirmed EPTB among all cases of TB in Africa, this is a high figure. According to a 2017 WHO report, the prevalence of EPTB in all cases of TB in Africa and the rest of the globe was 16% and 15%, respectively [7]. Furthermore, a systematic review and meta-analysis of the prevalence of bacteriologically-confirmed EPTB among patients living with HIV/AIDS in Sub-Saharan Africa revealed a lower prevalence of bacteriologically-confirmed EPTB than our findings [36]. However, in the current study, the funnel plot revealed that there is publication bias, where among 20 studies included in this study, 10 were above the 95% upper limit and 5 were below the 95% lower limit and only 5 were within the CI. This might be due to the low number of studies conducted so far in Ethiopia and their variations in

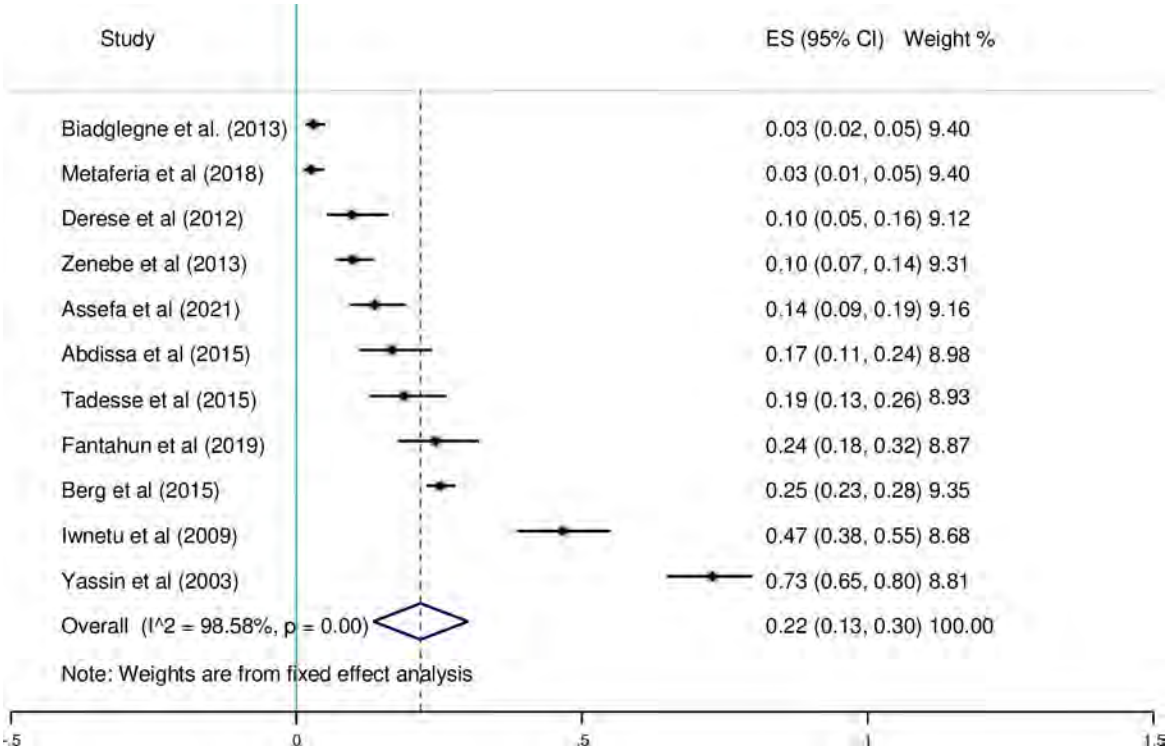

Fig 5. Pooled proportion of smear-positive EPTB using a fixed-effects model.

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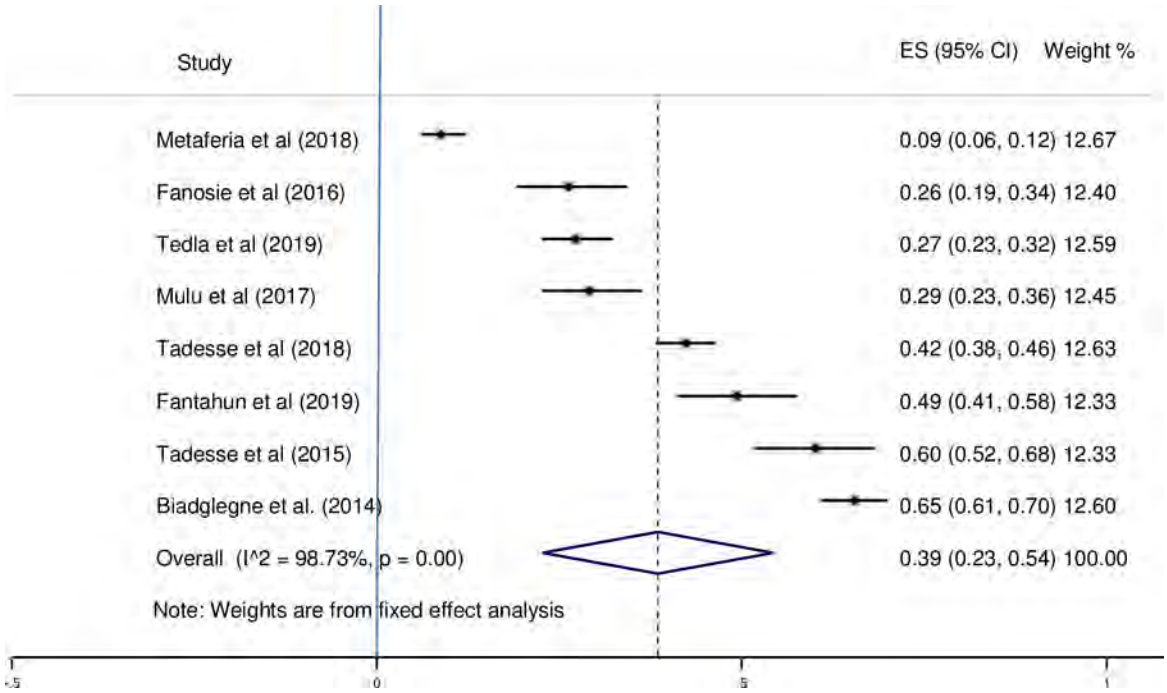

Fig 6. Pooled proportion of Xpert MTB/RIF assay positive EPTB using a fixed-effects model.

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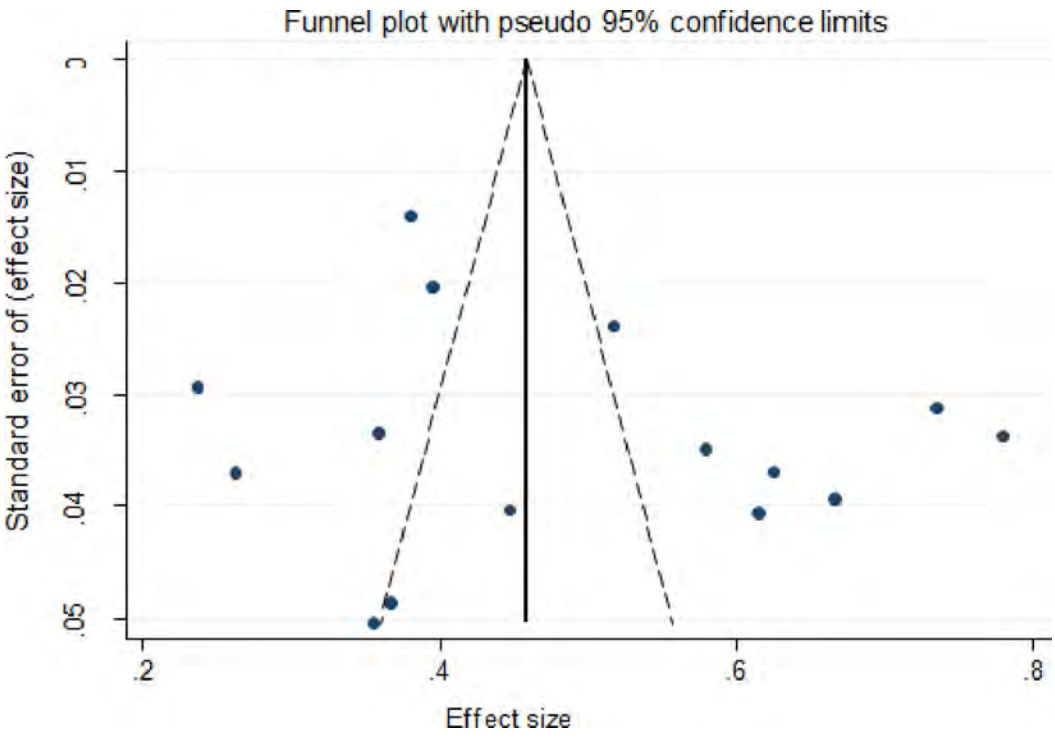

Fig 7. Funnel plot of a subgroup of 15 of the 20 selected studies for culture-positive EPTB.

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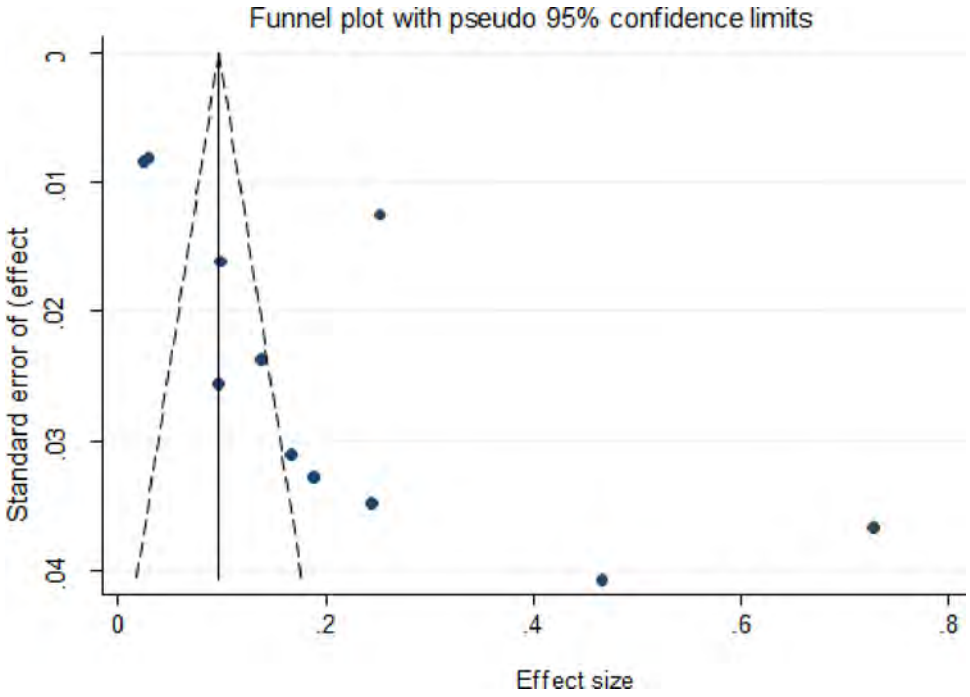

Fig 8. Funnel plot of a subgroup of 11 of the 20 selected studies for smear-positive EPTB.

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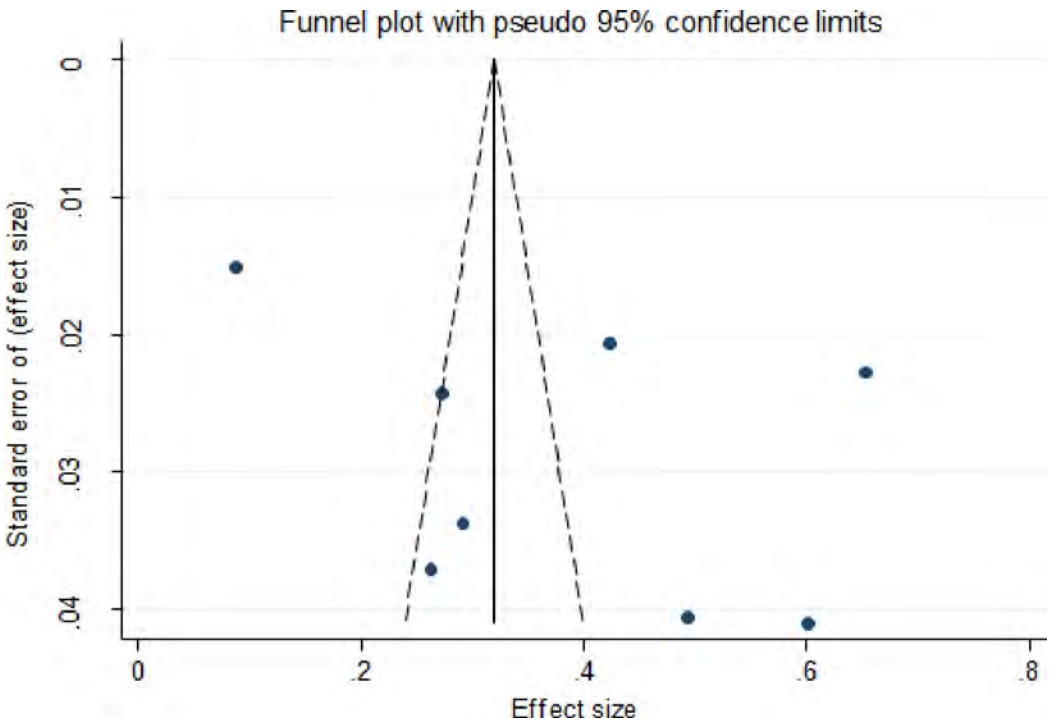

Fig 9. Funnel plot of a subgroup of 8 of the 20 selected studies for Xpert MTB/RIF assay positive EPTB.

https://doi.org/10.1371/journal.pone.0276701.g009

using laboratory methods. Thus, this may underestimate the pooled bacteriologically confirmed EPTB prevalence among EPTB presumptive cases in Ethiopia.

In this current systematic review and meta-analysis investigation, HIV-1 infected patients were the most significant risk factors for EPTB infection [19,20,22]. Similarly, several studies have examined the association between HIV-1 infection and EPTB infection [6,37]. Furthermore, nearly half of EPTB patients were HIV-1 infected, according to a prior study [38]. This is due to the virus's immune deficiency condition, which allows the bacteria to spread from the primary infection site, the lung, to other parts of the body. During TB-HIV-1 co-infection, there is a lack of granuloma growth and functional disruption of the local immune response within the granuloma [39].

Our study showed that having a history of TB and a history of contact with known pulmonary TB patients was found to be significant risk factors for EPTB development [16,19–22]. Similarly, it is well known that patients with a history of anti-TB treatment cases have an increased risk of EPTB [37].

In this study, we also discovered that men had a higher prevalence of EPTB involvement than women [15,20], which is consistent with similar findings in the previous study [40]. However, another systematic review and meta-analysis study in Africa found that refers to women with lymphadenitis with a higher rate of EPTB than men [41]. Likewise, women had a higher rate of EPTB infections than men [42]. In addition, another study reported women with a higher rate of EPTB than men [43].

In the end, the current study had its limitations. Firstly, the degree of EPTB prevalence in many parts of the country has yet to be addressed, making it impossible to conclude the true burden of EPTB in Ethiopia. Secondly, the observed publication bias that could be due to the differences in the laboratory methods might underestimate the estimated prevalence. Thirdly, Only three databases were searched. This could lead to publication bias. Finally, there is high

heterogeneity among studies that might affect the true estimates. However, the findings are still significant, because the rising rate of EPTB patients in the general population is concerning.

Conclusions

The finding of this study revealed that there is a high bacteriologically confirmed EPTB among persons suspected to have EPTB in Ethiopia. Patients having a history of previous tuberculosis, a poor income, a history of tuberculosis contact with a known PTB case, being HIV-1 positive, and having contact with PTB patients and a history of underlying diseases was with the most reported risk factors for EPTB. Thus, we recommend strengthening laboratory services for the diagnosis of EPTB in Ethiopia.

Supporting information

S1 File. PRISMA checklist.
(DOC)

S2 File. Literature search strategy from searched databases.
(DOCX)

S3 File. Detailed data of the included studies.
(XLSX)

S4 File. Newcastle-Ottawa quality assessment scale for cross-sectional studies.
(DOCX)

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Validation: Ayinalem Alemu, Kirubel Eshetu, Bazezew Yenew.

Writing – original draft: Getu Diriba.

Writing – review & editing: Ayinalem Alemu, Kirubel Eshetu, Habteyes Hailu Tola.

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PERSPECTIVES

Coronavirus Disease 2019 Diagnosis in Low- and Middle-Income Countries

The Big New Bully Disrupting TB and HIV Diagnostic Services

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Coronavirus disease 2019 (COVID-19) undermines control of other infectious diseases. Diagnostics are critical in health care. This opinion paper explores approaches for leveraging diagnostics for COVID-19 while retaining diagnostics for other infectious diseases, including tuberculosis (TB) and HIV. The authors reflect on experiences with GeneXpert technology for TB detection and opportunities for integration with other diseases. They also reflect on benefits and risks of integration. Placement of diagnostics in laboratory networks is largely nonintegrated and designated for specific diseases. Restricting the use of diagnostics leaves gaps in detection of TB, HIV, malaria, and COVID-19. Integrated laboratory systems can lead to more efficient testing while increasing access to critical diagnostics. However, the authors have observed that HIV diagnosis within the TB diagnostic network displaced TB diagnosis. Subsequently, COVID-19 disrupted both TB and HIV diagnosis. The World Health Organization recommended rapid molecular diagnostic networks for infectious diseases and there is a need for more investment to achieve diagnostic capacity for TB, HIV, COVID-19, and other emerging infectious diseases. Integrated laboratory systems require mapping laboratory networks, assessing needs for each infectious disease, and identifying resources. Otherwise, diagnostic capacity for one infectious disease may displace another. Further, not all aspects of optimal diagnostic networks fit all infectious diseases, but many efficiencies can be gained where integration is possible. *(J Mol Diagn 2022, 24: 289—293; https://doi.org/10.1016/j.jmoldx.2021.12.008)*

The roll-out of new technologies and the substantial growth in political and financial commitment by countries, regions, and bilateral and international donors (such as the Global Fund to Fight AIDS, Tuberculosis and Malaria; President's Emergency Plan for AIDS Relief [PEPFAR]; and US Agency for International Development) and their global partners have facilitated a surge of global progress in health over the past 15 years.[1] Despite major progress in the global HIV and tuberculosis (TB) responses, these diseases continue to represent a public health burden in all regions, with inequitable coverage of diagnosis, prevention, and treatment.[2]

Globally, an estimated 10 million individuals fell ill with TB in 2019, a number that has been declining very slowly in recent years; although, in 2019, there was an estimated reduction of 1.2 million TB deaths among HIV-negative individuals.[3] Access to TB treatment has grown from 6 million in 2015 to 7.1 million in 2019, with increased access to TB preventive treatment as well, to 4.1 million.[4] New HIV infections among women aged 15 to 24 years fell by 25% between 2010 and 2018, and since 2010, AIDS-related mortality has declined by 33%.[5] Other diseases, such as hepatitis C and sexually transmitted diseases, have gained global prominence, with many low- and middle-income

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countries (LMICs) beginning to implement services to reduce morbidity and mortality.

The coronavirus disease 2019 (COVID-19) pandemic has significantly disrupted health services due to cases overburdening the health system or response measures that limit normal health program activities and care-seeking. As of October 14, 2021, there have been 239,007,759 confirmed cases of COVID-19, including 4,871,841 deaths, reported to the World Health Organization (WHO) globally, and 6,471,051,151 vaccine doses have been administered. The pandemic has undermined the progress made in the last decade in part because access to timely diagnostics for TB, HIV, and other opportunistic infections has been compromised; for example, to illustrate a few impacts of COVID-19, TB domestic resources have been diverted to COVID-19 response, affecting also staffing and facilities used to isolate COVID-19 cases. WHO has indicated that TB diagnosis has gone down 21% in 2020 compared with 2019 due to COVID, which translates into one-half million more deaths due to TB. If new strategies are not developed, implemented, and coordinated effectively at the global and national levels, long-term setbacks will result.[2–6] Effective interventions and services must be targeted to the most vulnerable individuals and populations—for example, pregnant women, young children, individuals living with HIV/AIDS or TB, the poor, and the elderly—while maintaining quality and efficiency in existing health programs.[6]

As countries make progress toward universal health care (UHC), diagnostics are a critical component of health benefits packages because most diseases or conditions cannot be managed without a clear diagnosis and laboratory tests for follow-up. COVID-19 exposes the need for a fundamental shift in service delivery models, including diagnostic integration and involvement of the private sector as highlighted in the last Lancet Commission report[7,8] (for a supplementary perspective, see *https://www.statnews.com/2019/05/20/diagnostics-universal-health-coverage-succeed*, last accessed December 8, 2020). The pandemic reveals that reality by exacerbating the gaps in detection of TB, HIV, and other opportunistic infections due, on one hand, to lack of laboratory capacity (eg, physical infrastructure and human resources) in some LMICs, even before the pandemic, and on the other hand, to mitigation strategies undertaken to respond to COVID-19.[7,8] These mitigation steps and shifting of resources have drastically reduced the capacity of health systems in LMICs to respond to other health issues because of overwhelmingly high demand for the care of patients with COVID-19 and interruptions within the supply chain.

Because the diagnostics have been built and funded specifically for certain diseases, the use of new advances that enable technology designed for one disease to detect other diseases is often not permitted. For example, GeneXpert, a technology that revolutionized TB molecular diagnostic testing and has a massive footprint in 145 LMICs, can now be used for HIV (viral load, early infant diagnosis) and COVID-19 testing through the recent release of the new Xpert Xpress SARS-CoV-2 cartridge (Cepheid, Sunnyvale, CA). However, financial and operational barriers generate concerns about how the utilization of this technology in weak laboratory systems and public health programs will undermine, for example, TB and HIV diagnostic capacity in some countries. Improper integration of technology may lead to suboptimal diagnosis and ultimately greater TB and HIV mortality. The newly introduced diagnostics need to be integrated in a phased, systematic manner, and optimized to meet program needs and targets for both existing diseases and new ones.[4–8]

Current Situation

Application of nucleic acid amplification tests (NAATs) has revolutionized rapid and accurate diagnostic testing for most pathogens for a decade. Automated batched or modular cartridge—based NAATs offer a combination of excellent sensitivity and specificity and reproducible, accurate test results, with minimal manipulation and decreased risk of cross-contamination, that has made PCR technology an appealing alternative to culture- or immunoassay-based testing for disease diagnosis. Although NAATs are more sensitive than most other tests for TB, culture remains the gold standard. However, culture can take months, whereas NAATs can be performed in less than 2 hours (*http://www.stoptb.org/assets/documents/resources/wd/ERPD%20approved%20TB%20diagnostics%20info%20note.pdf?*, last accessed January 25, 2022).[9–11] The opportunity for decentralization to lower levels of the health system makes NAATs an essential tool to implement the End TB Strategy and realize the UNAIDS 95-95-95 goals.[12]

For the past 10 years, the Xpert assay has represented the first major advance in TB diagnosis, allowing peripheral detection of rifampicin resistance, which enabled detection of drug-resistant TB and exponentially increased the numbers of cases treated. Additionally, the Xpert Ultra test increases the sensitivity of TB diagnosis in children, HIV-infected individuals, and paucibacillary and extrapulmonary TB; and since its endorsement by WHO, most countries have quickly started rolling out Xpert.[9–11] As of December 31, 2018, 10,562 GeneXpert machines (47,567 modules) had been procured across 136 of the 145 countries eligible for concessional prices (Cepheid, 2018; W. Van Gemert, unpublished data). However, existing GeneXpert technologies typically have low overall utilization, although this is site-dependent in several countries. Countries are not procuring enough cartridges to reach testing targets or fully utilize instruments due to algorithm constraints on implementation, weak specimen referral linkages to testing, and inadequate attention to maintenance and prompt repair.

High-throughput platforms, mostly at centralized levels, have been introduced on a massive scale for HIV early infant diagnosis, drug resistance detection, and viral load

monitoring for treatment response, with funding from the Global Fund, PEPFAR, and other agencies. The volume of viral load tests performed has increased significantly from the 15 million viral load tests conducted in 2017, and the number is projected to double to nearly 30 million by 2022. The UNAIDS 2020 report released during the COVID-19 pandemic showed that only 14 countries have achieved the 90-90-90 HIV treatment targets (90% of individuals living with HIV know their HIV status, of whom 90% are on antiretroviral treatment and of whom 90% are virally suppressed), including Eswatini, which has one of the highest HIV prevalence rates in the world. However, in many parts of the world, COVID-19 is colliding with the ongoing HIV epidemic.[6–8] A recent WHO HIV guideline recommends point-of-care diagnosis and monitoring as preferred over centralized laboratory testing because they significantly reduce turnaround time and result in saving lives.[10] Further, the WHO Health Assembly recommends integrated services; donors such as the Global Fund may reduce funding and expect further integration.

To control the spread of COVID-19, experts agree that an aggressive strategy of vaccination along with test, trace, and treatment is needed, combined with physical distancing measures and the use of masks. However, SARS-CoV-2 detection in some countries is limited by weak and uncoordinated laboratory systems, as well as insufficient laboratory equipment and test kits for PCR or access to rapid diagnostic tests. This insufficient capacity compels governments, for example, to restrict testing to individuals who meet specific narrow criteria.[13] Many efforts and partnerships to increase the response to COVID-19 in Africa and around the world have been launched, such as the Access to COVID-19 Tools Accelerator, which is coordinated by the Global Fund, WHO, UNICEF, and the Partnership to Accelerate COVID-19 Testing in Africa. However, after 19 months into the pandemic, lessons and progress in diagnostic pipelines are demonstrating the efficiency of antigen tests. The Global Fund is advocating for using antigen tests (3 USD, rather than GX for COVID-19 at 20 USD), and WHO is updating its antigen rapid diagnostic test guidance as well as preparing interim guidance on Recommendations for National SARS-CoV-2 Testing Strategies and Diagnostic Capacities.

Discussion

This paper aims to identify the best approach to using both existing and new technologies to address the COVID-19 pandemic and coexisting major public health challenges without jeopardizing the gains in diagnostic access for TB, HIV, and other opportunistic infections.

COVID-19 illustrates our common vulnerability to disease across borders, the public–private divide, and the limits of our fragmented approach to health.[2,11–13] A more coordinated, comprehensive, and integrated decentralization of services at the community level is urgently needed. In their paper, Pooran et al[11] make a case for value for money for point-of-care TB diagnostic services because such services reduce, not only death, but also economic loss in Africa. It also reduces transport costs to have testing performed more locally.

Governments and donors will need to revisit public health programs and systems in line with UHC in LMICs. Doing so will require a paradigm shift, with change management, task shifting, and bold policies. Centralized testing of patients for initial diagnosis should be shifted to the lowest administrative level possible (district), ideally at the point of care. Centralized laboratory staff will continue to have opportunities for leadership of the entire network, for example, quality assurance, introduction of new diagnostics, research, training, and mentoring.

The current diagnostic gaps in the HIV, TB, and COVID-19 response could be greatly mitigated by intensively investing in public health laboratory systems and optimizing use of existing technologies already introduced in many LMICs. However, many of the multiplex technologies are centralized in biosafety level 2 or 3 laboratories, due to high requirements for safety, human skills, resources, and alignment with vertical diagnostic programs.

The US Food and Drug Administration approved Xpert Xpress SARS-CoV-2 on March 21, 2020.[9,13] The test kit can deliver a COVID-19 diagnosis in 45 minutes. The machine can be placed in a biosafety level 1 or 2 laboratory or in mobile vehicles with similar safety requirements, making it ideal for community testing. This will reduce the costs of referral, from both the patient and health system perspectives. Other affordable point-of-care or near-patient multiplex platforms endorsed by WHO are available, such as TrueNat (Molbio Diagnostics, Goa, India) or TB loop-mediated isothermal amplification assay); and more platforms are in development or in clinical trials that can diagnose and monitor multiple diseases, including drug-resistant malaria [refer to: *https://www.devex.com/news/afterthe-pandemic-how-will-covid-19-transform-global-health-and-development-96936*, last accessed December 8, 2020; *http://www.stoptb.org/assets/documents/covid/Considerations%20for%20selection%20of%20SARS-CoV-2%20diagnostics.pdf*, last accessed December 8, 2020; *https://www.finddx.org/mal-fev/improved-malaria-rdts*, last accessed December 8, 2020].[14,15]

Multidisease molecular platforms [eg, Abbott's RealTime m2000sp and m-PIMA (Abbott, Abbott Park, IL); Cepheid's GeneXpert GX-4, -16, -48, and -80 modules; Hologic Panther, Roche COBAS AmpliPrep/COBAS TaqMan CAP/CTM 96; Roche cobas 4800/6800/8800 (Roche, Basel, Switzerland); Thermo Fisher's Applied Biosystems 7500 Fast Real-Time PCR system (Thermo Fisher, Waltham, MA); Becton Dickinson's BD MAX (Becton Dickinson, Franklin Lakes, NJ); and genesig Easy qPCR Detection Kit for nCoV-2019 (genesig, Chandler's Ford, UK)][6,7,10] have already been introduced for HIV, influenza,

hepatitis, and other diseases in many national reference laboratories and research institutes in LMICs. Additionally, the Food and Drug Administration has authorized—for emergency use—some of the test kits that can be accommodated by some of the platforms listed above for SARS-CoV-2.

Given these developments, the diagnostic pipeline for COVID-19 and other priority diseases is growing. Integrated technologies, such as next-generation sequencing, at peripheral levels might also be used for detection of drug resistance across diseases. Furthermore, treatment monitoring, such as viral load and bacterial load testing, might also be conducted using integrated platforms. Having well-functioning laboratory systems to detect multiple infectious diseases, their drug resistance patterns, and treatment responses at lower levels of the health system would enable a more equitable, human-centered approach, with increased access and decreased turn-around time, ultimately reducing morbidity and mortality from infectious disease, particularly TB and HIV.

Integration of diagnostic networks is at an early stage in LMICs. A few African, Asian, and Latin American countries have piloted diagnostic integration, mainly at selected central and intermediate laboratories; they include Cameroon (HIV and TB), Malawi (HIV and TB), Nigeria (hepatitis C and TB), Zimbabwe (HIV and TB), Brazil, the Caribbean countries, Democratic Republic of Congo, India, and Malaysia.[11] Best practices and lessons from these pilots are urgently needed to inform the development and scale-up of an integrated diagnostic laboratory network approach. This network will form the basis for a robust public health laboratory system in each country, with strong international and government collaboration, which will benefit all health programs, including reproductive health, maternal and child health, communicable diseases, emerging diseases, and cancer, in line with UHC.[7]

Several LMICs have already used GeneXpert technology to diagnose both TB and COVID-19,[8,14,16,17] but such integration has not been uniform across countries, revealing better approaches to follow in the future. The authors believe that no one size fits all, because countries vary in infrastructure, disease burden, and geographic peculiarities. Further, some countries have vector-borne diseases such as malaria and cholera that are relevant only in certain areas of the country. Nonetheless, many common links can be made across most LMICs to integrate their laboratory systems for infectious diseases and create a more resilient response on all tiers of their public health laboratory network, shifted closer and targeted to the communities that need them.

Recommendations

LMICs should take advantage of existing multiplex platforms, such as GeneXpert, high-throughput platform technologies, and laboratory networks, to introduce COVID-19 testing. These networks are already established and working well to make laboratory diagnostic services available in several countries. By integrating diagnostics for COVID-19 and other infectious diseases into a well-articulated laboratory system, we will gain efficiencies as well as move closer to UHC even during the COVID-19 pandemic. Introducing a vertical COVID-19 diagnostic service model would be expensive and inefficient in reaching the individuals who need the services—and it would not be sustainable.

Integrated, affordable multiplex technologies, particularly at the point of care, local and community levels, have the advantages of avoiding parallel diagnostic systems and duplication of activities such as referral and transport, equipment maintenance, human resource management, quality assurance, supply chain and quantification, and training—and duplication of the costs of those activities. In providing increased capacity and uptake for TB, HIV, COVID-19, and other existing or future opportunistic infections, integrated technologies offer better value for money and sustainability.

Innovative approaches to diagnostic integration can maximize investments while increasing access but require a strategic approach tailored to each country context based on mapping and optimizing the laboratory network, assessing the needs for detection capacity for each disease, and identifying the gaps so resources can be mobilized. Merely having the machines will not translate into great improvements. We must also strengthen:

- Political leadership to remove barriers to diagnostic integration, and roadmaps and strategic plans focused on increasing investment in diagnostic capacity in a holistic, coordinated way, with robust policies;
- Structures for supplies of consumables, maintenance, and sample transportation;
- Coordination and communication among disease control programs, including donors and the private sector;
- Technical assistance to ministries of health, local public health programs and institutions, and the private sector;
- Quality-assured, connected, and sustainable laboratory networks, led by a national public health laboratory or other governance body, to guarantee universal access to prevention, diagnostics, treatment, and care services; and
- Integrated laboratory information systems and dashboards to increase use of data and inform decision-making for patient management, program planning, and service delivery, while ensuring confidentiality.

Conclusion: Looking Ahead

Effective interventions and services will require transforming our way of diagnosing and treating individuals to enable countries to reach the End TB milestones and UNAIDS 95-95-95 goals, even while containing other diseases. If we do not act to mitigate the threat, COVID-19 will

lead to an upsurge in deaths from TB, HIV, and other opportunistic infections. If we take an integrated approach, leveraging the infrastructure and resources we have already invested in and moving swiftly to strengthen the health system as a whole, we can step up the fight against both COVID-19 and other diseases of major public health importance.

The authors call on all ministries of health, donors, implementers, partners, and supported countries to revisit their strategies by looking at all these opportunities. The authors recommend that donors focus investments in COVID-19 testing by taking advantage of existing platforms and infrastructures to maximize service coverage to save lives during the pandemic while serving as a benchmark to gauge progress toward implementing guidelines such as the WHO Essential Diagnostics List and investing in long-term UHC goals. This approach will cost far less than setting up parallel systems or centralizing testing in a few laboratories. This is a time to be bold and act fast.

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Author Contributions

A.U.N. wrote the manuscript; A.U.N., J.N.S., M.G. and P.G.S. wrote, reviewed, edited, and approved the final manuscript equally.

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RESEARCH ARTICLE

Poor treatment outcome and associated risk factors among patients with isoniazid mono-resistant tuberculosis: A systematic review and meta-analysis

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Abstract

Background

To date, isoniazid mono-resistant tuberculosis (TB) is becoming an emerging global public health problem. It is associated with poor treatment outcome. Different studies have assessed the treatment outcome of isoniazid mono-resistant TB cases, however, the findings are inconsistent and there is limited global comprehensive report. Thus, this study aimed to assess the poor treatment outcome and its associated risk factors among patients with isoniazid mono-resistant TB.

Methods

Studies that reported the treatment outcomes and associated factors among isoniazid mono-resistant TB were searched from electronic databases and other sources. We used Joana Briggs Institute critical appraisal tool to assess the study's quality. We assessed publication bias through visual inspection of the funnel plot and confirmed by Egger's regression test. We used STATA version 17 for statistical analysis.

Results

Among 347 studies identified from the whole search, data were extracted from 25 studies reported from 47 countries. The pooled successful and poor treatment outcomes were 78% (95%CI; 74%-83%) and 22% (95%CI; 17%-26%), respectively. Specifically, complete, cure, treatment failure, mortality, loss to follow-up and relapse rates were 34%(95%CI; 17%-52%), 62% (95%CI; 50%-73%), 5% (95%CI; 3%-7%), 6% (95%CI; 4%-8%), 12% (95%CI; 8%-17%), and 1.7% (95%CI; 0.4%-3.1%), respectively. Higher prevalence of pooled poor treatment outcome was found in the South East Asian Region (estimate; 40%, 95%C; 34%-45%), and African Region (estimate; 33%, 95%CI; 24%-42%). Previous TB treatment (OR;

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1.74, 95%CI; 1.15–2.33), having cancer (OR; 3.53, 95%CI; 1.43–5.62), and being initially smear positive (OR; 1.26, 95%CI; 1.08–1.43) were associated with poor treatment outcome. While those patients who took rifampicin in the continuation phase (OR; 0.22, 95%CI; 0.04–0.41), had extrapulmonary TB (OR; 0.70, 95%CI; 0.55–0.85), and took second-line injectable drugs (OR; 0.54, 95%CI; 0.33–0.75) had reduced risk of poor treatment outcome.

Conclusion

Isoniazid mono-resistant TB patients had high poor treatment outcome. Thus, determination of isoniazid resistance pattern for all bacteriologically confirmed TB cases is critical for successful treatment outcome.

PROSPERO registration number: CRD42022372367

Introduction

Tuberculosis (TB) is causing a huge public health impact being the second cause of mortality among infectious diseases. There were 9.9 million TB cases and more than 1.5 million deaths due to TB in 2020 [1]. The efforts for the prevention and control of TB becomes challenging due to the emergence of drug resistant TB mainly with respect to treatment outcome. Drug-resistant TB is associated with poor treatment outcome [1, 2]. Based on the 2021 global TB report, the global successful treatment outcome among drug susceptible and Multi-drug resistant TB (MDR-TB)/ Rifampicin resistant TB (RR-TB) cases were 86% and 59%, respectively [1]. Drug resistant TB have different categories including mono-resistant TB. When TB is caused by *Mycobacterium tuberculosis* strains which are resistant only to one anti-TB drug it is called mono-resistant TB and isoniazid mono-resistant TB is among the categories [1, 2].

The world health organization (WHO) through the END TB Strategic document recommends calls for the early TB diagnosis drug sensitivity testing (DST) [3]. The drug resistance pattern should be determined for all bacteriologically confirmed TB cases to put patients on the right treatment for successful treatment outcome and to prevent the emergence of additional drug-resistance. Even though, there are improvements in the recent years, this becomes difficult in many TB endemic low and middle-income countries having resource limitations. To date, due to the implementation of Xpert MTB/RIF assay many countries reported RR-TB to the WHO [1, 2]. In this assay, the resistance profile for the other potent anti-TB drug isoniazid is unknown that might have made the isoniazid mono-resistant TB cases to be less reported and be treated as drug susceptible TB [2]. However, about 11% of TB patients worldwide are estimated to have isoniazid resistant, rifampicin susceptible TB [2].

Studies conducted in different settings indicated that isoniazid mono-resistant TB is a problem in different countries [4–8]. The incidence of isoniazid mono-resistant TB is increasing and it is higher than RR-TB globally [9]. In addition, studies revealed that those isoniazid mono-resistant TB cases had higher rate of poor treatment outcome compared to the drug-susceptible TB cases [10–13]. There are studies that assessed the treatment outcome of isoniazid mono-resistant TB cases [4–7, 10–30], however, the findings are inconsistent. In addition, there is no comprehensive report at the global level. Thus, this study aimed to assess the poor treatment outcome and the associated risk factors among patients with isoniazid mono-resistant TB.

Methods

Protocol registration

The protocol for this study is registered on the international prospective register of systematic reviews (PROSPERO) with a registration number CRD42022372367.

Information source and search strategy

This study was developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting checklist [31] (**S1 Table**). Article searching was conducted systematically from the electronic databases including PubMed, CINAHL, Global Health, Global Health Medicus and Environment Index. In addition, our search extends to other grey literature sources such as Google and Google Scholar. The search was conducted up to 20 November 2022 for studies published in English language. Two authors (AA, EG) have conducted the article searching independently. The third author (ZWB) managed the inconsistencies arose between the two authors. The search was conducted using the keywords; isoniazid mono-resistant tuberculosis, treatment outcome and risk factors/determinants. The Boolean operators OR and AND were used accordingly. The search string for PubMed was ("Treatment Outcome"[MeSH Terms] OR (("poverty"[MeSH Terms] OR "poverty"[All Fields] OR "poor"[All Fields]) AND ("Treatment Outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "Treatment Outcome"[All Fields])) OR ("Treatment Outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "Treatment Outcome"[All Fields])) AND (("isoniazid"[MeSH Terms] OR "isoniazid"[All Fields] OR "isoniazide"[All Fields]) AND "mono-resistant"[All Fields]) (**S2 Table**).

Study selection procedure

We have followed a step-wise approach to select the eligible studies. Primarily, all the studies identified from the whole search were exported to EndNote X8 citation manager, and we have removed the duplicates. In the next step, we have screened the articles by title and abstract. Then, full-text assessment was conducted for the remaining articles. Finally, we have included the articles that passed the full-text review in the final analysis. The article selection procedure was conducted by two independent authors (GD, GS) using pre-defined criteria that considered study subjects, study designs, quality, and outcome (**Fig 1**).

PICOS criteria

Participants: Isoniazid mono-resistant tuberculosis patients
Intervention: Anti-TB treatment
Comparator: Successful treatment outcome
Outcome: Poor treatment outcome
Study design: Observational studies.
Study setting: Any setting in any country across the globe

Inclusion and exclusion criteria

Studies that reported either TB treatment outcome or risk factors of poor treatment outcome or both in patients with isoniazid mono-resistant TB were included in the study. There was no restriction on entering the study in terms of sample size. The exclusion criteria were review studies, and not differentiated the target population.

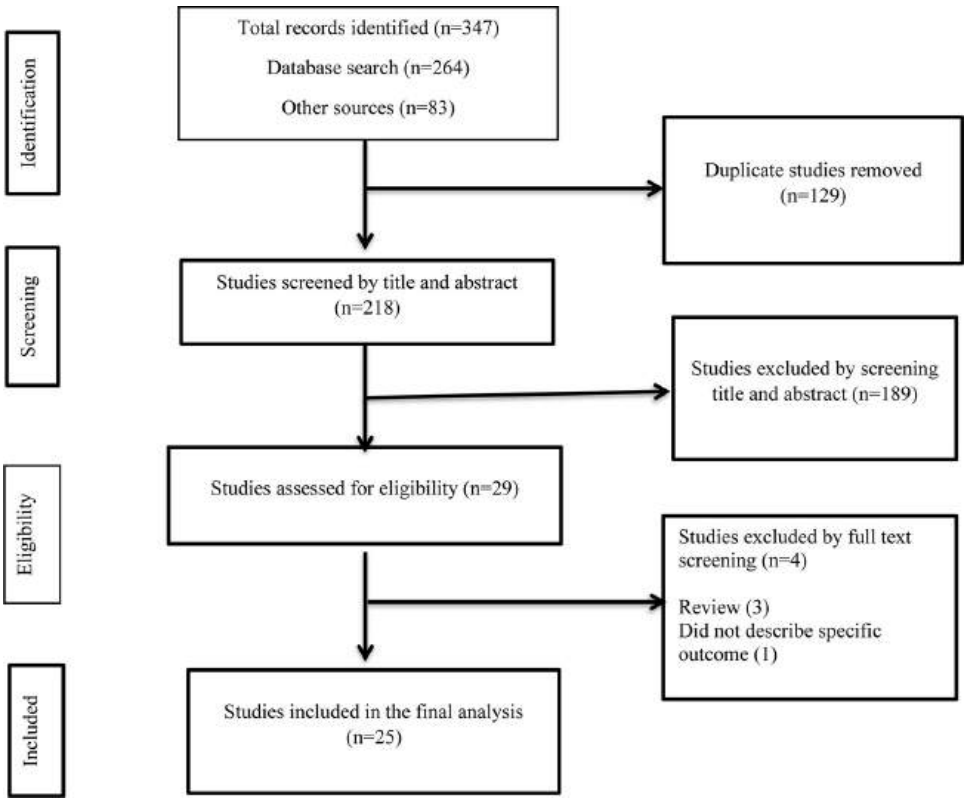

Fig 1. Flowchart describing the selection of studies for the systematic review and meta-analysis of poor treatment outcome and its associated factors among patients with isoniazid mono-resistant tuberculosis.

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Data extraction

Data were extracted from the articles included in the final analysis using Microsoft Excel 2016 spreadsheet. The extracted data included; primary author name, publication year, country, data collection period, study design, data collection time (prospective vs retrospective), study setting/place, age of study participants, number of study participants, number having successful (completed, cured) and poor treatment outcomes (mortality, treatment failure, loss to follow-up), number of relapse in successfully treated cases, and factors associated with poor treatment outcomes. Data were extracted by two independent authors (AA, ZWB), and the third author (GD) managed the inconsistencies that arose between the two authors.

Risk of bias (quality) assessment of included studies

We have evaluated the methodological reputability and quality of the findings of the included studies using the Joanna Briggs Institute (JBI) critical appraisal tools for observational studies [32]. Two independent authors (GS, KE) conducted the quality assessment, and the third author (ZWB) resolved the inconsistencies. The checklist for cross-sectional, case control and cohort studies consists of 8, 10, and 11 indicators, respectively. Each indicator was equally scored and summed up to give 100%. The quality of the studies was scored to have high, medium and low quality if the overall quality score was >80%, 60–80% and <60%, respectively (**S3 Table**). The presence of publication bias was explored through visual evaluation of the funnel plot such that asymmetry of the funnel plot indicated the presence of publication bias.

Furthermore, we have conducted egger's regression test to confirm the presence of publication bias ($P<0.05$).

Outcomes

The primary outcome of this study was the treatment outcomes such as the successful and poor treatment outcomes along with different categories among patients with isoniazid mono-resistant tuberculosis. The secondary outcomes were the factors that associated with poor treatment outcomes in those patients.

Operational definition

The operational definition for isoniazid mono-resistant tuberculosis was based on the WHO definition. This type of tuberculosis is caused by *Mycobacterium tuberculosis* strains that are resistant to isoniazid but susceptible to rifampicin confirmed in vitro [33]. The definitions for the treatment outcomes is based on the WHO classification of TB treatment outcomes as described in the guideline [34].

Ethical approval and consent to participate

Since this study is based on a review of published articles, ethical approval is not mandatory. The protocol is registered on PROSPERO.

Data synthesis and statistical analysis

The pooled estimates of successful and poor treatment outcomes among patients with isoniazid mono-resistant TB was determined with its 95%CI by assuming the true effect size varies between studies. The pooled estimate for successful and poor treatment outcomes were determined as the ratio of numbers of isoniazid mono-resistant TB patients with successful and poor treatment outcomes to the total treated isoniazid mono-resistant TB patients, respectively. Besides, the pooled OR along with 95%CI was estimated for each factor to determine the factors associated with poor treatment outcomes. We have also performed a stratified analysis. We presented the data using the forest plot. The heterogeneity among the studies was assessed using the I^2 heterogeneity test and a value above 50% indicated the presence of substantial heterogeneity among studies [35, 36]. We have performed bi-variable and multi-variable meta-regression to assess the association of study year and sample size on poor treatment outcome. To assess the presence of publication bias, the funnel plot was inspected visually and Egger's regression test was conducted. For those parameters that had a publication bias ($P<0.05$) in the Egger's regression test [37, 38], we have performed a trim and fill analysis to adjust the publication bias. The statistical analysis was conducted using STATA version 17.

Results

Characteristics of included studies

From the whole search, we identified 347 studies and after removing 129 duplicates, 218 were screened by title and abstract. At this stage, 189 studies were excluded and the remaining 29 studies were screened by full text review. Finally, 25 studies were included in this study [4–7, 10–30]. These studies were reported from five continents and from all the six WHO regions. Accordingly, the most frequent number of studies were reported from Asia with 11 studies followed by North America (5 studies), Africa (4 studies), Europe (3 studies), and South America (2 studies). Per WHO regional classification, relatively higher number of studies were reported from the Region of Americas (AMR) with 7 studies. The frequencies of studies in the other

regions were; West Pacific Region (WPR) (5 studies), African Region (AFR) (4 studies), European Region (EUR) (4 studies), South Eastern Asian Region (SEAR) (3 studies), and Eastern Mediterranean Region (EMR) (2 studies). The studies were reported from 47 countries and a maximum of two studies were reported from a single country (South Africa, Taiwan, China, Portugal, USA, Canada, India, and Peru). A single study conducted in Europe comprises data collected from 31 countries [20] that made the number of countries included in the current systematic review and meta-analysis study to be 47 in number.

The studies were published from 2009 [15, 29] to 2022 [28]. The data collection period for most of the studies were after 2000 except two studies where the data collection period was from October 1992 to October 2005 for one study [15] and from 1995 to 2010 for the other study [11]. In the majority of the studies (88%, 22), data were collected retrospectively. The data in these studies were collected either from a health facility or from the national surveillance data registry database (**Table 1**).

Pooled treatment outcomes among isoniazid mono-resistant tuberculosis patients

In the current study, we extracted data to estimate the pooled prevalence of successful treatment outcome including cure rate and treatment completion rate, poor treatment outcome including death rate, treatment failure rate and loss to follow-up, relapse after successful treatment outcome, and factors associated with poor treatment outcome among patients with isoniazid mono-resistant tuberculosis.

Data were extracted from 24 and 23 studies to estimate the pooled prevalence of successful treatment outcome and poor treatment outcome, respectively. The largest sample size was 6796 in a study that comprises 31 European countries [20], while the smallest sample size was 9 in a study conducted in Saudi Arabia [21]. Among the studies, 11 studies had a sample size below 100 while the remaining studies had a sample size of 132 and above.

Based on data collected from 24 studies comprising 10, 698 isoniazid mono-resistant TB patients, 8606 had successful treatment outcome that gave a pooled estimate of 78% (95%CI; 74–83, I^2; 94.02%) (**Fig 2**). The symmetry of the funnel plot (**Fig 3**) and the statistical insignificance of the egger's regression test showed there is no publication bias (P = 0.080). Specifically, the pooled treatment completed and cured rate among isoniazid mono-resistant TB patients were 34% (95%CI; 17–52, I^2; 99.26%) (**S1 and S2 Figs**) and 62% (95%CI; 50–73, I^2; 96.91%) (**S3 and S4 Figs**), respectively. Based on the WHO regional classification, the pooled prevalence of successful treatment outcome from the highest to lowest pooled estimate were; AMR (estimate; 84%; 95%CI; 78–90, I^2; 87.66%), EUR (estimate; 84%; 95%CI; 77–91, I^2; 91.21%), WPR (estimate; 82%; 95%CI; 77–86, I^2; 64.67%), EMR (estimate; 75%; 95%CI; 44–106, I^2; 73.41%), AFR (estimate; 67%; 95%CI; 58–76, I^2; 74.28%), and SEAR (estimate; 62%; 95%CI; 56–69, I^2; 13.74%) (**Fig 2**) (**Table 2**).

The poor treatment outcome was estimated from 23 studies having 10,670 isoniazid mono-resistant TB patients. From these individuals, 2084 had poor treatment outcome that yield a pooled estimate of 22% (95%CI; 17–26, I^2; 94.08%) (**Fig 4**). The egger's regression test showed there is no publication bias (P = 0.107) (**Fig 5**). Specifically, the pooled treatment failure, mortality and loss to follow-up rates were 5% (95%CI; 3–7, I^2; 93.97%) (**S5 and S6 Figs**), 6% (95% CI; 4–8, I^2; 88.73%) (**S7 and S9 Figs**), and 12% (95%CI; 8–17, I^2; 96.58%) (**S9 and S10 Figs**), respectively. Based on the WHO regional classification, the pooled prevalence of poor treatment outcome from the highest to lowest pooled estimate was; SEAR (estimate; 40%; 95%C; I34-45, I^2; 0.00%), AFR (estimate; 33%; 95%CI; 24–42, I^2; 74.28%), EMR (estimate; 25%; 95% CI; -0.06–56, I^2; 73.41%), WPR (estimate; 18%; 95%CI; 14–23, I^2; 64.63%), EUR (estimate;

Table 1. Characteristics of individual studies on the poor treatment outcome and associated risk factors among patients with isoniazid mono-resistant tuberculosis included in the current systematic review and meta-analysis.

Author year	Publication year	Country	Study period	Study design	Data collection time	Study setting	Age group	Sample size	Successful outcome		Poor outcome	
									N	%	N	%
Chien et al., 2014	2014	Taiwan	January 2004 to October 2011	Retrospective cohort study	Retrospectively	Four hospitals in northern, central, southern and eastern Taiwan	All age groups (Median age was 64 years)	395	328	83.04	67	16.96
Bachir et al., 2021	2021	France	January 1, 2016 to December 31, 2017	Multicenter case-control study	Retrospectively	University hospitals of Paris, Lille, Caen and Strasbourg	Median age was 35 years	97	75	77.32	22	22.68
Cattamanchi et al., 2009*	2009	USA	October 1992 to October 2005	Retrospective cohort study	Retrospectively	San Francisco Department of Public Health Tuberculosis Control Section	Median age was 47 years	137	-	-	-	-
Kwak et al., 2020	2020	South Korea	January 2005 to December 2018	Retrospective record review	Retrospectively	South Korean tertiary referral hospital	≥18 years	195	164	84.10	31	15.90
Binkhamis et al., 2021	2021	Saudi Arabia	May 2015 and April 2019	Cross-sectional analytical study	Retrospectively	King Khalid University Hospital	All age groups (range:1–90 years)	9	5	55.56	4	44.44
Murwira, et al., 2020	2020	Zimbabwe	March 2017 and December 2018	Retrospective cohort study	Retrospectively	National TB Reference Laboratory (NTBRL) in Bulawayo City and National TB programme	All age groups (Median age was 36 years, Interquartile range, was 29–45 years)	31	25	80.65	6	19.35
Chierakul et al., 2014	2014	Thailand	July 2009 and July 2011	Retrospective cohort study	Retrospectively	Siriraj Hospital	> 15 years	28	20	71.43	-	-
Jacobson et al., 2011	2011	South Africa	28 November 2000 to 28 May 2009	Retrospective cohort study	Retrospectively	22 clinics in the rural Cape Winelands East and Overberg Districts, Western Cape Province	All age groups (range:11–67 years)	151	101	66.89	50	33.11
Garcia et al., 2018	2018	Peru	January 2012 and December 2014	Cross-sectional study	Retrospectively	National registry of drug-resistant tuberculosis	All age groups	947	731	77.19	216	22.81
Karo et al., 2018	2018	31 European countries	2002 to 2014	Observational study	Retrospectively	European Surveillance System (TESSy)	All age groups (Median age was 41 years)	6796	5611	82.56	1185	17.44
Saldaña et al., 2016	2016	Mexico	1995 to 2010	Prospective cohort study	Prospectively	12 municipalities in the Orizaba Health Jurisdiction in Veracruz State	> 15 years	85	64	75.29	21	24.71
Villegas et al., 2016	2016	Peru	March 2010 to December 2011	Prospective cohort study	Prospectively	34 health facilities in a northern district of Lima	All age groups	82	63	76.83	19	23.17

(*Continued*)

Table 1. (Continued)

Author year	Publication year	Country	Study period	Study design	Data collection time	Study setting	Age group	Sample size	Successful outcome		Poor outcome	
									N	%	N	%
Edwards et al., 2020	2020	Canada	2007 to 2017	Retrospective cohort study	Retrospectively	One of three centralized comprehensive clinics in the province of Alberta	Median age was 37 years	98	90	91.84	8	8.16
Wang et al., 2014	2014	Taiwan	2006 January to 2007 December	Retrospective cohort study	Retrospectively	Chang Gung Memorial Hospital	All age groups	134	114	85.07	20	14.93
Sayfutdinov et al., 2021	2021	Uzbekistan	2017 to 2018	Retrospective cohort study	Retrospectively	Two regions of Uzbekistan (Fergana and Bukhara)	All age groups	132	105	79.55	27	20.45
der Heijden et al., 2017	2017	South Africa	2000 to 2012	Longitudinal study	Retrospectively	Prince Cyril Zulu Communicable Diseases Centre (PCZCDC)	All age groups (Median age was 34 years)	405	235	58.02	170	41.98
Romanowski et al., 2017	2017	Canada	2002 to 2014	Retrospective record review	Retrospectively	BC Centre for Disease Control (BCCDC)	All age groups (Median age was 46 years)	152	140	92.11	12	7.89
Santos et al., 2018	2018	Portugal	01 January 2008 to 31 December 2014	Retrospective record review	Retrospectively	National-Tuberculosis-Surveillance-System (SVIG-TB)	All age groups (Median age was 44 years)	232	210	90.52	22	9.48
Shao et al., 2020	2020	China	2013 to 2018	Retrospective cohort study	Retrospectively	Four national DR-TB surveillance sites of Jiangsu Province	All age groups (Median age was 48 years)	63	52	82.54	11	17.46
Kuaban et al., 2020	2020	Cameroon	January 2012 to March 2015	Retrospective record review	Retrospectively	In all the TB diagnostic and treatment centres (DTCs) in four regions of Cameroon namely the North West, South West, West, and Littoral regions	All age groups (range: 17–79 years)	45	32	71.11	13	28.89
Salindri et al., 2018	2018	USA	2009 to 2014	Retrospective cohort study	Retrospectively	Georgia State Electronic Notifiable Disease Surveillance System (SENDSS)	≥15 years	140	124	88.57	16	11.43
Nagar et al., 2022	2022	India	January 2019 to December 2020	Retrospective record review	Retrospectively	Ahmedabad city from Ni-kshay, an online web-based portal	≥18 years	243	144	59.26	99	40.74
Tabarsi et al., 2009	2009	Iran	2003 to 2005	Prospective cohort study	Prospectively	Masih Daneshvari Hospital	All age groups	42	37	88.10	5	11.90
Chunrong et al., 2020	2020	China	January 2016 to January 2019	Retrospective record review	Retrospectively	Shenzhen's drug-resistant TB project	All age groups (17–75 years)	144	102	70.83	42	29.17

(*Continued*)

Table 1. (Continued)

Author year	Publication year	Country	Study period	Study design	Data collection time	Study setting	Age group	Sample size	Successful outcome		Poor outcome	
									N	%	N	%
Garg et al., 2019	2019	India	January 1 to December 31, 2017	Retrospective record review	Retrospectively	At the nodal DRTB centre, Department of Pulmonary Medicine, Government Medical College and Hospital, Chandigarh	All age groups	52	34	65.38	18	34.62

"-"; Not specifically indicated

* the study only indicated the treatment completion rate the total successful treatment outcome including the cured cases and the poor treatment outcome (failure, death and lost to follow-up) are not indicated in the study.

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17%; 95%CI; 11–22, I^2; 85.06%), and AMR (estimate; 16%; 95%CI; 10–22, I^2; 87.75%) (Fig 4) (Table 2).

Pooled prevalence of relapse among successfully treated isoniazid mono-resistant tuberculosis patients

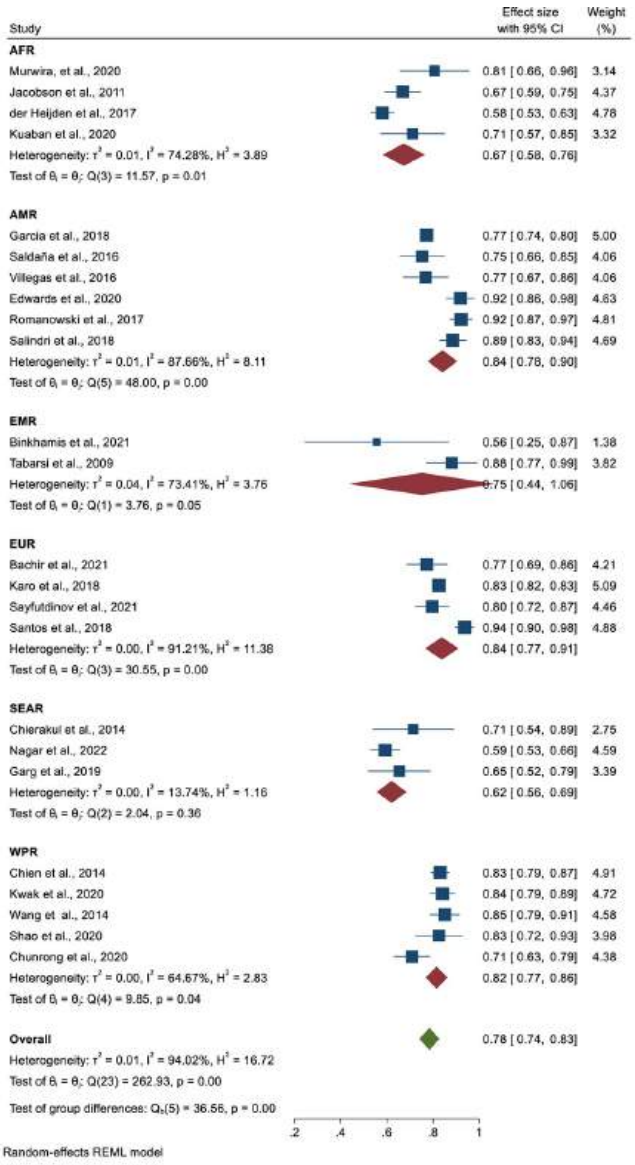
In this study, we have also assessed the relapse rate among isoniazid mono-resistant TB patients who had successful treatment outcome. We extracted data from eight studies comprising 970 successfully treated isoniazid mono-resistant TB cases. From these individuals, 28 developed relapse. The relapse period started from treatment completion and extends up to two years after treatment. Based on the random-effects model, the pooled prevalence of relapse among successfully treated isoniazid mono-resistant TB cases was 1.7% (95%CI; 0.4–3.1, I^2; 44.58%) (Fig 6).

Meta-regression

Besides, we have conducted a meta-regression analysis to assess the effect of sample size and publication year on the heterogeneity among studies that reported poor treatment outcome among isoniazid mono-resistant TB patients. The multivariable meta-regression model revealed that sample size (P = 0.713) and publication year (P = 0.464) did not significantly affected heterogeneity among studies (Table 3).

Risk factors of poor treatment outcome in isoniazid mono-resistant tuberculosis patients

In the current study, we assessed the risk factors associated with poor treatment outcome in isoniazid mono-resistant TB patients. We have performed the pooled estimate for the factors reported at least by two studies. We have estimated the pooled OR for 19 variables. The risk factors analyzed included demographic (sex, age group), smoking status, clinical factors such as having co-morbidities including diabetes, cancer, end-stage renal failure, and HIV, presence of cavity lesion in the chest radiograph, type of TB (extra-pulmonary vs pulmonary), initial smear status (smear positive vs smear negative), culture conversion after 2 months, drug-resistance level of isoniazid (high level vs low-level), and per taking different anti-TB drugs during



τ2; Tau (between-study variance), I^2; I-squared heterogeneity statistic (variability between studies), H^2; H-squared heterogeneity statistic (variability between studies).

Fig 2. Forest plot for the pooled successful treatment outcome rate among patients with isoniazid mono-resistant tuberculosis.

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initiation phase isoniazid (INH), streptomycin (STR), fluoroquinolones (FLQ), second-line injectable drugs (SLIDs) and continuation phase (rifampicin (RIF), (pyrazinamide (PZA)).

Statistically significant association was found for previous TB history (pooled OR; 1.74; 95%CI; 1.15–2.33, I^2; 45.10%) (Fig 7), having cancer, (pooled OR; 3.53; 95%CI; 1.43–5.62, I^2; 0.00%) (S11 Fig), initially smear positive (pooled OR; 1.26, 95%CI; 1.08–1.43, I^2; 2.13%) (Fig 8), taking RIF in the continuation phase (pooled OR; 0.22, 95%CI; 0.04–0.41, I^2; 0.00%) (S12 Fig), having EPTB (pooled OR; 0.70, 95%CI; 0.55–0.85, I^2; 0.00%) (S13 Fig), and taking SLIDs (pooled OR; 0.54, 95%CI; 0.33–0.75, I^2; 0.00%) (S14 Fig). Accordingly, individuals with previous TB treatment history had 1.74 times the odds to had poor treatment outcome compared to

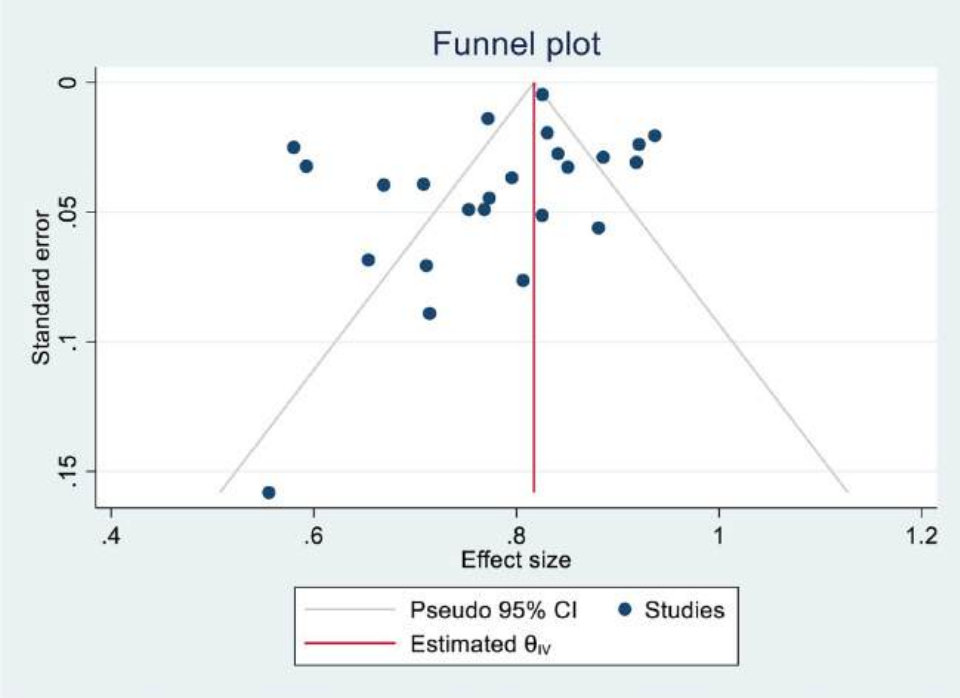

Fig 3. Funnel plot for the pooled successful treatment outcome rate among patients with isoniazid mono-resistant tuberculosis.

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new patients. Those patients who had cancer had 3.53 times the odds to develop poor treatment outcome compared to the counterparts. In addition, those patients who were smear positive initially had 1.26 times the odds to develop poor treatment outcome compared to those having smear negative TB initially. Patients who took RIF in the continuation phase had 78% reduced risk to have poor treatment outcome compared to their counterparts. Furthermore, those who took SLIDs had 45% reduced risk to have poor treatment outcome compared to their counterparts. Besides, those patients with EPTB had 30% reduced risk of poor treatment outcomes compared to those who had pulmonary TB (Table 2).

Statistically significant association was not found for being male (pooled OR; 1.34, 95%CI; 0.90–1.77, I^2; 43.67%) (S15 Fig), older age (pooled OR; 0.97, 95%CI; 0.62–1,32, I^2;85.56%) (S16 Fig), being smoker (pooled OR; 95%CI; 0.89–4.20, I^2; 13.69%) (S17 Fig), having DM (pooled OR; 1.16, 95%CI; 0.70–1.63, I^2; 0.00%) (S18 Fig), having end-stage renal failure (pooled OR; 3.15, 95%CI; -0.07–6.38, I^2; 0.00%) (S19 Fig), being HIV positive (pooled OR; 2.26, 95%CI; 0.60–3.91, I^2; 43.47%) (S20 Fig), being high level INH resistance (pooled OR; 0.79, 5%CI; 0.36–1.21, I^2; 28.22%) (S21 Fig), taking INH in the initiation phase (pooled OR; 0.72, 95%CI; 0.33–1.11, I^2; 0.00%) (S22 Fig), taking STR in the initiation phase (pooled OR; 0.76, 95%CI; 0.15–1.37, I^2; 0.00%) (S23 Fig), taking FLQ in the initiation phase (pooled OR; 0.94, 95%CI; 0.48–1.39, I^2; 0.00%) (S24 Fig), taking PZA in the continuation phase (pooled OR; 0.87, 95%CI; 0.27–1.47, I^2; 0.00%) (S25 Fig), not culture converted after 2 months (pooled OR; 1.30, 95%CI; 0.59–2.00, I^2; 0.00%) (S26 Fig), and the presence cavity lesion in the chest radiograph (pooled OR; 1.23, 95%CI; 0.62–1.84, I^2; 0.00%) (S27 Fig) (Table 2).

Discussion

Based on the pooled estimates, about one fifth of isoniazid mono-resistant TB patients had poor treatment outcomes and different factors are associated with this. The study findings of

Table 2. The summary of the pooled on the poor treatment outcome and associated risk factors among patients with isoniazid mono-resistant tuberculosis per different categories.

Indicators	Number of studies	Pooled estimates	
		Estimate (prevalence/OR), 95%CI	Heterogeneity I^2
Successful treatment outcome			
Over all	24	78% (74–83)	94.02%
AFR	4	67% (58–76)	74.28%
AMR	6	84% (78–90)	87.66%
EMR	2	75% (44–106)	73.41%
EUR	4	84% (77–91)	91.21%
SEAR	3	62% (56–69)	13.74%
WPR	5	82% (77–86)	64.67%
Cure rate	15	62% (50–73)	96.91%
Complete rate	14	34% (17–52)	99.26%
Poor treatment outcome			
Over all	23	22% (17–26)	94.08%
AFR	4	33% (24–42)	74.28%
AMR	6	16%(10–22)	87.75%
EMR	2	25% (-6-56)	73.41%
EUR	4	17% (11–22)	85.06%
SEAR	2	40% (34–45)	0.00%
WPR	5	18% (14–23)	64.63%
Treatment failure	16	5% (3–7)	93.97%
Loss to follow-up	18	12% (8–17)	96.58%
Mortality	23	6% (4–8)	88.73%
Relapse after successful outcome	8	1.7% (0.4–3.1)	n33.58%
Risk factors of poor treatment outcome			
Previous anti-TB treatment	9	**1.74 (1.15–2.33)**	45.10%
Male sex	9	1.34 (0.90–1.77)	43.67%
Older age	9	0.97 (0.62, 1.32)	87.56%
Had HIV co-infection	6	2.26 (0.60–3.91)	43.47%
Smoking	2	2.54 (0.89–4.20)	13.69%
Had diabetes	3	1.16 (0.70–1.63)	0.00%
Had cancer	2	**3.53 (1.43–5.62)**	0.00%
Had end stage renal disease	2	3.15 (-0.07–6.38)	0.00%
Being smear positive initially	7	**1.26 (1.08–1.43)**	2.13%
Had high level INH resistance	6	0.79 (0.38–1.21)	28.22%
Took INH in the initiation phase	2	0.72(0.33–1.11)	0.00%
Took STR in the initiation phase	2	0.76 (0.15–1.37)	0.00%
Took FLQ in the initiation phase	3	0.94 (0.48–1.39)	0.00%
Took RIF in the continuation phase	2	**0.22 (0.04–0.41)**	0.00%
Took PZA in the continuation phase	2	0.87 (0.27–1.47)	0.005
Had extrapulmonary tuberculosis	4	**0.70 (0.55–0.85)**	0.00%
Not culture converted after 2 months of treatment	4	1.30 (0.59–2.00)	0.00%
Took SLIDs	2	**0.54 (0.33–0.75)**	0.00%
Had cavity lesion on the chest radiograph	3	1.23 (0.62–1.84)	0.00%

AFR; African region, AMR; Region of the Americas, EMR; Eastern Mediterranean Region, EUR; European Region, SEAR; South Eastern region, WPR; West Pacific Region, HIV; Human Immunodeficiency Virus, INH; Isoniazid, RIF; Rifampicin, STR; Streptomycin; FLQ; Fluoroquinolones, PZA; Pyrazinamide; SLIDs; Second Line Injectable Drugs, OR; Odds Ratio

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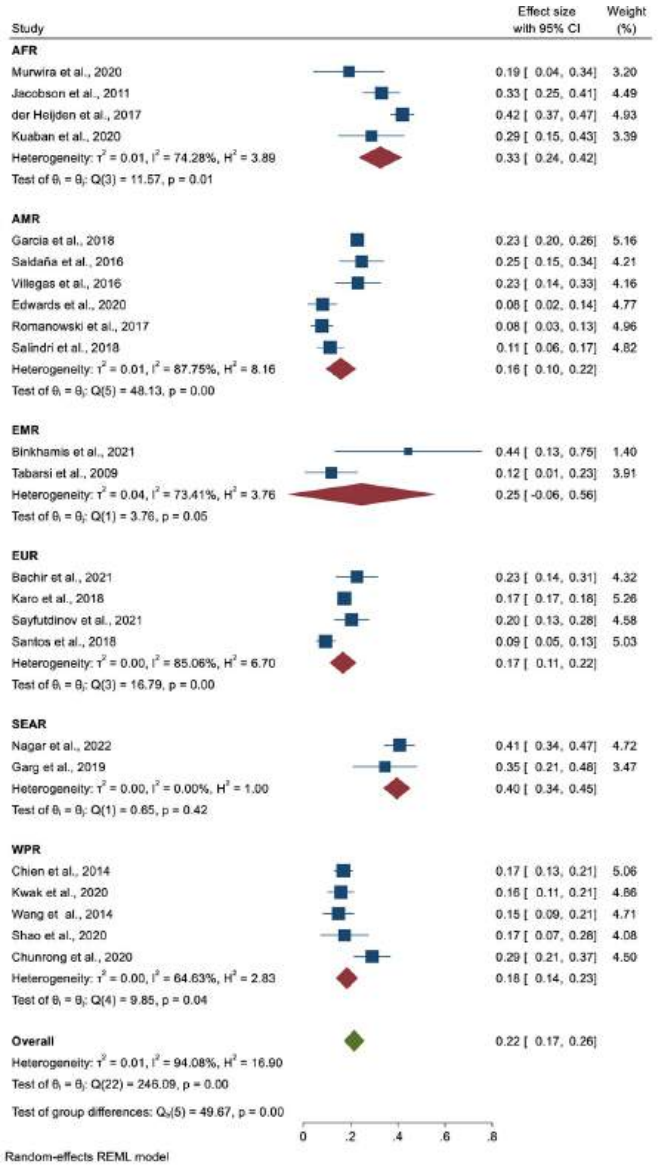

τ2; Tau (between-study variance), I^2; I-squared heterogeneity statistic (variability between studies), H^2; H-squared heterogeneity statistic (variability between studies).

Fig 4. Forest plot for the pooled poor treatment outcome rate among patients with isoniazid mono-resistant tuberculosis.

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this study revealed that the successful treatment rate among isoniazid mono-resistant TB patients was 79%. This finding is lower than the global average of the successful treatment outcome among drug-susceptible TB cases which was 85% and 86% for people newly enrolled on treatment in 2018 and in 2019, respectively [1, 2]. However, this is higher than MDR/RR-TB cases which was 59% based on the latest cohort [1], thus determining isoniazid resistant status for all bacteriologically confirmed TB cases may contribute for better treatment outcome and prevention of additional drug resistance. The successful treatment outcome among isoniazid mono-resistant TB cases had regional disparities, where better treatment success rate was

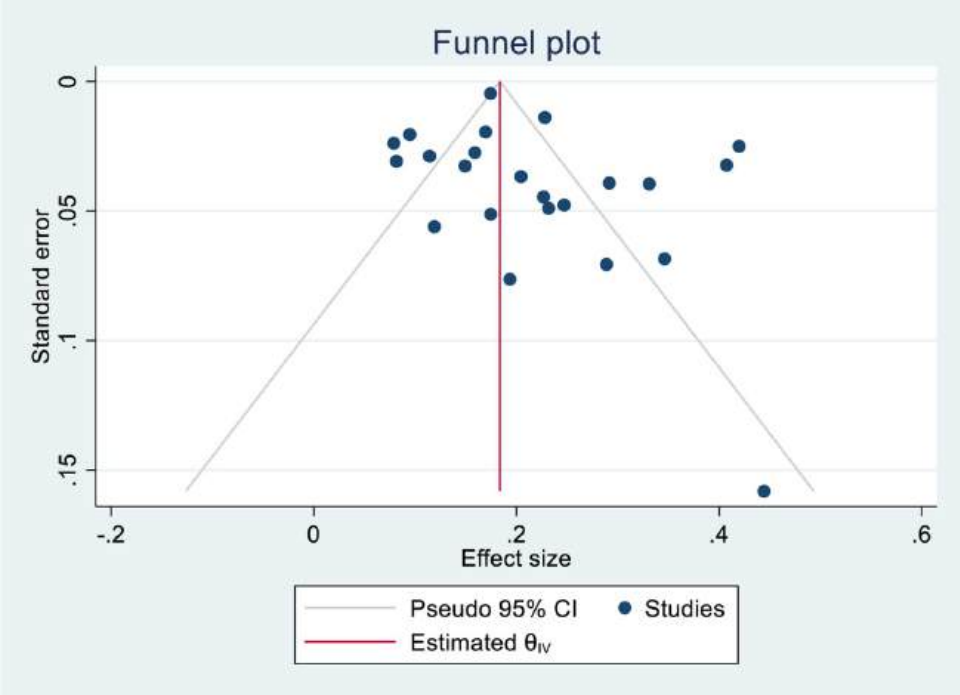

Fig 5. Funnel plot for the pooled poor treatment outcome rate among patients with isoniazid mono-resistant tuberculosis.

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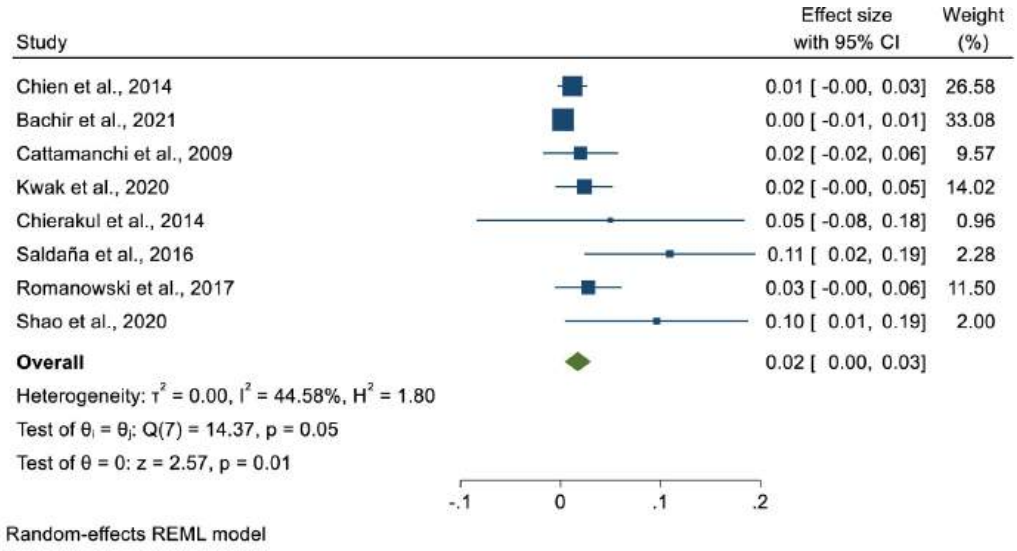

τ2; Tau (between-study variance), I^2; I-squared heterogeneity statistic (variability between studies), H^2; H-squared heterogeneity statistic (variability between studies).

Fig 6. Forest plot for the pooled relapse rate among successfully treated patients with isoniazid mono-resistant tuberculosis.

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Table 3. Meta-regression analysis of heterogeneity using sample size and publication year on poor treatment outcome.

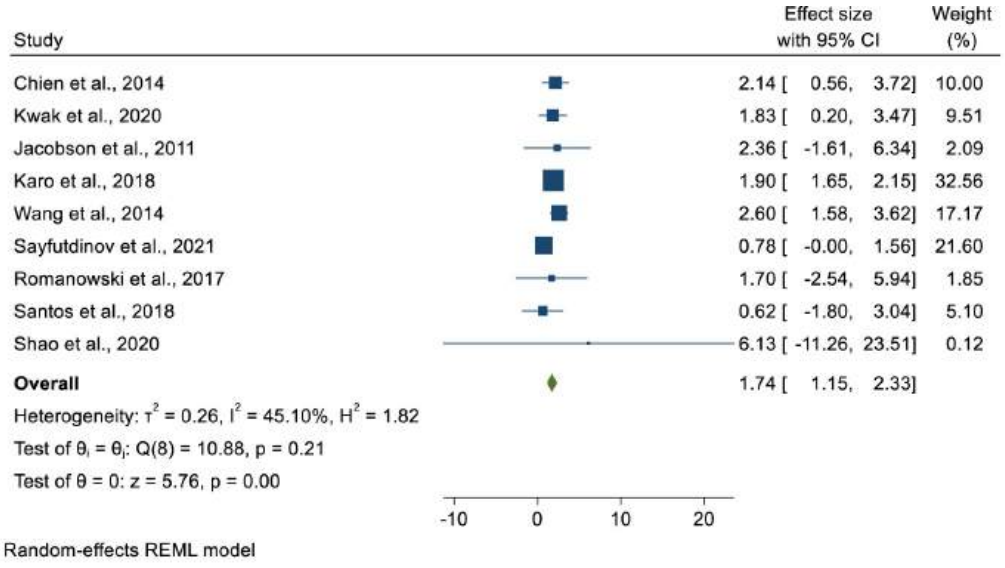
Variable	Unadjusted model		Adjusted model	
	Coefficient (95%CI)	P-value	Coefficient (95%CI)	P-value
Sample size	-5.76e-06 (-0.000035, 0.0000241)	0.719	-5.64e-06 (-0.0000357, 0.0000244)	0.713
Publication year	0.0051572 (-0.0085616, 0.0188759)	0.461	.0052476 (-0.0087989, 0.0192942)	0.464

https://doi.org/10.1371/journal.pone.0286194.t003

noted from AMR, EUR, and WPR having a successful treatment outcome above 80%, while lower treatment outcome was noted in AFR and SEAR having 71% and 62%, respectively. This revealed the importance of taking regional and country specific interventions.

The pooled poor treatment outcome among isoniazid-mono resistant TB patients estimated in this study is higher compared to drug-susceptible TB patients at the global level [1, 2]. Thus, determining isoniazid resistance level for all bacteriologically confirmed TB cases is important. In developing countries there is a gap in addressing the universal access to DST. Besides, most of the countries are using GeneXpert for the simultaneous detection of TB and rifampicin resistance. This test determines only the drug resistance pattern to rifampicin. Thus, the isoniazid resistance level may be underestimated and may be treated as drug susceptible TB. This might have resulted with poor treatment outcomes and increasing drug resistance [2]. Based on the sub-group analysis, higher poor treatment outcome is noted in the SEAR. Likewise, based on the 2020 global TB report, lower MDR/RR-TB treatment success rate was noted in SEAR [2].

We have estimated the pooled proportion of relapse among successfully treated isoniazid mono-resistant TB cases. The finding revealed that two percent of those patients had a relapse that extends up to two years after treatment completion. This relapse rate is relatively lower than the 3.7% relapse rate in a pooled estimate among patients enrolled on DOTs program



τ2; Tau (between-study variance), I^2; I-squared heterogeneity statistic (variability between studies), H^2; H-squared heterogeneity statistic (variability between studies).

Fig 7. Forest plot for the association of previous TB treatment history with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.

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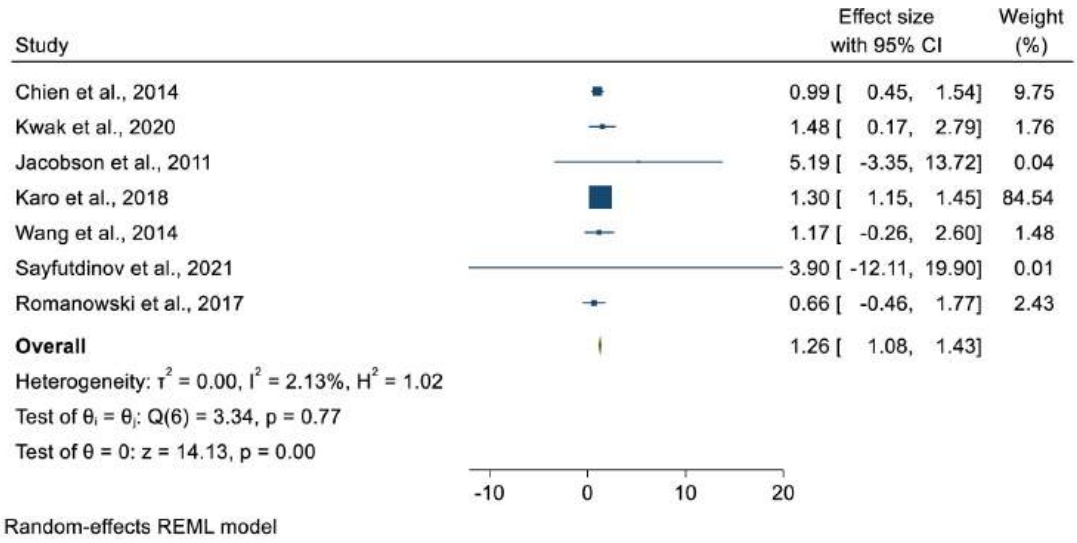

τ2; Tau (between-study variance), I^2; I-squared heterogeneity statistic (variability between studies), H^2; H-squared heterogeneity statistic (variability between studies).

Fig 8. Forest plot for the association of being initially smear positive with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.

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[39]. The pooled estimate in our study might be affected because the time of follow-up was different among the studies.

In the current study, we have conducted a pooled estimate to assess the factors associated with poor treatment outcome in isoniazid mono-resistant TB cases. The study findings revealed that, those patients who had a previous TB treatment history had 1.74 times the odds to develop poor treatment outcome compared to new cases. Association of previous TB treatment history for developing unsuccessful treatment outcome in TB patients for both drug-susceptible and drug-resistant TB was reported in different studies [40–44]. This risk factor is not specific to isoniazid mono-resistant TB, rather it is associated with unfavorable TB treatment outcome in general. The other identified risk factor is being smear positive initially. Initially smear positive patients had 1.26 times the odds to develop poor treatment outcome compared to smear negatives. Smear positive TB patients had higher bacterial load in their sputum reflecting the severity of the disease. Likewise, a global pooled estimate revealed that drug-resistant TB patients who were smear positive at the baseline had 1.58 times the risk to die [41]. Besides, those isoniazid mono-resistant TB cases who had cancer comorbid had 3.53 times the odds to had poor treatment outcome compared to the counter parts. Similarly, in a previous study it was reported that the 12-months all-cause mortality during TB in patients with malignancy was as high as 20.56% [45]. Thus, those patients with comorbid conditions should be critically followed during treatment.

The findings of this study also revealed that those patients who took rifampicin in the continuation phase had lower risk to develop poor treatment outcome. Including rifampicin for treatment of isoniazid-mono resistant TB cases is important to shorten the treatment duration. Our study also revealed that taking SLIDs lowered the risk of poor treatment outcome. However, in patients with confirmed rifampicin-susceptible and isoniazid-resistant TB, it is not recommended to add injectable agents to the treatment regimen [46]. In addition, compared to

PTB cases EPTB cases had 45% reduced risk to develop poor treatment outcome which needs further studies. It is difficult to document treatment cure in EPTB cases. In two studies conducted in Ethiopia, EPTB was reported as the risk factor for unsuccessful treatment outcome [47, 48].

Finally, the findings of this study should be interpreted by considering the limitations. The study findings of this study was based on a limited number of studies (24 studies) with small sample size for the majority that might affected the pooled estimates. In addition, in the majority of the primary studies data were collected retrospectively that might have introduced selection bias. Besides, there is high heterogeneity and publication bias was detected for some parameters that might affect the true estimates. However, we have performed a stratified analysis and we also performed a trim and fill analysis for those pooled estimates that had a publication bias that validated the findings of this study.

Conclusion

The findings of this study revealed that isoniazid mono-resistant TB patients had higher poor treatment outcome. The pooled estimates vary per geographical locations. Previous anti-TB treatment history, being smear positive initially, and having cancer were associated with poor treatment outcome in isoniazid mono-resistant TB patients. While, taking rifampicin in the continuation phase, taking SLIDs and having EPTB were associated with reduced risk of poor treatment outcome compared to their counter parts. Thus, determination of isoniazid resistance pattern for all bacteriological TB cases is critical to have successful treatment outcome.

Supporting information

S1 Table. Completed PRISMA 2009 checklist.
(DOCX)

S2 Table. Search engines.
(DOCX)

S3 Table. Quality assessment for the included studies in meta-analysis.
(DOCX)

S1 Fig. Forest plot for the complete rate among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S2 Fig. Funnel plot for the complete rate among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S3 Fig. Forest plot for the cure rate among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S4 Fig. Funnel plot for the cure rate among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S5 Fig. Forest plot for the treatment failure rate among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S6 Fig. Funnel plot for the treatment failure rate among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S7 Fig. Forest plot for the mortality rate among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S8 Fig. Funnel plot for the mortality rate among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S9 Fig. Forest plot for the lost to follow-up rate among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S10 Fig. Funnel plot for the lost to follow-up rate among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S11 Fig. Forest plot for the association of having cancer with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S12 Fig. Forest plot for the association of taking rifampicin in the continuation phase with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S13 Fig. Forest plot for the association of having extrapulmonary tuberculosis with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S14 Fig. Forest plot for the association of taking second-line injectable drugs with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S15 Fig. Forest plot for the association of being male with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S16 Fig. Forest plot for the association of older age with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S17 Fig. Forest plot for the association of smoking with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S18 Fig. Forest plot for the association of having diabetes with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S19 Fig. Forest plot for the association of having end stage renal disease with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S20 Fig. Forest plot for the association of being HIV positive with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S21 Fig. Forest plot for the association of having high-level isoniazid resistance with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S22 Fig. Forest plot for the association of taking isoniazid in the initiation phase with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S23 Fig. Forest plot for the association of taking streptomycin in the initiation phase with poor outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S24 Fig. Forest plot for the association of taking fluoroquinolones in the initiation phase with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S25 Fig. Forest plot for the association of taking pyrazinamide in the continuation phase with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S26 Fig. Forest plot for the association of not culture converted after 2 months' treatment of the initiation phase with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S27 Fig. Forest plot for the association of having cavity during chest radiograph with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

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The prevalence of latent tuberculosis infection in patients with chronic kidney disease: A systematic review and meta-analysis

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ABSTRACT

Objective: To estimate the prevalence of latent tuberculosis infection (LTBI) in chronic kidney disease (CKD) patients.

Methods: This study was conducted following the PRISMA guidelines. We identified, 3694 studies from the whole search, and 59 studies were included. Each study's quality was assessed using JBI checklist. We employed STATA version 17 for statistical analysis. We assessed heterogeneity using I^2 heterogeneity test. Publication bias was assessed using funnel plot and Egger's test. We estimated the pooled LTBI prevalence in CKD patients along with 95%CI.

Results: The pooled prevalence of LTBI among CKD patients using data collected from 53 studies having 12,772 patients was 30.2% (95%CI; 25.5, 34.8). The pooled prevalence among predialysis, hemodialysis, peritoneal dialysis, and renal transplanted patients was 17.8% (95%CI; 3.3, 32.4), 34.8% (95%CI; 29.1, 40.5), 25% (95%CI; 11, 38), and 16% (95%CI; 7, 25), respectively. The pooled prevalence of LTBI stratified by the laboratory screening methods was 25.3% (95%CI: 20.3–30.3) using TST, 28.0% (95%CI; 23.9–32.0) using QFT, and 32.6%, (95%CI: 23.7–41.5) using T-SPOT.

Conclusion: There is high prevalence of LTBI among CKD patients mainly in patients on dialysis. Thus, early diagnosis and treatment of LTBI in CKD patients should be performed to prevent active TB in CKD patients.

PROSPERO registration number: CRD42022372441.

1. Introduction

Tuberculosis (TB) continues to be a major public health issue across the globe. It is the second leading cause of mortality among

Abbreviations: CKD, Chronic Kidney Disease; IGRA, Interferon Gamma Release Assay; LTBI, Latent Tuberculosis Infection; TB, Tuberculosis; TST, Tuberculin Skin Test.

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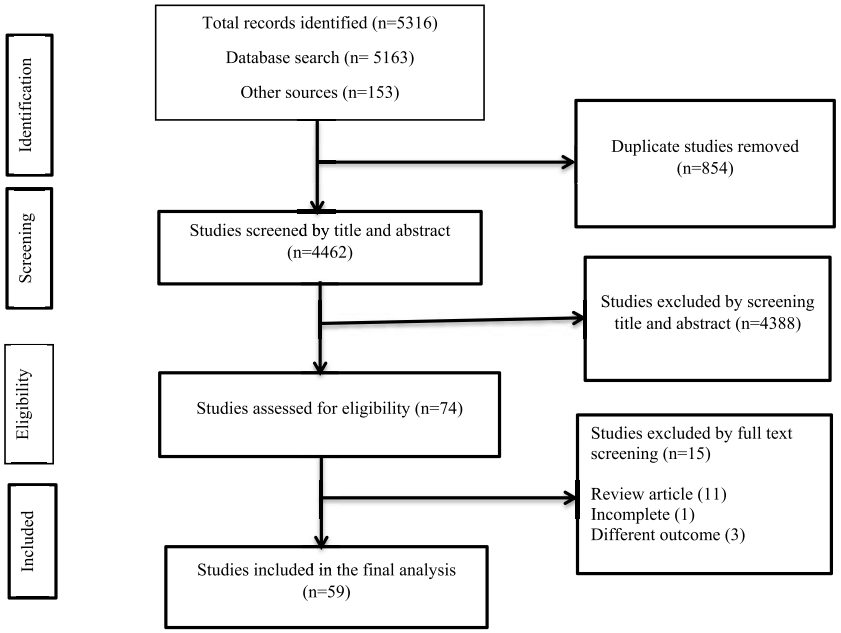

Fig. 1. Flowchart describing the selection of studies for the systematic review and meta-analysis of latent tuberculosis prevalence among patients with chronic kidney disease.

infectious diseases next to COVID-19 [1]. Countries are committed to control and prevent TB by developing and adapting different strategies and measurable targets. The World Health Organization (WHO) developed the END-TB strategy that aims to reduce the incidence of TB to less than 10 per 100,000 populations by 2035 [2]. However, achieving this ambitious objective may be challenging unless a specific intervention approach that addresses the burden in a high-risk population is created and implemented. For example, specific groups of people, such as those with chronic kidney disease (CKD), are at a higher risk of contracting TB than the overall population, necessitating a focused intervention [3]. According to our recent global systematic review and meta-analysis, the incidence of TB in CKD patients was 3718/100,000 population [4]. A pooled estimate revealed that patients on dialysis had 3.6 times the risk to develop TB compared to the general population [5]. Currently, the incidence of CKD is rising in developing countries where TB is also endemic which may halt the TB prevention and control efforts to achieve the END-TB strategy [6].

Early detection and treatment of latent tuberculosis infection (LTBI) among groups of people with weakened immune systems, such as CKD patients, is critical for preventing the development of active TB. In addition, dialysis patients frequently travel to health facilities for medical care, which may increase the risk of infection with *Mycobacterium tuberculosis* [7]. When compared to healthy adults, these patients have a 10–25 fold increased chance of risk of reactivating LTBI [7]. The WHO recommends that persons undergoing dialysis or preparing for an organ transplant be tested and treated for LTBI [8]. There have been studies undertaken in different countries and settings to determine the prevalence of LTBI in CKD patients [7,9–23]. The prevalence of LTBI in CKD patients has been found to range from 6% [24,25] to 82% [23]. The systematic reviews were primarily concerned with comparing the performance of diagnostic tools for detecting of LTBI in dialysis patients [26–28]. However, there is limited data that reported the global, and regional prevalence of LTBI among CKD patients in general and across different categories. A global data that comprehensively assessed the burden of LTBI in CKD patients can be an essential input for policy development and guidance to boost the effort for TB prevention and control, as well to improve the quality of life for this population group. Thus, this study aimed to estimate the global pooled prevalence of LTBI among patients with CKD.

2. Methods

2.1. Protocol registration

The protocol for this systematic review and meta-analysis study is registered on the International Prospective Register of Systematic Reviews (PROSPERO) with a registration number CRD42022372441.

2.2. Article search strategy and selection procedure

This systematic review and meta-analysis study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [29]. Two independent investigators (AA, ZWB) conducted article searching, and the third investigator (GD) resolved the inconsistencies. Both electronic databases and grey literature sources were searched for previously published studies that

reported LTBI among patients with any types of CKDs. We searched articles published in English language until November 21, 2022. PubMed, Global Index Medicus, Informit, Joanna Briggs Institute EBP Database (including OVID), and Global Health were among the electronic databases used. Whereas the grey literature sources were Google, and Google Scholar. The searching was carried out using the key terms in conjunction with the Boolean operators AND and OR. The keywords used in the current study includes; latent tuberculosis, chronic kidney disease patient, renal failure, dialysis, hemodialysis, peritoneal dialysis, renal-transplant, pre-renal transplant, and pre-dialysis. All of the articles identified during the entire search were exported to Endnote X8 citation manager. We have followed a stepwise approach to select the studies included in the final data-analysis. In the primary step, duplicates were removed and then the articles were screened by title and abstract. All the articles that passed the above stage were eligible for full-text screening and those that passed the full-text assessment were included in the final data analysis (Fig. 1) (Appendix).

2.3. PICOS criteria

Participants: Patients with chronic kidney disease.
Intervention: Not applicable.
Comparator: Not applicable.
Outcome: Latent TB infection.
Study design: Observational studies.
Study setting: Any setting in any country across the globe.

2.4. Inclusion and exclusion criteria

Studies that assessed prevalence of LTBI among different categories of CKD patients (pre-dialysis, hemodialysis, peritoneal dialysis, or renal transplanted) were included in the study. Review studies, incomplete studies and articles with different outcomes were excluded.

2.5. Data extraction

We extracted data from all studies included in the current systematic review and meta-analysis using the 2016 Microsoft Excel Spreadsheet. Two investigators (GS, EG) extracted data independently, and the inconsistencies were resolved through discussion and consensus was reached with the guidance of the third author (AA). The extracted data included; first author name, publication year, country, data collection period, study design, age group, type of CKD patients included, laboratory screening method, sample size, and number of patients who had LTBI. In addition to the above variables, the studies were categorized based on continent, WHO regional classification, and country TB burden category **(Table 1).**

2.6. Outcome

The primary outcome of this study was detection of LTBI among CKD patients with any category including pre-dialysis, hemodialysis, peritoneal dialysis, and renal transplant. The included studies used different laboratory screening methods alone or in combination for screening of LTBI in CDK patients; Tuberculin Skin Test (TST), QFT (QuantiFERON®-TB Gold), T-SPOT, and ELISPOT (enzyme-linked immunospot). The TST result was considered positive when the cut-off induration was $\geq$10 mm. From studies that employed a two-step TST, only the baseline results were taken to avoid a boosting phenomenon.

2.7. Quality assessment

Two independent investigators (AA, GS) assessed the quality and validity of individual studies included in this study using the Joanna Brigg's Institute critical appraisal tool [30]. The inconsistencies that arose between the two authors were resolved by the third investigator (ZWB). The JBI tool for prevalence study was used to assess the study's quality. Each question on the checklist was scored equally, and their total was calculated out of 100%. We classified the quality score as low, medium, and high quality when the score was $<$60%, 60–80%, and $>$80%, respectively.

2.8. Data synthesis and analysis

The data that were summarized in the 2016 Microsoft Excel Spreadsheet were exported to STATA version 17 for statistical analysis. The pooled prevalence of LTBI among CKD patients was estimated along with 95%CI. Sub-group analysis was performed based on CKD categories, LTBI laboratory screening methods, WHO regional classification, continent, country's income level, publication year, and TB burden category. We have presented the pooled estimates using forest plot. The presence of heterogeneity among studies was assessed using I^2 heterogeneity test where $I^2 >$50% was considered as the presence of substantial heterogeneity [31,32]. We have used the random-effect model considering the presence of substantial heterogeneity. We assessed the presence of publication bias through the visual inspection of the funnel plot and the statistical significance of the Egger's regression test ($P < 0.05$) [33,34]. A trim-and fill analysis was done to adjust the publication bias [35].

Table 1
Characteristics of individual studies on the prevalence of latent tuberculosis among patients with chronic kidney disease, included in the current systematic review and meta-analysis.

Author year	Country	Continent	TB burden category	Study period	Study design	Study group	Study setting	Age group	Diagnostic method
Wu et al., 2021	Taiwan	Asia	Not HBC	September 5, 2018 to September 5, 2019	Prospective study	HD	Kaohsiung Chang Gung Memorial Hospital	>18 years	QFT
Shu et al., 2015	Taiwan	Asia	Not HBC	January 2012 to June 2013	Cross-sectional	Patients undergoing dialysis, and those with severe CKD	National Taiwan University Hospital, a tertiary referral center, and its branches, regional teaching hospitals, and a local hemodialysis clinic.	≥20 years	QFT
Shu et al., 2012	Taiwan	Asia	Not HBC	March 2011 to February 2012	Cross-sectional	Dialysis	National Taiwan University Hospital, a tertiary referral center in northern Taiwan, and its branch in southern Taiwan.	≥20 years	QFT
Fonseca et al., 2013	Brazil	South America	HBC	December of 2008 to December of 2009	Cross-sectional	HD	Mineiro Institute of Nephrology	>18 years	TST
Gunluoglu et al., 2015	Turkey	Asia	Not HBC	September to November 2011	Cross-sectional	HD	Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital.	Mean age 62.2 years	TST and QFT
Passalent et al., 2007	Canada	North America	Not HBC	January 15 to April 15, 2005	Cross-sectional	HD	Toronto General Hospital site of the University Health Network	All	TST and T-SPOT
Ferreira et al., 2021	Brazil	South America	HBC	July to December 2018	Cross-sectional	HD	Clinical Hospital (HCFMRP-USP), of the Ribeirão Preto Nephrology Service (SENERP)	≥18 years	TST
Setyawati et al., 2021	Indonesia	Asia	HBC	May 2018	Cross-sectional	HD	Dr. Moewardi Surakarta Hospital	>18 years	TST and T-SPOT
Lee et al., 2010	Taiwan	Asia	Not HBC	October 2008	Cross-sectional	HD	Kaohsiung Veterans General Hospital	16.8–93.5 years	TST and QFT
Ahmadinejad et al., 2012	Iran	Asia	Not HBC	October 2009 to November 2010	Cross-sectional	Pre-transplantation	Tehran University of Medical Sciences.	16–65 years	TST and QFT
Sester et al., 2004	Germany	Europe	Not HBC	December 2001 to December 2002	Cross-sectional	HD	University of the Saarland	Mean age was 61.2 ± 15.2 years	TST
Al Jahdali et al., 2013	Saudi Arabia	Asia	Not HBC	August to December 2010	Cross-sectional	HD	KAMC-R	Mean age was 62.27 ± 11.79 years	TST and QFT
Kim et al., 2011	South Korea	Asia	Not HBC	June 2008 to December 2009	Cross-sectional	Transplant	University of Ulsan College of Medicine	>16 years	TST
Al Wakeel et al., 2015	Saudi Arabia	Asia	Not HBC	January 5, 2011 to March 31, 2013	Prospective study	Dialysis	King Khalid University Hospital, Security Forces Hospital and Lehbi Medical Center	≥18 years	TST and QFT
Lee et al., 2015	South Korea	Asia	Not HBC	–	Prospective study	Dialysis	Inje University Busan Paik hospital.	23–74 years	QFT
Ates et al., 2010	Turkey	Asia	Not HBC	15 February to July 15, 2008	Cross-sectional	HD	13 hemodialysis centers in five different cities	>15 years	TST
Chung et al., 2009	South Korea	Asia	Not HBC	1 March to April 30, 2008	Cross-sectional	HD	Gil Medical Centre, Gachon University of Medicine and Science	17–88 years	TST, QFT and T-SPOT
Shu et al., 2019	Taiwan	Asia	Not HBC	2014 to 2018	Cross-sectional	On pre transplantation and after transplantation	National Taiwan University Hospital,	≥20 years	QFT
Agarwal et al., 2015	India	Asia	HBC	May 2007 to August 2010	Cross-sectional	HD	All India Institute of Medical Sciences	18–88 years	TST and QFT

(*continued on next page*)

Table 1 (*continued*)

Author year	Country	Continent	TB burden category	Study period	Study design	Study group	Study setting	Age group	Diagnostic method
Sultan et al., 2016	Iraq	Asia	Not HBC	1st of April to December 15, 2014	Cross-sectional	HD	Baghdad teaching hospital	Mean age was 54.34 ± 15.25 years	TST
Hassen et al., 2013	Saudi Arabia	Asia	Not HBC	January 1 to May 30, 2009	Cross-sectional	HD	King Fahad specialist hospital in Dammam	≥18 years	TST and T-SPOT
Chagas et al., 2014	Brazil	South America	HBC	July 2011 to December 2013	Cross-sectional	HD	six existing dialysis services in Campo Grande, MS, Brazil	>18 years	TST
Romanowski., 2020	British Columbia, Canada	North America	Not HBC	January 1, 2012 to May 31, 2017	Retrospective cohort	Dialysis	British Columbia	≥18 years	IGRA (Not specified)
Hussein et al., 2017	Egypt	Africa	Not HBC	February to April 2016	Prospective study	HD	Sohag University Hospital	21–65 years	TST and QFT
Shankar et al., 2005	India	Asia	HBC	–	Prospective study	ESRD	Postgraduate Institute of Medical Education and Research Hospital, Chandigarh	18–60 years	TST
Triverio et al., 2009	Switzerland	Europe	Not HBC	–	Cross-sectional	HD	Geneva University Hospital	Mean age was 65 ± 15 years	TST, QFT and T-SPOT
Soysal et al., 2012	Turkey	Asia	Not HBC	May 2006 to May 2007	Prospective study	HD	Marmara University School of Medicine	19–84 years	TST and T-SPOT
Habesoglu et al., 2007	Turkey	Asia	Not HBC	–	Prospective study	HD	Adana Teaching and Training Hospital of Baskent University	Mean age was 50.0 ± 15.9 years	TST
Hoffmann et al., 2010	Switzerland	Europe	Not HBC	–	Prospective study	HD	Kantonsspital, St.Gallen	≥18 years	TST and QFT
Agarwal et al., 2010	India	Asia	HBC	May 2000 to May 2006	Prospective study	Transplant	All India Institute of Medical Sciences	14–60 years	TST
Lee et al., 2009	Taiwan	Asia	Not HBC	September 2005	Prospective study	HD	Kaohsiung Veterans General Hospital	34.4–77.7 years	TST, QFT and T-SPOT
Lin et al., 2020	Taiwan	Asia	Not HBC	March 1, 2017, to May 31, 2017	Cross-sectional	HD	Kaohsiung Medical University Hospital	≥20 years	QFT
Baek et al., 2019	South Korea	Asia	Not HBC	March 2017 to August 2019	Cross-sectional	Dialysis	Mediplex Sejong Hospital	All (mean age was 61.6 ± 12.6 years)	QFT
Bandiara et al., 2021	Indonesia	Asia	HBC	March to May 2020	Cross-sectional	HD	Dr. Hasan Sadikin Hospital	≥18 years	IGRA (Not specified)
Ogawa et al., 2021	Japan	Asia	Not HBC	–	Cross-sectional	HD	3 hospitals	62–79 years	QFT
SAYARLIOĞLU et al., 2011	Turkey	Asia	Not HBC	–	Cross-sectional	HD	Kahramanmaras State Hospital,	Mean age was 54.6 ± 14.9 years	TST and QFT
Carrazco-Ibarra et al., 2017	Mexico	North America	Not HBC	2011–2016	Retrospective cohort	Pre-transplantation	Hospital based study	–	TST
Seyhan et al., 2009	Turkey	Asia	Not HBC	November 2008 to December 2008	Cross-sectional	HD	Yedikule Chest Diseases and Thoracic Surgery Education and Research Hospital	Mean age was 56.2 ± 15.3 years	TST and QFT
Wauters et al., 2004	Belgium	Europe	Not HBC	September–October 2001	Cross-sectional	HD	University Hospital Gasthuisberg KU Leuven, Leuven and Virga Jesse Hospital, Hasselt	21–92 years	TST

(*continued on next page*)

Table 1 (*continued*)

Author year	Country	Continent	TB burden category	Study period	Study design	Study group	Study setting	Age group	Diagnostic method
Fang et al., 2002	Taiwan	Asia	Not HBC	June to July 1999	Cross-sectional	Dialysis	Kaoh siung Veterans General Hospital.	Mean age was 54.7 ± 17.3 years	TST
Winthrop et al., 2008	USA	North America	Not HBC	Oct-03	Cross-sectional	HD	Multisite study conducted by USA CDC	18–90 years	TST, QFT, and ELISPOT
Woeltje et al., 1998	USA	North America	Not HBC	June 1996 to August 1996	Cross-sectional	HD	Washington University School of Medicine, St Louis	19–91 years	TST
Smirnoff et al., 1998	USA	North America	Not HBC	1995	Cross-sectional	HD	The Mount Sinai Medical Center,	19–89 years	TST
Connel et al., 2010	United Kingdom	Europe	Not HBC	2008	Cross-sectional	CKD with different categories	Hammersmith Hospital	28–88 years	TST, QFT and T-SPOT
Cengiz et al., 2005	Turkey	Asia	Not HBC	–	Cross-sectional	HD	Ondokuz Mayıs University School of Medicine	Mean age was 49.9 ± 14.4 years	TST
Akcay et al., 2003	Turkey	Asia	Not HBC	January 1 to December 31, 1999	Cross-sectional	HD	Hacettepe University School of Medicine, Hemodialysis Unit	20–72 years	TST
Dogan et al., 2005	Turkey	Asia	Not HBC	June to December 2003	Prospective study	HD	Van (Yuzuncu Yil University Hospital, Yuksek Ihtisas Hospital) and the Mus State Hospital).	13–82 years	TST
Foster et al., 2016	Canada	North America	Not HBC	February 2008 to December 2008	Retrospective cohort	Dialysis	4 major hospital dialysis units in Winnipeg, Manitoba.	Mean age was 54.3 ± 14.7 years	TST
Khosroshahi et al., 2012	Iran	Asia	Not HBC	–	Cross-sectional	HD	two university hospitals in Tabriz	Mean age was 44.6 ± 15 years	TST
Altunoren et al., 2012	Turkey	Asia	Not HBC	–	Cross-sectional	Dialysis	Kahramanmara¸s Sutcu Imam University	Mean age was 51.9 ± 15.5 years	TST
Edathodu et al., 2016	Saudi Arabia	Asia	Not HBC	August 2008 to May 2013	Prospective study	ESRD	King Faisal Specialist Hospital and Research Centre	≥14 years	TST and QFT
Maciel et al., 2018	Brazil	South America	HBC	January 2011 to July 2013	Cross-sectional	Transplant	Federal University of Minas Gerais Hospital das Clínicas	≥18 years	TST
Igari et al., 2019	Japan	Asia	Not HBC	April 2017 to March 2018	Cross-sectional	Transplant	National Hospital Organization Chiba-East Hospital	20–79	QFT and T-SPOT
Meinerz et al., 2021	Brazil	South America	HBC	April 4th, 2014 to Oct 31st, 2018, follow-up until Oct 31st, 2019	Prospective study	Transplant	Hospital based study	18–80 years	TST and QFT
Grant et al., 2012	Canada	South America	Not HBC	–	Cross-sectional	HD	Vancouver General Hospital	≥18 years	TST, QFT and T-SPOT
Chung et al., 2010	South Korea	Asia	Not HBC	February 1st to March 31st, 2009	Cross-sectional	HD	Gil Medical Center	18–81 years	TST, QFT and T-SPOT
Mohtashami et al., 2022	Iran	Asia	Not HBC	2018	Cross-sectional	HD	Khorramabad teaching hospitals.	>15 years	TST
Wang et al., 2020	Taiwan	Asia	Not HBC	2016–2019	Cross-sectional	HD	two tertiary-care medical centers	Mean age was 56.7 ± 11.2 years	QFT
Harris et al., 2016	Canada	North America	Not HBC	2007 to 2014	Cross-sectional	ESRD	British Columbia Centre for Disease Control	All	TST and IGRA (Not specified)

CKD; Chronic Kidney Disease, HD; Hemodialysis, HBC; High TB Burden Country, TST; Tuberculin Skin Test, QFT; QuantiFERON®-TB Gold, ELISPOT; enzyme-linked immunospot, "-"; Not described.

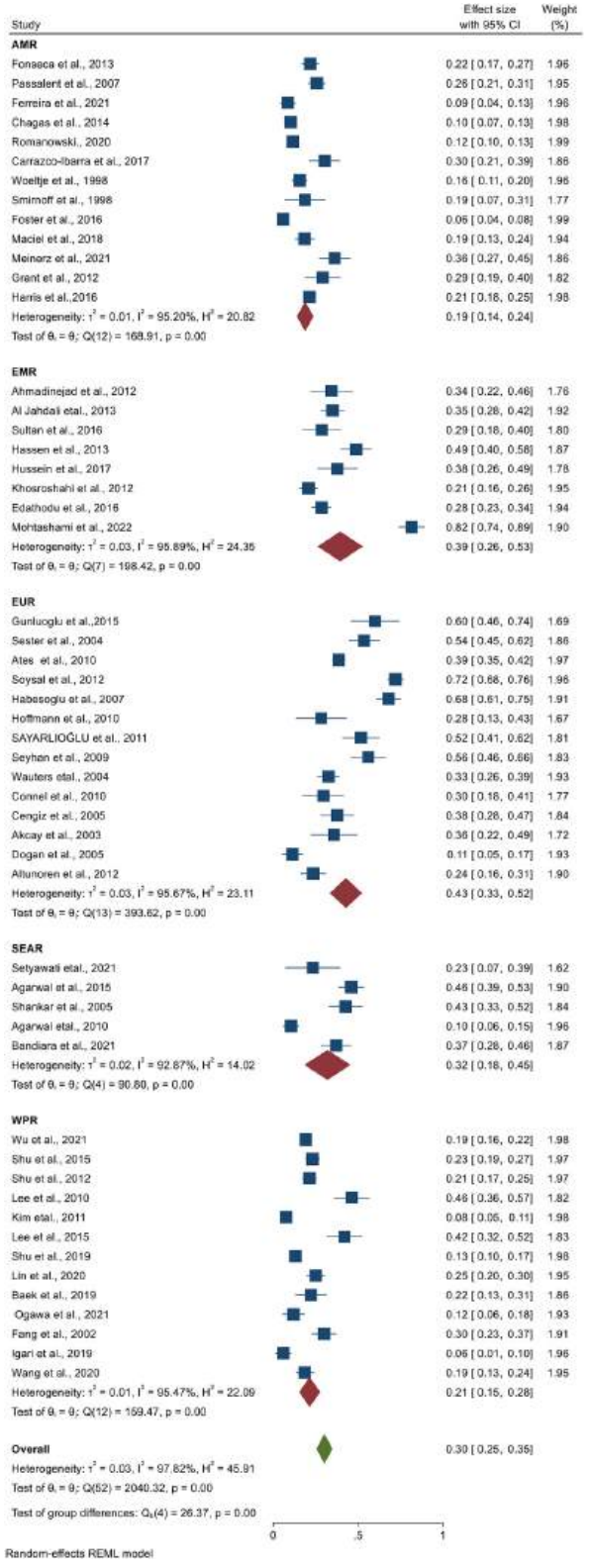

Fig. 2. Forest plot for the pooled prevalence of latent tuberculosis among patients with chronic kidney disease.

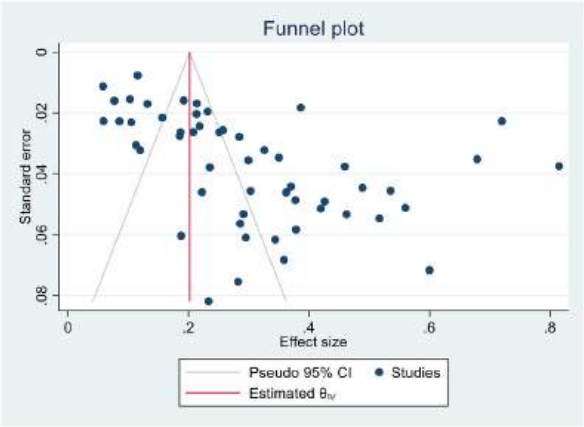

Fig. 3. Funnel plot for the pooled the pooled prevalence of latent tuberculosis among patients with chronic kidney disease.

Table 2
The summary of the pooled prevalence of latent tuberculosis among chronic kidney disease patients per different categories.

Latent tuberculosis prevalence among patients with chronic kidney disease across different categories		Number of studies	Sample size	Number of LTBI cases	Pooled LTBI prevalence	
					Estimate, 95% CI	Heterogeneity I^2
Over all latent tuberculosis prevalence		53	12,772	3219	30% (26, 35)	97.82%
Per continent	Europe	4	451	170	36% (25, 48)	82.78%
	Asia	35	7273	2253	33% (27, 40)	97.57%
	North America	7	3662	536	18% (12, 24)	95.78%
	South America	6	1005	163	20% (12, 28)	93.50%
	Africa	1	74	28	38% (26, 49)	–
Per WHO regional classification	Region of Americas	13	4974	766	19% (14, 24)	95.20%
	European Region	8	1193	434	43% (33, 52)	95.67%
	East Mediterranean Region	14	2440	1113	39% (26, 53)	95.89%
	South East Asian Region	5	643	206	32% (18, 45)	92.87%
	West Pacific Region	13	3522	700	21% (15, 28)	95.47%
	African Region	–	–	–	–	–
Per publication year	1998–2010	17	2994	1008	34% (26, 42)	95.41%
	2011–2015	16	3647	1099	34% (25, 43)	97.65%
	2016–2022	20	6131	1112	24% (17, 31)	98.31%
Per high TB burden category	Included	10	1876	413	25% (16, 34)	95.81%
	Not included	43	10,896	2806	31% (26, 37)	98.02%
Per World Bank Group income classification of countries	Lower Middle Income	6	717	234	33% (21, 44)	90.82%
	Upper Middle Income	20	3839	1375	37% (28, 47)	97.89%
	High Income	27	8216	1610	24% (20, 29)	96.75%
Per laboratory diagnostic method	TST	47	8208	1966	25% (20, 30)	97.71%
	QFT	29	4821	1285	28% (24, 32)	90.83%
	T-SPOT	13	1412	595	33% (24, 42)	97.53%
	ELISPOT	1	97	27	–	–
Per chronic kidney disease categories	Pre-dialysis	3	432	61	18% (3, 32)	90.61%
	Hemodialysis	39	7534	2396	35% (29, 41)	96.87%
	Peritoneal dialysis	5	253	60	25% (11, 38)	83.48%
	Post-renal transplantation	6	1100	159	16% (7, 25)	94.26%

TST; Tuberculin Skin Test, QFT; QuantiFERON®-TB Gold, ELISPOT; enzyme-linked immunospot, WHO; World Health Organization, "-"; Not available.

3. Results

3.1. Study characteristics

From the whole search, 5316 studies were identified and 854 duplicates were removed. Title and abstract screening was conducted for the 4462 studies and 4388 were excluded. Then, the remaining 74 studies were assessed for full text and 59 studies were included in the final analysis. While the remaining 15 studies were excluded due to different reasons (review articles, incomplete studies, articles

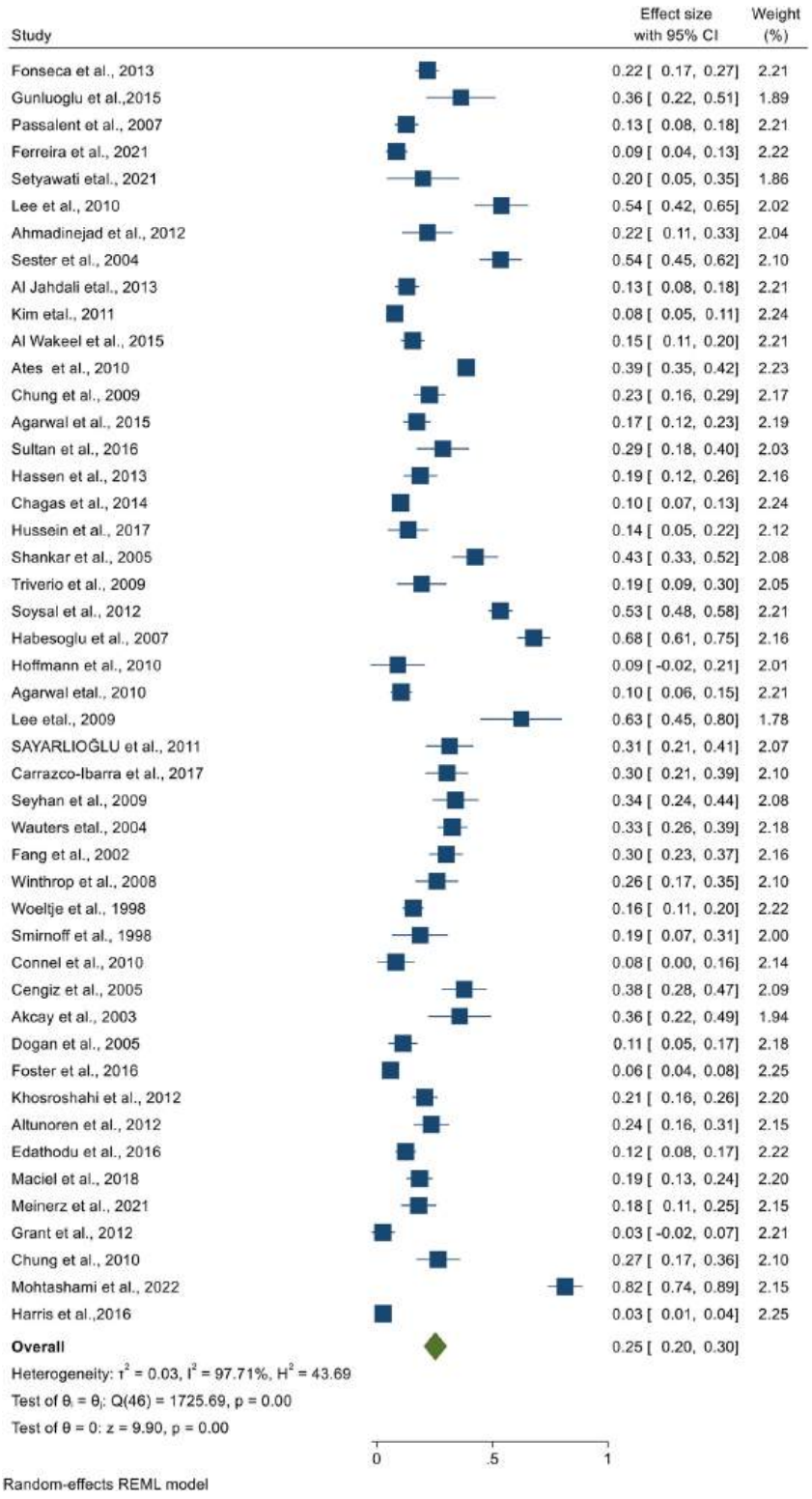

Fig. 4. Forest plot for the pooled prevalence of latent tuberculosis among patients with chronic kidney disease diagnosed using TST.

with different outcomes) (Fig. 1) (Appendix).

The studies were conducted in 18 countries from four continents. The highest number of studies were from Asia (39 studies) followed by North America (8 studies), South America (6 studies), and Europe (5 studies). The least number of study was from Africa with only one study conducted in Egypt. Based on the WHO regional classifications, the highest number of studies were from the West Pacific Region (WPR) with 16 studies followed by the European Region (EUR) (15 studies), the Region of Americans (AMR) (14 studies), Eastern Mediterranean Region (EMR) (9 studies), and South East Asian Region (SEAR) (5 studies). No study was reported from the WHO African Region (AFR). Specifically, the most frequent studies were from Turkeye (10 studies) followed by Taiwan (9 studies), South Korea (5 studies), Canada (5 studies), and Brazil (5 studies). The other studies were reported from Saudi Arabia, United States, India, Iran, Indonesia, Japan, Switzerland, Belgium, Egypt, Germany, Iraq, Mexico, and United Kingdom. Based on the World Bank income classification, 6, 20, and 27 studies were reported from lower middle income, upper middle income and high income countries, respectively.

Based on publication year, 22, 17, and 20 studies were published from 1998 to 2010, from 2011 to 2015 and from 2016 to 2022. Based on the 2021 global TB report, 10 studies were reported from high TB burden countries while the remaining 49 studies were reported from countries that were not included in the high TB burden country list. The majority of the studies (43 studies) were conducted using a cross-sectional study design **(Table 1)**.

Different laboratory diagnostic methods such as TST and IGRA (QFT, T-SPOT and ELISPOT) were used to detect LTBI in CKD patients. The IGRA method was used in 36 studies where QFT, T-SPOT, and ELISPOT were used in 29, 11 and 1 studies, respectively. However, the type of IGRA methods were not specified in three studies. Tuberculin skin test was used in 47 studies. These diagnostic methods were used alone or in different combinations **(Table 1)**.

3.2. Pooled prevalence of latent tuberculosis among patients with chronic kidney disease

We have extracted data from 59 studies, but the pooled prevalence of LTBI among CKD patients was determined by using 53 studies. In the remaining six studies, the studies used two or more laboratory screening methods and data was available for the specific method, but we were unable to get the overall LTBI prevalence in combination of the laboratory methods. The highest sample size was 1790 [13], while the lowest sample size was 30 [36]. The highest prevalence was 82% from Iran [23], and the lowest prevalence 6% from Canada [24] and from Japan [25]. When pooled together, 3219 CKD patients had LTBI from 12,772 patients. Based on the random effect model, the pooled prevalence of LTBI among CKD patients was estimated as 30.2% (95%CI; 25.5, 34.8, I^2; 97.82%) (Fig. 2). There was high heterogeneity among studies, and publication bias was revealed by funnel plot (Fig. 3) and Egger's regression test (P = 0.0006). However, after the trim-and-fill analysis, there was no change in the pooled estimate (Fig. 2) (Table 2).

Per continent, the highest pooled prevalence of LTBI among CKD patients was found in Europe (estimate; 36%, 95%CI; 25, 48, I^2; 82.78%) followed by Asia (estimate; 33%, 95%CI; 27, 40, I^2; 97.57%), South America (estimate; 20%, 95%CI; 12, 28, I^2; 93.50%), and North America (estimate; 18%, 95%CI; 12, 24, I^2; 95.78%). Since there is only one study from Africa conducted in Egypt with a prevalence of 38% (95% CI; 26, 49), we were unable to estimate the pooled prevalence. Per the WHO regional classification, the highest pooled estimate was found in EUR (estimate; 43%, 95%CI; 33, 52, I^2; 95.67%) followed by EMR (estimate; 39%, 95%CI; 26, 53, I^2; 95.89%), SEAR (estimate; 32%, 95%CI; 18, 45, I^2; 92.87%), WPR (estimate; 21%, 95%CI; 15, 28, I^2; 95.47%), and AMR (estimate; 19%, 95%CI; 14, 24, I^2; 95.20%) (Fig. 2). In addition, we have also performed a sub-group analysis based on publication year. The pooled prevalence of LTBI among CKD patients based on studies published from 1998 to 2010, from 2011 to 2015, and from 2016 to 2022, were 34% (95%CI; 26%, 42, I^2; 95.41%), 34% (95%CI; 25%, 43, I^2; 97.65%), and 24% (95%CI; 17%, 31, I^2; 98.31%), respectively. Besides, we performed a sub-group analysis considering classification of countries with TB burden category. Thus, the pooled prevalence of LTBI among CKD patients residing in high TB burden countries was 25% (95%CI; 16%, 34, I^2; 95.81%), while the pooled LTBI prevalence among CKD patients residing in the countries not included in the list of high TB burden countries was 31% (95%CI; 26%, 37, I^2; 98.02%). Furthermore, we have conducted a sub-group analysis based on the World Bank Group classification of countries by their income level**.** Accordingly, the pooled prevalence of LTBI was 24% **(**95%CI; 20%, 29, I^2; 96.75%), 33% (95%CI; 21%, 44, I^2; 90.82%), and 37% (95%CI; 28%, 47, I^2; 97.89%) in CKD patients living in high income, lower middle income and upper middle income countries, respectively **(Table 2) (Appendix).**

3.3. Pooled prevalence of latent tuberculosis per laboratory diagnostic method

We have performed a sub-group analysis, using the laboratory diagnostic method used to detect LTBI in CKD patients. Accordingly, TST, QFT, T-SPOT, ELISPOT, and unspecified IGRA were used. Tuberculin skin test was used by 47 studies, where the highest prevalence was 82% [23] and the lowest prevalence was 3% [37,38]. A total of 8208 CKD patients were screened by TST and 1966 were found to have LTBI. Based on the random effect model, the pooled prevalence of LTBI among CKD patients screened by TST was 25.3% (95%CI; 20.3%, 30.3%, I^2; 97.71%) (Fig. 4). The Egger's regression test (P = 0.002) revealed the presence of publication bias **(Appendix).** However, there is no change in the pooled prevalence after the trim and fill analysis. The QFT test was used in 29 studies where the largest and the smallest LTBI prevalence among CKD patients detected by QFT were 54% [39], and 6% [25], respectively. From 4821 CKD patients screened for LTBI using QFT, 1285 were found to have LTBI that gave a pooled prevalence of 28.0% (95%CI; 23.9, 32.0, $I^{2;}$ 90.83%) (Fig. 5). The presence of publication bias was revealed by the asymmetry of the funnel plot and the statistical significance of the Egger's regression test (P = 0.0003) **(Appendix)**. After the trim and fill analysis, the pooled estimate became 25.4% (95%CI; 21.1%, 29.8%). The other laboratory method used to detect LTBI in CKD patients was T-SPOT that is used by 13 studies. Based on this method, the smallest and the highest LTBI prevalence was found to be 4% [25] and 58% [40], respectively. Among 1412 CKD

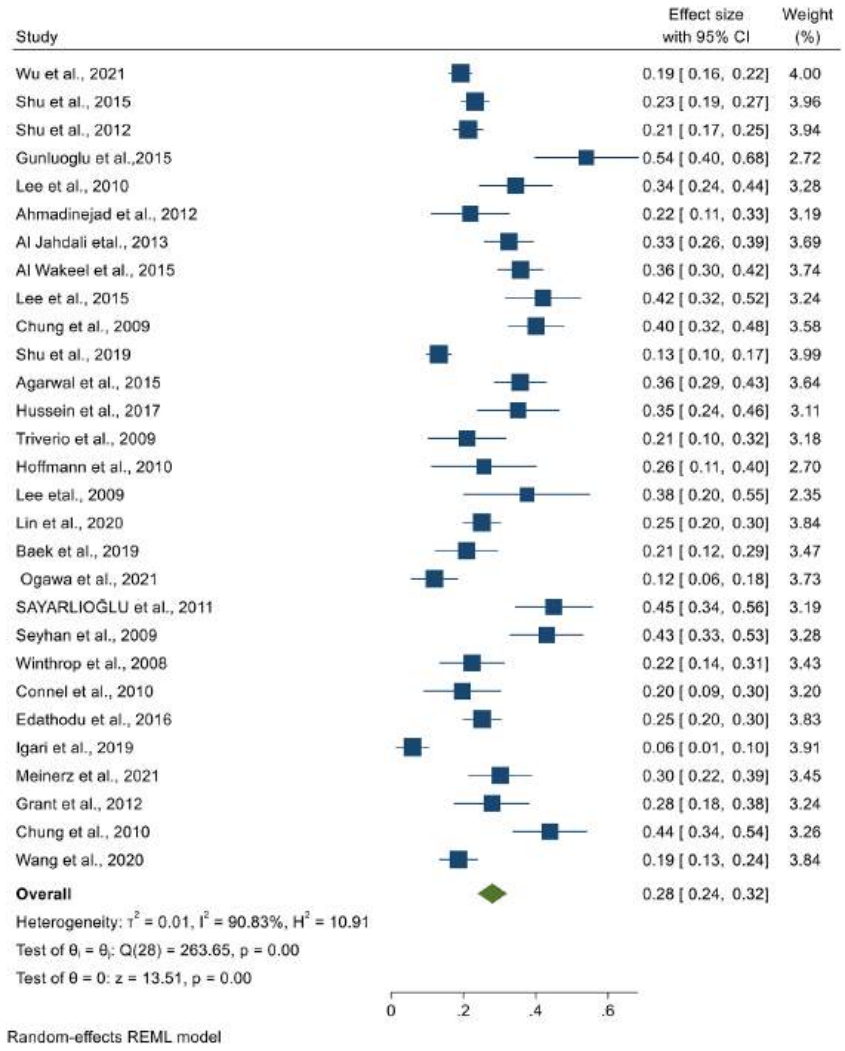

Fig. 5. Forest plot for the pooled prevalence of latent tuberculosis among patients with chronic kidney disease diagnosed using QFT.

patients screened for LTBI using T-SPOT, 595 patients were found to have LTBI. Based on the random effect model, the pooled prevalence of LTBI in CKD patients screened by T-SPOT was 32.6% (95% CI; 23.7, 41.5, I^2; 97.53%) (Fig. 6). Based on the Egger's regression test there is no publication bias (P = 0.306) **(Appendix).** Since there is only one study that used ELISPOT, it was difficult to estimate the pooled prevalence **(Table 2).**

3.4. Prevalence of latent tuberculosis across categories of chronic kidney disease

In this study, we have performed a sub-group analysis to estimate the pooled prevalence of LTBI based on the category of CKD such that pre-dialysis, hemodialysis, peritoneal dialysis and post-renal transplantation. Specifically, 39, 6, 5, and 3 studies assessed the prevalence of LTBI in hemodialysis, post-renal transplantation, peritoneal dialysis and pre-dialysis patients, respectively. Among 432 pre-dialysis patients, 61 were found to have LTBI that gave a pooled LTBI prevalence of 17.8% (95%CI; 3.3, 32.4, I^2; 90.61%) (Fig. 7). In hemodialysis patients, the smallest prevalence of LTBI was 9% [12], while the highest prevalence was 82% [23]. A total of 7534 hemodialysis patients were screened for LTBI and 2396 were found to have LTBI with a pooled LTBI prevalence of 34.8% (95%CI; 29.1, 40.5, I^2; 96.87%) (Fig. 8). The Egger's regression test was on the borderline (P = 0.049) that revealed the presence of publication bias. However, after the trim and fill analysis, there was no change in the pooled estimate. The third group of patients were those on peritoneal dialysis. We have estimated the pooled prevalence using four studies having 60 LTBI cases among 253 patients that gives a pooled prevalence of 25% (95%CI; 11, 38, I^2; 83.48%) (Fig. 9). The last group of CKD patients were those who had undergone renal transplantation. The pooled prevalence of LTBI among CKD patients who underwent transplantation was estimated using six studies that comprises 1100 renal transplanted patients. LTBI was detected in 159 patients that gave a pooled LTBI prevalence of 16% (95%CI; 7, 25, I^2; 94.26%) (Fig. 10) **(Table 2).**

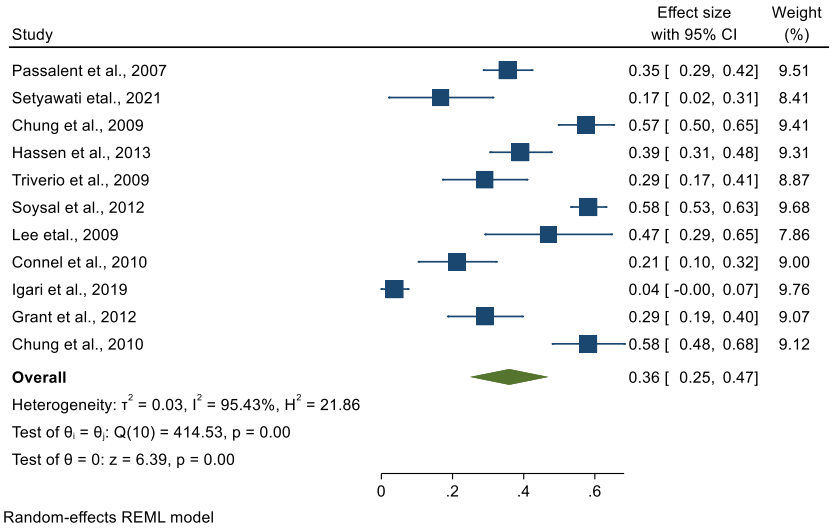

Fig. 6. Forest plot for the pooled prevalence of latent tuberculosis among patients with chronic kidney disease diagnosed using TST.

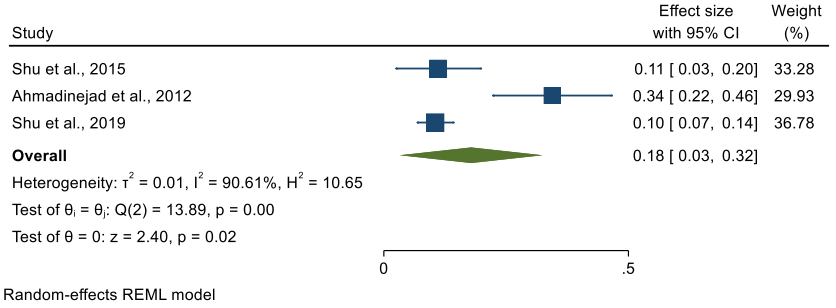

Fig. 7. Forest plot for the pooled prevalence of latent tuberculosis among pre-dialysis chronic kidney disease patients.

We conducted a meta-regression analysis to assess the effect of sample size and publication year on the heterogeneity among studies. The multivariate meta-regression model revealed that sample size (P = 0.064) and publication year (0.553) did not significantly predicted heterogeneity among studies. However, this model only explains 4.58% of the heterogeneity **(Table 3).**

4. Discussion

In this study, we estimated the pooled prevalence of latent tuberculosis among patients with chronic kidney disease based on data collected from 53 studies that included 12,772 CKD patients. The study findings indicated that nearly one-third of CKD patients had LTBI with regional disparities. In addition, we conducted a sub-group analysis to estimate the pooled prevalence of LTBI based on the type of CKD, the laboratory diagnostic methods, continent, WHO regional classification, country's income level, publication year, and TB burden classification.

This study revealed that, 30% of CKD patients had LTBI, which is higher compared to the prevalence in the general population, where one-fourth of the global population is infected with TB [1]. In addition, this pooled estimate exceeds the global pooled estimate obtained among the general population, which was less than 25% [41]. This higher LTBI prevalence among CKD patients indicated that this group of population are at higher risk to develop active TB. This was corroborated in our recent meta-analysis, in which 3718/100, 000 CKD patients got TB during their follow-up period, substantially above the TB incidence in the general population [4]. This emphasizes the necessity of early and active screening, testing and treatment of LTBI in CKD patients in order to strengthen active TB prevention and control, which can improve the quality of life in this population. The outcomes of this study can be used to develop future guidelines and guidance. According to the WHO regional classification of countries, the highest pooled estimate was found in EUR (43%), followed by EMR (39%), SEAR (32%), WPR (21%), and AMR (19%). In a previous global meta-analysis study the decreasing order of the pooled prevalence of LTBI among the general population stratified per WHO regional classification was SEAR, AFR, EMR, WPR, AMR and EUR. Since we did not get studies from the WHO African region, we were unable to find the estimate the pooled estimate.

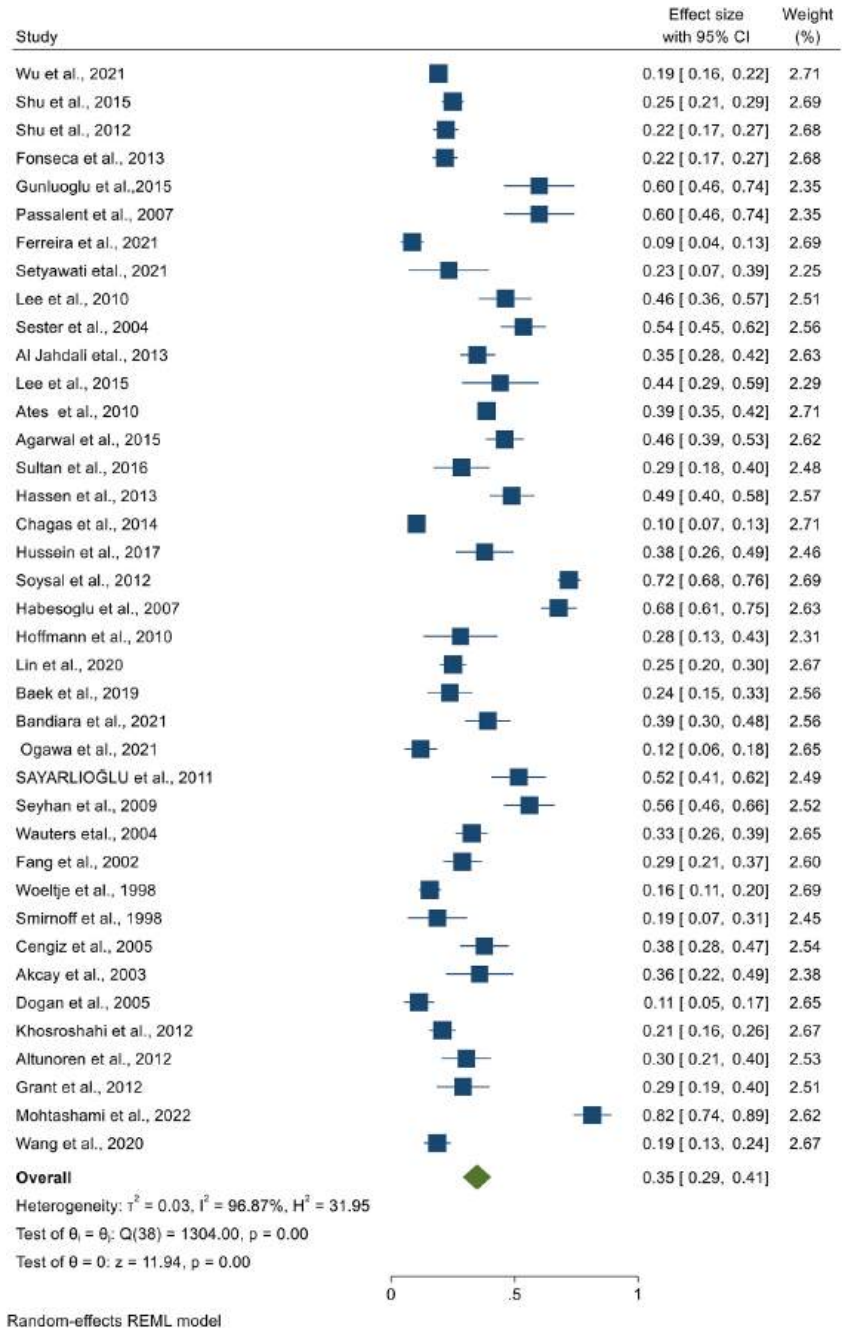

Fig. 8. Forest plot for the pooled prevalence of latent tuberculosis among hemodialysis patients.

We also conducted a sub-group analysis based on publication year, and the study findings revealed that the pooled estimate is lower in studies published after 2016 (24%) compared to studies published between 1998 and 2010 (34%), and between 2011 and 2015 (34%). A global study [42] similarly found a modest reduction in the prevalence of LTBI. In addition, we have also estimated the pooled prevalence based on country's TB burden classification. The findings revealed that countries not included in the high TB burden countries had a relatively greater prevalence than their counterparts did.

The current study found that dialysis patients in general and hemodialysis patients in particular, had higher LTBI prevalence as compared to pre-dialysis and post-renal transplanted patients. Dialysis patients, particularly those on hemodialysis, are at increased risk of contracting *Mycobacterium tuberculosis* through person-to-person transmission since they travel frequently and spend lengthy periods in health facilities.

Besides, we have performed a sub-group analysis based on the laboratory diagnostic method used to diagnose LTBI in CKD patients.

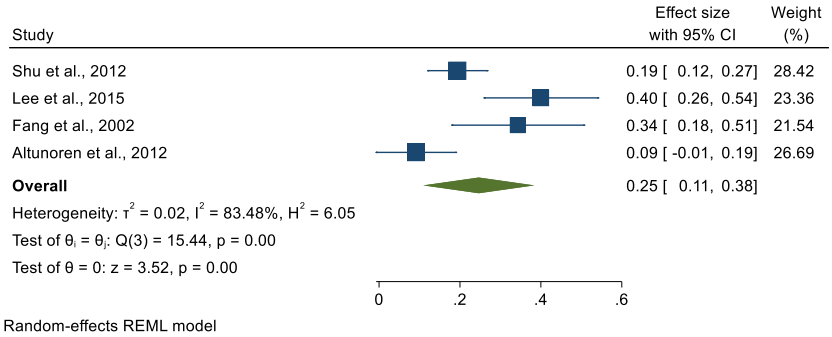

Fig. 9. Forest plot for the pooled prevalence of latent tuberculosis among peritoneal dialysis patients.

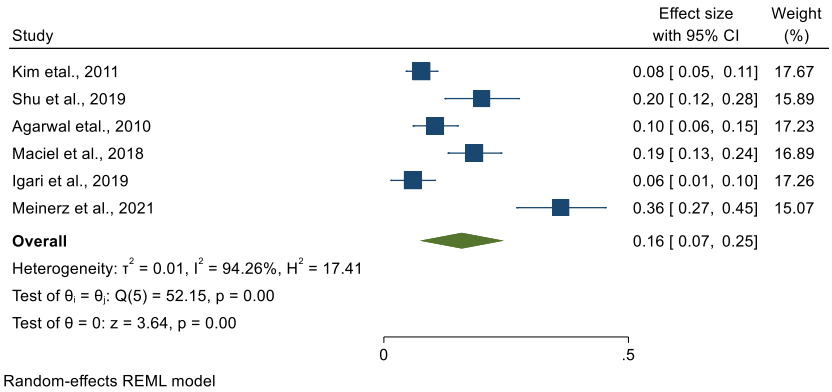

Fig. 10. Forest plot for the pooled prevalence of latent tuberculosis among patients who undergone renal transplantation.

Table 3
Meta-regression analysis of heterogeneity using sample size and publication year.

Variable	Unadjusted model		Adjusted model	
	Coefficient (95%CI)	P-value	Coefficient (95%CI)	P-value
Sample size	−.0001712 (-.0003371 -5.31e-06)	0.043	−.0001609 (−.0003313 9.56e-06)	0.064
Publication year	−.0037576 (−.0114016, .0038865)	0.335	−.002313 (−.0099455 .0053196)	0.553

We found a relatively a higher pooled estimate in CKD patients diagnosed with IGRAs compared with TST. One possible reason might be the use of 10 mm cut-off in the TST. Likewise, this was reported by a previous global pooled estimate conducted in the general population [31].

In general, CKD patients suffer from multitude complications ranging from anemia, psychiatric diseases, cardiovascular complications, endocrine and metabolic abnormalities that needs to be given a focus to decrease high morbidity, mortality and poor quality of life [43–45].

Finally, the findings of this study should be interpreted by considering the following limitations. Primarily, under representation of CDKs from Africa in this review may have affected the global prevalence of LTBI in CDK patients. Second, the high heterogeneity among studies and the presence of publication bias may affect the true estimates. Lastly, since most of the original studies did not use specific cutoffs based on age and immunosuppression status of CKD patients, we did not perform analysis based on the specific cutoffs. However, we have performed stratified analysis that validated the current study findings.

5. Conclusion

This study identified higher prevalence of LTBI among CKD patients that needs attention of all concerned bodies to early detect and treat LTBI in this group of individual. There is disparities in the prevalence of LTBI per WHO regional classification, where CKD patients residing in the EUR, EMR and SEAR had relatively higher LTBI prevalence. In addition, dialysis patients mainly hemodialysis patients had higher LTBI prevalence compared to pre-dialysis and post-renal transplanted CKD patients. Besides, the prevalence of LTBI is higher in patients diagnosed with IGRA compared with those CKD patients diagnosed with TST. The findings in this study

indicate the need to give attention for the early diagnosis and treatment of LTBI in CKD patients. We recommended more studies from the African Region where TB is endemic and the prevalence of CKD is increasing.

Author contribution statement

Ayinalem Alemu: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Zebenay Workneh Bitew: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Getu Diriba; Getachew Seid; Emebet Gashu: Performed the experiments.

Shewki Moga; Saro Abdella; Kirubel Eshetu; Getachew Tollera; Mesay Hailu Dangisso; Balako Gumi: Analyzed and interpreted the data; Wrote the paper.

Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2023.e17181.

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Effectiveness of healthcare workers and volunteers training on improving tuberculosis case detection: A systematic review and meta-analysis

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Abstract

Introduction

Tuberculosis is the second most common infectious cause of death globally. Low TB case detection remains a major challenge to achieve the global End TB targets. This systematic review and meta-analysis aimed to determine whether training of health professionals and volunteers increase TB case detection.

Methods

We performed a systematic review and meta-analysis of randomized control trials and non-randomized control trials reporting on the effectiveness of health professionals and volunteers training on TB case detection. We searched PubMed, SCOPUS, Cochrane Library, and reference sections of included articles from inception through to 15 February 2021, for studies published in English. Study screening, data extraction, and bias assessments were performed independently by two reviewers with third and fourth reviewers participating to resolve conflicts. The risk of bias was assessed using the Joanna Briggs Institute (JBI) checklist. Meta-analyses were performed with a random effect model to estimate the effectiveness of training intervention on TB case detection.

Results

Of the 2015 unique records identified through our search strategies, 2007 records were excluded following the screening, leaving eight studies to be included in the final systematic review and meta-analysis. The results showed that providing training to health professionals and volunteers significantly increased TB case detection (RR: 1.60, 95% CI: 1.53, 1.66). There was not a significant degree of heterogeneity across the included study on the outcome of interest (I^2 = 0.00%, p = 0.667).

Conclusions

Providing training to healthcare workers and volunteers can increase TB case detection.

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Abbreviations: CD, Case detection; JBI, Joanna Briggs Institute; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MeSH, Medical Subject heading; RCT, randomized control trial; TB, Tuberculosis; WHO, World Health Organization

Introduction

Despite Tuberculosis (TB) is a preventable and treatable disease, it remains an important cause of death from an infectious agent [1], especially, TB, the second-deadliest infectious killer (after COVID-19), is caused by Mycobacterium tuberculosis, which primarily affects the lungs [2]. Based on the World Health Organization (WHO) report, approximately 10 million people who

developed TB in 2020. More than 4 million people have tuberculosis but have not been diagnosed or have not reported the disease to national authorities, which means 40% of all incident cases were not reported to the national tuberculosis program [2,3]. India (41%), Indonesia (14%), the Philippines (12%), and China (8%) were the countries that contributed the most to the global reduction in TB notifications between 2019 and 2020 [2].

Failure of TB case detection can increase the risk of death, severe illness, and transmission of TB in households and communities [4–7]. Previous studies showed that missed pulmonary TB cases can transmit the infection to 10–15 people per year, a major challenge to achieving the global End TB targets [8–10].

The reason for low TB case detection can be related to the healthcare system or patient-related factors. Lack of f adequate training of health professionals on the diagnosis and treatment of TB a common healthcare system factor affecting TB case detection [11–14]. Different interventions were designed to enhance TB case detection in the national TB programs. Most of the interventions designed to improve TB case detection were targeted to TB patients and the communities [15,16]. Extensive advocacy and awareness-raising activities have been implemented to educate people about TB diagnosis [1]. Patient education can be as simple as a booklet or as comprehensive as multiple session programs. However, this approach alone does not increase TB case detection. Additional measures, such as training of health professionals, health extension workers, and community volunteers might be required to increase TB case detection. While few studies have investigated the effects of providing training to health professionals and volunteers on TB case detection, the findings were inconsistent across studies [17–19]. To our knowledge, no systematic review has examined whether health professionals and volunteers training is an effective intervention to increase TB case detection. Therefore, this systematic review and meta-analysis aimed to determine whether training of health professional and volunteers increase TB case detection.

Materials and methods

Eligibility criteria

Studies were included if they were randomised controlled trials; non-randomised trials with at least a defined intervention and parallel control groups; quasi-experimental studies; controlled before-after studies with outcome measures before and after the intervention. The interventions were a provision of training to health professionals or any volunteers for at least three days. Potential comparators were usual care, or no intervention (i.e. no training). We excluded conference and meeting abstracts, and non-English language articles, animal studies and those that had insufficient information on the main outcome of interest. The outcome of interest was the TB case detection rate. Our research eligibility in the PICO (Population, Intervention, Comparator, Outcome) format is included in (Table 1).

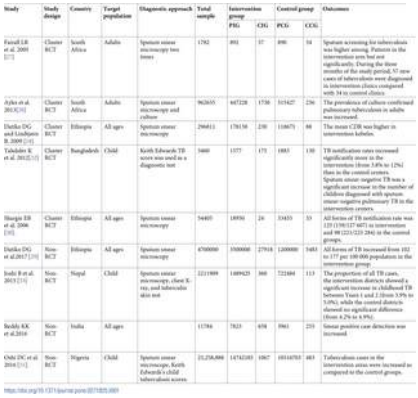

Table 1. The characteristics of the studies included in the systematic review and meta-analysis.
https://doi.org/10.1371/journal.pone.0271825.t001

Search strategy, information sources and selection criteria

We conducted an electronic medical literature search on PubMed, Cochrane Library, and Scopus databases for relevant randomized controlled trials describing training as an intervention to increase TB case detection, published from the date of each database inception to 15 February 2021. The review was performed according to the standard procedures of the Cochrane Collaboration [20]. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used to report the review [21]. The protocol was registered in PROSPERO with registration number CRD42021284106. A comprehensive search strategy was developed using the search terms and medical subject headings [22]. The complete PubMed search strategy is provided in the (S1 File). Reference lists of included papers were screened for additional relevant articles using forward and backward citation search. Corresponding authors were contacted by email in some instances when additional information was required. Key terms were used to search a library database (S1 Table).

Study selection

All studies identified through the search strategies were imported into EndNote version 7 for screening. After removing duplicate articles, screening of papers by title and abstract were carried out independently by two researchers (DA and GD). Screening of full-text papers was also carried out by the same two researchers for inclusion based on pre-defined eligibility criteria.

Disagreement on the inclusion or exclusion of selected papers was resolved through discussion and consensus with co-authors (MBS, EWM, TAD, and FAG).

Data extraction

Data were extracted from included studies using Microsoft Excel 2016 spreadsheet (Microsoft, Redmond, Washington, USA) by two researchers (DA, GD,). The spreadsheet was checked and refined before extraction began. Data extracted from each study included: name of the first author, year of publication, study design, place of study, type of participant, type of intervention (comparison groups and sample size of each group), outcomes (case detection rate), and the key findings. Information on the duration of implementation, frequency of interventions, site of intervention, and the number of interventions were also extracted.

Outcome measurement

The primary outcome was TB case detection, expressed by the proportion of all new cases of TB with a confirmed diagnosis.

Quality assessment

The quality of the included studies was independently assessed by two investigators (DA and EWM) using Joanna Briggs Institute (JBI). The JBI checklist is designed to assess 13 components of RCT study design including randomization method, allocation concealment, baseline characteristics, patient blinding, therapist blinding, observer blinding, co-intervention control, compliance, attrition rate, end-point assessment time point, intention to treat analysis, the same outcome measurement way and reliable outcome measurement [23]. The authors considered low risk of bias 'Yes' either the study protocol is available and all of the studies' pre-specified outcomes that are of interest in the review have been reported in the pre-specified way or the study protocol is not available but it is clear that the published reports include all of the study's pre-specified outcomes and all expected outcomes that are of interest in the review. Authors considered high risk of bias 'No' if any of the following is fulfilled: Not all of the study's pre-specified primary outcomes have been reported, one or more primary outcomes is reported using measurements analysis methods or subsets of the data that were not pre-specified, one or more reported primary outcomes were not pre-specified, one or more outcomes of interest in the review are reported incompletely, the study report fails to include results for a key outcome that would be expected to have been reported for such a study. Authors considered unclear if there is insufficient information to permit judgment of 'Yes' or 'No'.

Other sources of bias such as recruitment bias were considered as "No" if bias is detected due to problems not covered elsewhere and "Yes" if no other bias is detected. Blinding was classified as "Yes" if steps were taken to ensure that those recording the main outcome of the study were blind to the assigned interventions, and "No" if this was not the case, or if there was no description of the method for assessing the adequacy of the randomization procedure. Completeness of follow-up was assessed as "Yes" if steps to the handling of incomplete outcome data were complete and unlikely to have produced bias or "No" if the attrition amount or handling of incomplete outcome data was not maintained.

The instrument or tool used to assess the risk of bias, rigor, or study quality was reported along with some summary estimate of the quality of primary studies in the included research synthesis [24]. Therefore, the quality of each study was assessed based on JBI quality assessment criteria (S2 Table).

Data analysis

Meta-analysis with a random effect model was performed to calculate relative risk (RR) with 95% confidence intervals [25]. Heterogeneity between studies was assessed by the index of heterogeneity squared (I^2) statistics with 95% CI. The I^2 statistic measures the proportion of observed variance between trials that is not due to chance (rather due to real differences across studies populations and interventions). The I^2 value less than 30% was interpreted as low evidence of heterogeneity, between 30% and 60% was moderate heterogeneity and I^2 more than 60% was interpreted as evidence of substantial heterogeneity [26]. Meta-regression was used to explore whether study characteristics explained heterogeneity. Publication bias was assessed qualitatively by visual inspection of funnel plots and quantitatively by Egger's test. Sensitivity analysis was also conducted based on the quality and characteristics of the studies. The data analysis was performed by Stata version 16. All tests were 2-tailed, and $P < 0.05$ was considered statistically significant.

Results

Study selection

Of 4052 studies obtained from the database search, 2037 articles were excluded due to duplications. After removing duplicates, 2015 articles were screened by titles and abstracts and 1946 articles were excluded which resulted in 69 potential articles for full-text review. After a full-text review, 9 studies met the eligibility criteria and were included in the final analysis (Fig 1).

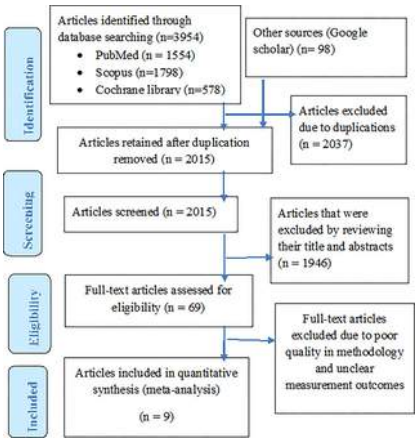

Fig 1. PRISMA flow chart of study selection.
https://doi.org/10.1371/journal.pone.0271825.g001

Study characteristics

Table 1 summarizes the characteristics of the included studies. Studies were conducted in five different countries. All the studies were from African and Asian continents. The population groups were children (under the age of 15) for three studies [29–31], adults for two studies [27,28], and both adults and children for four studies [18,19,29,30]. Interventional trials were included in this analysis. Five of the studies were cluster RCTs, whereas the other four were non–RCTs.

In all studies, the training provided for health workers and volunteers were focused on symptoms, diagnostic and screening methods, and treatment of TB cases. The duration of the intervention varied from 3 months [27] to 54 months [28,29]. Sputum smear microscopic and gene Xpert were used to diagnose TB (Table 1).

Most of the studies included in this study used instructor-led training, demonstration, hands-on training, group-based training, job training, and technology-based training (text message), but the method used by the three studies [19,28,31] is not clear. As a result, it is difficult to determine which training method is more effective in identifying TB case detection.

Effectiveness of healthcare workers and volunteers training on improving TB case detection

Nine interventional studies were included to investigate whether the intervention group had an effective improvement in TB case detection rate as compared to the control arms. Seven out of nine selected studies were effective to improve the case detection while the other two studies showed that the interventions had not improved the case detection rate. The overall pooled effect size estimate showed that healthcare workers and volunteers training was significantly improved TB case detection (RR: 1.60, 95% CI: 1.53, 1.66) (Fig 2). In addition, sensitivity analysis showed that there was no single study that affects the overall effect of the intervention (Fig 3).

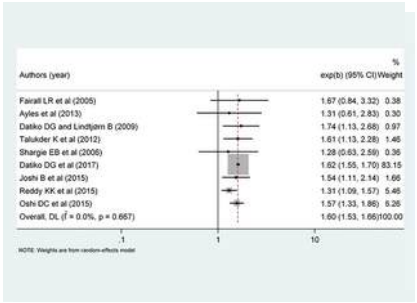

Fig 2. Forest plot of the effect size of training on tuberculosis case detection in TB high burden settings.
https://doi.org/10.1371/journal.pone.0271825.g002

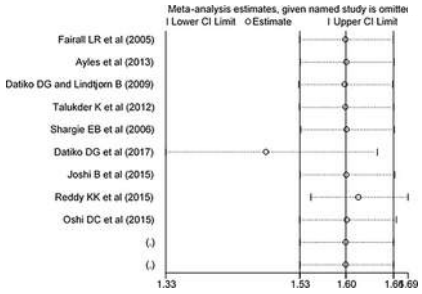

Fig 3. Sensitivity test on effect of training on tuberculosis case detection.
https://doi.org/10.1371/journal.pone.0271825.g003

Heterogeneity and publication bias

There was no a significant degree of heterogeneity across the included study on the outcome of interest (I^2 = 0.00%, p=0.667) (Fig 2). Neither the funnel plot (Fig 4) nor the egger tests showed evidence of significant publication bias (P = 0.244).

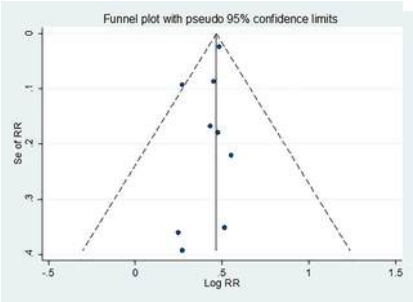

Fig 4. Funnel plot analysis of publication bias.
https://doi.org/10.1371/journal.pone.0271825.g004

Risks of bias assessment

The risk of bias assessment showed that seven studies had a low risk of bias for random sequence generation and adequate allocation concealment. A blind outcome assessment was reported from only one study (28). In all studies, there was no relevant outcome reporting bias observed. Also, there was no reporting in attrition and selective reporting bias (Table 2).

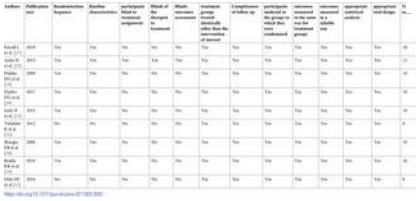

Table 2. Risk bias assessment using JBI checklist.
https://doi.org/10.1371/journal.pone.0271825.t002

Discussion

This is the first systematic review and meta-analysis that quantified the effectiveness of providing training for healthcare workers and volunteers on TB case detection. Our findings showed that providing training to healthcare workers and community volunteers significantly increased TB case detection. This is an important finding suggesting the need to scaling-up training to improve case detection and to achieve the global End TB targets [25,34,35].

Community healthcare workers being more familiar with the community and trusted by the community were involved in the intervention. Providing training to community volunteers may improve their knowledge of TB and they can refer suspected cases to TB programs. A previous study found that community-based case detection approach helps to empower patients to deal with their

problems [36]. Providing training to health professionals may also be useful for the proper diagnosis and treatment of TB patients [31,32]. Although different training approaches were used their effectiveness in increasing TB case detection were not significantly differ [18,29,31–33].

The World Health Organization (WHO) has a target to end TB by 2035 [37]. The findings from this systematic review provide important evidence that may contribute to achieve this ambitious target. This systematic review revealed that providing effective training to health professionals and community workers can improve TB case detection. It has therefore had a great impact on TB case findings by implementing educational training for healthcare providers and community volunteers. This systematic review and meta-analysis have also implications for health staff and researchers by increasing their knowledge on the effectiveness of training intervention on TB cases detection. Although many people with TB infection remain undiagnosed and had a lack of care [38], our study showed that the implementation of training packages considerably effective approach to case detection and helps to reduce unnecessary delays in diagnosis and received care. The implementation of interventions and using accurate diagnostic tests may improve TB case notification. Therefore, the findings of this study could in turn be implemented into practice.

Trained health workers and community volunteers were the keys to detecting TB cases in the community and primary health care settings and trained community volunteers were crucial to conduct household contact screening in detecting cases and refer cases to nearby TB diagnostic centers [33]. The finding of this systematic review supported the importance of providing educational training to improve the TB case detection rate.

Our review had several limitations. We have included articles published in English only. Most studies included in our study used a sputum smear microscope as a main diagnostic method for TB that mainly identifies positive pulmonary TB, and this type of diagnostic approach has limited ability to identify true positive cases. This evidence is substantiated with another report that conventional tests like microscopic examination have low accurate TB diagnosis as compared to Xpert [39]. Possibly, many people with TB infection are still undetected in resource-limited and TB high burden countries [40]. Study related characteristics were not explored using a meta-regression due to low number of available studies. Some studies show that the training method used is not clear, so it is difficult to know which training method is more effective to increase case detection. We find this to be one of the limitations of the study.

Conclusions

This systematic review and meta-analysis found that the TB case detection rate can be improved by providing training for healthcare workers and volunteers. Therefore, strengthened educational training interventions should be encouraged to improve TB case detections and to ultimately achieve the End-TB targets.

Supporting information

S1 File. PubMed advanced search terms.
https://doi.org/10.1371/journal.pone.0271825.s001
(DOCX)

S1 Table. Search key terms.
https://doi.org/10.1371/journal.pone.0271825.s002
(DOCX)

S2 Table. Data collection and risk assessment for RCTs and non-RCTs studies.
https://doi.org/10.1371/journal.pone.0271825.s003
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Prevalence and incidence of symptomatic pulmonary tuberculosis based on repeated population screening in a district in Ethiopia: a prospective cohort study

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ABSTRACT

Objective In Ethiopia, one-third of the estimated tuberculosis cases are not detected or reported. Incidence estimates are inaccurate and rarely measured directly. Assessing the 'real' incidence under programme conditions is useful to understand the situation. This study aimed to measure the prevalence and incidence of symptomatic pulmonary tuberculosis (PTB) during 1 year in the adult population of Dale in Ethiopia.

Design A prospective population-based cohort study.

Setting Every household in Dale was visited three times at 4-month intervals.

Participants Individuals aged ≥15 years.

Outcome measures Microscopy smear positive PTB (PTB s+), bacteriologically confirmed PTB (PTB b+) by microscopy, GeneXpert, or culture and clinically diagnosed PTB (PTB c+).

Results Among 136 181 individuals, 2052 had presumptive TB (persistent cough for 14 days or more with or without *haemoptysis, weight loss, fever, night sweats, chest pain or difficulty breathing*), in the first round of household visits including 93 with PTB s+, 98 with PTB b+ and 24 with PTB c+; adding those with PTB who were already on treatment, the total number of PTB was 201, and the prevalence was 147 (95% CI: 127 to 168)/100 000 population. Out of all patients with PTB, the proportion detected by symptom screening was in PTB s+ 65%, PTB b+ 67% and PTB c+44%. During 96 388 person-years follow-up, 1909 had presumptive TB, 320 had PTB and the total incidence of PTB was 332 (95% CI: 297 to 370)/100 000 person-years, while the incidence of PTB s+, PTB b+ and PTB c+ was 230 (95% CI: 201 to 262), 263 (95% CI: 232 to 297) and 68 (95% CI: 53 to 86)/100 000 person-years, respectively.

Conclusion The prevalence of symptomatic sputum smear-positive TB was still high, only one-third of prevalent PTB cases notified and the incidence rate highest in the age group 25–34 years, indicating ongoing transmission. Finding missing people with TB through repeated symptom screening can contribute to reducing transmission.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study included a large sample and worked closely with the national tuberculosis programme and the community structures that contributed to its sustainability.
⇒ We report not only the prevalence but also the incidence of symptomatic pulmonary tuberculosis during 1 year, which is often not reported elsewhere.
⇒ The study screened a very high proportion of households in the district, giving an accurate measure of the burden of tuberculosis, where the probability of missing people with tuberculosis is small.
⇒ Tuberculosis cases notified were chosen the year before the study because we could not separate the patients identified by the screening from those who attended the health services themselves.
⇒ Only symptomatic patients with tuberculosis were reported, and it is known that many patients are more or less asymptomatic.

BACKGROUND

Tuberculosis (TB) is an infectious disease transmitted by mycobacterial droplets from coughing patients. The global End TB strategy aims to reduce the sources of infection by curing infected individuals with effective anti-TB drugs and has helped reduce the incidence of TB worldwide. The estimated global incidence of TB has recently decreased by 9% from 2015 to 2019, but still 11% less than the End TB targets set for 2020. The incidence of TB is unevenly distributed globally with the highest estimated TB incidence rate in Africa, at 226/100 000 population in 2019. However, the TB incidence rate in Africa declined by 16% from 2015 to 2019, which is greater than the average global decline but still not fast enough to reach the Sustainable Development Goal milestones.[1–4] Ethiopia achieved the first milestone of End TB with a 31% decrease in the estimated incidence rate from 2015 to 2020 (192 to 132/100 000 population).

The national X-ray-based TB survey in Ethiopia in 2010 reported *prevalence* estimates of

108 per 100 000 population for smear-positive pulmonary tuberculosis (PTB s+) and 277/100 000 population for bacteriologically confirmed pulmonary tuberculosis (PTB b+).[5] Only two studies have investigated the pulmonary TB (PTB) *incidence,* both *based on screening of respiratory symptoms.* A study in a central district of Ethiopia in 2013 reported that the incidence of PTB s+ was 214/100 000 person-years and that of PTB b+ was 232/100 000 person-years,[6] while a study in the northern part of the country in 2011 reported that the incidence of PTB s+ was 311/100 000 person-years.[7] However, notifications in the country indicate that one-third of TB cases are still undetected, and more than half of them are in those aged 15–34 years old. Hence, the true incidence of TB is unknown and under-researched because generating these estimates requires massive resources.[8 9]

Therefore, locally available data using the existing health system may help to understand the epidemiology of the disease as well as to validate national estimates, since these are not accurate in areas with disparities in health outcomes and programme implementation. The 'missed' or 'diagnosed late' individuals are important sources of TB transmission.[5 10] Repeated assessment of subnational population-level incidence and prevalence patterns may help the programme quantify the impact of the control efforts to support local decision-making.[10–12]

Dale district was part of a community-based project with active TB case-finding implemented in 2010.[13] The study initially showed high notification rates in the district, which gradually decreased over time (215/100 000 in 2011 to 66/100 000 in 2015). It is not clear to what extent the decline reflects a real decline in TB incidence or is the result of going back to the routine health service delivery strategy without a systematic screening of the community. The impact has therefore not been sufficiently described and documented. Hence, this study aimed to measure the prevalence and incidence of symptomatic PTB through repeated population-based screening in the adult population of the Dale district in southern Ethiopia.

METHODS

Study design and population

This was a population-based prospective cohort study including repeated symptom screening in three consecutive rounds of household visits, from October 2016 to September 2017, in Dale district of southern Ethiopia. The target population was everyone who resided in the 36 administrative units (*kebeles*) in the district. The population data were obtained from the district health offices and each *kebele.* A persistent cough for 14 days or more with or without *haemoptysis, weight loss, fever, night sweats, chest pain or difficulty breathing* was taken as a sign of presumptive TB. Individuals with presumptive TB were enrolled after informed consent, and the population ≥15 years are included in this report. The total population denominator for the population aged ≥15 years was 136 181, based on official data from the Central Statistics Agency in Ethiopia.[14] The coverage of households screened is based on the number of households visited over the number of households registered at each time point. The prevalence of PTB was calculated by dividing the number of patients diagnosed during the first round of visits by the population covered. The incidence rate was calculated by dividing the number of patients with PTB identified during the follow-up period (ie, in the second and third rounds of household visits) by person-years of observation-time. We used the strengthening of the Reporting of Observational Studies in Epidemiology cohort reporting guidelines (online supplemental file 1).[15]

Study setting

The Dale district is a densely populated rural community with 10 health centres, 2 clinics and 36 health posts; TB care follows the End TB strategy.[16] Since 2010, the non-governmental organisation REACH Ethiopia has been developing an innovative model using close-to-community providers, including in the Dale district, contributing to community TB care implementation in Ethiopia.[6 13] Microscopy, but not GeneXpert nor X-ray examination, can be performed at health centres. The primary test for PTB diagnosis is sputum smear microscopy, which is cost-efficient and accessible, but has low sensitivity.[17–19] The only GeneXpert equipment in the area is located outside of Dale district in the town administration of Yirgalem.

Patient and public involvement

No patients were involved in setting the research question or the outcomes, the conduct, interpretation, writing or dissemination of the results. The study was conducted in close collaboration with the Dale district National TB and Leprosy Programme (NTLP). They were informed about the study in advance and were actively involved throughout the design and implementation and in dissemination of the results. The project team organised consultative meetings with participants from regional, zonal and woreda level organisations, non-governmental organisations and religious institutions throughout the full study period. Village-women were included as representatives for the population in Dale.

Data collection

As a first step of the screening, trained female health extension workers (HEWs) familiar with the village went door-to-door, asking if any household member had respiratory symptoms compatible with TB, including those not at home during the survey. HEWs are well-established and trusted by the communities. Those identified with symptoms were carefully followed and asked to come to the health post for a test. This also applied to household members not at home at the time of the visit. Health personnel offered to come to the home to collect sputum for persons having difficulties in reaching the health facilities.

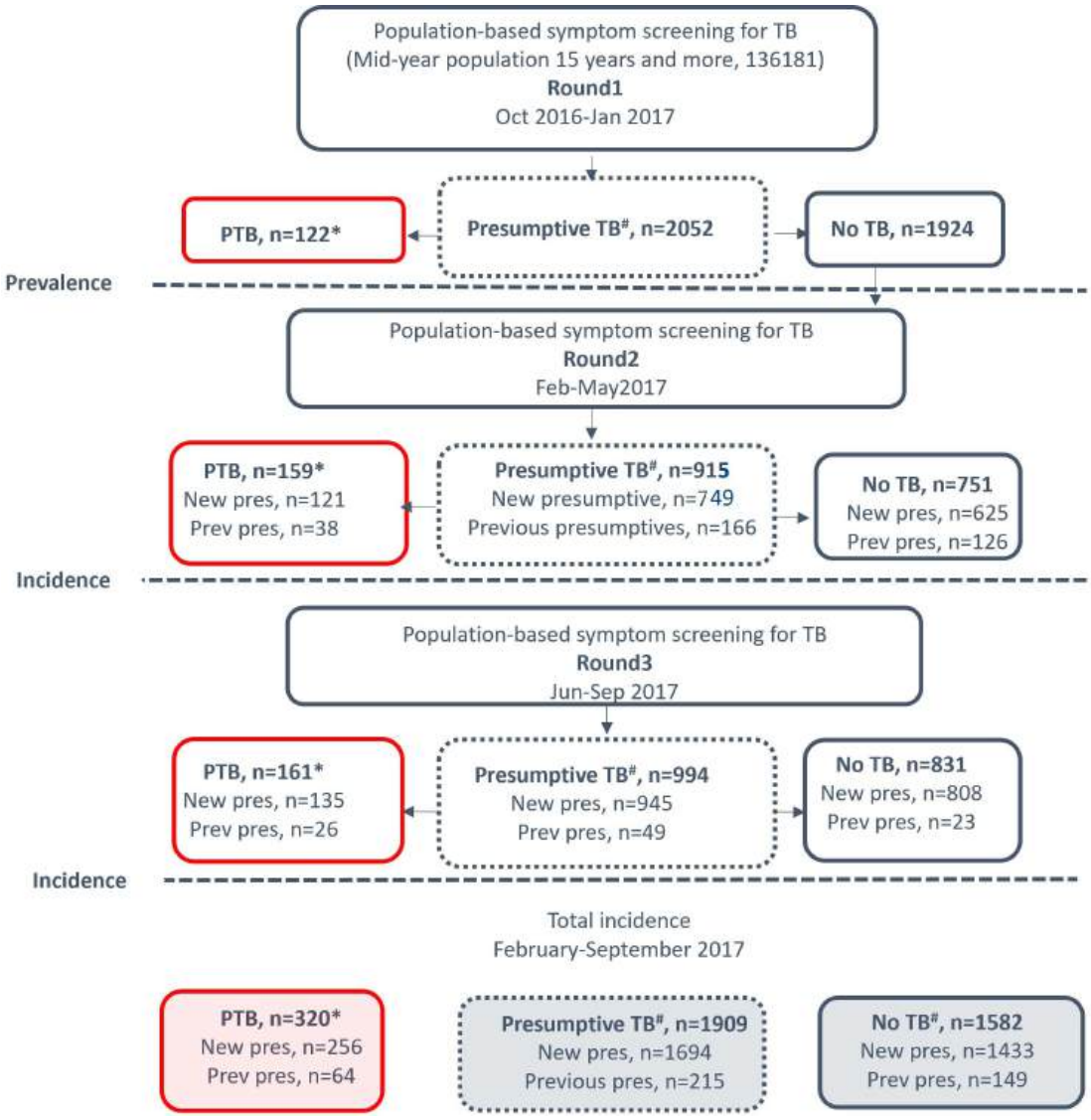

Figure 1 Study flow chart showing three rounds of household screening for TB in Dale district, 2016–2017. PTB, pulmonary TB; TB, tuberculosis. PTB: pulmonary tuberculosis. New pres: first episode of presumptive TB. Prev presumptive: the participant has been identified with presumptive TB in a previous round of household visits and enrolment dates were minimum 30 days apart. ‡Population denominator, estimates from Central Statistics Agency (CSA) in Ethiopia (estimated from a population census of 2007); Some patients had more than one episode.

Pretested semi-structured questionnaires were used to identify individuals with respiratory symptoms compatible with PTB and to collect clinical, demographic and socioeconomic data (online supplemental file 2). Individuals identified with presumptive TB were asked to come to the health post to provide sputum. The sputum samples were collected and transported to the health centre for smear microscopy. Once identified by the study, participants received care, free of charge, as in the routine TB programme. If individuals were diagnosed with TB, they were treated according to the NTLP guidelines.[20] For patients diagnosed with drug-resistant TB, second-line drugs and follow-up were available at the nearby Yirgalem Hospital that initiates drug resistance TB treatment—free of charge. Individuals diagnosed with other diseases were referred for treatment. To ensure the quality of the laboratory, 50% of the slides were randomly selected from participating catchment facilities and retested at the regional laboratory. Smear-positive samples were further validated by GeneXpert. Those already on TB treatment at the time of the survey were not included in the screening data of new incident cases. However, aggregate surveillance data from the NTLP on the number of patients already on TB treatment were added to those detected by screening in the prevalence calculation to facilitate comparison with other studies. Aggregated notification data were obtained from the NTLP from 2011 to 2018. Quarterly TB data were used to track those notified with PTB s+ or PTB c+ before, during, and after the study period to evaluate the impact of interventions on routine TB notification. The project ensured that all patients with TB identified through the project were registered in the TB register.[21]

Table 1 Results of three rounds of testing individuals with presumptive tuberculosis in Dale, 2016–2017

Household visits		Presumptive TB episodes*, n	PTB, n	PTB b+, n	PTB c+, n	% presumptive PTB with PTB		
						PTB[1]	PTB b+[1]	PTB c+[1]
Round 1	New presumptive; only tested once	1729	76	71	5	4	4	0.3
	New presumptive; TB with a repeat test	323	46	27	19	14	8	5.9
	New presumptive; all†	2052	122	98	24	6	5	1.2
Round 2	New presumptive; only tested once	630	72	71	1	11	11	0.2
	New presumptive; TB with a repeat test	119	49	19	30	41	16	25.2
	New presumptive; all†	753	121	90	31	16	12	4.1
	Previous presumptive	166	38	19	19	23	11	11.4
	Total	919	159	109	50	17	12	5.4
Round 3	New presumptive; only tested once	900	121	119	2	13	13	0.2
	New presumptive; TB with a repeat test	45	14	11	3	31	24	6.7
	New presumptive; all†	945	135	130	5	14	14	0.5
	Previous presumptive	49	26	15	11	53	31	22.4
	Total	994	161	145	16	16	15	1.6
Rounds 1+2+3	New presumptive	3746	378	318	60	10	8	2.0
	Previous presumptive	215	64	34	30	30	16	14.0

*The number of episodes is higher than the number of individuals as some were identified more than once.
†New presumptive all means only tested once plus repeat tests within the same round.
PTB[1], PTB means the proportion of presumptive TB cases with a positive bacteriological test result plus clinically diagnosed PTB; PTB, pulmonary TB; PTB b+, bacteriologically confirmed PTB; PTB c+, clinically diagnosed; TB, tuberculosis.

Operational definitions

As mentioned above, the term 'presumptive TB' was used to define individuals who had respiratory symptoms compatible with TB.[22] 'New presumptive' *was used the first time an individual was identified in the study as having symptoms of TB.* Those with presumptive TB who tested negative for TB were included in the denominator for the consecutive rounds. If they were identified as having presumptive TB in a consecutive round of household visits (more than 30 days apart), they were classified as 'previous presumptive with a new episode'. *PTB s+ was defined as at least one positive result by smear microscopy. PTB b+ included having at least one positive result by smear microscopy, GeneXpert or culture. PTB c+ was based on a clinical decision to start anti-TB treatment in those with persistent symptoms and negative bacteriological results; this diagnosis was usually (if not always) also supported by radiological findings. PTB b+ and PTB c+ both indicated a diagnosis of PTB. The* 'screening prevalence' *of PTB was calculated based on individuals identified with PTB in the first round (October 2016 to January 2017) of household visits divided by the total adult population (per 100 000 population). The* 'total prevalence' *also included patients who were already on TB treatment at the time of the first screening round. The incidence was calculated based on the number of individuals newly identified with PTB in the second (February to May 2017) and third (June to September 2017) rounds of household visits divided by the person-years observation time (per 100 000 person-years). Person-years were calculated from the date of enrolment for screening or the end of follow-up on 31 September 2017, for all study participants.* 'Notification' is based on TB register.

Diagnosis

For diagnosis, two spot sputum samples were collected according to standard procedures. Sputum smear-positive samples were sent for confirmation of diagnosis by GeneXpert at Yirgalem Hospital and by culture at the Armauer Hansen Research Institute in Addis Ababa. The use of GeneXpert for all samples was not feasible at the time of the study and was mainly limited to validation for smear-positive (drug-resistant TB diagnosis). In addition, smear-negative samples from HIV positive persons and persistent coughers still symptomatic after a course of broad-spectrum antibiotic were sent for analysis by GeneXpert and cultured in line with NTLP guidelines. Data on TB diagnosis, treatment and treatment outcome

were obtained from the TB register in the health centre. It was not possible to disentangle those identified through the household screening from those who approached the health centre on their own initiative. Individuals with chest X-ray abnormalities[23] were transferred to Yirgalem Hospital for clinical diagnosis of TB.

Data quality and analysis

Data were entered into Excel (Microsoft Office Proofing Tool 2016, Microsoft Corporation). The data quality was assessed by frequency distributions, cross-tabulations and double-entry of a 10% random sample of the data. The difference between the first and second data entries was 0.1%, and no systematic errors were detected. Stata V.14 and OpenEpi[24] were used for analyses.

RESULTS

Population-based symptom screening

The coverage of households screened was high, ranging from 96% to 98% in the three rounds of household visits, (online supplemental file 3). Figure 1 shows a flow chart of the population in the three rounds of household screening. During the study-period, 3746 out of 136 181 persons in the screened target population were identified with presumptive TB. Of these, 442 persons were diagnosed with PTB. In total 352 cases had PTB b+; among them 263 were positive by smear microscopy, GeneXpert and culture, and 52 were positive by smear microscopy only, 34 were positive by GeneXpert only and 3 were positive by culture only. Of the 90 PTB c+ cases, 72 had the GeneXpert test (71 negatives and 1 error test), and none had culture tests. Chest X-ray was taken of 142 persistent coughers who needed further examination after broad spectrum antibiotic treatment; 86 had findings suggestive of PTB, 55 had normal and one unclear X-ray finding.

Table 1 shows results of three rounds of testing individuals with presumptive TB. The number of individuals presumed to have PTB was highest in the first round and halved in the two following rounds. The proportions of PTB cases among individuals with presumptive TB were 6%, 17% and 16% across the three rounds; the proportions of individuals with PTB b+ were 5%, 12% and 15%, respectively; and the proportions of PTB c+ were 5%, 10% and 13%, respectively. The proportion of PTB among individuals with presumptive TB who completed a course of broad-spectrum antibiotics and returned for another test was higher in the second and third rounds (14%, 41% and 31% for rounds 1, 2 and 3, respectively). Seventeen TB cases with symptoms of PTB were eventually diagnosed with extrapulmonary TB but not PTB, and excluded from the study (online supplemental table 1). Four individuals were identified with rifampicin resistance among 263 PTB b+ cases with rifampicin resistance test results. Women had a significantly higher prevalence and incidence of presumptive TB, a lower proportion with PTB b+ cases and a lower prevalence and incidence of PTB than men.

Prevalence of symptomatic PTB

Table 2 shows the total prevalence of PTB in the study area in first round of visits. Among the population of 136 181, 2052 had presumptive TB, 93 were diagnosed with PTB s+, 98 with PTB b+ and 24 with PTB c+. The total number of patients with PTB detected by symptom screening was 122; adding 49 PTB b+ (all of them PTB s+) and 30 PTB c+ patients who were already on TB treatment at the first round, the total number of PTB cases was 201, and the prevalence rate of PTB was 147 (95% CI: 127 to 168)/100 000 population. In those detected by screening, the prevalence rates of PTB b+ and PTB

Table 2 Total prevalence and percentage detected with pulmonary tuberculosis in the first round of visits in Dale, October 2016 to January 2017

	Number of PTB during screening		Number of PTB before screening		Total prevalence of PTB		% detected by screening	
Covariate	PTB b+	PTB c+	PTB b+	PTB c+	PTB b+ per 100 000 (95% CI)	PTB c+ per 100 000 (95% CI)	PTB b+	PTB c+
Total	98	24	49	30	108 (90 to 125)	39 (29 to 50)	67	44
Age in years								
15–24	27	7	23	5	100 (76 to 132)	24 (13 to 41)	54	58
25–34	31	7	15	6	135 (100 to 179)	38 (21 to 64)	67	54
35–44	26	2	4	2	126 (86 to 177)	17 (5 to 40)	87	50
45–54	7	4	4	5	82 (43 to 143)	67 (33 to 123)	64	44
55+	7	4	3	12	65 (33 to 116)	104 (61 to 166)	70	25
Sex								
Male	56	15	27	17	122 (98 to 151)	47 (33 to 66)	67	47
Female	42	9	22	13	93 (72 to 118)	32 (21 to 48)	66	41

n, number; PTB, pulmonary TB; PTB b+, bacteriologically confirmed PTB; PTB c+, clinically diagnosed PTB; TB, tuberculosis.

c+ were 72 (95% CI: 57 to 86) and 17 (95% CI: 10 to 24)/100 000 population, respectively. The prevalence rate of PTB s+ was 68 (95% CI: 54 to 82)/100 000 population from screening and 104 (95% CI: 87 to 121)/100 000 population including patients already on treatment. The percentages of patients detected by screening were as follows: PTB s+, 65%; PTB b+, 67%; and PTB c+, 44%. Among both PTB b+ and PTB c+ patients detected, only one out of three had been identified by the health system (online supplemental tables 2–6).

Incidence of symptomatic PTB

The overall observation time was 96 388 person-years, with 1909 individuals identified with presumptive TB, 254 with PTB b+ (including 222 smear-positive) and 66 with PTB c+ (table 3). The total number of PTB cases

Table 3 Incidence of presumptive and pulmonary tuberculosis in the adult population in Dale, February to September 2017

		Presumptive TB	PTB incidence			Proportion of presumptive TB with PTB (%)		
Visits	Covariate	Episode per 100 000	PTB[1] per 100 000 (95% CI)	PTB b+ per 100 000 (95% CI)	PTB c+ per 100 000 (95% CI)	PTB[1]	PTB b+	PTB c+
Round 2	Total	1920 (1798–2047)	333 (284 to 388)	228 (188 to 274)	104 (78 to 137)	17	12	5
	Age in years							
	15–24	1034 (891–1194)	281 (210 to 369)	212 (151 to 289)	68 (37 to 117)	27	21	7
	25–34	1750 (1524–2000)	429 (322 to 559)	336 (244 to 453)	92 (48 to 160)	25	19	5
	35–44	2065 (1773–2392)	324 (218 to 465)	228 (141 to 350)	96 (44 to 182)	16	11	5
	45–54	3096 (2652–3595)	298 (176 to 474)	130 (257 to 258)	167 (82 to 308)	10	4	5
	55+	4039 (3493–4647)	342 (202 to 543)	106 (39 to 236)	235 (123 to 408)	8	3	6
	Sex							
	Male	1697 (1537–1869)	337 (269 to 418)	223 (169 to 290)	114 (76 to 163)	20	13	7
	Female	2140 (1960–2331)	329 (262 to 408)	233 (178 to 303)	96 (62 to 141)	15	11	4
Round 3	Total	2040 (1916–2170)	330 (282 to 384)	297 (252 to 349)	32 (194 to 522)	16	15	2
	Age in years							
	15–24	895 (763–1043)	322 (246 to 415)	305 (232 to 396)	17 (4 to 46)	36	34	2
	25–34	2126 (1878–2399)	521 (403 to 662)	455 (346 to 587)	66 (30 to 125)	25	21	3
	35–44	2222 (1923–2556)	187 (110 to 297)	152 (84 to 253)	35 (9 to 95)	8	7	2
	45–54	3617 (3142–4144)	180 (91 to 320)	162 (78 to 297)	18 (1 to 89)	5	4	0.50
	55+	3856 (3334–4438)	307 (178 to 496)	287 (163 to 470)	20 (10 to 100)	8	7	1
	Sex							
	Male	1757 (1595–1930)	319 (253 to 396)	294 (231 to 369)	25 (10 to 52)	18	17	1
	Female	2318 (2134–2516)	341 (274 to 420)	300 (238 to 375)	40 (20 to 72)	15	13	2
Round 2+3	Overall	1981 (1893–2071)	332 (297 to 370)	263 (232 to 297)	68 (53 to 86)	18	14	4
	Age in years							
	15–24	964 (865–1071)	302 (248 to 364)	259 (210 to 317)	43 (25 to 69)	32	27	5
	25–34	1940 (1769–2122)	475 (394 to 569)	396 (322 to 482)	79 (49 to 121)	25	21	4
	35–44	2145 (1932–2374)	254 (186 to 340)	189 (132 to 264)	65 (34 to 113)	12	9	3
	45–54	3361 (3031–3719)	238 (159 to 344)	146 (86 to 234)	91 (46 to 160)	7	4	3
	55+	3946 (3562–4359)	324 (224 to 454)	198 (123 to 304)	125 (68 to 213)	8	5	3
	Sex							
	Male	1727 (1612–1848)	328 (279 to 382)	259 (216 to 308)	69 (48 to 95)	19	15	4
	Female	2230 (2100–2366)	336 (287 to 391)	268 (224 to 317)	67 (47 to 94)	15	12	3

PTB, pulmonary TB; PTB[1], PTB means the proportion of presumptive TB cases with a positive bacteriological test result plus clinically diagnosed PTB; PTB b+, bacteriologically confirmed PTB; PTB c+, clinically diagnosed.

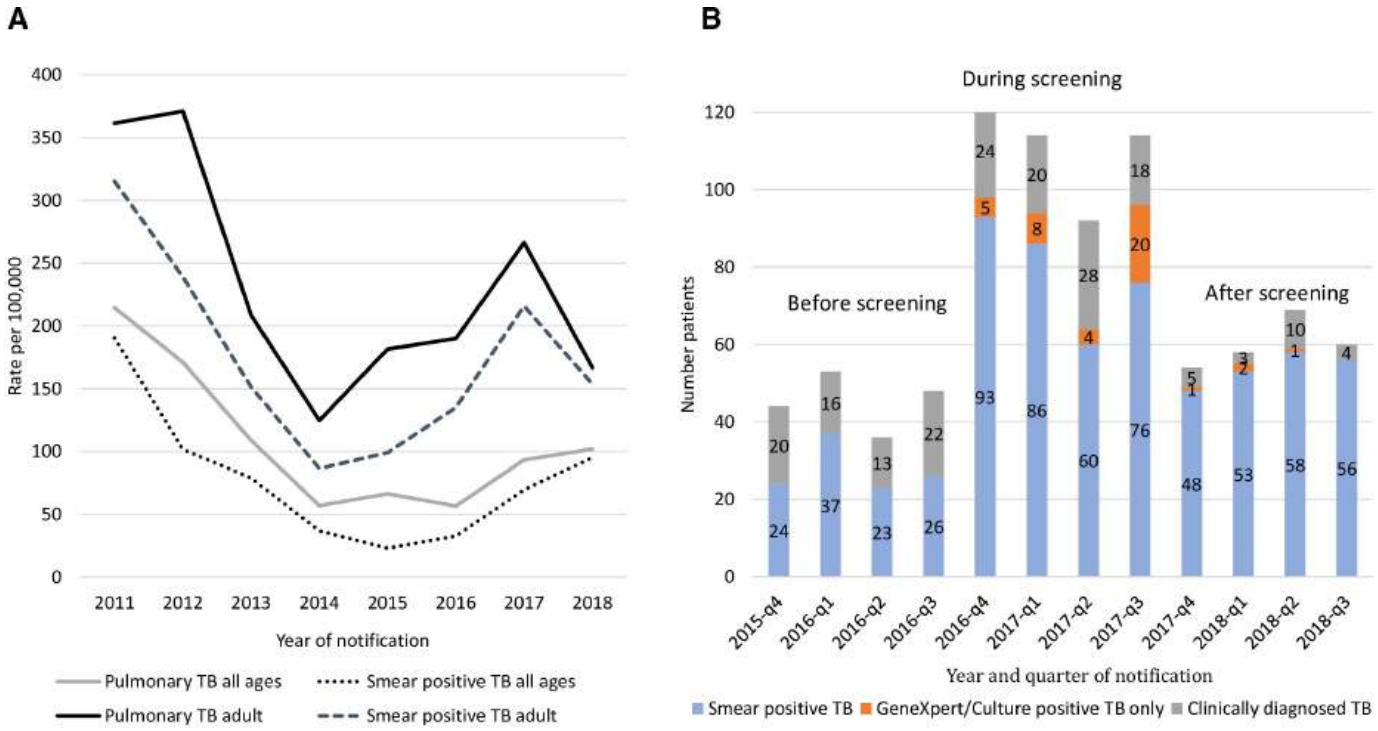

Figure 2 Case notification of patients with pulmonary TB in Dale district (A) rate per 100 000 population by category 2011–2018, and (B) absolute number of patients before, during and after screening from quarter 4 2015 to quarter 3 2018 (source National TB and Leprosy Programme). TB, tuberculosis.

was 320. The incidence of PTB was 332 (95% CI: 297 to 370)/100 000 person-years; the incidence rates of PTB s+, PTB b+ and PTB c+ were 230 (95% CI: 201 to 262), 263 (95% CI: 232 to 297) and 68 (95% CI: 53 to 86)/100 000 person-years, respectively (online supplemental table 7). The incidence rates of PTB s+ and PTB b+ were highest among 25–34 years old (online supplemental table 8).

PTB rate ratio comparison by sex

We estimated the ratios of the notification rate to the total prevalence rate (including cases already on TB treatment in the first round of the survey) as well as to the incidence rates for PTB b+, PTB c+ and PTB s+. The prevalence-to-notification rate ratios for PTB s+ were 1.28:1 for all adults, 1.2:1 for men and 1.4:1 for women. The ratios of the prevalence rate to the incidence rate were 0.45:1 for all adults, 0.52:1 for men and 0.40:1 for women. The ratios of the notification rate to the incidence rate of PTB b+ were 0.35:1 for all adults, 0.42:1 for men and 0.28:1 for women (online supplemental table 9).

PTB notification trend by year

Figure 2 shows (A) case notification rate 2011–2018 (B) and the number of patients before (four-quarters), during and after screening. The PTB s+ notification rates were 81 (95% CI: 66 to 96), 231 (95% CI: 206 to 257) and 150 (95% CI: 130 to 170)/100 000 population, respectively. The notification rates increased threefold during the project year and then decreased after the project but were higher than before the project. The notification rates had wide ranges between catchment areas, particularly before the start of the current project (online supplemental tables 10–12).

DISCUSSION

This systematic symptom-based population-based TB screening in a district of Ethiopia found a point prevalence of smear-positive TB of 104/100 000 population, twice the level found in Ethiopia's 2010 national prevalence survey using smear-microscopy among symptomatic (58/100 000), where half of the cases were identified not by symptoms but by X-ray screening alone.[5] Only one-third of individuals with TB were detected by the routine NTLP services. The incidence of PTB was 332/100 000 person-years, highest among those with persistent symptoms and in those aged 25–34 years old. Higher TB rates in young people in a community indicates high transmission, since with falling rates the median age of patients with TB increases as the infected population becomes older.[2 25 26]

Our study showed a prevalence similar to that found in a 2013 local symptom-based survey from central Ethiopia, with a PTB s+ prevalence rate of 109 (67–150)/100 000 population,[6] while other symptom-based studies reported a higher prevalence of PTB s+: 169/100 000 population in northern Ethiopia in 2011,[27] 139/100 000 population in southern Ethiopia in 2016[28] and 78–174/100 000 population in other studies from different rural areas in Ethiopia, demonstrating how the disease burden varies across the country.[12 29–31] Compared with our data from

Ethiopia, a systematic review of national TB prevalence surveys (including X-ray and not based on symptoms) in Africa has revealed a higher prevalence of PTB s+ in Kenya (230/100 000) and Uganda (174/100 000), but a comparable prevalence in Ghana (111/100 000) and a lower prevalence in Gambia (90/100 000) and Rwanda (74/100 000). The difference in prevalence rates across studies could be due to differences in methods, year of study and location. Studies based on smear microscopy alone had lower prevalence rates than studies using the more sensitive tools GeneXpert and culture.[27 28 32]

In the current study, two out of three individuals with PTB s+ remained undetected in the communities, which is in agreement with a systematic review in Ethiopia showing a point prevalence of undiagnosed PTB s+ of 79 (56–113)/100 000, with an active-to-passive case finding ratio of 2.3:1,[32] which is also comparable to our prevalence of 72 (57–86)/100 000 population. Similarly, two individuals out of five with PTB c+ remained undetected. PTB c+ contributed 20–36% to the total prevalence and incidence of PTB in our study; 44% of PTB c+cases were detected by screening. In general, all PTB c+ diagnoses were based on chest X-ray. Overall, active TB case finding increases TB detection through community engagement with HEWs, thereby improving community awareness and access to TB treatment.[33 34] A lower prevalence of HIV and TB-HIV co-infections in the region[35] may have contributed to a lower prevalence of TB compared with the other studies. TB mainly affects women due to socioeconomic disadvantages and domestic responsibilities. Women accounted for only 44% of the nationally notified cases in 2020 in Ethiopia, and such trends persisted for several years.[11] The prevalence of PTB was not statistically different by sex in this study.

The incidence of PTB s+ was 230 (201–262)/100 000 person-years, which is similar to the most recent report based on symptom screening, 214 (163–263)/100 000 person-years for PTB s+ from central Ethiopia in 2013, but lower than 311 (240–382)/100 000 person-years in northern Ethiopia in 2011.[6 7] The age group 25–34 years had the highest incidence of PTB s+ cases, with no difference by sex; this may indicate heightened recent community transmission.

Individuals with presumptive TB for more than one round of screening (previous presumptive) were more likely to have PTB b+ (16%) than a new presumptive TB case (8%).[36] Similar trends were seen in a study in Guinea-Bissau, where smear-negative chronic coughers had a 5% higher smear-positivity rate after a month than new presumptive TB cases.[37] As expected, this study found more cases of PTB with a longer follow-up of chronic coughers after negative results than those initially identified with presumptive TB, thus emphasising the need to reach this population with feasible interventions and follow-up that can improve the identification of more TB cases.[37 38]

Our study allowed us to directly calculate the prevalence-to-incidence ratio. In an ideal world where the duration of the TB disease episode is not much more than 6 months (from disease onset to rapid start and completion of treatment) the ratio should be close to 0.5. In our study, of those with PTB s+, the ratio was 0.45:1 overall; 0.52:1 in men and 0.4:1 in women. These findings with a low ratio are likely due to the systematic and repeated screening with high coverage. Our prevalence-to-incidence ratio was lower than the study from another region of Ethiopia that reported rate ratio of 0.6:1.[6]

In prevalence surveys, the true incidence is normally unknown, and notification rates are used to estimate the incidence while taking into consideration underdiagnoses and under-reporting. The prevalence-to-notification rate ratio in PTB s+ cases in our study was 1.28:1, consistent with the finding that only one-third of patients with TB were detected and notified; therefore, showing that they had TB for a long time before diagnosis. In national surveys, the prevalence-to-notification rate ratios in PTB s+ patients have been reported to be 1.19:1 in Ethiopia, 0.62:1 in Gambia and 5.8:1 in Nigeria.[39]

The notification rate increased threefold during the intervention year, indicating that the decline of TB notifications since the previous intervention did not only reflect decline in TB incidence but also less case-finding activities. The decreasing incidence is a function of early detection and effective treatment of infectious cases. In our study, it may be too early to see that the reduced transmission leads to lower TB incidence. Besides, we may have missed TB cases during our initial screening since we only included symptomatic persons and mainly confirmed the diagnosis using smear-positive microscopy. Although some smear-negative patients were started on treatment as clinical cases, others could be identified as smear-positive during subsequent rounds of screening. This delay may have resulted in continued transmission and persistently high incidence.

This study had two main strengths. First, the project worked in close collaboration with the NTLP, and very few people declined to participate. Due to the large study population, the data provide precise estimates of the prevalence and incidence of PTB. Second, the engagement of existing health systems and community structures increased the community involvement, thus contributing to its sustainability. Challenges include that only symptomatic patients with TB were reported, and it is known that many patients are more or less asymptomatic.[40 41] However, since the same screening method is used in three rounds of visits, we are able to compare prevalence and incidence and assess changes over time. Individuals who did not participate in the first round of household visits, either because they were unavailable at the time of the visit or they did not come for sputum testing, may have been diagnosed with PTB in the second round (ie, prevalent but counted as incident cases). This may have overestimated the incidence. However, the number should be low because the coverage of households screened was high and screening-questions included household members who were not at home at the time of

the visit. We cannot rule out that there was some drop-off in the referral process of presumptive TB and sample collection, but none were reported as lost to follow-up and the proportion was probably very low. Finally, since the patients detected by screening could not be separated from those who attended health services by themselves, the year before the study was chosen as 'notification'.

From a public health perspective, in this study, two-thirds of symptomatic individuals with smear-positive PTB were undetected and transmitting TB in the community. Why individuals with symptoms of the deadly disease in a setting with reasonably accessible health services do not seek treatment is a major question. Increasing access by lowering the cost of care (patients should not have travel and other-related expenses to seek care), better diagnostic tools and addressing the impact of stigma are important factors to consider. Based on the study results, community screening for respiratory symptoms at intervals (every 3–4 months) may improve case findings and reduce delay in TB diagnosis in the community.

CONCLUSIONS

The prevalence rate of symptomatic sputum microscopy-positive TB was still high and similar to the magnitude found in the district at the start of a previous project and only one-third of PTB cases were notified. The incidence rate was highest in the age group 25–34 years. These findings indicate low TB case finding in the community and ongoing transmission of PTB. Cost-effective interventions implemented under routine programme conditions that engage the existing health system structures are needed to find the missing people with TB, decrease transmission and contribute to a sustained decline in the incidence of TB in a society.

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Effect of multicomponent interventions on tuberculosis notification in mining and pastoralist districts of Oromia region in Ethiopia: a longitudinal quasi-experimental study

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ABSTRACT

Objective To demonstrate the impact of interventions on tuberculosis (TB) case detection in mining and pastoralist districts in southeastern Ethiopia over a 10-year period.

Design Longitudinal quasi-experimental study.

Setting Health centres and hospitals in six mining districts implemented interventions and seven nearby districts functioned as controls.

Participants Data from the national District Health Information System (DHIS-2) were used for this study; therefore, people did not participate in this study.

Interventions Directed at training, active case finding and improving treatment outcomes.

Primary and secondary outcome measures Primarily, trends in TB case notification and percentage of bacteriologically confirmed TB—as collected by DHIS-2—between pre-intervention (2012–2015) and post-intervention (2016–2021) were analysed. Secondarily, post-intervention was split into early post-intervention (2016–2018) and late post-intervention (2019–2021) to also study the long-term effects of the intervention.

Results For all forms of TB, case notification significantly increased between pre-intervention and early post-intervention (incidence rate ratio (IRR): 1.21, 95% CI: 1.13, 1.31; p<0.001) and significantly decreased between pre-intervention/early post-intervention and late post-intervention (IRR: 0.82, 95% CI: 0.76, 0.89; p<0.001 and IRR: 0.67, 95% CI: 0.62, 0.73; p<0.001). For bacteriologically confirmed cases, we found a significant decrease between pre-intervention/early post-intervention and late post-intervention (IRR: 0.88, 95% CI: 0.81, 0.97; p<0.001 and IRR: 0.81, 95% CI: 0.74, 0.89; p<0.001). The percentage of bacteriologically confirmed cases was significantly lower in the intervention districts during pre-intervention (B: −14.24 percentage points, 95% CI: −19.27, −9.21) and early post-intervention (B: −7.78, 95% CI: −15.46, −0.010; p=0.047). From early post-intervention to late post-intervention, we found a significant increase (B: 9.12, 95% CI: 0.92 to 17.33; p=0.032).

Conclusions The decrease in TB notifications in intervention districts during late post-intervention is possibly due to a decline in actual TB burden as a result of the interventions. The unabated increase in case notification in control districts may be due to continued TB transmission in the community.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Trends in case notification over a longer period of time (10 years) have not been studied often.
⇒ The use of case notification data from control districts enabled us to analyse the effect of interventions.
⇒ Use of difference-in-differences analyses confirmed the impact of the interventions.
⇒ The parallel outcome assumption criteria were not met for the difference-in-differences analyses.
⇒ The quasi-experimental design did not enable us to control the implemented interventions.

INTRODUCTION

Tuberculosis (TB) continues to be among the leading causes of infectious morbidity and mortality, claiming the lives of 1.6 million people in 2022.[1] Moreover, the health system misses nearly one-third of the estimated number of patients, and <90% of those detected are successfully treated. Reasons for missing people along the care cascade include limited access to healthcare services, underdeveloped health reporting systems, insufficient human resources, and poor linkages between private providers and national TB programmes.[2] The COVID-19 pandemic led to disruptions in TB care services, further constraining case detection efforts.[3] To achieve the End TB Strategy goals of '95% reduction in TB deaths' and '90% reduction in TB incidence', strengthening the detection and treatment of TB is crucial.[4] High-impact and sustainable interventions that

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can be implemented across high TB burden settings are urgently needed.[2]

Ethiopia is 1 of the 30 high TB and HIV-associated TB burden countries, with an incidence of 119 per 100 000 people in 2020.[1] In 2019, 29.3% of TB cases were not notified to the national TB programme.[5] Oromia region has 37% of Ethiopia's TB cases, with high rates in its southeastern zones of Guji and Borena.[6 7]

Guji and Borena zones are home to some of Ethiopia's major traditional mines. Several studies showed that TB is more prevalent among miners than in the general population.[7–9] This high prevalence is due to unhealthy working and living conditions, such as exposure to silica dust, crowded environments with insufficient ventilation, and excessive alcohol and tobacco use. The flourishing sex industry at mining sites induces the risk of sexually transmitted infections, such as HIV, which in turn increases the risk of active TB.[10] In general, HIV is one factor that contributes to the occurrence of TB in Ethiopia.[11] Additionally, many miners are also migrants and are associated with even more risk factors, including limited access to TB diagnosis and treatment. Moreover, their migration might enable TB transmission to the general population.[7 12] Furthermore, mining shafts are often located in hard-to-reach rural areas where access to care, and thus diagnosis and treatment of TB, are challenging.[13] Because the mining industry is one of the largest employers of men in sub-Saharan Africa and miners face multiple risk factors for TB, mining populations are important targets for TB case finding and treatment outcome interventions,[12] especially in Ethiopia where the number of TB cases is disproportionately high.

Pastoralists comprise about 12% of the Ethiopian population. They live in drought areas and often face food scarcity and stress, which are risk factors for TB.[14] Access to healthcare is problematic due to long distances to health facilities.[15] Hence, disease control activities, including TB diagnosis and treatment, are often delayed. Improving diagnostic and treatment services tailored to pastoralists' needs should be prioritised.[14 15]

Several interventions, including active case finding, have been implemented in other high burden settings.[16–18] For interventions implemented for a period of 1–2 years, an increase in case notification is expected. Yet, in the long term, a decline in TB prevalence and incidence is an expected result of these interventions.[19] A few studies from Africa and Asia show the long-term impact of different active case finding strategies.[20 21] In Zimbabwe, for example, six rounds of mobile van-based active case finding over a period of 3 years were associated with a 41% reduction in TB prevalence.[20] A modelling study from Pakistan suggested a sustained reduction in TB prevalence and incidence after 5 years of communication-oriented active case finding.[21] However, there is no clear guidance on the cut-off point when programmes should set a decline in the case notification rate (CNR) as an indicator of intervention success. Therefore, national and subnational programmes use an increase in the CNR as the best indicator of success in programme performance without regard to the duration of past and ongoing interventions. Context-specific target setting is rarely done due to a lack of local data and knowledge on how prior interventions can lead to declining prevalence and incidence.

The mining and pastoralist populations described in this study form an important target group for CNR improvement. The availability of intervention data over a relatively long span of time also makes it suitable for comparing the short-term and long-term impacts of the interventions. Data are scarce on the effectiveness of such interventions among mining and pastoralist populations. Our objective was to demonstrate the impact of multifaceted interventions on case detection in mining and pastoralist districts in southeastern Ethiopia.

METHODS

Study design

This study has a longitudinal quasi-experimental design embedded within an ongoing comprehensive TB programme. We categorised districts that received intensive programme support as intervention districts and those that received regular support as control districts. For the aim of this study, districts were monitored over a period of 10 years.

Study setting

Persistently high numbers of TB incidence in Guji and Borena zones in the Oromia region in Ethiopia and the presence of at-risk groups (miners, migrant workers and pastoralist communities) triggered designing this project. Six mining woredas (districts) were pinpointed to implement the multifaceted interventions, and seven nearby districts were selected as control districts for this study. Figure 1 and table 2 show the location and demographics of the selected woredas, respectively.

Patient and public involvement

None.

Interventions

Following the initial site visit (February–July 2015), a series of actions and interventions were designed (August–October 2015) and implemented (November 2015–June 2016) under technical assistance from three successive US Agency for International Development-funded projects: HEAL TB, Challenge TB and Eliminate TB (figure 2).[22–24] See table 1 for a detailed description of implemented interventions.

Data sources and analysis

We used TB case notification data (all forms (AFs) of TB and bacteriologically confirmed (BC) TB) from the national District Health Information System (DHIS-2) in this study for 2012–2021. With the use of DHIS-2 data, no identifiable patient data were used. We analysed trends in TB case notification, CNR and percentage of BC TB cases over time and between intervention and control

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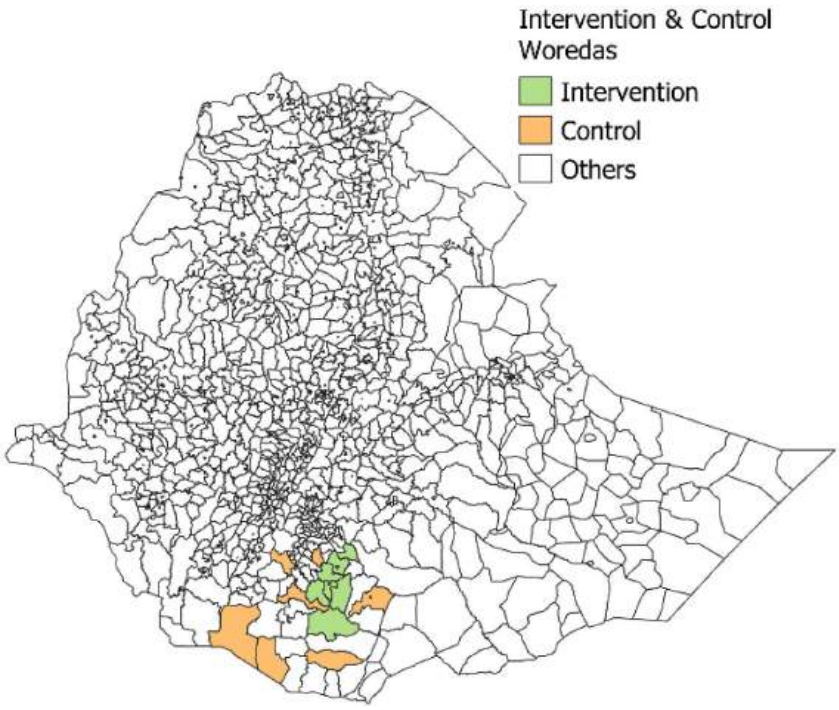

Figure 1 Map of Ethiopia with selected intervention and control woredas.

districts. We computed CNR per 100 000 population and the percentage of BC TB cases.

We used line graphs to describe and visualise differences between control and intervention districts in trends of cases notified, CNR and percentage of BC TB cases over the 10 years of follow-up. To study whether differences and patterns found in the graphs are statistically significant, we performed a difference-in-differences (DID) analysis using a Poisson regression technique. The DID method has origins in John Snow's cholera study in 1855, but it is currently more widely used in social sciences research.[25] This technique is suitable for making a combination of before–after and treatment–control comparisons. Moreover, it allows data use on a group level rather than on an individual level, which is necessary in this study. DID analysis allowed us to estimate the effect of the interventions on the people living in intervention districts. The technique controls for unobservable time and group characteristics that confound the effect of the treatment on the outcome.[26]

We used the number of TB notifications as the dependent count variable (AFs of TB and BC TB separately). As predictor variables, we used district (0=control, 1=intervention) and time. To assess changes over time, we dichotomised the follow-up period into pre-intervention (2012–2015) and post-intervention (2016–2021). Additionally, to analyse the impact of interventions in both the short and long term, we categorised time into three periods: pre-intervention (2012–2015), early post-intervention (2016–2018) and late post-intervention (2019–2021).

We performed Poisson regression analyses and used the exponential estimates of the beta values as measures of effect, described as incidence rate ratios (IRRs). We described the results as IRRs with its 95% CI, and a p value of <0.05 was considered statistically significant. We used interaction terms to analyse how the effect (difference between control and intervention districts) found at baseline (pre-intervention) changed over time; significance was determined at p<0.05. The control districts and pre-intervention time were used as reference categories. Yet, we changed the time reference category once to early post-intervention in DID with categorised time to assess the difference between early-post intervention and late post-intervention. Subsequently, we analysed trends in the percentage of BC TB cases out of AFs of TB cases between intervention and control districts and over time. We treated the percentage of BC TB cases out of AFs



Figure 2 Timeline of intervention implementation. ETB, Eliminate TB; TB, tuberculosis.

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Table 1 Key study interventions, coordination and management

Intervention districts	Control districts
A. Key interventions	A. Key interventions
1. Action plan: set and endorsed by senior management at regional health bureau level	1. Action plan: district-level TB and other communicable diseases management
2. Six-day training: provided for newly deployed health extension workers (HEWs)[1 21]	2. Training: quota-based training for health extension training every 3–5 years
3. Gap-filling training: provided for existing HEWs	3. No such service
4. One Xpert machine: placed at a health centre to serve all districts	4. Patient referral: for Xpert service in nearby districts
5. Training on slide fixing and transportation: provided to 146 health workers from non-diagnostic health centres	5. No such service—patient referral applied
6. 29 motor bikes: provided to the woredas	6. One motor bike for all district health services
7. Billboard messages (in local language) on TB prevention: prepared and placed at five major market sites	7. No such service
8. Sensitisation workshop: conducted on Xpert utilisation, childhood TB and infection control; recording provided to TB focal persons from all woredas	8. No such service
9. Basic comprehensive TB/HIV training: provided to health workers in TB clinics	9. Basic TB/HIV training once a year
10. Other supportive actions: supported zonal review meetings, one-on-one review meetings and supervision	10. Participate in regional cluster review meeting
B. Coordination and programme management	B. Coordination and programme management
1. Coordination and programme management a. Supporting and capacitating woreda health offices and health facilities in overall planning, coordination, implementation, and monitoring and evaluation	1. No such service
2. Community mobilisation and sensitisation a. Providing health education at mining shafts for mine workers and at schools b. Social mobilisation at gatherings: selection and training of active TB volunteers, supporting women health development armies and supporting catchment area meetings c. Distributing leaflets/brochures with messages on TB prevention and control	2. Occasional health education on TB by HEWs or community volunteers
3. Improving diagnostic capacity a. Slide fixing and referral, integrated refresher training and comprehensive TB/HIV training b. Strengthening sample transportation from mining shafts to diagnostic centres	3. Postal service engaged in specimen transportation
4. Active case finding a. TB screening of mine workers at mining shafts b. TB screening at houses/tents c. Strengthening facility and community-level case findings: strengthening outpatient department screening at facilities within the mining woredas and strengthening community presumptive TB identification and referral d. Strengthening and conducting retrospective and prospective contact investigation at both the facility and community levels e. Selecting, training and engaging active community TB volunteers in presumptive identification and referral f. Strengthening the referral linkage between health centres and health posts	4. Active case finding a. Facility-based TB screening b. Routine or prospective contact screening c. HEW-led referral linkage between health posts and health facilities
5. Treatment and adherence support packages a. Ensuring strict Directly Observed Therapy Shortcourse (DOTS) provision is in place at health posts and health centres through supportive supervision/mentorship b. Selecting, training and supervising volunteer TB treatment supporters c. Retrieval of absentees, treatment interrupters and patients who are lost to follow-up	5. DOTS: mainly at health centres by health providers
6. Strengthening monitoring and evaluation a. Supporting improvement of data quality through on-site verification and checking b. Regular supportive supervision and quarterly review meetings c. Organising and preparing monthly progress reports	6. Supportive supervision and review meetings twice a year

TB, tuberculosis.

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Table 2 Information on the intervention and control districts

Zones	Name of woreda	Population in 2018	Public health facilities			Total
			Hospital	Health centre	Health post	
Intervention districts						
Guji*	Adolla Redde	195 101	1	5	28	34
	Gerja	67 065	0	4	20	24
	Odo Shakiso	130 630	0	5	31	36
	Saba-Boru	177 139	1	5	11	17
West Guji	Melkasoda	79 996	1	4	12	17
Borena	Arero	44 733	1	2	18	21
Total		694 664	4	25	120	149
Control districts						
Guji*	Uraga	152 828	1	5	33	39
	Liben	83 695	0	3	17	20
West Guji	Dugda Dawa	115 947	0	3	11	14
	Gelana	94 508	0	3	29	32
Borena	Teltele	78 367	1	4	24	29
	Dhas	21 649	0	4	8	12
	Dillo	27 057	0	3	10	13
Total		458 104	2	25	132	159

*This woreda has recently been divided into two (Saba-Boru and Aga Woyu); the information is the sum of the two.

of TB as a continuous dependent variable and district and time as predictor variables, as specified above. We performed a linear regression analysis and used beta values (including 95% CI) as measures of effect. We also used interaction terms between time and interventions to study differences over time. Statistical significance was set at p<0.05. All analyses were performed in STATA V.17.0.

RESULTS

Background information on the intervention and control districts participating in this study is provided in table 2.

Trends in number of cases notified

AFs of TB

In the intervention districts, the number of AFs of TB cases notified increased during the pre-intervention period, from 1076 cases in 2012 to 1276 cases in 2015 (+19%). This increase continued through the early post-intervention period with 1554 cases in 2018 (+22%) but declined to 1179 in 2021 (−24%). In the control districts, a steady decline was seen in the number of cases reported between 2012 and 2017 (−46%). It reached a nadir in 2017 (432 cases), after which it steadily increased, reaching a peak of 897 cases in 2021 (+108%). Figure 3A shows trends in the number of notified AFs of TB cases in the intervention and control districts.

When analysing differences in cases notified between intervention and control districts with dichotomised intervention time, we found an IRR of 1.92 (95% CI: 1.84, 2.02). The rate ratio for case notification was 1.92 times higher in the intervention districts than in the control districts before the intervention was implemented. This baseline effect did not change statistically significant in the period after the interventions were implemented (IRR: 0.99, 95% CI: 0.93, 1.05) (see table 3).

The DID analysis with categorised intervention time also showed an IRR of 1.92 (95% CI: 1.84, 2.02) for notification within intervention districts compared with control in the pre-intervention period. This effect increased statistically significant by a factor of 1.21 (95% CI: 1.13, 1.31) during the early post-intervention period. The rate ratio for notification was 2.34 (1.92×1.21) times higher in intervention than in control districts. The baseline effect of 1.92 decreased statistically significant by a factor of 0.82 (95% CI: 0.76, 0.88) during the late post-intervention period. The rate ratio for notification was 1.57 (1.92×0.82) times higher in the intervention districts than in the control districts. When changing the time reference category to the early post-intervention period, the difference in rate ratio for notification between the intervention and control districts decreased from early post-intervention to late post-intervention by a factor of 0.67 (95% CI: 0.62, 0.73). Thus, the pattern seen in figure 3A is confirmed to be statistically significant (p<0.05).

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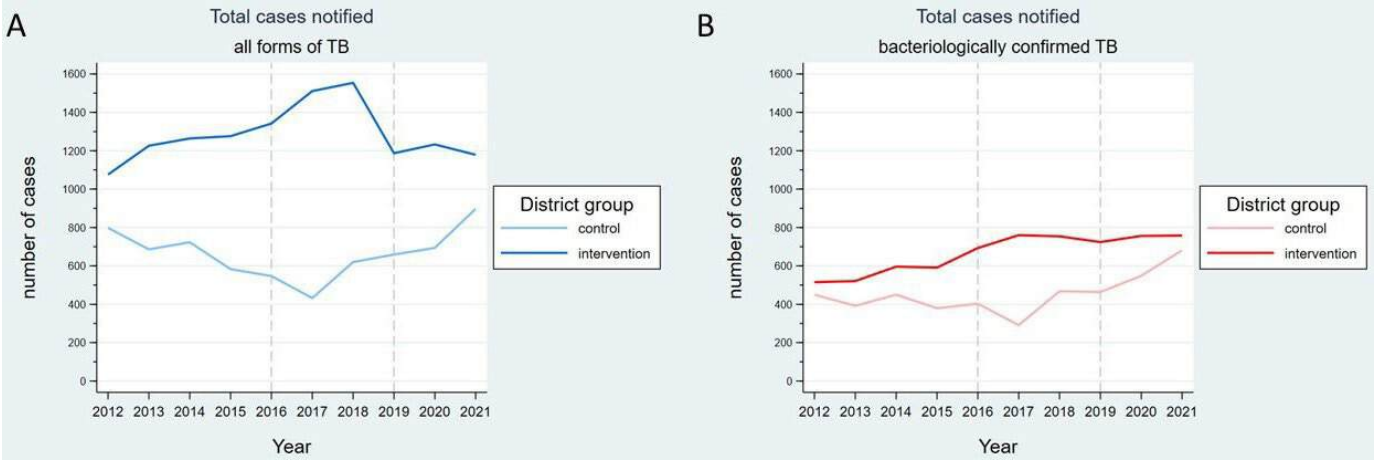

Figure 3 Visualisation of time trends in number of cases notified for (A) all forms of TB and (B) bacteriologically confirmed TB. The two lines in the figures represent the trends in case notification in the control (lighter colour) and intervention (darker colour) districts. The dashed lines in the figures represent the different intervention periods: pre-intervention (2012–2015), early post-intervention (2016–2018) and late post-intervention (2019–2021). TB, tuberculosis.

Bacteriologically confirmed TB

Similarly, the number of BC cases of TB in the intervention districts increased during the pre-intervention period from 515 cases in 2012 to 591 cases in 2015 (+15%). This increase continued through the early post-intervention period with 754 cases in 2018 (+28%), thereafter the number of cases notified stayed almost stable until 2021 (+0.5%). In contrast, the number of cases reported between 2012 and 2017 decreased in the control districts, reaching a nadir of 291 cases in 2017 (−35%). Afterwards, the number of cases notified increased steadily, reaching a peak in 2021 (+134%). Figure 3B shows trends in the number of notified BC TB cases in the intervention and control districts.

When analysing differences in cases notified between the intervention and control districts with dichotomised intervention time, we found an IRR of 1.47 (95% CI: 1.38, 1.57). The rate ratio for notification was 1.47 times higher in the intervention districts than in the control districts before the intervention was implemented. This effect did not change significantly in the period after the intervention was implemented (IRR 0.96, 95% CI: 0.89, 1.04), as shown in table 4.

The DID analysis with categorised treatment time also showed an IRR of 1.47 (95% CI: 1.38, 1.57) for BC TB notification in the pre-intervention period. The effect changed by a factor of 1.05 (95% CI: 0.99, 1.20) during the early post-intervention period, but this difference was not statistically significant. Yet, the effect of 1.47 changed by a factor of 0.88 (95% CI: 0.81, 0.97) from the pre-intervention to late post-intervention period. The rate ratio for notification was 1.29 (1.47×0.88) times higher in intervention districts than in control districts during the late post-intervention period, which was a

Table 3 Results of DID Poisson regression analyses for case notification of all forms of TB

	IRR	95% CI	SE	P value
DID model 1: analysis with dichotomised time				
Intervention districts	1.92	1.84, 2.02	0.046	<0.001
Post-intervention period	1.00	0.95, 1.05	0.025	0.989
Intervention districts×post-intervention period	0.99	0.93, 1.05	0.030	0.672
DID model 2: analysis with categorised time				
Intervention districts	1.92	1.84, 2.02	0.046	<0.001
Early post-intervention period	0.86	0.81, 0.92	0.027	<0.001
Late post-intervention period	1.13	1.07, 1.19	0.032	<0.001
Intervention districts×early post-intervention period	1.21	1.13, 1.31	0.046	<0.001
Intervention districts×late post-intervention period	0.82	0.76, 0.89	0.029	<0.001
Intervention districts×late post-intervention* period	0.67	0.62, 0.73	0.027	<0.001

Reference category: control (district group), pre-intervention (time).
*Time reference group changed to early post-intervention.
DID, difference-in-differences; IRR, incidence rate ratio; TB, tuberculosis.

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Table 4 Results of DID Poisson regression analyses for case notification of bacteriologically confirmed TB

	IRR	95% CI	SE	P value
DID model 1: analysis with dichotomised time				
Intervention districts	1.47	1.38, 1.57	0.048	<0.001
Post-intervention period	1.24	1.17, 1.31	0.038	<0.001
Intervention districts×post-intervention period	0.96	0.89, 1.04	0.039	0.360
DID model 2: analysis with categorised time				
Intervention districts	1.47	1.38, 1.57	0.048	<0.001
Early post-intervention period	1.05	0.97, 1.13	0.040	0.240
Late post-intervention period	1.42	1.32, 1.52	0.049	<0.001
Intervention districts×early post-intervention period	1.09	0.99, 1.20	0.053	0.076
Intervention districts×late post-intervention period	0.88	0.81, 0.97	0.040	0.006
Intervention districts×late post-intervention* period	0.81	0.74, 0.89	0.039	<0.001

Reference category: control (district group), pre-intervention (time).
*Time reference group changed to early post-intervention.
DID, difference-in-differences; IRR, incidence rate ratio; TB, tuberculosis.

significant decrease from the pre-intervention period. When changing the time reference category to early post-intervention, the difference in rate ratio for notification between the intervention and control districts decreased significantly between the early post-intervention and late post-intervention periods by a factor of 0.81 (95% CI: 0.74 to 0.89) (see table 4).

Trends in CNR

During the study period (2012–2021), the CNR for AFs of TB was higher in the intervention districts than in the control districts (figure 4A). When analysing the lines for control and intervention districts over time separately, we see different time patterns. For the intervention districts, we see an increase in CNR followed by a decrease, whereas we see a decrease followed by an increase in the control districts. CNR of intervention districts increased throughout the pre-intervention and early post-intervention periods: from 200.1 cases per 100 000 in 2012 to 223.7 cases per 100 000 in 2018 (+12%). Afterwards, it declined to 184.9 per 100 000 in 2021 (−17%). In control districts, CNR decreased from 131.7 per 100 000 in 2012 to 76.5 per 100 000 in 2017 (−42%), and from 2017 onwards, it reversed, reaching a peak of 144.2 per 100 000 in 2021 (+88%).

Figure 4B shows that during the study period, the CNR for BC TB was higher in the intervention districts than in the control districts. When analysing the lines for control and intervention districts over time separately, we see a more parallel time pattern compared with CNR for AFs of TB. In the intervention districts, the CNR of BC TB showed an overall increasing trend, but CNR between 2 consecutive years fluctuated. From 2012 to 2021, we saw an increase of 24%, but in the control districts, we saw a fluctuating decline in CNR until a drop in 2017 (51.6 per

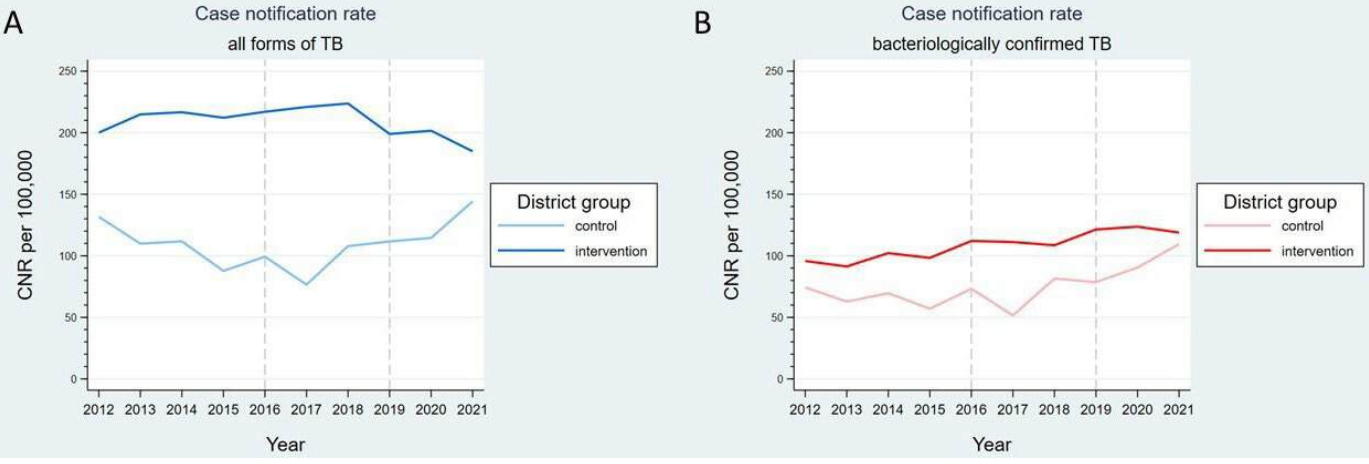

Figure 4 Visualisations of time trends in case notification rate (CNR) of (A) all forms of TB and (B) bacteriologically confirmed TB. The two lines in the figures represent the trends in case notification in the control (lighter colour) and intervention (darker colour) districts. The dashed lines in the figures represent the different intervention periods: pre-intervention (2012–2015), early post-intervention (2016–2018) and late post-intervention (2019–2021). TB, tuberculosis.

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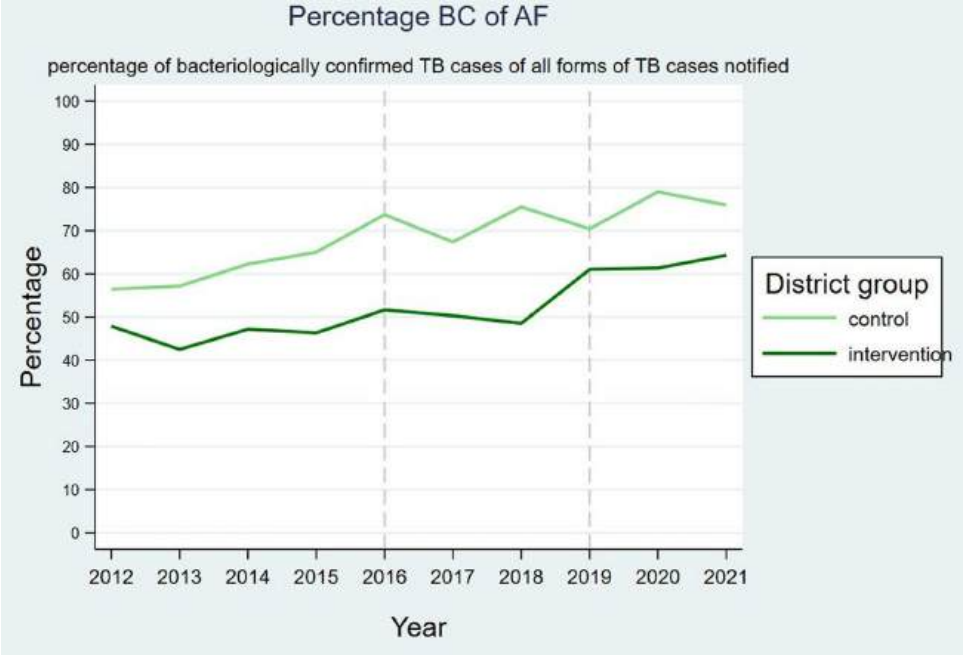

Figure 5 Visualisation of time trends in percentage of bacteriologically confirmed (BC) TB cases out of all forms (AFs) of TB cases. The two lines in the figure represent the trends in case notification in the control (lighter colour) and intervention (darker colour) districts. The dashed lines in the figures represent the different intervention periods: pre-intervention (2012–2015), early post-intervention (2016–2018) and late post-intervention (2019–2021). TB, tuberculosis.

100 000 people, −31%). CNR then increased to a peak in 2021 (+112%).

Both control groups (AFs of TB and BC TB) showed a decline in CNR during the pre-intervention period and 1 year after, with a nadir in 2017 (figure 4A,B). In contrast, the intervention districts showed an increase in CNR at the beginning without a drop in 2017. CNR for AFs of TB in the intervention groups declined from 2018 onwards, while CNR for BC TB increased. This could suggest that more people were accurately diagnosed over time in the intervention zones.

Trends in percentage of BC TB out of AFs of TB

Figure 5 shows the percentage of BC cases out of AFs of TB notified. The percentage is always higher in the control districts than in the intervention districts. However, the dark green line (reflecting the intervention group) shows a stable increase over time, while the lighter green line fluctuates.

The DID analysis with dichotomised intervention time shows a significant difference of −14.24 percentage points (95% CI: −21.58, −6.89) for the intervention districts compared with the control districts during the pre-intervention period. This baseline effect did not change significantly in the period after the intervention was implemented (B: −3.22, 95% CI: −12.7, 6.26). See table 5 for the results of the DID analysis.

When analysing the percentage of BC cases out of AFs of TB over the three time periods, we found that the intervention districts had a statistically significantly lower percentage at baseline (pre-intervention) than the control districts (B: −14.24, 95% CI: −19.27, −9.21). This difference got bigger during the early post-intervention period: −7.78 (95% CI: −15.46, −0.010) to −14.24+−7.78=−22.02. During the late post-intervention period, the difference in percentages between control and intervention districts decreased but not significantly. When comparing the late post-intervention with the early post-intervention period, we saw an increase of 9.12 percentage points (95% CI: 0.92, 17.33), which is significant. Table 5 shows the results of the DID analysis of the percentage of BC TB cases out of AFs of TB.

DISCUSSION

In this study, we found significant differences between intervention and control districts over time in the number of notified TB cases and percentage of BC TB cases. There was a significant increase in the number of notified AFs of TB cases in the intervention districts from the pre-intervention to the early post-intervention period, while it reached a nadir in control districts over the same period. During the late post-intervention period, these trends were reversed significantly. The number of notified BC TB cases in intervention districts increased during the early post-intervention period; however, this was not significant. During the late post-intervention period, we saw a significant decrease in BC TB and AFs of TB notifications in intervention districts compared with control districts. Furthermore, the comparison of CNR showed a similar pattern, and the proportion of BC TB cases out of AFs of TB increased steadily over time in both control and intervention districts, although it was always significantly lower in intervention districts.

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Table 5 Results of DID linear regression analyses on the percentage of all forms of TB notified that are bacteriologically confirmed

	B	95% CI	SE	P value
DID model 1: analysis with dichotomised time				
Intervention districts	−14.24	−21.58, 6.89	3.466	<0.001
Post-intervention period	13.44	6.73, 20.14	3.163	<0.001
Intervention districts×post-intervention period	−3.22	−12.7, 6.26	4.474	0.482
DID model 2: analysis with categorised time				
Intervention districts	−14.24	−19.27, 9.21	2.344	<0.001
Early post-intervention period	11.98	6.55, 17.41	2.531	<0.001
Late post-intervention period	14.90	9.47, 20.33	2.531	<0.001
Intervention districts×early post-intervention period	−7.78	−15.46, 0.010	3.58	0.047
Intervention districts×late post-intervention period	1.34	−6.34, 9.02	3.58	0.713
Intervention districts×late post-intervention* period	9.12	0.92, 17.33	3.83	0.032

Reference category: control (district group), pre-intervention (time).
*Time reference group changed to early post-intervention.
DID, difference-in-differences; TB, tuberculosis.

These findings highlight the importance of careful analysis of post-intervention outcomes before drawing conclusions on the impact of interventions. Traditionally, increase in notifications is taken as a positive impact, which may be true for the immediate post-intervention period. However, even when there is a decline in cases or no change at all, it could still be a positive impact. In 2017, for example, the decline in the number of AFs of TB notified cases was significantly higher in the control districts, and for BC TB, this difference was close to significant (p=0.076). This appears to be linked to the major political instability (leadership transition) that affected Ethiopia at that time. These numbers suggest that the intervention improved the resilience of the health system in certain districts. In the future, resilience of TB programmes in projects and research should get more attention.

Another striking finding in this study is the unabated increase in case notification (AFs of TB and BC TB) in the control districts after the 2017 dip. In the absence of any significant investment in case finding, the increase in case notification is unlikely to be a measure of success. Rather, this could be an indicator of unchecked disease transmission due to late diagnosis, poor infection control practices, or inaccurate recording and reporting.[27] This shows that contextual analysis might be needed to rate TB management progress.

The increase in the number of notified cases shortly after intervention implementation was as expected, since multiple studies showed comparable findings in the past. In Nigeria, a multifaceted active case finding approach, similar to this study, was used in a low-resource setting. This led to a 112.9% increase in case finding during implementation compared with baseline.[28] A study in Nepal on active case finding placed GeneXpert machines throughout intervention districts, among other interventions. In these intervention districts, 29% more TB cases were found than in control zones.[29] A previous study in southern Ethiopia focused on community-based interventions that led to an increase in case notification from 64 per 100 000 at baseline to 127 per 100 000 during implementation.[30]

Analysing the effect of interventions on the long term is more challenging. Our study found a significant decrease in AFs of TB and BC TB cases notified in the intervention districts during the late post-intervention period compared with both the pre-intervention and early post-intervention periods. Meanwhile, case notification in control districts increased during the early and late post-intervention periods; this could mean that the actual prevalence was dropping in intervention districts compared with control districts. This decrease could be due to COVID-19 measures. However, TB notifications did not drop in control districts and not for BC TB only; therefore, we think it reflects an actual decrease in case notifications. A study in Vietnam found a similar pattern: during the fourth year after implementation, a decline in prevalence was seen.[31] Furthermore, the steady increase we found in case notification of BC TB and the proportion of BC TB cases could suggest that diagnosis is done more accurately in intervention districts over time than in control districts, where we saw a fluctuating pattern. A recent systematic review of interventions found that active case finding might increase TB notifications in high-risk populations.[32]

The study has both strengths and limitations. In the DID analysis, three key assumptions should be fulfilled: stable unit treatment value assumption (outcomes are equal for patients in control and intervention districts

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and treatment that is given is the same for all in control and all in intervention districts); intervention is unrelated to outcome at baseline (allocation of intervention was not determined by outcome); and control/intervention have parallel trends in outcome. In this study, the latter assumption is violated, as we see a different pattern in notification in the years before the intervention was implemented. Since the other assumptions were met, the DID analysis was the best available rigorous statistical method and allowed us to do statistical analysis on top of descriptive analysis. This adds value to the research field. Since most district coordinators are qualified at the postgraduate level, they are trained (or could be trained) to conduct analyses like these to evaluate subnational programme performance. Moreover, DID allows us to interpret results intuitively and use group-level data, and it could provide causal relationships. This study focused on two risk groups in Ethiopia: miners and pastoralists. Those two populations are likely to face challenges when it comes to seeking healthcare.[8 33] Multiple studies suggest that proper TB diagnosis and treatment of pastoralists and miners require service expansion, adaptation of TB programmes to the specific context of pastoralist and miner communities, and decentralisation management.[33 34] The one-size-fits-all approach regarding TB diagnosis and treatment hampers timely and accurate TB care for pastoralists and probably miners as well.[35] This study considered the characteristics of both populations when designing suitable and sustainable interventions and support actions that can be scaled up in similar settings.

A weakness of this study was the disruption of intervention intensity due to the transition between projects. The decline in the number of notified cases between 2018 and 2020, for example, could be due to less technical support rather than actual decline. We did not have control over what was implemented in the control districts.

Conclusions

This study gives fresh perspective about the way TB case finding efforts should be evaluated at the subnational level in settings with a dual burden of risk factors. Our analysis shows that after about 4 years of intensive case finding efforts, the number of reported cases tends to decline. This provides an important clue about when national TB programmes should start adjusting their case notification targets after well-supported interventions have been in place. The multifaceted interventions in mining and pastoralist areas of Ethiopia have a clear impact on TB case notification and burden. We recommend that these interventions be scaled up to other settings, and the results should be further evaluated on a broader scale. DID analysis could be used by national programmes to measure both the short-term and long-term effects of interventions.

Contributors DJ and PGS conceptualised the study. DJ and DGD designed the study. DJ, DGD and PGS acquired resources. ZGD and SNG supervised implementation. NH and SNG collected data. LMdG and DJ analysed data. LMdG and DJ interpreted data. LMdG and DJ wrote first and subsequent drafts. PGS, DGD, ZGD and NH reviewed the final manuscript. PGS, DGD, ZGD, NH, SNG, DJ and LMdG approved the final version. DJ is the guarantor of the study.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval Although ethics approval was not needed for the aggregate data analysis, the study was reviewed and approved by the Oromia Regional Health Bureau Research Ethics Committee (BFYHBOFU/1-10), because there was a general plan to analyse and publish lessons and key results from the project.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study. Data may be obtained from a third party and are not publicly available. All data used in this study are from the national District Health Information System (DHIS-2), which are owned on national level and shared with us. Data sharing is not applicable for this study as no datasets were generated for this study.

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Epidemiology of extensively drug-resistant tuberculosis among patients with multidrug-resistant tuberculosis: A systematic review and meta-analysis

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ABSTRACT

Objectives: To estimate the pooled proportion of extensively drug-resistant tuberculosis (XDR-TB) and pre-extensively drug-resistant tuberculosis (pre-XDR-TB) in patients with multidrug-resistant TB (MDR-TB).

Methods: We systematically searched articles from electronic databases: MEDLINE (PubMed), ScienceDirect, and Google Scholar. We also searched gray literature from the different literature sources main outcome of the review was either XDR-TB or pre-XDR-TB in patients with MDR-TB. We used the random-effects model, considering the substantial heterogeneity among studies. Heterogeneity was assessed by subgroup analyses. STATA version 14 was used for analysis.

Results: A total of 64 studies that reported on 12,711 patients with MDR-TB from 22 countries were retrieved. The pooled proportion of pre-XDR-TB was 26% (95% confidence interval [CI]: 22-31%), whereas XDR-TB in MDR-TB cases was 9% (95% CI: 7-11%) in patients treated for MDR-TB. The pooled proportion of resistance to fluoroquinolones was 27% (95% CI: 22-33%) and second-line injectable drugs was 11% (95% CI: 9-13%). Whereas the pooled resistance proportions to bedaquiline, clofazimine, delamanid, and linezolid were 5% (95% CI: 1-8%), 4% (95% CI: 0-10%), 5% (95% CI; 2-8%), and 4% (95% CI: 2-10%), respectively.

Conclusion: The burden of pre-XDR-TB and XDR-TB in MDR-TB were considerable. The high burdens of pre-XDR-TB and XDR-TB in patients treated for MDR-TB suggests the need to strengthen TB programs and drug resistance surveillance.

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Introduction

The rise of drug-resistant (DR) bacterial infections is becoming a major public health concern worldwide. It threatens global tuberculosis (TB) control programs and makes TB diagnosis and treatment challenging. In the past 20 years, DR-TB has spread across the world and continued to be a challenge to global TB control efforts [1]. A recent estimate indicated 465,000 incident cases of multidrug resistance/rifampicin (RIF) resistance (MDR/RR-TB) occurred worldwide [2]. In addition, an estimated 3.6% of new TB cases and 18% of previously treated TB cases have developed MDR-TB in 2021 [3]. Moreover, on average, 6.2% of XDR-TB was esti-

Abbreviations: AFR, African region; AMR, Region of the Americas; BDQ, Bedaquiline; CFZ, Clofazimine; CI, Confidence interval; DLM, Delamanid; DR-TB, Drug-resistant tuberculosis; EMR, Eastern Mediterranean reegion; ES, Effect size; EUR, European region; FQs, Fluoroquinolone; INH, Isoniazid; LZD, Linezolid; MDR-TB, Multidrug-resistant tuberculosis; pre-XDR-TB, pre-extensively drug-resistant tuberculosis; RIF, Rifampicin; SEAR, South-East Asian region; SLID, Second-line injectable drug; TB, Tuberculosis; WHO, World Health Organization; WPR, Western Pacific region; XDR-TB, Extensively drug-resistant tuberculosis.

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mated in 2019 among patients treated for MDR-TB [2]. Prolonged duration required for the treatment, low cure rates, and the cost of drugs and toxicity make DR-TB treatment the most costly challenge [4].

Migration, housing conditions, poverty, and the emergence of other diseases, such as HIV and diabetes, are the factors fueled the burden of MDR/XDR-TB [5,6]. Furthermore, low laboratory diagnosis capabilities that delay DR-TB diagnosis and limited access to second-line MDR-TB treatment are associated with the transmission of resistant strains. Therefore, to stop the emergency of DR-TB strain, the best strategy is evidence-based diagnosis and treatment [7].

Before 2021, XDR-TB was defined as a disease caused by *Mycobacterium tuberculosis* with resistance to at least isoniazid (INH) and RIF (MDR-TB), with further resistance to any fluoroquinolones (FQs) and a second-line injectable drug (SLID) (kanamycin, amikacin, or capreomycin). Pre-XDR-TB is defined as TB with resistance to INH, RIF, and either an FQ or a second-line injectable agent but not both [4]. Based on new experimental and observational data, the World Health Organization (WHO) recently updated its guidelines, in which the late-generation FQs (levofloxacin and moxifloxacin) and WHO group A drugs (linezolid and bedaquiline) are recommended for the treatment of MDR-TB. In this guideline, XDR-TB is defined as an infection with MDR *M. tuberculosis* that is resistant to any FQs and at least one of the group A drugs. The most effective use of group A drugs to improve MDR-TB treatment requires appropriate drug susceptibility testing results [8].

The DR-TB treatment method has been updated in 2022. This document includes two new recommendations. The first regimen is the use of bedaquiline, pretomanid, linezolid, and moxifloxacin regimen for 6 months. This regimen is composed of bedaquiline, pretomanid, linezolid, and moxifloxacin and given to patients with MDR/RR-TB. However, patients with MDR/RR-TB with FQs additional resistance (pre-XDR-TB) should be treated for 9 months with all oral regimens. The consolidated guidelines includes the existing recommendations in the treatment regimens for INH-resistant TB with longer all oral regimens, monitoring of treatment response, timing of antiretroviral therapy in MDR/RR-TB for the patients infected with HIV, and the use of surgery for patients receiving MDR-TB treatment [8].

Several review studies have attempted to pool the proportion of MDR-TB cases. However, there are few review studies that attempted to estimate the pooled proportion of pre-XDR-TB and XDR-TB. Thus, we aimed to determine the pooled proportion of pre-XDR-TB and XDR-TB among patients diagnosed with MDR-TB from published primary studies.

Methods

Protocol registration

To prevent duplicates, the review study databases were searched for similar systematic reviews before this review commenced. The protocol of this systematic review and meta-analysis was registered in International Prospective Register of Systematic Reviews at the University of York database and obtained registration number PROSPERO ID: CRD42022343112.

Databases and search strategy

We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines for reporting systematic reviews and meta-analyses [9,10]. We estimated the pooled proportion of pre-XDR-TB and XDR-TB in patients with MDR-TB for global occurrence. We conducted systematic searches of the following electronic databases: MEDLINE (PubMed), ScienceDirect, and Google Scholar, until July 20, 2022 for articles published in English, without limiting the year of publication. Studies that reported pre-XDR-TB and XDR-TB globally were included in the analysis. We used search terms: "(extensively drug-resistant tuberculosis OR XDR-TB) AND (pre-extensively drug-resistant tuberculosis OR Pre-XDR-TB) AND (drug-resistant tuberculosis OR DR-TB) AND (second-line drug resistance)" for the PubMed database search in both free text and medical subject heading.

Inclusion and exclusion criteria

We included cross-sectional studies that reported the proportion of either pre-XDR or XDR-TB among patients diagnosed with MDR-TB. However, we excluded studies that compared or validated the diagnostic methods for the detection of DR-TB and treatment outcomes. In addition, we excluded case studies, editorials, author comments, commentaries, general evaluations, and professional opinions to avoid duplicates.

Study selection

To identify potential studies, two authors (GD and BY) independently searched the electronic databases. Two reviewers (GD and DFG) independently screened the full-text papers to choose relevant articles based on the inclusion criteria. Differences between the two reviewers were resolved through discussion between the two authors (GD and DFG).

PICOS criteria

- Participants: patients with MDR-TB with pre-XDR-TB and XDR-TB.
- Intervention: not applicable.
- Comparator: not applicable.
- Outcome: pre-XDR-TB and XDR-TB among patients with MDR-TB.
- Study design: observational studies.
- Study setting: any setting in any country worldwide.

Definition of terms

Based on a previous 2021 definition, pre-XDR-TB and XDR-TB were defined as:

- Pre-XDR-TB was defined as TB with resistance to INH and RIF and either an FQ or a second-line injectables.
- XDR-TB referred to MDR-TB that is resistant to INH and rifampin plus any fluoroquinolone and at least one of the three SLIDs.
- New TB case is defined as a newly registered episode of TB in a patient who has never been treated for TB or has taken anti-TB drugs for less than a month.
- Previously treated TB case refers to a patient who has received anti-TB drugs in the past for a month or longer.

Data extraction

We extracted the data in a standard prepared Microsoft Excel sheet. Two authors (GD and BY) independently extracted the data from the selected primary studies. Data were extracted on the variables: first author name; year of publication; study period; study area (country); study design; a number of MDR-TB; a number of XDR-TB; a number of pre-XDR-TB; FLQ resistance; SLIDs resistance, new drugs resistance Bedaquiline (BDQ), Clofazimine (CFZ), Delamanid (DLM), and Linezolid (LZD), and previous treatment history.

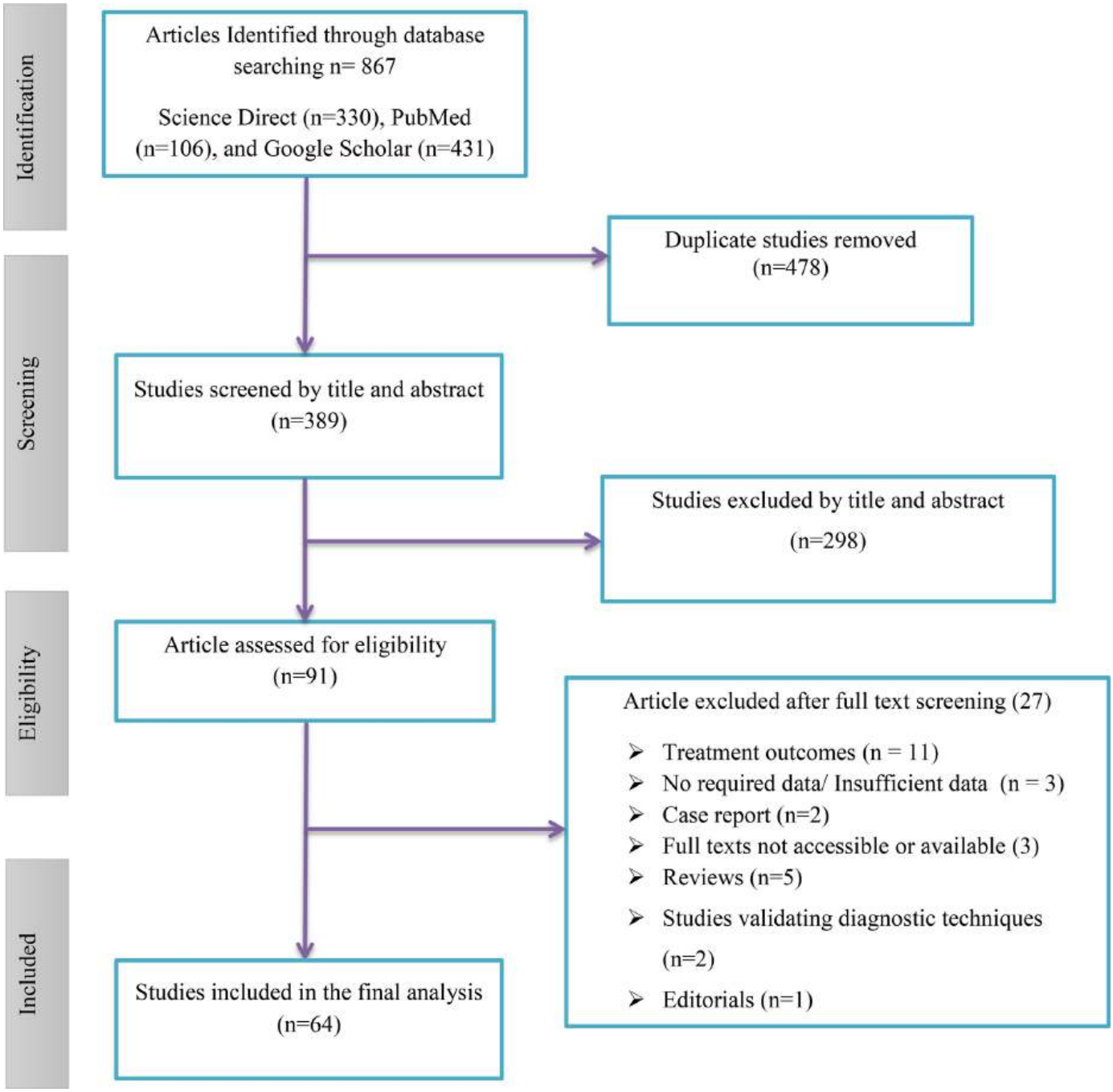

Figure 1. Flowchart describing the selection of studies for the systematic review and meta-analysis of extensively drug-resistant-TB and pre- extensively drug-resistant-TB TB in globally. TB, tuberculosis.

Discrepancies between the two authors' on data records were resolved by consensus.

Risk of bias assessment and quality assessment

Two authors (GD and AA) evaluated the quality of the selected studies independently and in cases of inconsistencies a third reviewer (BY) was involved. We used Newcastle-Ottawa scale adapted for cross-sectional studies to assess the quality of the included studies. Newcastle-Ottawa scale rates the likelihood of bias in three domains of observational studies. These are the (1) selection of participants, (2) comparability, and (3) outcomes. For each numbered item in the selection and outcome categories, a study receives up to one point, and for comparability, a study may receive up to two points [11]. For low-, moderate-, and high-quality studies, the corresponding scores of 0-3, 4-6, and 7-9 were given, respectively. We used the *I*-squared statistic (I^2) to assess the heterogeneity in the reported proportion. I^2 $\geq$50% was used to indicate the presence of heterogeneity [12]. Moreover, a funnel plot was used to examine the possibility of publication bias.

Statistical analysis

We used the random-effects model to pool the proportion of pre-XDR-TB and XDR-TB and their 95% confidence interval (CI). The pooled proportion of pre-XDR-TB and XDR-TB in patients with

Table 1
Characteristics of the individual studies on XDR-TB and pre-XDR-TB among DR-TB patients in globally included in the current systematic review and meta-analysis.

First author, year	Study design	Country	WHO regions	Study period	MDR-TB	XDR-TB	Pre-XDR-TB	XDR-TB New	XDR-TB Previous treated	Pre- XDR-TB New	Pre- XDR-TB Previous treated	FQs resistance	SLIDs resistance
Adwani et al. [14]	cross-sectional	India	SEAR	2014	227	11	127	11	0	127	0	127	19
Agonafir et al. [15]	cross-sectional	Ethiopia	AFR	2005-2006	46	2	0	0	2	0	0	2	0
Araujo et al. [75]	cross-sectional	Brazil	AMR	2013-2019	33	2	3	1	1	1	2	5	2
Elion Assiana et al. [16]	cross-sectional	Congo	AFR	2018-2019	9	1	1	NR	NR	NR	NR	2	1
Banerjee et al. [17]	cross-sectional	California	AMR	1993-2006	424	18	77	NR	NR	NR	NR	NR	NR
Bedru et al. [18]	cross-sectional	Ethiopia	AFR	2017-2018	30	3	1	1	2	0	1	NR	NR
Calver et al. [19]	cross-sectional	South Africa	AFR	2003-2005	77	5	26	NR	NR	NR	NR	NR	NR
Chen et al. [20]	cross-sectional	China	WPR	2014 -2015	51	0	24	0	0	10	14	24	0
Cheng et al. [21]	cross-sectional	Cambodia	WPR	2012- 2017	118	3	16	NR	NR	NR	NR	15	5
Dagne et al. [20]	cross-sectional	Ethiopia	AFR	2019	99	1	8	NR	NR	NR	NR	7	3
Dala et al. [21]	cross-sectional	India	SEAR	2005-2013	340	33	193	NR	NR	NR	NR	179	41
Daniel et al. [24]	cross-sectional	Nigeria	AFR	2007-2011	50	0	10	0	10	0	10	8	NR
Diriba et al. [25]	cross-sectional	Ethiopia	AFR	2019	14	0	3	0	0	2	1	2	1
Ennassiri et al. [26]	cross-sectional	Morocco	EMR	2015	155	4	18	NR	NR	NR	NR	16	6
Gadhav et al. [27]	cross-sectional	India	SEAR	2019	700	23	143	NR	NR	NR	NR	106	58
Gallo et al. [28]	cross-sectional	Brazil	AMR	2011-2013	313	32	60	6	26	1	47	59	33
He et al. [29]	cross-sectional	China	WPR	2015	102	9	30	NR	NR	NR	NR	24	6
Jabbar et al. [30]	cross-sectional	Pakistan	EMR	2016-2017	62	5	0	NR	NR	NR	NR	5	5
Jain et al. [31]	retrospective	India	SEAR	2007-2009	130	11	55	NR	NR	NR	NR	36	19
Jaksuwan et al. [32]	cross-sectional	Thailand	SEAR	2005-2012	24	1	9	NR	NR	NR	NR	NR	NR
James et al. [33]	cross-sectional	India	SEAR	2003 -2007	103	45	0	NR	NR	NR	NR	NR	NR
Javaid et al. [34]	cross-sectional	Pakistan	EMR	2011-2012	132	2	65	NR	NR	NR	NR	67	5
Kozińska et al. [5]	cross-sectional	Poland	EUR	2000-2009	297	36	19	NR	NR	NR	NR	NR	NR
Kumar et al. [35]	cross-sectional	India	SEAR	2014-2016	173	3	33	1	2	5	28	NR	NR
Kuo et al. [36]	cross-sectional	Taiwan	WPR	2011-2015	63	4	0	NR	NR	0	0	4	4
Lai et al. [37]	cross-sectional	Taiwan	WPR	2000-2006	150	10	0	1	9	NR	NR	6	4
Lee et al. [38]	cross-sectional	South Korea	WPR	2011-2017	85	9	29	NR	NR	NR	NR	32	15
Lee et al. [39]	cross-sectional	Korea	WPR	2006-2013	145	55	0	27	28	0	0	43	12
Macedo et al. [40]	cross-sectional	Portugal	EUR	2008-2010	50	12	0	NR	NR	NR	NR	NR	NR
Madukaji et al. [41]	cross-sectional	Nigeria	AFR	2018-2019	101	12	16	NR	NR	NR	NR	5	12
Matsui et al. [42]	cross-sectional	Brazil	AMR	2016-2017	92	5	11	1	4	5	6	NR	NR
Mbuh et al. [43]	cross-sectional	Cameroon	AFR	2016-2017	75	1	2	0	1	0	2	NR	NR
Misra et al. [44]	cohort study	India	SEAR	2017-2019	62	48	11	NR	NR	NR	NR	48	11

(*continued on next page*)

Table 1 (*continued*)

First author, year	Study design	Country	WHO regions	Study period	MDR-TB	XDR-TB	Pre-XDR-TB	XDR-TB New	XDR-TB Previous treated	Pre- XDR-TB New	Pre- XDR-TB Previous treated	FQs resistance	SLIDs resistance
Mohan et al. [45]	cross-sectional	India	SEAR	2012	87	3	0	NR	NR	NR	NR	NR	NR
Mok et al. [46]	cross-sectional	Korea	WPR	2010-2014	378	47	78	20	27	37	41	96	68
Momen et al. [47]	cross-sectional	Morocco	EMR	2015-2018	200	5	48	2	3	5	42	27	25
Namburete et al. [48]	cross-sectional	Mozambique	AFR	2014–2015	25	0	6	0	0	NR	NR	6	0
Nguyen et al. [49]	cross-sectional	Vietnamese	WPR	2011	91	5	15	2	3	8	7	15	5
Noor et al. [50]	cross-sectional	Bangladesh	SEAR	2011-2012	59	2	9	0	2	0	9	7	2
Park et al. [51]	retrospective	Korea	WPR	2008	2,472	749	0	313	436	0	0	NR	NR
Poudel et al. [52]	cross-sectional	Nepal	SEAR	2007-2010	109	13	43	NR	NR	NR	NR	NR	NR
Qi et al. [53]	cross-sectional	China	WPR	2009-2011	249	31	77	10	21	NR	NR	89	41
Ramachandran et al. [54]	cross-sectional	India	SEAR	2005	216	7	0	0	7	NR	NR	52	10
Riccardi et al. [55]	retrospective	Italy	EUR	2000-2015	370	0	83	0	0	NR	NR	NR	NR
Salvato et al. [56]	cross-sectional	Brazil	AMR	2013-2014	87	4	8	NR	NR	NR	NR	NR	NR
Sethi et al. [57]	cross-sectional	India	SEAR	2018	687	59	265	6	53	103	192	295	70
Sharma et al. [58]	retrospective	India	SEAR	2003	211	5	25		5	NR	NR	21	14
Sharma et al. [59]	cross-sectional	India	SEAR	2014-2016	49	1	9	NR	NR	NR	NR	NR	NR
Shibabaw et al. [60]	cross-sectional	Ethiopia	AFR	2016-2018	176	1	10	1	0	1	9	NR	NR
Singhal et al. [61]	cross-sectional	India	SEAR	2012-2013	87	10	43	NR	NR	NR	NR	41	16
Tasnim et al. [62]	cross-sectional	Bangladesh	SEAR	2016-2017	68	4	11	1	3	3	8	9	2
Tuladhar et al. [63]	cross-sectional	Nepal	SEAR	2015	57	1	29	NR	NR	NR	NR	21	8
Ullah et al. [64]	retrospective	Pakistan	EMR	2019-2020	180	8	62	NR	NR	NR	NR	62	8
Vashakidze et al. [65]	cross-sectional	Georgia	EUR	2005-2007	261	33	96	6	27	NR	NR	75	54
Wang et al. [66]	cross-sectional	china	WPR	2008-2012	206	41	90	NR	NR	NR	NR	90	35
Wang et al. [67]	cross-sectional	china	WPR	2020	391	28	94	NR	NR	NR	NR	68	NR
Welekidan et al. [68]	cross-sectional	Ethiopia	AFR	2018-2019	38	0	2	NR	NR	NR	2	2	0
Xu et al. [69]	cross-sectional	China	WPR	2015-2018	17	0	9	NR	NR	1	8	9	NR
Yang et al. [70]	cross-sectional	China	WPR	2008-2009	239	29	138	14	15	64	74	134	77
Yang et al. [71]	cross-sectional	Korea	WPR	2017	420	9	17	NR	NR	NR	NR	NR	NR
Yao et al. [13]	cross-sectional	China	WPR	2018-2019	425	29	282	NR	NR	NR	NR	311	171
Yuan et al. [72]	cross-sectional	China	WPR	2010-2011	77	16	26	NR	NR	NR	NR	16	13
Yuan et al. [73]	cross-sectional	China	WPR	2010-2011	159	13	0	3	10	NR	NR	NR	NR
Zheng et al. [74]	cross-sectional	China	WPR	2014-2016	88	9	44	NR	NR	NR	NR	34	11

AFR, African region; AMR, region of the Americas; DR-TB, drug-resistant tuberculosis; EMR, Eastern Mediterranean eegion; EUR, European region; FQs, fluoroquinolone; MDR-TB, multidrug-resistant tuberculosis; SEAR, South-East Asian region; SLID, second-line injectable drug; WPR, Western Pacific region; XDR-TB, extensively drug-resistant tuberculosis.

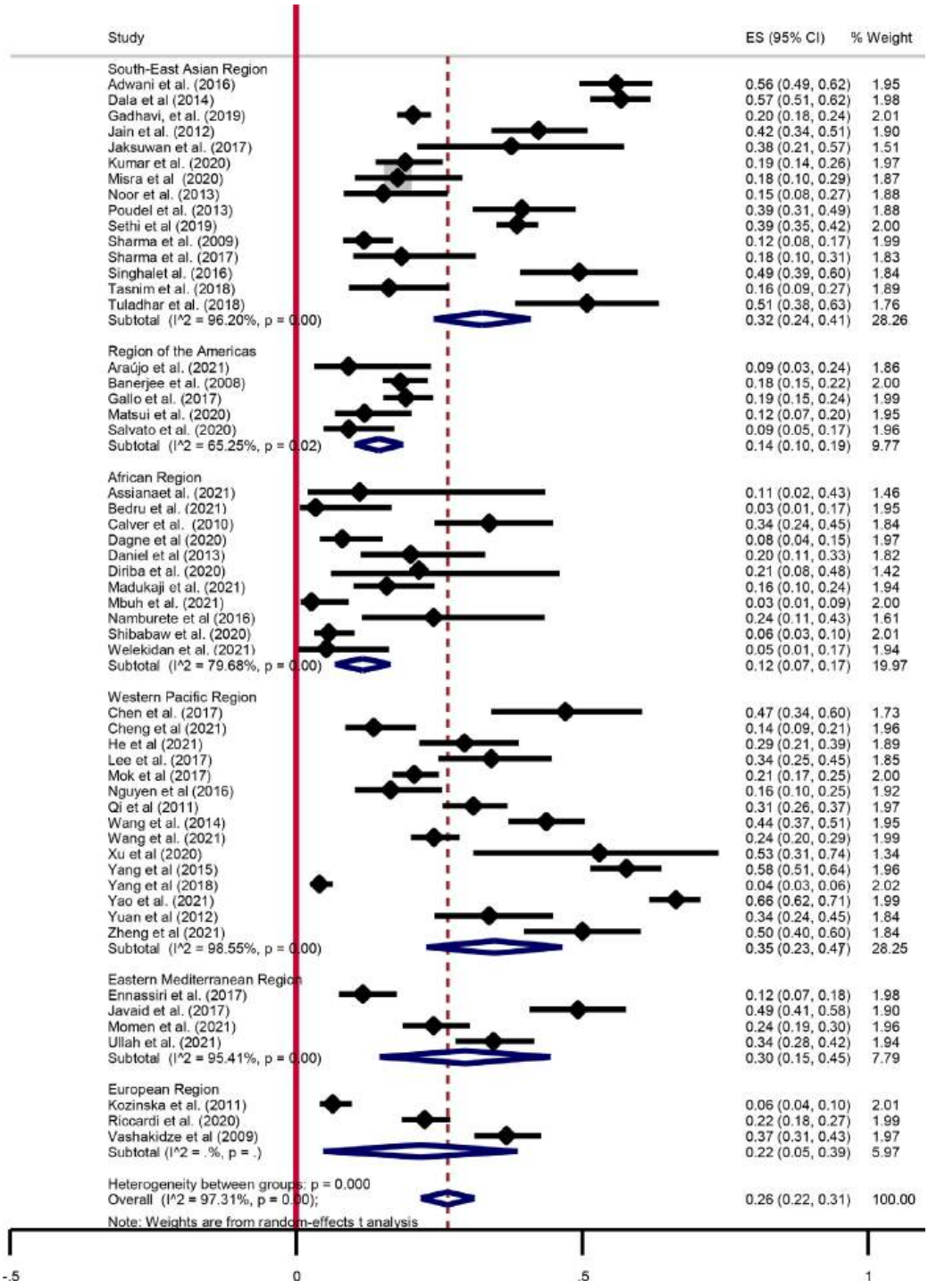

Figure 2. Summary of pooled estimates of pre-extensively drug-resistant-tuberculosis among multi drug-resistant-tuberculosis patients. CI, confidence interval; ES, effect size. New diagnosed cases Previously treated diagnosed cases.

MDR-TB was estimated using the "metaprop" command in STATA 14 (STATA Corporation, College Station, TX, USA). The estimates of pre-XDR-TB and XDR-TB pooled proportion were compared descriptively by the WHO regional categories and patient TB treatment history.

Results

Study selection

A total of 867 records were retrieved from the electronic and gray literature search and imported to EndNote reference manager. Of the total retrieved record, 389 remained after the duplicates were removed; Of 389 records, 298 were excluded by reviewing the title and abstract for population, intervention, and outcome difference with the current review. A total of 91 original articles were retrieved and fully articles were reviewed, and 27 were removed based on exclusion criteria. Finally, total of 64 articles were included in this review [5,13–75] (Figure 1).

Characteristics of the studies included in the review

Detailed characteristics of included studies are depicted in Table 1. The included studies were reported from 22

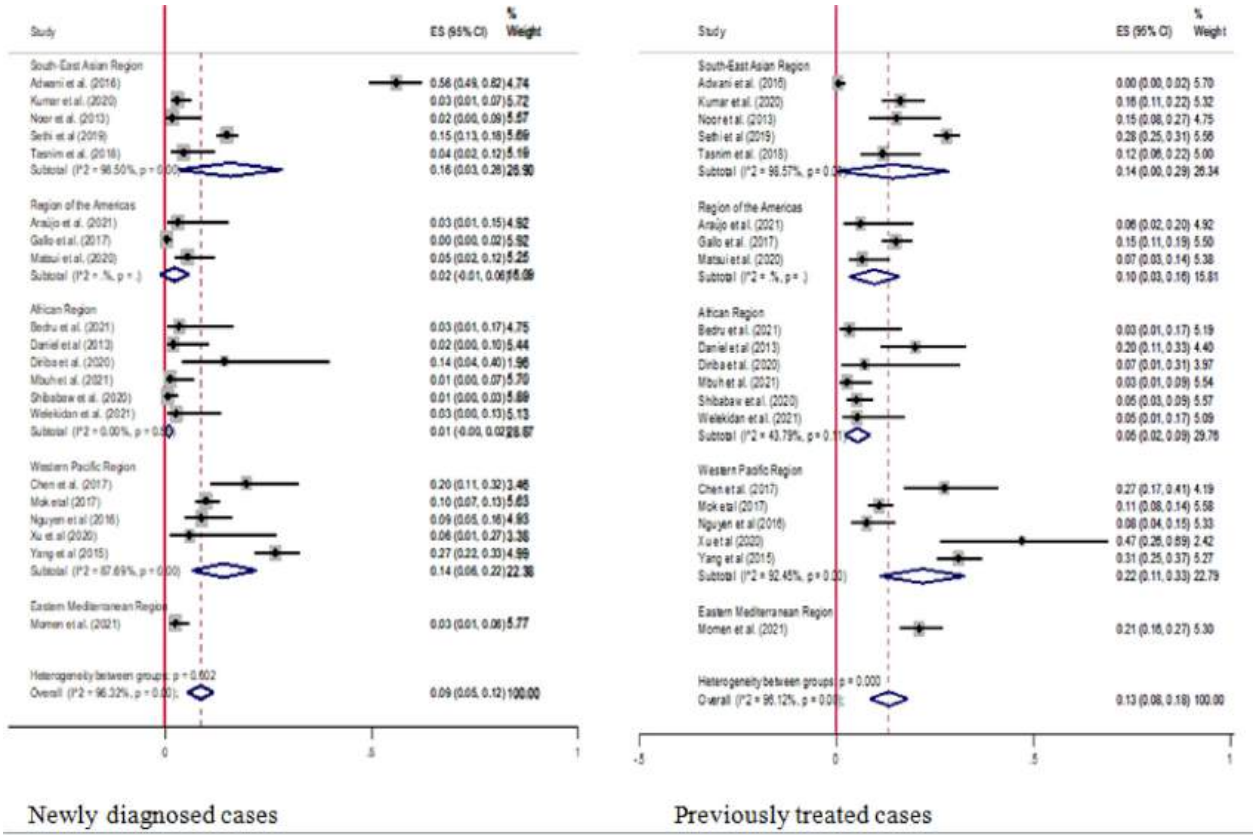

Figure 3. Pooled estimates of pre-extensively drug-resistant-tuberculosis among new and previous treated multi drug-resistant-tuberculosis patients. CI, confidence interval; ES, effect size.

countries across the WHO regions. A total of 13 studies were reported from in India [14,23,27,31,33,35,44,45,54,57–59,61] and 11 from China [13,20,29,53,66,67,69,70,72–74]. A total of 20 studies were reported from the Western Pacific [13,20,21,29,36–39,46,49,51,53,66,67,69–74] and 18 from South-East Asian regions [14,23,27,31–33,35,44,45,50,52,54,57–59,61–63]. A total of 12 studies reported from African region [15,16,18,19,22,24,25,41,43,48,60,68]. The remaining 14 studies were reported from the Eastern Mediterranean, Americas, and European regions [5,17,26,28,30,34,40,42,47,55,56,64,65,75].

The data were extracted from 64 studies involving a total of 12,711 patients with MDR-TB who were treated from 2003 to 2020, with publication years ranging from 2008 to 2021. The sample size of MDR-TB in the included studies varied from nine [16] to 2472 [51]. Among the 64 studies, 53 reported pre-XDR cases, whereas 57 reported XDR-TB cases.

Pooled proportion of pre-XDR-TB

The pooled proportion of pre-XDR-TB among MDR-TB cases was 26% (95% CI: 22-31; I^2 = 97.31%). China had the highest proportion of pre-XDR-TB (66%) [13] and Ethiopia the lowest (3%) [18]. In the Western Pacific, South-East Asian, Eastern Mediterranean, European, Americas, and African regions, the pooled proportions of pre-XDR-TB were 35% (95% CI: 23-47, I^2 = 98.55%), 32% (95% CI: 24-41; I^2 = 96.2%), 30% (95% CI: 15-45; I^2 = 95.41%), 22% (95% CI: 5-39), 14% (95% CI: 10-19; I^2 =65.25%), and 12% (95% CI: 7-17; I^2 = 79.68%), respectively (Figure 2).

In the current study, we also performed a subgroup analysis based on the treatment history of patients with MDR-TB (newly diagnosed and previously treated cases). In the newly diagnosed group, the data were extracted from 23 studies, with the sample sizes ranging from 14 [25] to 687 [57]. A study in China had the highest proportion of pre-XDR-TB (27%) [70], whereas Ethiopia and Cameroon had the lowest (1%) [43,60]. The pooled proportion of pre-XDR-TB among newly diagnosed MDR-TB cases was 9% (95% CI: 5-12; I^2 = 96.32%). In the previously treated group, the data were extracted from 19 studies with sample sizes ranging from 14 [25] to 687 [57]. Similarly, the highest proportion of pre-XDR-TB (47%) was reported in China (69), whereas Ethiopia and Cameroon had the lowest (3%) [18,43]. The pooled proportion estimate of pre-XDR-TB proportion was 13% (95% CI: 8-18; I^2 = 96.12%) (Figure 3).

Pooled proportion of XDR-TB

The proportion of XDR-TB was reported in all WHO regions. The estimated pooled proportion of XDR-TB among patients with MDR-TB was 9% (95% CI: 7-11; I^2 = 95.98%). The highest proportion of XDR-TB was reported in India (77%) [44] and the lowest in Ethiopia [60] and Cameron (1%) [43]. The pooled proportions of XDR-TB in the Western Pacific, South-East Asian, Americas, African, and Eastern Mediterranean regions were 12% (95% CI: 7-17; I^2 = 19.62%), 10% (95% CI: 6-13%; I^2 = 94.54%), 6% (95% CI: 3-9; I^2 = 57.54%), and 3% (95% CI: 1-5%; I^2 = 65.68%), 3% (95% CI: 1-4; I^2 = 19.62%), respectively (Figure 4).

In the current study, we performed a subgroup analysis based on the treatment history of patients with MDR-TB (newly diagnosed and previously treated cases). In the newly diagnosed group, the data were extracted from 23 studies with a sample size ranges from nine [16] to 2472 [51]. Whereas the data was extracted from 25 studies, with sample sizes ranging from 33 [75] to 2472 [51], on previously treated patients. The pooled estimates of XDR-TB among newly diagnosed patients with MDR-TB were 3% (95% CI:

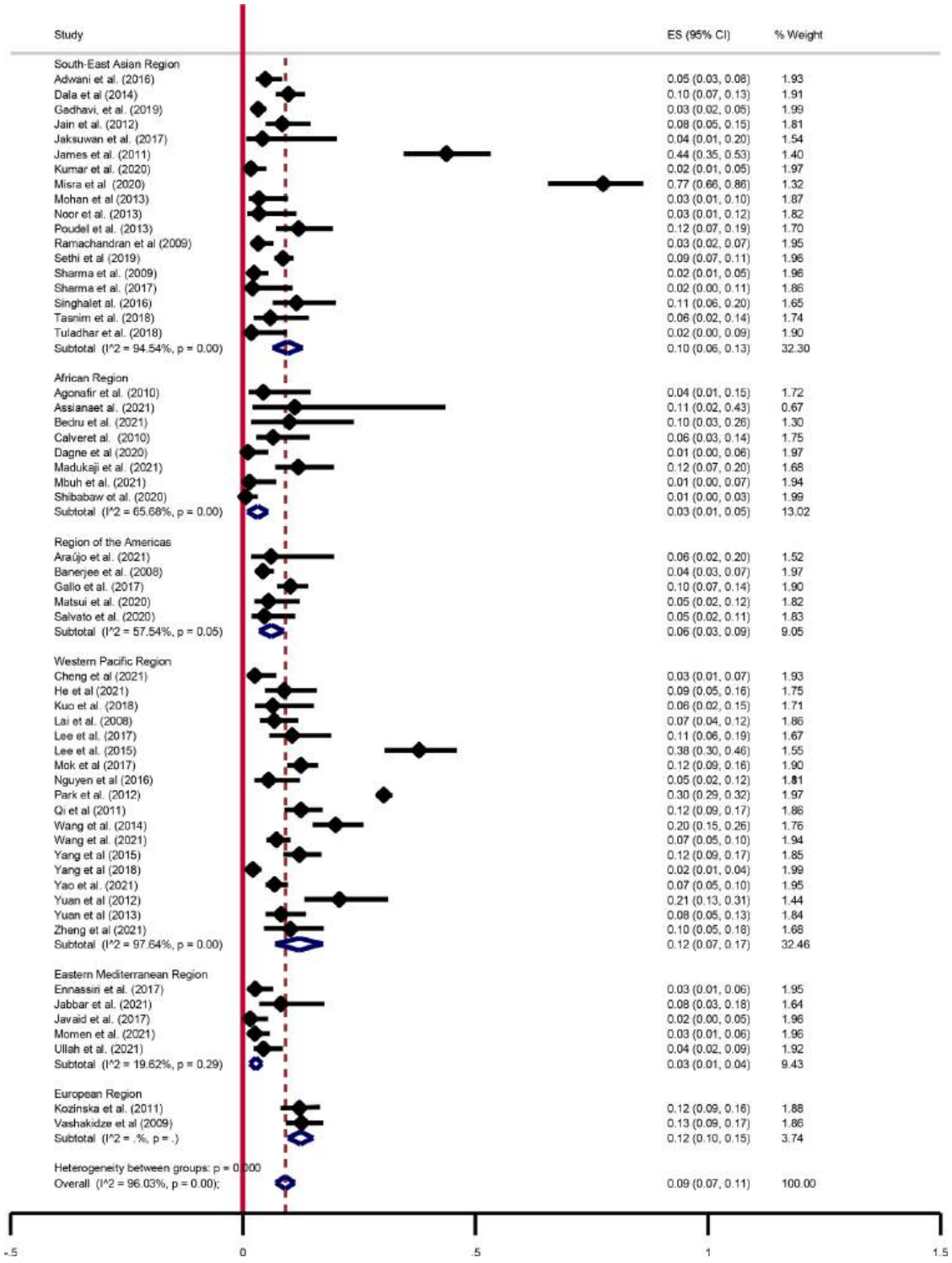

Figure 4. Pooled estimates of extensively drug-resistant-tuberculosis among multi drug-resistant-tuberculosis patients. CI, confidence interval; ES, effect size.

2-5; I^2 = 93.58%) and 6% (95% CI: 4-8; I^2 = 95.62%) among previously treated patients (Figure 5).

Pooled proportion estimates of FQs, SLID, and new drugs (BDQ, CFZ, DLM, and LZD)

In this study, we estimated the pooled proportion of resistance to FQs, SLIDs, and new drugs among patients with MDR-TB. The highest proportion of FQs resistance was 77% [44], whereas the lowest proportion was 4% [15,37]. Furthermore, the highest proportion of SLIDs resistance was 40% [13], whereas the lowest proportion was 3% [50,62]. The overall pooled proportion of FQs resistance among MDR-TB cases were 27% (95% CI: 22-33; I^2 = 97.53%) and 11% (95% CI: 9-13; I^2 = 91.31%) SLIDs resistance (Figure 6).

In this study, we performed a subgroup analysis to estimate the pooled new drug resistance among patients with MDR-TB. The pooled proportion of new drugs resistance was estimated from five studies for BDQ and LZD, four studies for DLM, and three stud-

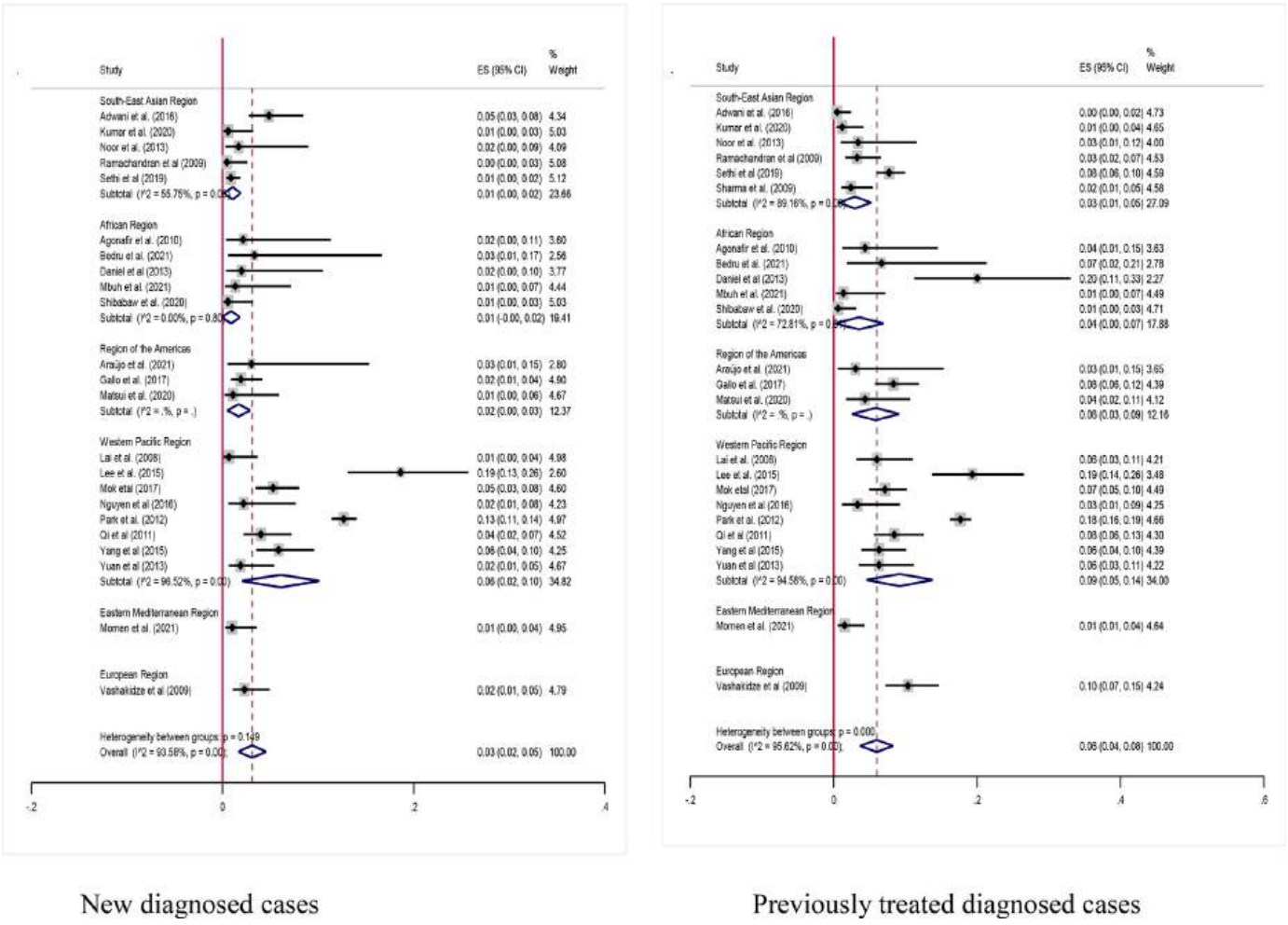

Figure 5. Pooled estimates of extensively drug-resistant-tuberculosis among new and previous treated multi drug-resistant-tuberculosis patients. CI, confidence interval; ES, effect size.

ies for CFZ [13,29,67,71,74]. The sample size of the included studies ranged from 88 [74] to 425 [13]. The pooled proportion of resistance to new drugs among patients with MDR-TB was 5% (95% CI: 1-8; I^2 = 90.84%) for BDQ, 4% (95% CI: 0-10; I^2 = 84.27%) for CFZ, 5% (95% CI: 2-8; I^2 = 80.80%) for DLM, and 4% (95% CI: 2-10; I^2 = 67.39%) for LZD (Figure 7).

Publication bias

We assessed the publication bias using funnel plots with the effect size and their standard errors. Visual inspection showed that the presence of publication bias was observed for the majority of the estimation of pre-XDR-TB, with fewer studies clustered at the tip of the funnel and the others distributed to the right and left corners of the funnel. The funnel plot for XDR-TB patients was relatively symmetrical, with only few studies visible in the right corners (Figure 8).

Discussion

This systematic review and meta-analysis estimated the pooled proportion of pre-XDR and XDR-TB among patients diagnosed with MDR-TB from the study reported worldwide. The pooled proportions of XDR-TB among new patients with MDR-TB were 3% and 6% in previously treated patients. The pooled proportions of pre-XDR-TB among new patients with MDR-TB were 9% and 13% among previously treated patients. The overall pooled proportion of pre-XDR was 26%, whereas the proportion of XDR-TB was 9% among patients diagnosed with MDR-TB. The pooled proportion of FQs resistance was 27% and the proportion of SLIDs resistance was 11%. A considerable proportion of resistance to new drugs BDQ (5%), CFZ (4%), DLM (5%), and LZD (4%) were also reported worldwide.

In the current review, the pooled proportion of XDR-TB was 9%. This is relatively higher than the proportion reported by the WHO global TB report in 2019, in which the proportion of XDR-TB was 6.2% [4]. This substantial difference could be due to the fact that the current meta-analysis was based on the findings from published clinical studies that reported data from diverse patient populations in various settings. The data, therefore, effectively entails regional influences and different epidemiological factors contribute to drug resistance and do not involve selective sampling of patients. Moreover, the proportion reported in the current review might reflect the status of suspected isolates referred for resistance testing rather than the might actual prevalence that estimated from representative participates. In contrast, the proportion given by WHO is based on the estimation from the TB program report, which could lead to underestimation, whereas the current review is based on the primary studies reported by independent researchers worldwide, which could be more representative. The results of the current review findings were relatively similar to the 2018 WHO global TB report, in which the proportion of XDR-TB was 8.5% [76].

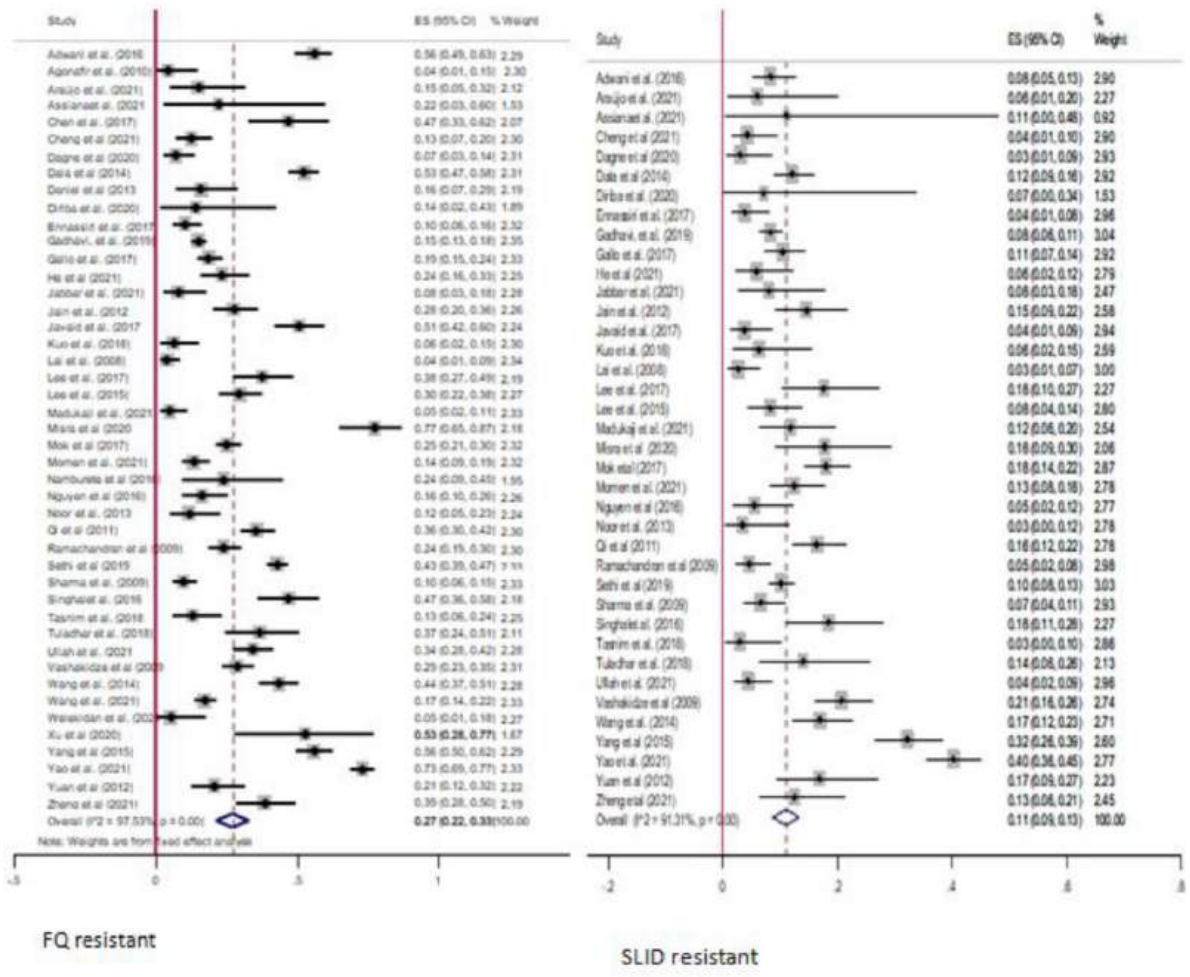

Figure 6. Summary of pooled estimates of FQs resistance and SLIDs resistance among multi drug-resistant-tuberculosis patients. CI, confidence interval; ES, effect size; FQs, fluoroquinolone; SLID, second-line injectable drug.

The proportion of XDR-TB among newly diagnosed patients with MDR-TB was 3% and 6% in previously treated patients. The combined proportion of pre-XDR-TB patients among the newly diagnosed patients with MDR-TB was 9% and 13% in the previously treated patients. The WHO estimate showed that 25,038 cases of pre-XDR-TB or XDR-TB were detected worldwide in 2022 [3]. However, there is limited information on the burden of pre-XDR-TB and XDR-TB among MDR-TB cases based on their previous treatment history.

The findings of the current study showed that more than a quarter of patients with MDR-TB had pre-XDR-TB with the majority were resistant to FQs. The pooled proportion of pre-XDR-TB in the current review is higher than the WHO estimate of 2021 [77]. The study results show that the proportion of pre-XDR-TB is higher and strains remains a major global public health concern in the area of antimicrobial resistance.

Based on the subgroup analysis, there are differences in the proportion of pre-XDR and XDR-TB in the WHO-defined regions of the world. The Western Pacific and South-East Asian regions have the highest rates of pre-XDR-TB and XDR-TB proportion. These regions should primarily examine the major risk factors for the high rates of DR-TB and intensify their efforts to address factors associated with high prevalence of DR-TB. The Beijing family is highly prevalent in these two regions and could be among the factors associated with the high proportion of DR-TB in the region [61]. The higher proportion of pre-XDR and XDR-TB might be due to the considerable variation in the coverage of high MDR/RR-TB burden countries and the high burden of the Beijing family.

The current review determined the proportion of FQs resistance cases. The pooled proportion of FQs resistance among MDR-TB cases was 27%. This finding is higher than the estimate of WHO in 2019, in which the proportion of FQs was 20.8% [4]. This difference is most likely due to the fact that majority of the included publications being from countries with high proportion of DR-TB. In addition, the possible reasons behind the high proportion of FQs are access and indiscriminate use of some of the commonly available FQ antibiotics for the treatment of various infection diseases [78]. Furthermore, the pooled proportion of SLID resistance among patients with MDR-TB was found to be 11%. The proportion of FQs resistance was equal to resistance to SLID proportion. This might be due to the fact that injectable drugs are less frequently used than FQs to treat common infections.

WHO has updated the MDR-TB treatment recommendations, in which injectable drugs are replaced by new drugs (BDQ, CFZ, DLM, and LZD). The update is required because the SLIDs are associated with an increase in deaths, treatment failures, relapses, and severe side effects, including permanent hearing loss [79]. Despite the limited evidence on new drugs, five published studies were included in the current review. In the current review, the proportion of resistance to new drugs (BDQ, CFZ, DLM, and LZD) among patients with MDR-TB was considerable. The occurrence of drug resistance among these four new anti-TB drugs was highlighted by

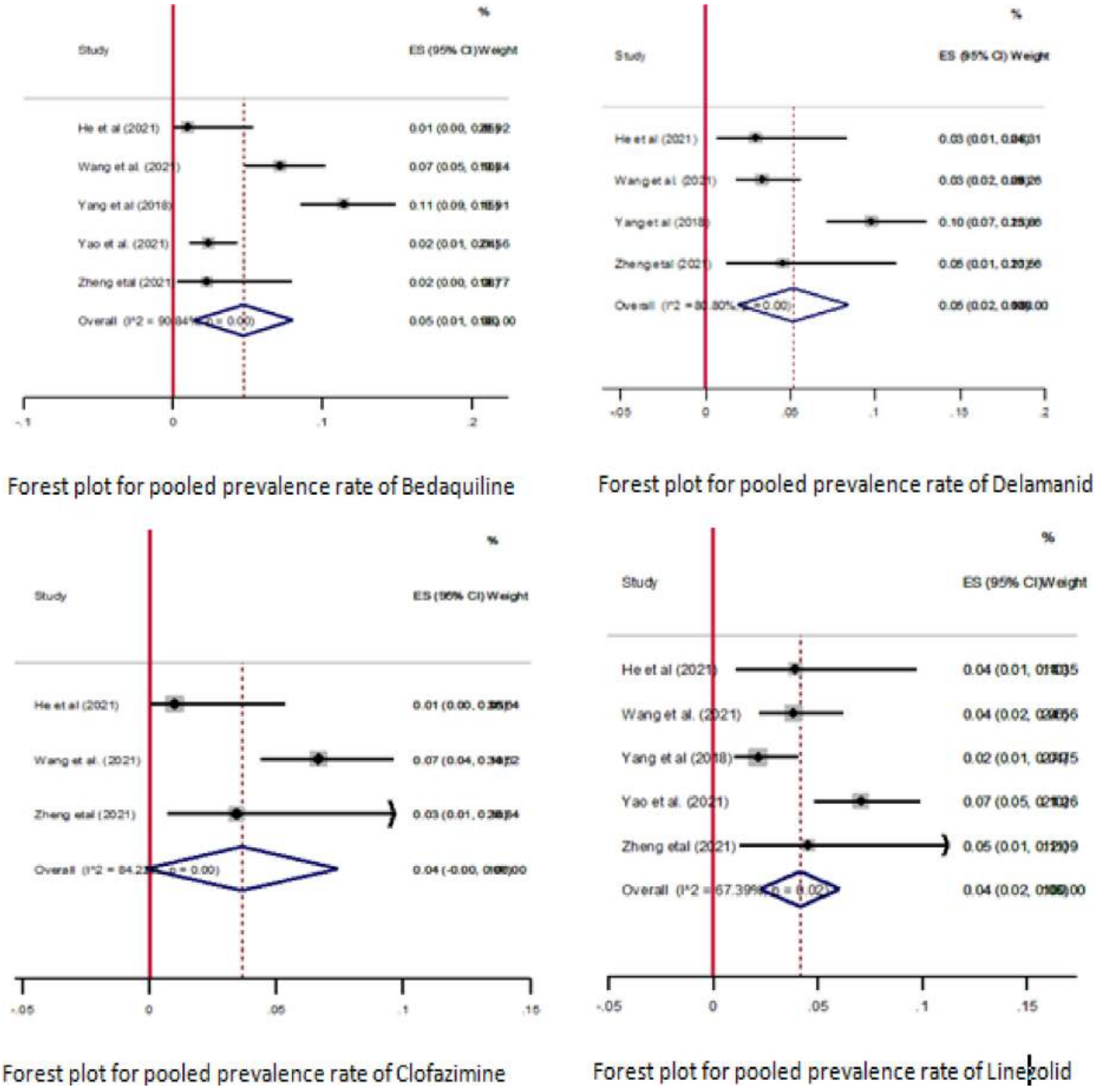

Figure 7. Summary of the pooled prevalence of new drug resistance among multi drug-resistant-tuberculosis patients. CI, confidence interval; ES, effect size.

the relatively higher proportion of resistance to BDQ and DLM. The introduction of new drugs may represent a new era in the care of patients with DR-TB by minimizing the toxicity associated with injectable drugs, reducing the spread of disease, reducing mortality rates, and improving successful treatment outcomes [31]. However, our findings revealed that 4-5% of patients with MDR-TB developed resistance to new drugs. Our findings imply that appropriate strategies are required to reduce resistance acquired during treatment.

Our review has several strengths. We used a random-effects model to address the problem of heterogeneity on the effect sizes between the included studies. In addition, we conducted a subgroup analysis using previous TB treatment history to determine the potential sources of heterogeneity. Although we cannot exclude the risk of publication bias, we used a sensitive search strategy and included a large number of studies. Moreover, we included a large number of studies that published from different parts of the world, which increases the generalizability of our findings. The current review study has some limitations. We included the studies that were published in English only, which could induce publication bias. In addition, the majority of the included studies were reported from the Western Pacific and South-East Asian regions, which could have overestimated the proportion of pre-XDR-TB and XDR-TB in this region and might have induced variation in the coverage of high MDR/RR-TB burden among the countries. Moreover, we did not evaluate the effect of HIV and other factors that could have predicted the proportion of pre-XDR-TB and XDR-TB due to the lack of data on potential predictors from the included stud-

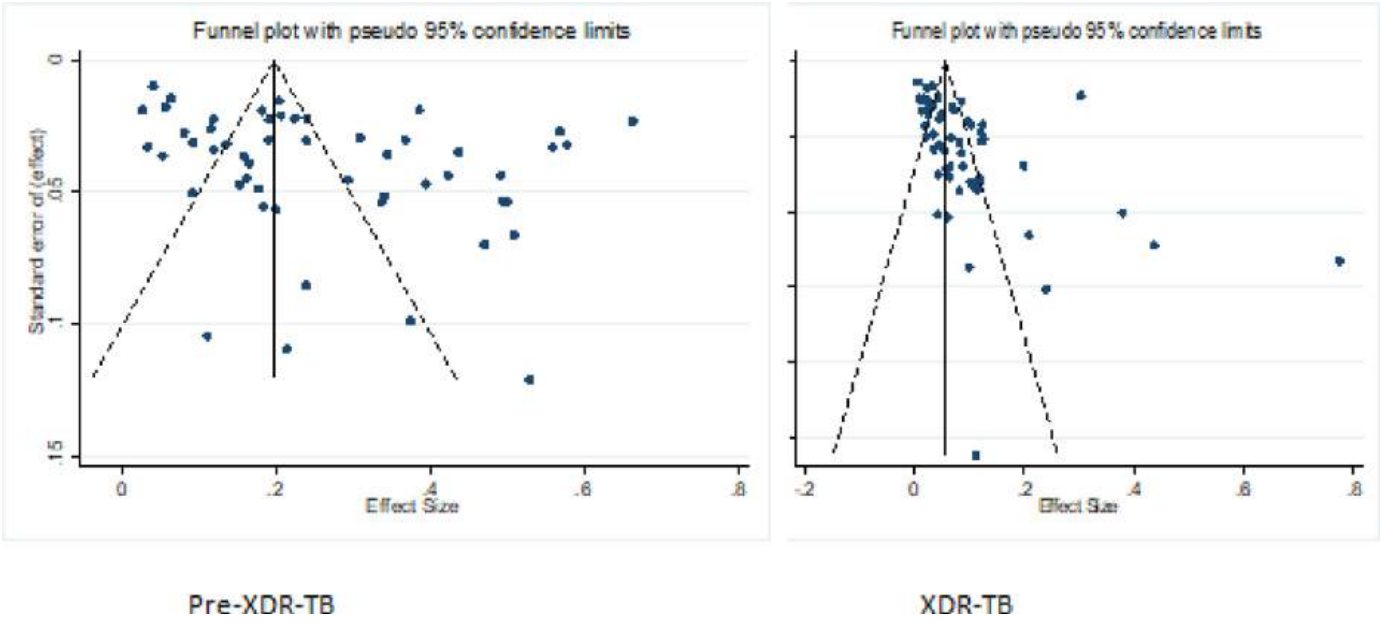

Figure 8. Funnel plots analyzing publication bias among studies evaluated for pre-XDR-TB and XDR-TB. XDR-TB, extensively drug-resistant-tuberculosis

ies. Despite these limitations listed previously, the current study results would not be affected by these limitations.

Conclusion

The current review study showed the presence of a higher proportion of pre-XDR-TB and XDR-TB than the WHO estimates. The highest proportions of pre-XDR-TB and XDR-TB were observed in the Western Pacific and South-East Asian regions. A considerable proportion of resistance to new drugs was also observed. Programmatic interventions are required to reduce the occurrence of pre-XDR-TB and XDR-TB. Countries should implement robust passive or active surveillance of DR-TB to understand the current burden of resistance to second-line and newly introduced drugs.

Declaration of competing interests

The authors have no competing interests to declare.

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Ethical approval and consent to participate

Not applicable.

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Author contributions

GD conceptualized, designed, and drafted the manuscript. GD, AA, BY, HHT, HM, DFG, KE, and AK: article searching, data extraction, and quality assessment. GD, AA, DFG, and BY: data analysis of the manuscript. AA, HHT, AK, SM, SA, GT, and MHD: writing, review, and editing of the final manuscript. All authors read, reviewed, and approved the final manuscript.

Availability of data and materials

All relevant data are available from the corresponding author upon request.

Consent for publication

Not applicable.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.04.392.

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The Contribution of Private Health Facilities to the Urban Tuberculosis Program of Afghanistan

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ABSTRACT

SETTING: Although the prevalence of tuberculosis (TB) is generally higher in urban areas than in rural areas, coordination between the private and public sectors for TB control is weak.

OBJECTIVE: To share experience from an urban DOTS program in five cities of Afghanistan.

DESIGN: An urban DOTS project was designed in 2009 in Kabul, Afghanistan, and later expanded to Kandahar, Jalalabad, Herat, Mazari-i-Sharif, and Paul-i-Khomri cities.

RESULTS: In total, 57 public health facilities and 49 private facilities provided DOTS services in the five cities from 2015 to 2018. A total of 28,542 (10.6%) adults (aged ≥ 15) screened were diagnosed with TB (all forms). The private sector contributed 5,618 (19.7%) of those. Positivity rates among presumptive TB cases in public facilities were 18.9%, 12.5%, 14.4%, and 4.8% in 2015, 2016, 2017, and 2018, respectively. In private facilities, positivity rates were 25.8%, 39.5%, and 27.4 % in 2016, 2017, and 2018, respectively.

CONCLUSION: The private sector's contribution to case detection was very high and the TB positivity rate among people screened in the private sector was high, which could be due to more selective screening rather than all health facility visitors done by public health facilities.

INTRODUCTION

With rapid urbanization of the world, we expect population health to improve overall because people will have better access to health services and infrastructure. However, other factors, including overcrowding, proliferation of slums, and lack of access to health services because of cost or cultural factors, aggravate TB transmission in cities [1]. In one European study, the rate of TB in cities was two times higher than the national notification rates [2]. In many countries, the urban TB burden is much higher than the rural one; for example, in Bangladesh the prevalence of TB in urban areas was 334 per 100,000 population, while it was 274 per 100,000 in rural areas [3]. In the same national survey of TB in Bangladesh, the TB death rate was higher in urban areas, at 8.5% versus 4% in rural areas [3]. In a Kenyan national prevalence survey, the urban TB prevalence rate was 760 per 100,000 population, while rural TB prevalence was 453 per 100,000 [4]. In Pakistan, the reverse is true: prevalence of TB in rural areas was 471 per 100,000 population, while it was 309 per 100,000 in urban areas [5]. A study comparing multidrug-resistant TB isolates in rural India and Mumbai city found that 51% of isolates from Mumbai residents were multidrug-resistant, while the proportion was only 2% in patients who lived in a nearby rural region. The authors posit that Mumbai has become a hot spot for MDR-TB because private-sector practitioners, a major source of health care in the city, are not regulated and do not follow the nationally approved regimens for treatment of TB [6]. In a South African study, cases of extremely drug-resistant TB(X-DR TB) were clustered in poor neighborhoods, characterized by lower educational attainment (12% vs. 9%), higher unemployment (29% vs. 20%), and a lower proportion of homes with flush toilets (36.4% vs. 68.9%) [7].

In Afghanistan the incidence of TB was estimated at 189 per 100,000 in 2017, a level that has remained the same for the past 17 years, while the case notification rate increased from 103.7 per 100,000 in 2008 to 131.3 per 100,000 in 2017 [8]. The case notification rate varies by province, from as low as 46 per 100,000 in Panjshir Province to 300.2 per 100,000 population in Kunar Province (WHO database, 2017), but no disaggregated data for urban and rural areas exist for Afghanistan. In Kabul, a TB project performance report reported that case notification increased from 59 per 100,000 in 2009 to 125 per 100,000 population in 2015 [9].

We analyzed the data collected in the routine health information system for five cities, excluding Kabul, to show the increase in case notification and treatment outcomes.

STUDY POPULATION, DESIGN, AND METHODS

Settings

In 2017 we published an analysis of six years of experience in Kabul with urban DOTS [9], a successful approach that was expanded to five other cities of Afghanistan with a combined population of 1.9 million: Kandahar, Jalalabad, Herat, Mazari-i-Sharif, and Paul-i-Khomri [10]. In 2015, 35 (42%) of 83 public health facilities were providing DOTS services, and 18 (18.3%) of 98 private health facilities were DOTS centers (National TB Program [NTP], surveillance database, 2015).

The DOTS Expansion Approaches

We also published information about the approaches we used for DOTS expansion in 2017 [9], so this article briefly summarizes them. Two types of health care providers serve urban areas: the public sector managed and funded by the government, and the private for-profit sector. TB diagnosis and treatment services are free even in the private sector, except for the consultation fee for the first visit of a client to a private health facility. The Ministry of Public Health recognized some of the private health facilities as DOTS centers, based on criteria such as existence of a laboratory and outpatient department (OPD), and advised clients to use those facilities, as well as public-sector health facilities, to obtain TB prevention and care services.

A baseline assessments of both the public and private health facilities at the beginning of the expansion was done with the objective of assessing human resources, and diagnostics capacities, as well facilities space adequacy to give TB services. Based on the findings, training as given to health workers on the national comprehensive TB care and prevention guideline, and standard

operating procedures, reagents for diagnostics, drugs, and other supplies supplied. Provincial or NTP program officers supervised and mentored both the private and public DOTS centers quarterly.

Data Collection and Analysis

The data we used were collected in Excel using the routine NTP recording and reporting forms and reported quarterly to the provincial offices and the NTP. Although TB services were provided in urban areas, clients came from both rural and urban areas. In our analysis we included patients aged 15 years and above. Data were entered in Excel and analyzed manually. Proportions, rates, and ratios were used to analyze the secondary data.

Ethical Statement

We used only routine program data for this analysis, and we solicited approval from the NTP to publish the data. The research was implemented in close collaboration with the NTP, which reviewed and approved the manuscript for publication.

RESULTS

In total 181 health facilities had DOTS capacity as per the nationals standard, and we were able to engage 106 (58.5%) of them as DOTS centers. The number of DOTS centers in the private sector grew from 18 in 2015 to 57 in 2018. Of the total of 3,581,079 OPD visitors over the age of 15 years old, the majority of patients (2,960,718 [(89.6%]), visited public health facilities. The number of people seeking care in public health facilities increased from 502,112 in 2015 to 862,191 in 2018. The same trend of increase in patient load, from 65,547 in 2015 to 107,868 in 2018, was also observed in private health facilities. The striking difference between the public and private health facilities was that the private health facilities did not screen all OPD visitors except those whose major complaints coincided with sign and symptoms of TB. Of all screened OPD visitors (unfortunately the number screened was not recorded), 268,677 were reported to be presumptive TB cases and 28,542 (10.5%) were diagnosed with TB (all forms). The positivity rates for the public health facilities were 18.2%, 12.2%, 13.9%, and 4.5% in 2015, 2016, 2017, and 2018, respectively. In the private sector, the positivity rates were higher, at 25.1%, 38.1%, and 26.2 % in 2016, 2017, and 2018 respectively (Table 1).

Out of 28,542 TB cases (all forms) diagnosed in the public and private health facilities in the four years, 10,156 (35.5%) were bacteriologically confirmed. There was a large difference in the proportion of bacteriologically confirmed TB cases between the public and private health facilities. In the public sector, 8,891 (38.1%) cases were bacteriologically confirmed TB, while the proportion was 1,265 (22.5%) in the private health facilities. Clinically diagnosed TB (11,822 [41.4%]) and extrapulmonary TB (6,564 [23.0%]) constituted the majority of the TB diagnoses in both public and private DOTS centers.

Treatment success rates also improved, from 81% in 2015 to 86% in 2018. The treatment success rate was not different between the public and private health facilities: it was 81% in 2015 and increased to 85% in 2018 in the public sector, and it rose from 82% in 2016 to 85% in 2018 in the private health facilities.

DISCUSSION

Based on the experience gained in Kabul, the NTP and Challenge TB together expanded the urban DOTS program to five more cities, which resulted in increasing case notification of all forms of TB from 5,520 in 2015 to 7,988 in 2018. Many of the changes came from private-sector engagement. In 2015 only 329 cases were notified by the private sector. This number reached 2,093 in 2018—an almost 536% increase, while the increase in public health facilities was only 30%. The increases can be explained by the expansion of TB DOTS to the private sector and the capacity-building efforts in the public sector. The TB positivity rate out of all presumptive TB cases has decreased from 18.9% in 2015 to 4.8% ($p < 0.05$) in 2018 in the public health facilities. In the private sector, the all forms of TB positivity rate was 25.8%, 39.5%, and 27.4% in 2016, 2017, and 2018 respectively. Because all visitors in the OPD are screened for TB in the public health facilities, the positivity rate is low in the public sector.

In an evaluation of passive and active case-finding approaches in health facilities of Afghanistan, the rate of TB (all forms) diagnosed was 0.3% in the first year and 0.5% in the second year [11], which is a little lower than our findings in the public sector. The NTP should decide if blanket TB screening in OPDs is effective in Afghanistan, from a time and cost perspective, as compared to targeted screening of contacts and people from high-risk groups.

We saw also a difference in the proportions of extrapulmonary TB and bacteriologically confirmed TB diagnoses between the public and private centers. Of all forms of TB diagnosed, 8,891 (38.8%) were bacteriologically confirmed in the public centers, while only 5,618 (22.5%) were bacteriologically confirmed in the private sector ($P < 0.05$). The proportion of

bacteriologically confirmed cases was lower than the proportion reported in 2017, which was 61% of pulmonary TB cases [8]. One possible reason for the discrepancy in the proportion of bacteriologically confirmed cases between the reported national proportion and the proportion in the five cities in this study could be that the capacity to diagnose non-pulmonary presumptive TB is low in peripheral health centers, and cases are referred to secondary and tertiary hospitals in the cities. As a result, most of the referred cases diagnoses would be either extrapulmonary TB or smear-negative clinically diagnosed pulmonary TB cases.

The private sector is usually attracted to TB diagnosis because patients can pay for registration and investigations, and it is in the interest of the private sector to provide comprehensive clinical services to retain clients who have the ability to pay. The challenge comes in administering daily DOT and following up with patients, which are free services. In Afghanistan the treatment success rate in the private sector is equivalent to the rate in the public sector, which was 85% in 2018. In Kenya the private-sector treatment success rate ranged from 74% to 85% in a four-year report, and the reason for such a high rate was that the patients seen in the private sector can pay for registration and diagnostic tests, while the government provides drugs free of charge [12]. We recommend research on incentives for the private sector to provide free TB prevention and care services in Afghanistan.

CONCLUSIONS

We found that the private-sector contribution to case detection in Afghanistan was high and the treatment success rate was also high and equivalent to that of the public sector. Although the contribution is high, what we do not know is that what factors motivate private practitioners to give full or partial free services to patients. Studying these factors will help to include more private health facilities, including those at the lower level, such as pharmacies, in TB screening.

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AUTHORS' CONTRIBUTIONS

Designed the study and led the research: : A. Hammim, M.K. Seddiq, S.M Sayedi, K.M. Rashidi, G.Q. Qader, L. Manzoor, M. Melese, P. G. Suarez. All others participated in the data analysis and writing. All authors have approved the manuscript for submission.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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Table 1. Screening for TB and TB cases diagnosed in public and private health facilities, 2014-2019

Year	2015		2016		2017		2018		Total
Indicator	**Public**	**Private**	**Public**	**Private**	**Public**	**Private**	**Public**	**Private**	
Total number of Health facilities (HFs) with DOTS capacity	67	71	70	83	83	90	83	98	181
Number (%) of HFs that were DOTS centers	35	18	38	37	42	45	49	57	106
Number of patients ≥15 years who visited OPDs	502,112	65,547	792,000	73,036	804,415	94,765	862,191	107,868	3,301,934
Total number of presumptive TB cases identified	27,444	NA	41,278	4,511	39,921	5,134	142,761	7,628	268,677
Total number of all forms of TB patients diagnosed	5,191 (18.9)	329	5,196 (12.5)	1,166 (25.8)	5,757 (14.4)	2,030 (39.5)	6,780 (4.7)	2,093 (27.4)	28,542 (10.6)
Number (%) bacteriologically confirmed TB patients	1,918 (36.9)	50 (15.2)	2,037 (39.2)	310 (26.6)	2,222 (38.6)	401 (19.7)	2,714 (40.0)	504 (24.1)	10,156 (35.5)
Treatment success rate	81	NA	82	83	85	84	85	85	NA

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Uptake and Completion of Tuberculosis Preventive Treatment Using 12-Dose, Weekly Isoniazid–Rifapentine Regimen in Bangladesh: A Community-Based Implementation Study

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Uptake and Completion of Tuberculosis Preventive Treatment Using 12-Dose, Weekly Isoniazid–Rifapentine Regimen in Bangladesh: A Community-Based Implementation Study

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Abstract: Background: The United Nations high-level meeting (UNHLM) pledged to enroll 30 million in tuberculosis preventive treatment (TPT) by 2022, necessitating TPT expansion to all at tuberculosis (TB) risk. We assessed the uptake and completion of a 12-dose, weekly isoniazid–rifapentine (3HP) TPT regimen. Methods: Between February 2018 and March 2019 in Dhaka, community-based TPT using 3HP targeted household contacts of 883 confirmed drug-sensitive pulmonary TB patients. Adhering to World Health Organization guidelines, contacts underwent active TB screening before TPT initiation. Results: Of 3193 contacts who were advised health facility visits for screening, 67% (n = 2149) complied. Among these, 1804 (84%) received chest X-rays. Active TB was diagnosed in 39 (2%) contacts; they commenced TB treatment. Over 97% of 1216 contacts began TPT, with completion rates higher among females, those with more education and income, non-slum residents, and those without 3HP-related adverse events. Adverse events, mainly mild, occurred in 5% of participants. Conclusions: The 3HP regimen, with its short duration, self-administered option, and minimal side effects, achieved satisfactory completion rates. A community-focused TPT approach is feasible, scalable nationally, and aligns with UNHLM targets.

Keywords: TB preventive treatment; UNHLM; End TB; TPT; 3HP; Bangladesh

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1. Introduction

Tuberculosis (TB) infection (TBI) is an important reservoir of TB disease, and it is important to treat individuals with TBI to break the chain of transmission and prevent the further spread of the disease in the community [1]. It is estimated that over one-fourth of the world's population is infected with *Mycobacterium tuberculosis*, the bacteria responsible for TB disease [2]. If TB infection remains untreated, 5–10% of individuals with TBI develop active TB in their lifetime, with 50% developing the active disease within two years after infection [3,4]. A study by Dye et al. showed that to meet World Health Organization (WHO) End TB targets, TBI treatment will need to be incorporated into TB programs, as merely treating the active disease will not result in a significant reduction in the burden

given the large number of individuals infected with TB. These individuals with TBI will continue to give rise to TB cases because of reactivation [5]. The WHO recommends that TB preventive treatment (TPT) should be prioritized for contacts of TB patients [6]. Thus, the prevention of new TB infections and their progression to active TB disease is critical to reducing the burden of the disease and resulting deaths, as well as to achieving the United Nations high-level meeting (UNHLM) on TB and End TB Strategy targets for 2022 and 2030/2035.

TB remains a major public health concern in Bangladesh, with an estimated 360,000 people who developed TB and 44,000 died from TB in 2020 in the country [7]. The country's annual report on TB shows that, although TB case detection and notification in Bangladesh is increasing steadily (approximately 5% annually), the estimated TB incidence has remained static—between 225/100,000 and 221/100,000 since 2001 [8]. The current National Tuberculosis Control Program (NTP) in Bangladesh focuses heavily on detecting new TB cases and treating these new patients with a limited focus on TPT. Children younger than five years and people living with human immunodeficiency virus (HIV) are prioritized for isoniazid preventive treatment (IPT) with a daily dose for six months. Although the NTP and partners have been implementing IPT among children of <5 years for years, the coverage is only 51% among all eligible children, with a completion rate of around 75% [7]. In Bangladesh, the implementation of TPT strategies is hindered by limited resources that affect healthcare capacity and cultural barriers such as health literacy that affect the public perception of TPT and adherence to it. Global evidence also suggests that the acceptance and completion rates of IPT are often low (30–64%) because of the long duration of treatment [9], and implementation of TPT is challenging. The current initiatives are not enough to achieve a significant reduction in TB infection in line with the UNHLM and End TB targets for TPT.

The recent WHO guideline recommends several shorter regimens, which can minimize the burden on both patients and health systems. One of the recommended TPT regimens is a once-weekly dose of rifapentine and isoniazid for three months (3HP). This regimen has comparable adverse events and better treatment completion rates [10–17]. The experience with this regimen in low-resource programmatic settings is lacking, but given once-weekly dosing and higher completion rates, as observed in other trials, it is expected to improve adherence and address the operational challenges associated with IPT. At present, there are no data available in Bangladesh on the eligibility, initiation, and completion of TPT for child contacts and the feasibility of TPT for other household (HH) contacts. Understanding this implementation feasibility can potentially inform the effective development of future TPT programs and thus warrants comprehensive programmatic research. The current study was conducted to assess the uptake and completion of the 3HP regimen and better understand the programmatic challenges with the intervention delivery, uptake, and completion of the 3HP regimen for TPT.

2. Materials and Methods

2.1. Ethical Approval

Ethical approval for the study was obtained from the Bangladesh Medical Research Council (Registration Number 127 14 06 2018). Written informed consent for participation was obtained by project staff prior to enrollment into the study from adults and from guardians/parents of children. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee. All participants enrolled in this study received free services, including costs for investigation and TPT with 3HP.

2.2. Study Design and Location

A community-based implementation study was conducted under routine programmatic settings in Dhaka (South City Corporation Zones 3, 4, and 5), Bangladesh, between February 2018 and March 2019 to assess the uptake and completion of TPT with 3HP. The

design of this study and the intervention packages were supported by a prior qualitative study on the barriers to and facilitators of existing IPT program in Bangladesh [18].

2.3. Study Population

The study population comprised the HH contacts of bacteriologically confirmed (B+) pulmonary-drug-susceptible TB (DS-TB) patients (index patients) enrolled for TB treatment at all 12 NTP-linked treatment facilities in the selected areas during the study period.

2.4. Inclusion and Exclusion Criteria

All HH contacts of index DS-TB patients were considered eligible if (i) both the index DS-TB patients and their families lived in our selected study sites and (ii) the individual was aged over two years. The HH contacts were excluded from the study for the following reasons: (i) they were already receiving TB disease treatment or IPT at the time of the HH contact investigation; (ii) they were women who were pregnant or planning pregnancy during the study period; (iii) the HH contact was under two years of age, as rifapentine is not recommended for this age group. Pregnant women were excluded given the limited safety data on the 3HP regimen during pregnancy. This precaution, reflecting ethical considerations and the need to mitigate unknown fetal health risks, aligns with the principle of safeguarding participant safety in clinical research, especially in populations with insufficiently studied treatment effects.

2.5. Identification of HH Contacts for TPT

Field Supervisors (FSs) who had prior experience working with TB were recruited by the study and received training on the study implementation process. The FSs extracted the contact details of the index TB patients from the treatment registers and interviewed each index patient over the phone to enumerate the HH contacts. They encouraged the index patient to bring their HH contacts to the nearest health facility for contact screening and clinical evaluation. Once HH contacts arrived at the facility, Treatment Counselors (TCs) counseled the index TB patients and the HH contacts on the risk of developing TB and the importance of TPT. Then, the TCs conducted verbal screening for the presence of TB symptoms, and a physician conducted a clinical assessment. Based on the advice of the physician, free chest X-rays (CXRs) were offered to all contacts to rule out TB disease as per the NTP protocol. Rapid molecular tests (if sputum was available) were performed for the contacts with abnormal CXRs to detect active TB disease. When active TB disease was confirmed, the project field staff connected the patient with an NTP-linked TB treatment facility for treatment initiation. Those HH contacts considered not to have active TB disease were counseled by the treatment counselor and invited to initiate TPT with a 3HP regimen. For HH contacts with self-reported previous episode(s) of TB, the NTP records were reviewed to verify previous treatment and outcome history. If the individual had not completed TB treatment, was not declared cured/had not completed treatment, or did not have documented proof, he or she was referred to the TB treatment facility for further evaluation before being fully eligible for TPT.

In instances where the HH contacts did not come for evaluation or were reluctant to come within one week of the initial phone call, the TCs made at least three reminder phone calls, and then, community health workers (CHWs) from the NTP visited the HHs within three weeks to talk with the contacts face-to-face and motivated them to go for evaluation.

2.6. Initiation of TPT with 3HP

The HH contacts who were willing to participate and met the inclusion criteria were considered eligible. The eligible HH contacts took the recommended first dose of the TPT in front of the physician within seven days of the initial evaluation. The 3HP regimen was used among eligible contacts >2 years old and as a self-administered treatment procedure by the participants with support from the project team and the CHWs [11,12].

2.7. Treatment Support and Monitoring of Adverse Events

A trained CHW (acting as a treatment supporter) from a local non-governmental organization (NGO) visited the participant at home bi-weekly to follow up on treatment progress and to assess any adverse drug reactions. The treatment adherence was assessed through self-reported pill intake by the HH contacts over the phone and reconfirmed by pill count and reviewing the household diaries of CHWs during follow-up household visits. The treatment completion was defined as completing at least 11 doses of 3HP within 3 months. The TCs called the HH contacts on TPT every two weeks during the treatment period. In addition, the FSs visited all HHs monthly, quantified adherence, asked about adverse events, and recorded the results. If either CHWs or FSs identified a possible adverse event, they immediately communicated with the physician and referred the participant to the hospital for clinical evaluation if needed. Contacts on 3HP visited the health facility every month for follow-up evaluation by the physician. Enablers (USD 36 per month) to promote treatment adherence were provided to CHWs, and travel and investigation costs were reimbursed to the participating families. The HH contacts could also self-report any adverse events to the CHWs or to the project physician, which were recorded on a standardized open-ended adverse event reporting tool. The reported adverse events were immediately assessed, graded, and managed by the physicians. In cases of drop-out from the TPT, the CHWs explored the reason for discontinuation and recorded the reasons.

2.8. Data Analysis

All data were analyzed using the Statistical Package for Social Sciences, version 24 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to report the data. The data involving continuous variables (age, schooling, income, etc.) were analyzed using a rank-sum test, and the results are presented as the median value plus the minimum and maximum values. Sex, residence, occupation, comorbidity, etc., variables are presented as frequency and percentage. The cumulative probability of an HH contact completing all stages of the TB preventive care cascade was assessed in all eligible participants, and the proportion of HH contacts completing 3HP was assessed among all those who initiated the regimen. Univariate logistic regression analysis was used to analyze the relationships between various factors and the subjects' completion of TPT, and the results were calculated as an odds ratio (OR) and its 95% confidence interval (95% CI). A multivariable non-conditional logistic regression analysis was then performed on univariate variables that were statistically significant, with the criteria for inclusion being a p-value ≤ 0.050.

3. Results

3.1. Demographic and Clinical Characteristics

During the study period, 3193 HH contacts of 883 index TB patients were enumerated and counseled to visit health facilities for evaluation. Of 3193 HH contacts, 67% (n = 2149) showed up at the health facilities and were verbally screened, of whom 54% (n = 1167) were female, and the mean age of the contacts was 21.2 years (Standard Deviation (SD) $\pm$ 17.5). Of the 1216 contacts initiated into TPT, the mean age was 27.4 (SD $\pm$ 23.8), and 56% (n = 675) were female. Diabetes was the predominant comorbidity among contacts. It was observed that most of the contacts needed two phone calls from the project team to get them to the facilities for evaluation (Table 1).

Table 1. Socio-demographic characteristics of the household contacts of index TB patients who were verbally screened (*n* = 2149) and initiated TB preventive treatment (*n* = 1216) using the 3HP regimen.

Variables	Household Contacts Verbally Screened (*n* = 2149)	Household Contacts Who Initiated TPT with 3HP (*n* = 1216)
Age—mean age (± SD)	21.2 (±17.5)	27.4 (±23.8)
<5	65 (3.0%)	40 (3.3%)
5–<15	484 (22.5%)	272 (22.4%)
15 and above	1600 (74.5%)	904 (74.3%)
Female	1178 (54.8%)	675 (56.0%)
Schooling in year		
No schooling	323 (15.0%)	146 (12.0%)
1–5 years	726 (33.8%)	383 (31.5%)
6–10 years	710 (33.0%)	345 (28.4%)
10+ years	390 (18.1%)	342 (28.1%)
Household income/month in BDT (mean ± SD) *	14,532 ± 9853	15,251 ± 10,235
≤5000	14 (0.7%)	7 (0.5%)
5001–10,000	321 (14.9%)	165 (13.6%)
10,001–20,000+	1814 (84.4%)	1044 (85.9%)
Original residence		
Permanent resident of Dhaka	677 (31.5%)	398 (32.7%)
Tenant (rural-to-urban migrant)	1472 (68.5%)	818 (67.3%)
Current dwelling status		
Living in slums	1027 (47.8%)	589 (48.4%)
Non-slum households	1122 (52.2%)	627 (51.6%)
Occupation		
Student and dependent child	543 (25.3%)	361 (29.7%)
Day labor/garments/factory work	605 (28.2%)	234 (19.2%)
Self-employed and business	359 (16.7%)	138 (11.3%)
Public/private service	246 (11.4%)	132 (10.9%)
Homemaker	380 (19.9%)	341 (28.0%)
Unemployed	16 (0.7%)	10 (0.8%)
Current or past smoker	892 (41.4%)	483 (39.7%)
Comorbidity		
No comorbidity	1372 (68.5%)	1194 (98.2%)
Diabetes mellitus	95 (4.4%)	16 (1.3%)
Hypertension	409 (19.0%)	04 (0.3%)
Asthma	14 (0.7%)	01 (0.1%)
Thyroid dysfunction	159 (7.4%)	01 (0.1%)
Experienced any adverse events	NA	65 (5.3%)

* USD 1 = BDT 110.

3.2. Evaluation, Initiation, and Completion of TPT among HH Contacts

Of the 2149 contacts who visited the health facilities and were verbally screened, 1804 contacts (84%) completed an evaluation with CXRs. Among CXRs performed, 39 (2%) contacts were found to have active TB (abnormal CXR and molecular test), and 92 (5%) were below two years and initiated on IPT. The remaining 1673 (93%) eligible contacts were invited to enroll on TPT with the 3HP regimen. Of those eligible, 1216 (73%) initiated the 3HP regimen, 97% (*n* = 1175) of whom completed the regimen (Figure 1). The TPT completion among adults was 99.8%, and in females, 99.9%. The cumulative probability of completing all steps of the TB prevention cascade was 63% among the study population.

Among the HH contacts who did not complete the treatment, 78% (*n* = 32) dropped out between 2 and 5 weeks after the treatment initiation. The most common reason for noncompletion of TPT was a refusal to continue treatment due to side effects or fear of side effects (*n* = 32; 78%). Furthermore, 14.6% (*n* = 6) migrated to a different area where 3HP intervention was not available. Only a small proportion (*n* = 3; 7.3%) was advised by a doctor to stop treatment because of unusual events experienced during TPT (Table 2).

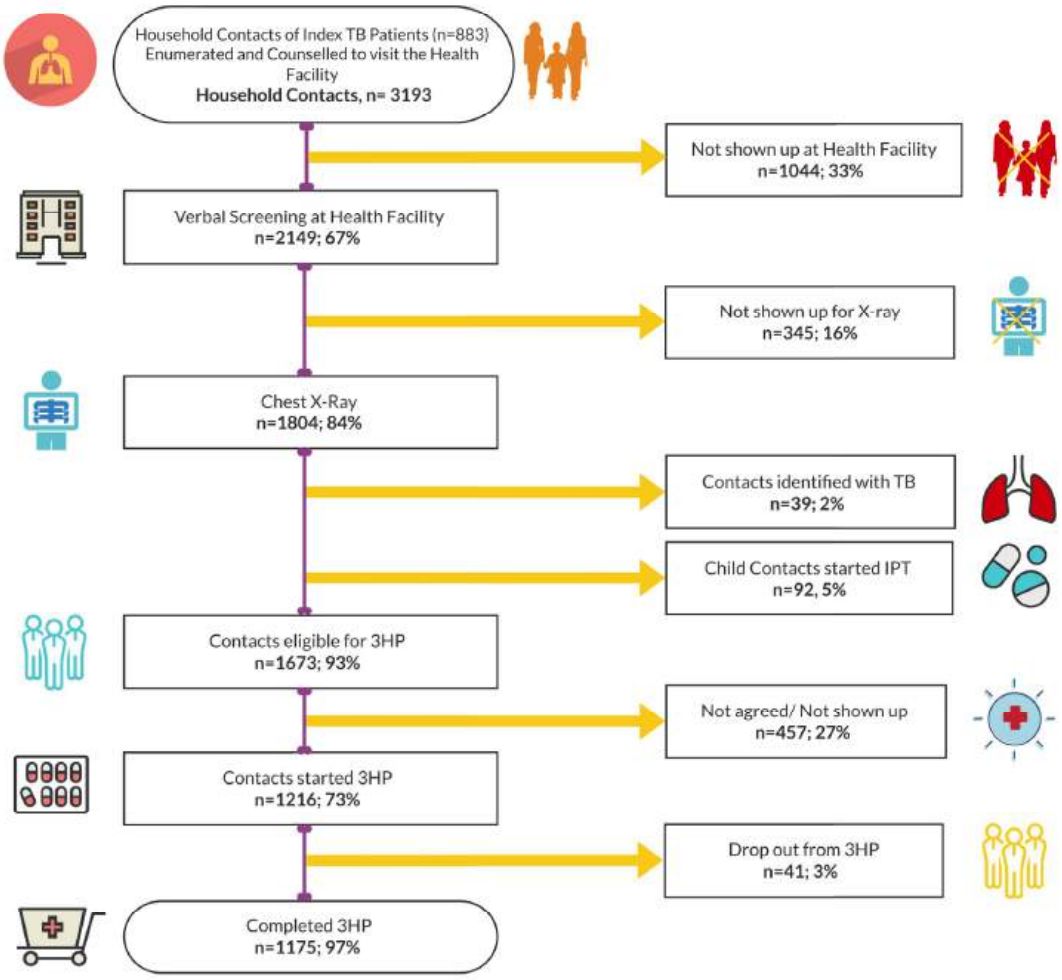

Figure 1. TPT enrollment and completion cascade with 3HP, February 2018–March 2019.

Table 2. Number and percentage of household contacts with adverse events after any 3HP dose by type and grade (*n* = 65).

Experienced Adverse Events after Any 3HP Dose by Type *	Frequency ** with Grading ***			
	Not Graded	Grade 1	Grade 2	Grades 3, 4, and 5
Gastrointestinal—nausea/vomiting	-	20 (1.64%)	01 (0.08%)	-
Neurological symptoms	-	01 (0.08%)	-	-
Muscle pain	-	02 (0.16%)	-	-
Hepatotoxicity	-	00 (0.00%)	-	-
Flu-like symptoms	-	10 (0.82%)	01 (0.08%)	-
Dermal—itching/skin rash	01 (0.08%)	09 (0.74%)	-	-
Respiratory symptoms	-	02 (0.16%)	-	-
Fatigue	-	07 (0.58%)	-	-
Headache	-	06 (0.49%)	-	-
Other symptoms ‡	-	05 (0.41%)	-	-
Total experiencing adverse events	01 (0.08%)	62 (5.09%)	02 (0.16%)	00 (0.00%)

* Includes all adverse events reported by the participants deemed to be "related" or "possibly related" to 3HP medication by the project physician. ** Number of participants experiencing an adverse event of a certain severity with one or more doses where each participant is counted only once at the highest level of severity for that type, and the percentages are taken out of the total number of patients on TPT. *** Grade 1 = mild—discomfort noticed but no disruption of normal daily activity; Grade 2 = moderate—discomfort sufficient to reduce or affect daily activity; Grade 3 = severe—inability to work or perform a normal daily activity; Grade 4 = life-threatening or disabling—represents an immediate threat to life; Grade 5 = death—death related to an adverse event. ‡ Other related or possibly related adverse events included dizziness, insomnia, increased blood pressure, and gynecologic symptoms (spotting) (all Grade 1).

3.3. Reported Adverse Events

During the TPT, 5.3% (n = 65) of HH contacts on TPT experienced adverse events. However, no major adverse events were observed, nor were any hospitalizations required. Most of the adverse events were Grade 1, and symptomatic management alone resolved the presenting issues (Table 2). The majority of adverse events were reported in subjects aged 15 years and older (n = 51; 4.2%) and among females (n = 35; 2.9%). Of the three contacts who stopped TPT as per the suggestion of the physician, one was hypertensive and had poor adherence to antihypertensive medications, and two female patients had gynecologic symptoms (spotting).

3.4. Factors Associated with TPT Completion with the 3HP Regimen

Table 3 presents bivariate and multivariable logistic regression models examining the association between TPT completion with 3HP and demographic characteristics and clinical factors. The multivariable model reveals that TPT completion was higher in contacts aged 15 years or more (OR 1.5; 95% CI 1.1–2.0; p 0.043); female contacts (OR 1.7; 95% CI 1.3–2.1; p 0.009); contacts with higher education (OR 1.4; 95% CI 1.1–1.9; p 0.044); contacts with high HH income (OR 1.5; 95% CI 1.0–2.1; p 0.047); contacts those with no comorbidities (OR 1.7; 95% CI 1.1–2.2; p 0.046); and those who did not experience any adverse events while on the 3HP regimen (OR 1.6; 95% CI 1.2–2.1; p 0.009).

Table 3. Bivariate and multivariable logistic regression examining the association between TPT completion with 3HP and demographic characteristics and clinical factors.

Variables	Bivariate Model		Multivariable Model *	
	OR (95% CI)	***p* Value**	**OR (95% CI)**	***p* Value**
Current age (r = age < 15 years)	2.1 (1.8–2.4)	0.004	1.5 (1.1–2.0)	0.043
Female (r = male)	2.5 (1.7–2.8)	0.002	1.7 (1.3–2.1)	0.009
Schooling in year (r = 0)	2.2 (1.7–2.5)	0.004	1.4 (1.1–1.9)	0.044
Monthly household income > BDT 10,000 (r = ≤ BDT 10,000) [a]	1.7 (1.3–2.1)	0.005	1.5 (1.0–2.1)	0.047
Permeant urban resident (r = rural-to-urban migrant with temporary settlement)	1.2 (0.8–2.3)	0.098	NA	
Lives in non-slum household (r = lives in slum)	1.6 (1.3–2.1)	0.049	1.1 (0.7–2.4)	0.088
Occupation: non-manual work (r = manual work)	1.1 (0.7–2.7)	0.106	NA	
No comorbidities (r = have had any comorbidities)	2.3 (1.8–2.5)	0.008	1.7 (1.1–2.2)	0.046
Experienced no adverse events (r = experienced any adverse events)	1.8 (1.3–2.4)	0.003	1.6 (1.2–2.1)	0.009
Intervention Approaches				
Reminder phone calls + treatment counseling (r = reminder phone calls only for the next dose schedule)	2.7 (2.1–3.2)	0.002	1.9 (1.5–2.4)	0.007
Reminder phone calls + treatment counseling + follow-up home visit by health workers (r = reminder phone calls only)	3.2 (2.7–3.6)	0.001	2.1 (1.5–2.7)	0.005

* The multivariable model only included the variables that were found to be statistically significant in the bivariate model, with the criteria for inclusion being a p-value ≤ 0.050; [a] USD 1 = BDT 105; r = reference category; OR, odds ratio; CI, confidence interval.

The multivariable logistic regression model identified the significant independent predictors of TPT completion with the 3HP regimen. Female sex, higher schooling, higher income, older age, contacts with no comorbidities, and contacts who did not experience any adverse events while on a 3HP regimen were all found to be independent predictors of TPT completion with a 3HP regimen.

3.5. Intervention Approaches

We used multiple intervention approaches for contact investigation and TPT enrollment during treatment. They included phone calls only, phone calls plus counseling, and phone calls plus counseling plus home visits. Among those who attended the health facility (n = 2149), 88% (n = 1890) came based on the phone calls made to the index patients by the project staff; 9.1% (n = 196) came based on phone calls plus counseling; and the remaining 2.9% (n = 63) came as a result of the combined efforts of phone calls, counseling, and HH visits. Further, during the treatment, reminder phone calls to inform subjects about the next dose schedule, phone-based and/or face-to-face treatment counseling, and follow-up home visits by the project staff and NGO CHWs were all found to be associated with the completion of the 3HP regimen (Table 3).

4. Discussion

This is the first population-based study in Bangladesh that has assessed the implementation feasibility of TPT under routine programmatic settings with a 12-dose, weekly 3HP regimen among the HH contacts of DS-TB patients. The use of 3HP for the treatment of TBI was found to be feasible and well accepted. Consistent with the findings of other studies, we found that a weekly 3HP regimen has higher treatment completion rates (97.3%) compared with under-five children in the ongoing IPT program (74.6%) in Bangladesh, with fewer adverse events, and the results were similar across subgroups of people without HIV [19–21].

Several other studies that included shorter TPT regimens have shown a better completion rate compared with longer regimens [11,12,22]. The treatment completion rates in this study were also higher than in other large randomized controlled studies, phase 4 studies, and other cohort studies conducted among adults and children in developed and developing country settings [11,12,22–32]. A recent prospective cohort study conducted on children and adolescents in Pakistan using a 1HP regimen reported a 94% completion rate [33].

In Bangladesh, the national TB program provides IPT to children aged under five years who are contacts of B+ TB patients, and there is no provision of TPT for adult contacts. The majority (about 62%) of the HH contacts who were enrolled for the TPT in our study were adults, and treatment completion rates among the adults were also as high as children. Our study generated solid evidence that it is possible to implement TPT among adult populations through the existing routine TB program in Bangladesh. We observed that a higher percentage of our study population (56%) were female, and TPT completion was significantly higher among the female participants. This result will help in shaping the healthcare-seeking behavior of female HH contacts.

We noted a low frequency (5.3%) of adverse events with 3HP among the study participants, mostly of mild severity, and they were comparable with previous studies [22,24,34–36]. A recent systematic review including data from 23 randomized and 55 non-randomized studies also reported a similar low frequency of adverse events with 3HP compared with INH monotherapy [36]. The low adverse events observed in our study might also be attributed to the low drop-out and high treatment completion rates among the contacts who initiated the TPT with 3HP.

The project's field activities were carried out by its project field staff and NGO CHWs alongside their regular community health interventions. The data indicated that intervention approaches resulted in a high level of TPT enrollment, adherence to treatment, and TPT completion. The possible explanations for this high participation and completion rate may be related to the use of multiple approaches like counseling, phone calls only, phone calls plus counseling, and phone calls plus counseling plus home visits. During the treatment period, we also used reminder phone calls to inform subjects about the next dose schedule, phone-based and face-to-face treatment support and counseling, and follow-up home visits—all of these may have had cumulative effects on the outcomes and helped the participants to make informed decisions to adhere to and complete the TPT. Moreover,

the CHWs used in this study were involved in community mobilization, and they were well accepted and trusted by the community, which created an enabling environment for the target community [37]. The study demonstrated that it is feasible to implement a TPT intervention utilizing ongoing TB program infrastructure and the facilities of the government and NGOs in a resource-limited setting.

The prevention of active TB disease with TPT is a critical component of the WHO's End TB Strategy. This study proved that a convenient and easy-to-administer TPT regimen should be considered to achieve END TB and UNHLM targets. Considering the high completion rate of this TPT, the abundant care in managing HH contacts (evaluation and enrollment to TPT) and the interventions used to support the TPT can be adopted by the national program. However, the NTP should also consider critical issues with the programmatic scale-up of TPT, including policy considerations, ruling out active TB, diagnostic tests and evaluation, the time to start treatment, safety, uninterrupted drug supplies, treatment adherence monitoring, recording, reporting, etc., before adopting a countrywide TPT imitative. Utilizing CXR as an initial diagnostic tool is also critical given its heightened sensitivity, even though our study did not achieve complete coverage. This experience underscores the importance of advocating for CXR usage in early TB detection, particularly in identifying subclinical or asymptomatic patients.

One of the limitations of this study was that it only implemented TPT in the urban settings of Dhaka, and it is essential to recognize that the experience may differ in rural areas. This may not represent the entire country and limits the generalizability of our results. Specifically, healthcare infrastructure, community dynamics, and patient behaviors may vary in rural settings. However, considering that urban TB is the most challenging aspect of TB control efforts and the presence of extensive community programs (the Sasthya Sebika model) in the rural areas of Bangladesh [38], we believe this study will help in formulating appropriately targeted measures and future TPT programs in Bangladesh. Future research efforts should aim to assess the feasibility and implementation of TPT programs in rural areas considering the specific challenges and opportunities posed by these contexts. The study also did not have a true comparative group for the HH contacts for whom TPT was initiated using 3HP. Future research should aim to explore the effectiveness of the 3HP regimen across various demographic groups and settings. Additionally, comparative studies between the 3HP regimen and the standard 6-month IPT regimen would provide valuable insights into the relative benefits of these approaches. Furthermore, investigations into the long-term outcomes and cost-effectiveness of the 3HP regimen would be beneficial for informing policy decisions and optimizing TB prevention strategies. Further, the study did not use any test to confirm the presence of TBI. The Interferon-Gamma Release Assay is not used in this country, so the tuberculin skin test (TST) was the only test we could use. However, mass, population-wide TBI testing was not feasible considering the high TB burden setting, and the TST is inconclusive. The absence of TBI confirmation in our study could potentially result in some misclassification of TBI status, and this may impact the generalizability of our results to settings with routine TBI testing. In such settings, the decision to initiate TPT might be guided by a combination of clinical evaluation, TBI test results, and individual risk factors. Therefore, the applicability of our findings to areas with robust TBI testing should be made with an awareness of this limitation.

5. Conclusions

In this community-based implementation study, TPT using 3HP was found to have a high completion rate. The convenient weekly regimen of 3HP, the shorter treatment duration, and minimal adverse events resulted in higher treatment adherence among those who were enrolled in this study. The study findings exhibited a strong case for considering the integration of the 3HP regimen into the national TB control program in Bangladesh. The study demonstrated that the identification of potential HH contacts for TPT in urban areas and high treatment completion could be achieved through a well-designed, community-based program using the existing program structure and involving

appropriately trained CHWs. Targeted awareness creation, counseling, rigorous follow-up, and a self-administered TPT option also contributed to achieving higher TPT adherence.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and ethical approval was obtained from the Bangladesh Medical Research Council (Registration Number 127 14 06 2018).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: All data are fully available without restriction. However, data cannot be shared publicly because the detailed data were generated under programmatic conditions. The data are available from the National TB Control Program (directormbdc@gmail.com) for researchers who meet the criteria for access to confidential data.

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Conflicts of Interest: The authors declare that no competing interest exist.

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SHORT COMMUNICATION

Descriptors of multidrug-resistant TB deaths in Ethiopia

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Deaths related to multidrug-resistant TB among patients who had received a second-line anti-TB drugs in Ethiopia were analysed. Respectively 38/704 (5.4%) and 44/995 (4.4%) deaths were identified in two cohorts (2015 and 2022). In the 2015 cohort, severe malnutrition was less prevalent, previous treatment rates were three times higher, hypokalaemia was more frequent, and the use of the Xpert® MTB/RIF assay, respiratory failure and severe anaemia/pancytopenia were less common than in the 2022 cohort. We observed that there were variations in adverse events when different treatment regimens were used over different time periods. To ensure proper patient care, correct guidance must be consistently implemented.

Drug-resistant TB (DR-TB) remains a critical concern for public health. According to 2019 data from Ethiopia, an estimated 1.1% of the new TB cases and 7.5% of those who had previously undergone TB treatment among the reported TB cases were found to have rifampicin-resistant TB (RR-TB).[1,2] In 2020, Ethiopia was removed from the list of 30 countries with a high burden of rifampicin-resistant/multidrug-resistant TB (RR/MDR-TB).[2]

COVID-19 pandemic has reversed years of progress in providing essential TB services, including the reduced numbers of TB notifications, access to TB diagnostics tests, enrolment for effective treatments and provision of quality services.[1] The overall number of TB deaths have also increased due to reduced access to TB diagnosis and treatment because of the pandemic.[1] This may have also had adverse consequences for DR-TB mortality. Improving patient-centred care delivery to DR-TB patients by implementing regular clinical analysis of unfavourable outcomes, specifically, DR-TB-related deaths helps to identify common cause of deaths that could guide the development of targeted interventions and provide practical recommendations to healthcare workers (HCWs) in the field.

METHODS

Study area, period, population, and data collection procedure

A hospital-based review was conducted in selected high-load RR/MDR-TB treatment initiating centres (TICs). We analysed RR/MDR-TB patient charts and registers using structured checklists to describe the case fatality of RR/MDR-TB, the distribution and magnitude of clinical parameters related to RR/MDR-TB deaths. Data were collected from June 2012 to June 2015 (the 2015 cohort) from Amhara and Oromia Regions; and from July 2020 to June 2022 (the 2022 cohort) from the Oromia, Amhara, Addis Ababa, South Nation and Nationalities and Peoples (SNNP) Regions to compare relevant variables related to TB deaths. Sociodemographic variables (age, sex), HIV status, previous TB treatment and comorbid diseases were some of the variables included in the analysis. All deaths in selected treatment centres were line-listed and their charts were reviewed to get the necessary information.

We conducted descriptive statistical analyses. This review was carried out after obtaining approval for the extraction of the secondary data from the regional ethical clearance committee.

ASPECTS OF INTEREST

Sociodemographic and clinical characteristics

In the 2015 cohort of patients, a total of 38 MDR/RR-TB deaths out of a total of 704 RR/MDR-TB patients were documented in Oromia and Amhara Regions of the country. In the 2022 cohort of patients, a total of 44 MDR/RR-TB deaths out of a total of 995 RR/MDR-TB patients were registered and reviewed from Addis Ababa, SNNP, Oromia and Amhara. RR/MDR-TB-related death rates were 5.4% in the 2015 cohort and 4.4% in 2022 cohort. In the 2022 cohort, more than 93% of patients had severe form of disease at the time of diagnosis, which may have contributed to early death. Compared to the 2022 cohort, severe malnutrition was less prevalent (odds ratio [OR] 0.24, 95% confidence interval [CI] 0.93–0.63), history of previous treatment was three times higher (OR 2.77, 95% CI 1.05–7.24), electrolyte imbalance (hypokalaemia) was more frequent (28% vs. 3%, Fisher's Exact test,P = 0.001), and Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) testing (37% vs. 95%, $P < 0.001$), respiratory failure (3% vs. 29%, Fisher's Exact test, P = 0.013) and severe anaemia/pancytopenia were less common (3% vs. 35%, Fisher's Exact test, P = 0.003) in the 2015 cohort. Early death (within 2 months of treatment initiation) and other factors such as comorbidities (HIV and diabetes mellitus) in the two cohorts were similar (Table). In the 2022 cohort, 41/44 (93%) of patients who died had severe forms of TB (mainly disseminated TB, miliary TB and extensive bilateral lung disease) at the time of diagnosis (Figure).

In the 2015 cohort, the standard long treatment regimen that included injectables was the predominant treatment regimen, with over 95% of patients receiving it in all TICs across the country. In the 2022

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KEY WORDS
Ethiopia; drug-resistant TB deaths; rifampicin-resistant TB; RR/MDR-TB; TB-related mortality

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TABLE Sociodemographic and clinical data among RR/MDR-TB patients who died during the review period in 2015 and 2022

Variables	2015 (*n* = 38) *n* (%)	2022 (*n* = 44) *n* (%)	OR (95% CI)	*P* value
Male sex	16 (43)	25 (57)	0.58 (0.24–1.39)	0.224
Mean age, years	37.1	38.7		
Severe malnutrition	8 (39)	23 (51)	0.24 (0.93–0.63)	0.004*
Early death, less than 2 months	31 (80)	40 (93)	—	0.331
HIV-positive	10 (30.3)	12 (27.9)	0.98 (0.36–2.60)	0.980
DM	3 (14)	4 (15)	—	1.000
Confirmed using Xpert MTB/Rif	14 (37)	42 (95)	—	<0.001*
Confirmed using culture/LPA	21 (60)	2 (5)	—	—
Missed	3	0		
Previous treatment history	32 (84)	26 (61)	2.77 (1.05–7.24)	0.038*
Home death	23 (42.4)	20 (45.5)	1.84 (0.77–4.41)	0.173
Adverse events	30 (66)	31 (70.4)	1.57 (0.58–4.24)	0.379
Hypokalaemia	11 (28)	1 (3)	—	0.001*
Renal failure/ uraemia	4 (13)	2 (6)	—	0.424
Refractory vomiting/severe dyspepsia	5 (17)	2 (6)	—	0.255
Hepatitis	3 (10)	1 (3)	—	0.354
Severe anaemia/ pancytopenia	1 (3)	11 (35)	—	0.003*
Psychosis	2 (7)	4 (13)	—	0.671
Respiratory failure	1 (3)	9 (29)	—	0.013*
Congestive heart failure	1 (3)	1 (3)	—	1.000

*Statistically significant.
RR/MDR-TB = rifampicin-resistant/multidrug-resistant TB; OR = odds ratio; CI = confidence interval; DM = diabetes mellitus; LPA = line-probe assay.

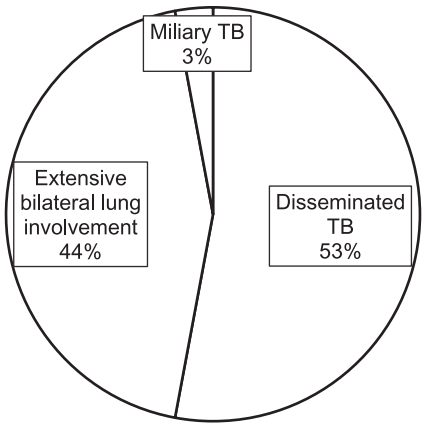

FIGURE RR/MDR-TB disease severity status in 2022 cohort (*n* = 44). RR/MDR-TB = rifampicin-resistant/multidrug-resistant TB.

cohort, the all-oral bedaquiline (BDQ) and linezolid (LZD) containing longer treatment regimens were administered to 57% of patients, followed by the short, all-oral, BDQ-containing regimen (23%). The remainder (16%) were on individualised regimens. Only 5% of patients were on injectable-containing treatment regimens. RR/MDR-TB patients were managed in line with Ethiopian national guideline recommendations for the management of RR/MDR-TB.[2]

DISCUSSION

Our review indicates that RR/MDR-TB-related mortality is more prevalent in patients with malnutrition, which has been worsening over time. Malnutrition was observed in individuals with severe disease and typically manifested within the initial months of presentation during the study periods. Almost all patients had severe forms of the disease at the time of diagnosis, which may have contributed to early death. Although the use of molecular diagnostic testing (GeneXpert) has increased, the rate of early deaths remained similar in the two cohorts. Risk factors such as previous treatment and comorbidities like malnutrition, diabetes mellitus and HIV/AIDS, were frequent in both cohorts, which is in concordance with other studies.[3–6] We identified variations in adverse events, including the shift from an injectable-based regimen with notable electrolyte imbalances in the 2015 cohort to an all-oral BDQ and LZD-based regimen with a significant occurrence of severe anaemia/pancytopenia in the more recent 2022 cohort. These variations in adverse events are consistent with reports from other countries.[7,8]

CONCLUSION

This hospital-based TB mortality review showed severe malnutrition was more prevalent among patients who died of RR/MDR-TB. The persistence of early deaths underscores the need for additional prospective studies to gain a clearer understanding of the underlying causes of these fatalities. Patients experienced adverse events while on treatment, and these varied according to regimen type and the presence of risk factors like severe malnutrition and a history of previous treatment. We strongly recommend adjunctive nutritional care, including therapeutic feeding, for all DR-TB patients as standard of care. We also recommend the use of emergency care management services for RR/MDR-TB patients to prevent early death. Similarly, patients experiencing adverse events including drug toxicities, those with comorbid conditions and risk factors should be managed in consultation with senior experts based on guidelines and global recommendations. We also recommend implementing community awareness programmes that promote psychosocial support and encourage early healthcare-seeking behaviour.

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Les décès liés à la TB multirésistante chez les patients ayant reçu des médicaments antituberculeux de seconde ligne en Éthiopie ont été analysés. Respectivement 38/704 (5,4%) et 44/995 (4,4%) décès ont été identifiés dans deux cohortes (2015 et 2022). Dans la cohorte 2015, la malnutrition sévère était moins fréquente, les taux de traitement antérieur étaient trois fois plus élevés, l'hypokaliémie était plus fréquente, et l'utilisation du test Xpert® MTB/RIF, l'insuffisance respiratoire et l'anémie/pancytopénie sévère étaient moins fréquentes que dans la cohorte 2022. Nous avons observé des variations dans les effets indésirables lorsque différents schémas thérapeutiques étaient utilisés sur différentes périodes. Pour garantir des soins adéquats aux patients, des consignes appropriées doivent être appliquées de manière régulière.

Public Health Action (PHA) welcomes the submission of articles on all aspects of operational research, including quality improvements, cost-benefit analysis, ethics, equity, access to services and capacity building, with a focus on relevant areas of public health (e.g. infection control, nutrition, TB, HIV, vaccines, smoking, COVID-19, microbial resistance, outbreaks etc).

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LETTER

TB-related catastrophic costs and associated factors for patients in Ethiopia

Dear Editor,

TB predominately affects the disadvantaged and the most vulnerable communities in precarious socio-economic situations, with vicious cycles of poverty and disease.[1] Despite the widespread adoption of 'free TB care' policies, TB-affected households still face prohibitive direct medical costs.[2] TB illness is often compounded by high out-of-pocket (OOP) spending for direct costs (i.e., costs for diagnosis, treatment, transportation, and temporary accommodations when visiting health facilities) and indirect costs incurred due to the income foregone when looking for and receiving treatment or lost employment due to disability, stigma or discrimination.[1] Catastrophic cost, defined as an OOP spending of more than 20% of a household's annual income, forces many patients and their families to cut down on their daily necessities.[1,3,4] TB services are exempted in Ethiopia, and yet the proportion of TB patients facing TB-related catastrophic costs has been estimated at 40%.[5] The COVID-19 pandemic and associated economic crisis (alongside the ongoing conflict), could have further exacerbated the TB catastrophic cost. Nevertheless, nationally representative TB patient cost surveys have not been conducted. This study aimed thus to determine the magnitude and main drivers of costs incurred by TB patients and their households.

We conducted a health facility-based cross-sectional survey from November 2020 to February 2021 in 19 study zones in four regions in Ethiopia: Oromia, Amhara, Sidama, and Southern Nations, Nationalities and Peoples (SNNP). An estimated 80,481,771 people reside in these regions, representing 80% of the national population in 2020[6] and contributing to 54% of the national TB burden.[7] One-third of the public health facilities that provide TB treatment were randomly selected from all the districts within the study zones. The participants were selected randomly among patients receiving treatment during the study period, one from low TB load health facilities (<100 TB patients per year) and two from high TB load health facilities (<100 TB patients per year). TB patients who were receiving TB treatment in the sampled health facilities for at least 14 days, regardless of age and type of TB, were considered for inclusion in the study. The WHO generic TB cost survey questionnaire[8] was customized to the local context and translated into three local languages (Amharic, Oromiffa and Sidama). Data were collected from patients or their parents/guardians while attending their TB treatment follow-up visits. The analysis included basic descriptive statistics to present sociodemographic factors and the extent of catastrophic costs. The average spending during the continuation phase was used to estimate the cost for the whole TB treatment period and of patients in the initiation phase. Catastrophic costs were determined by giving a binary value for whether patients incurred catastrophic costs or not. Bivariate and multivariate analyses were applied to assess the factors associated with TB patients' catastrophic costs. All variables with a *P*-value of less than 0.05 in the bivariate analysis were entered into the multivariable regression. We obtained support letters and permission from each study region's ethical review committee. Oral consent was obtained prior to the interview of TB patients. Assent was obtained from the parent or guardian for children under 14 years of age.

A total of 433 TB patients participated: 56% were male, the mean age was 33.6 (male: 35.8 and female: 30.8), the median age was 30 (male 33 and female 28), 59.4% had attended school grades 1–12, and 39.3% were farmers. One average, a TB patient incurred a total of USD715.5 for TB-related costs: with 87.8% and 12.2% direct and indirect costs (income lost related to time lost), respectively. Direct costs attributed to non-medical (food, drink, and accommodations) (55.5%), transport (20.7%) and medical cost for TB treatment (11.6%). Of the 433 study participants, 66.1% experienced catastrophic costs related to TB diagnosis and treatment when using a threshold of more than 20% of their annual income. Additionally, 39% faced catastrophic costs at a higher threshold of more than 30% of their annual income. Compared with TB patients from Amhara, Sidama TB patients were 71% less likely to face TB-related catastrophic costs (adjusted odds ratio [aOR] 0.29, 95% confidence interval [CI] 0.11–0.76). Farmers were 74% (aOR 0.26, 95% CI 0.11–0.62) more likely than government employees and 66% (aOR 0.34, 95% CI 0.18–0.61) more likely than the self-employed to experience catastrophic costs. TB patients with directly observed treatment (DOT) at home were 61% less likely to experience catastrophic costs than those who attended DOT at a health facility (aOR 0.39, 95% CI 0.24–0.65). TB patients with at least one family member on TB treatment were 93% more likely to experience catastrophic costs than those with no family member on TB treatment (aOR 1.93, 95% CI 1.10–3.42; Table).

Our findings indicated approximately two-thirds of TB patients and their families experienced TB-related

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Table. TB-related costs, catastrophic costs (>20% of household annual income), and bivariate and multivariable analysis based on the sociodemographic characteristics of TB patients ($n = 433$).

A) Sociodemographic characteristics of TB patients

Variables	Not catastrophic *n* (%)	Catastrophic *n* (%)	Bivariate analysis cOR (95% CI)	Multivariable analysis aOR (95% CI)
Region				
Amhara	43 (40)	64 (60)	1	
Oromia	76 (47.8)	83 (52.2)	0.73 (0.45–1.21)	0.65 (0.39–1.09)
Sidama	15 (65.2)	9 (34.8)	0.36 (0.14–0.92)	0.29 (0.11–0.76*)
SNNP	79 (55.2)	64 (44.8)	0.54 (0.33–0.90)	0.61 (0.36–1.04)
Sex				
Female	66 (34.4)	126 (65.6)	1	
Male	81 (33.6)	160 (66.4)	1.03 (0.70–1.54)	
Age, years				
<15	6 (40)	9 (60)	1	
15–24	35 (23.5)	76 (68.5)	1.45 (0.48–4.38)	
25–49	78 (32.6)	161 (67.4)	1.38 (0.47–4.00)	
>49	28 (41.2)	40 (58.8)	0.95 (0.30–2.98)	
Education				
Illiterate	49 (35.5)	89 (64.5)	0.86 (0.57–1.35)	
≤Grade 12	84 (32.6)	174 (67.4)	1	
>Grade 12	14 (37.8)	23 (62.2)	0.77 (0.38–1.61)	
Occupation				
Farmer	48 (28.6)	122 (71.8)	1	
Government employment	20 (45.5)	24 (54.6)	0.47 (0.24–0.93)	0.29 (0.1–0.66*)
Self-employed	50 (44.3)	63 (55.8)	0.5 (0.30–0.82)	0.44 (0.20–0.68*)
Unemployed	29 (27.4)	77 (72.6)	1.04 (0.61–1.80)	0.73 (0.39–1.40)
Treating health facility				
Private facility	53 (47.3)	59 (52.7)	1	
Public health center	31 (52.5)	28 (47.5)	0.52 (0.14–1.92)	
DOT support provider				
Health facility	77 (30)	170 (70)	1	
Self or home-based	70 (39.6)	107 (60.4)	0.44 (0.28–0.69)	0.39 (0.24–065*)

B) TB-related direct and indirect costs

	Direct costs (USD)			Indirect costs (USD)	
	Transport costs	Drink, food and accommodation	Medical cost of TB treatment	Income lost related to time lost	Total costs (USD)
Cost in number	148.1	397.1	83.0	87.3	715.5
Proportion of total cost, %	20.7	55.5	11.6	12.2	100

* Statistically significant.
cOR = crude odds ratio; CI = confidence interval; aOR = adjusted OR; SNNP = Southern Nations, Nationalities and Peoples; DOT = directly observed therapy; USD = US dollar.

catastrophic costs. This is higher than the 2014 estimate of 58% across all low- and middle-income countries,[9] 43% of global estimates,[10] and 40% from Ethiopia[5] and other African[9] and Asian countries.[3] This is despite the exempted cost of TB services in Ethiopia, with direct costs contributing the highest share. The prohibitively high direct non-medical costs, and medical costs representing less than 20%, have been reported by many studies conducted in Ethiopia[11] and other African countries[12] and systematic reviews.[9] Therefore, the policy in Ethiopia may consider implementing a 'TB patients' exemption' rather than a 'TB service exemption'. Receiving TB DOT at home is associated with a lower likelihood of experiencing catastrophic costs, which may be due to the reduced costs for transportation, food and accommodation associated with at-home treatment with fewer visits to health facilities.[13] Further decentralization of DOT services near the patient, through self or home-based DOT, may reduce catastrophic costs. The higher financial impact of TB on farmers has repercussions often extending beyond the patient to the family and caregivers. Farmers often reside in rural areas, requiring them to overcome many barriers to adhere to DOT, such as travelling long distances to facilities.[2] The regional differences in catastrophic costs are mainly due to differences in the type of TB: the Sidama region has a higher number of bacteriologically confirmed TB cases, whereas Ahmara has higher extrapulmonary TB.[14] The diagnostic and treatment service for extrapulmonary TB is usually delayed, expensive and requires a longer period of treatment.[15]

In conclusion, the high burden of catastrophic costs necessitates a decentralization of TB diagnosis and treatment services, the scaling up of community and home-based DOT, and the need to establish a community support system to help with nutrition and transportation costs.

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KEY WORDS: tuberculosis; decentralized healthcare; DOT; directly observed treatment; out-of-pocket expenses

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TB-related catastrophic costs in Ethiopia

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OBJECTIVES: To measure the progress towards reducing TB-related catastrophic costs in 19 zones of Amhara, Oromia, SNNP (Southern Nations and Nationalities, and Peoples) and Sidama Regions of Ethiopia.

METHODS: A baseline survey was conducted in randomly selected health facilities from all districts within the 19 zones from November 2020 to February 2021. Interventions targeting the major drivers of catastrophic costs identified in the baseline survey, such as installation of 126 GeneXpert and 13 Truenat machines, securing connectivity of 372 GeneXpert, establishing alternative specimen referral systems, and capacity-building of health workers, were implemented. A follow-up survey was conducted from October to December 2022. The WHO generic tool was used to collect data based on probability proportional to size. Data were entered into STATA software, and the proportion of catastrophic costs was calculated and compared between the two surveys.

RESULTS: A total of 433 and 397 patients participated in the baseline and follow-up surveys, respectively. The proportion of catastrophic costs reduced from 64.7% to 43.8% ($P < 0.0001$). The share of direct non-medical costs decreased from 76.2% to 19.2%, while medical and indirect costs increased from 11.6% and 12.3% to 30.4% and 52.4 %.

CONCLUSION: The proportion of households facing TB-related catastrophic costs has significantly reduced over the 2-year period. However, it remains unacceptably high and varies among regions. Further reducing the catastrophic costs requires multisectoral response, reviewing the TB service exemption policy, further decentralisation and improving the quality of TB services.

TB is one of the top infectious disease killers worldwide, and the emergence of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) poses a significant challenge to global health. TB causes significant productivity losses due to illness, disability, and premature death, leading to economic hardship for patients and their families.[1]

Particularly in low-income settings where access to affordable healthcare is limited, the costs associated with diagnosis and treatment of TB force many households to cut down on necessities such as food, clothing, and children's education or they decide not to use services simply because they cannot afford them, which in turn contribute to poor health outcomes and increase the risk of disease transmission.[2,3] Particularly, the poor and vulnerable segments of society are pushed into a vicious cycle of ill health and poverty.[4]

The WHO report indicates that, globally, approximately 50% of TB patients and their families faced catastrophic costs in 2022, defined as direct medical expenditures, direct non-medical expenditures, and indirect costs (e.g., income losses) that total more than 20% of household income.[5] The average income loss due to TB illness can be equivalent to more than one year's income,[6] and even more among MDR-TB patients and their households.[7]

Ethiopia has made significant progress in extending healthcare services to rural and disadvantaged urban areas, with over 94% of the population now having access to primary healthcare.[8] TB diagnosis and treatment has been integrated within the primary healthcare settings to enable early detection and prompt initiation of treatment and is offered free of charge at all public health facilities.[9] TB confirmatory diagnosis services such as Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) and X-rays for clinical diagnosis have been expanded to diagnostics in more than 350 hospitals and high TB burden health centres, while advanced diagnosis such as liquid and solid culture and whole genome sequencing are also available at regional and zonal levels. Community-based TB care, engaging community health workers and volunteers, has also been initiated to enhance TB case identification, treatment adherence, and monitoring, especially in remote and underserved areas.

Consequently, the incidence of TB has decreased from 421/100,000 people in 2000 to 119/100,000 people in 2022. Despite this significant decline, Ethiopia remains among the 30 countries with a high burden of TB, with over 145,000 people contracting the disease and more than 19,000 deaths attributed to TB. Additionally, the WHO estimates that approximately 30% of TB cases go undetected by the healthcare system.[10] While a national study on the TB catastrophic cost survey has not been conducted, a smaller-scale study focusing solely on direct costs and another meta-analysis study suggested that 40% and 51% of TB patients face catastrophic costs.[11,12] These studies also showed that private facility diagnosis, drug-resistant TB, TB-HIV co-infection, hospitalisation, household income, and diagnosis delays were the major factors associated with catastrophic costs.[11–13]

Ethiopia has adopted the WHO End TB strategy,[14] which achieves 'Zero TB-related catastrophic costs' by 2025.[15] The Management Sciences for Health, through the USAID Eliminate TB Project, provides support for national TB control efforts in Amhara, Oromia, Southern Nations, Nationalities, and Peoples (SNNP), and Sidama Regions. Therefore, this study seeks to

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assess the advancement in reducing catastrophic costs within the framework of the project, serving as valuable information for policymakers at all levels to make evidence-based decisions.

METHODS

Study setting and design

We conducted health facility-based cross-sectional TB cost surveys at two different points in 19 zones of Amhara, Oromia, SNNP, and Sidama Regions of Ethiopia, where the project is functioning. Based on projections from the 2007 Census, these zones constitute an estimated 42,806,707 people in 2022,[16] and more than 1,050 public health centres, 58 hospitals, and 26 private health facilities provide TB diagnosis and treatment services. The is health centres serve as the first point of contact for TB diagnosis and treatment, where they collect samples from presumptive cases, transport them to the nearest diagnostic sites, or refer patients for clinical diagnosis. They also initiate DOTS for confirmed TB cases, provide adherence support, and monitor treatment outcomes using sputum smear microscopy. Assuming a TB incidence rate of 132 cases per 100,000 population and a case detection rate of 70%, during the baseline survey, we anticipate approximately 19,638 TB patients per 6 months. distributed among the health facilities, and 2–4 patients visit the health facility for follow-up or medication collection each month.

As part of the project, we conducted a baseline survey from November 2020 to February 2021 to understand the extent and factors associated with TB-related catastrophic costs. After implementing various interventions, a follow-up survey was conducted from October to December 2022.

Intervention

Various interventions targeting the major drivers of catastrophic cost and improving access to diagnostic and treatment services have been implemented. This included installing an additional 126 GeneXpert machines and 13 Truenat (Molbio Diagnostics, Verna, India) machines and ensuring the connectivity of 372 GeneXpert machines. In addition, an alternative specimen referral system was established that enabled remote health facilities to transport TB specimens to diagnostic centres using non-healthcare workers, thereby ensuring continuous service while healthcare workers focus on their duties. In addition, enhanced support was provided to further decentralise TB DOTS services to health posts and the community level, particularly for those in remote areas. This was crucial for reducing the time and financial costs of long-distance travel and improving treatment outcomes.

Furthermore, several capacity-building training sessions and supportive supervision programmes were conducted to improve the quality of TB diagnosis and treatment and ensure a consistent supply of drugs and supplies. Overall, these interventions not only enhance access to and quality of TB diagnosis and treatment services but also reduce the need for long-distance travel and multiple healthcare visits before diagnosis. They also reduce the time and expenses associated with patient referrals for diagnosis and travel to health centres for DOT services.

Sampling method

The sample size was determined using the single point calculation formula, 41% catastrophic costs,[2] and an absolute precision of 4%. This yielded, with an additional 10 % contingency, a sample of 460 patients and 424 patients in the baseline and follow-up surveys, respectively. Consequently, one-third of the health facilities providing DOTs were selected from each district using the rule of thumb, and the estimated sample size was distributed proportionally across all health facilities.

The data collection involved customising the WHO generic TB cost survey,[1] which was previously used in Vietnam[17] and China,[18] adopted to local language and context. The project staff, who were also trained on the questionnaire, data collection approach, and ethical considerations, collected the data via a paper-based questionnaire while patients visited the health facility for follow-up or to collect their drugs. The average household annual income and direct and indirect costs incurred (operational definition in Table 1) in the intensive and continuous phases of treatment were collected on the basis of patient response.

Data management, validation, and analysis

The data were entered into STATA software (Stata, College Station, TX, USA) by clerks who received a 1-day orientation, and double entry was performed for every twentieth questionnaire to ensure data quality. Based on the WHO protocol,[19] we calculated the total medical costs, total travel costs, total food costs, total accommodation costs, and total income lost for the particular episode phase the patient is in, and the cost for other phases was estimated from similar patients (matched by type of TB and facility) interviewed in the other phases of illness. Then, we calculated the total cost of each patient during the DOTS period, and if the total costs, net of transfers and reimbursements, exceeded 20% of the total annual household's pre-TB income, they were considered catastrophic. We used a binary response model to identify the factors most significantly associated with catastrophic costs, using a χ^2 test with two-tailed $P < 0.05$ considered to be the threshold for statistical significance. In addition, the proportion and mean difference of the direct and indirect costs in the two surveys were compared, and $P < 0.05$ were used to determine the level of significance difference.

Ethical considerations

We obtained support letters and permission from each study region's ethical review committee. Oral consent was obtained before the interview of patients with TB. Consent was obtained from the parent or guardian of children under 14 years of age.

RESULTS

Data were collected from 433 (94.1%) TB patients from 342 health facilities in the baseline survey and from 397 (90.2%) TB patients in 300 health facilities in the follow-up survey. Despite the slight difference in the number of patients with TB between the two surveys, the demographic and socioeconomic characteristics of the study participants were similar (Table 2). The average annual income of patients with TB in the baseline and follow-up surveys was US$715.50 and US$690.10, respectively. The number of patients enrolled from public hospitals was 74 (16.8%) during the baseline survey and 93 (23.4%) in the follow-up survey (Z-score 2.4, $P = 0.02$; Table 2).

Costs faced by patients with TB during baseline and follow-up surveys

The mean medical and non-medical costs were US$117.90 and US$213.00 at baseline and declined to US$41.80 and US$50.40 at follow-up ($P < 0.0001$). The mean indirect cost slightly increased from US$41.20 at baseline to US$45.70 at follow-up; however, this increase was not statistically significant (Table 3).

Proportion of the catastrophic cost

In the baseline survey, 64.7% of TB patients faced catastrophic costs, which decreased to 43.8% in the follow-up surveys ($P <$

TABLE 1. Definitions of indirect, direct, and catastrophic costs.

Type of cost	Elements included in cost type	Methods used to calculate costs
Direct medical costs	Cost of consultations, laboratory tests, and other medical procedures	Sum of all medical costs net of any reimbursements
Direct non-medical costs	• Transportation costs • Cost of accommodations, food, nutritional supplements • Hourly wage lost due to time loss, visiting health facilities for diagnosis and DOT, or a visit to pick up TB drugs	Sum of direct non-medical and direct medical costs net of any reimbursements
Indirect costs	• Lost productivity or wage due to illness	Sum of the reported product or wages during the TB episode, as reported by an individual

DOT = directly observed therapy.

TABLE 2. Summary of demographic and socioeconomic characteristics of TB patients at baseline and follow-up surveys.

		TB cost survey		
Variables		Baseline survey (n = 433) n (%)	Follow-up survey (n = 397) n (%)	P-value
Regions	Oromia	159 (36.8)	161 (40.6)	0.52
	Amhara	107 (24.8)	87 (21.9)	
	Sidama	24 (5.3)	40 (10.1)	
	SNNP	143 (33.1)	109 (27.5)	
Sex	Female	192 (44.3)	171 (43.0)	0.43
	Male	241 (55.7)	226 (57.0)	
Age, years	<15	15 (3.5)	16 (4.1)	0.73
	15–24	111 (25.6)	101 (25.5)	
	25–49	239 (55.2)	225 (56.7)	
	>49	68 (15.7)	54 (13.7)	
Educational status	Illiterate	138 (31.9)	130 (32.8)	0.62
	Grade 1–12	257 (59.4)	231 (58.3)	
	College/university	38 (8.8)	36 (9.0)	
Treating health facilities	Private facility	14 (3.2)	6 (1.5)	0.08
	Public health centre	345 (80.0)	298 (75.1)	0.08
	Public hospital	74 (16.8)	93 (23.4)	0.02
Treatment phase	Intensive	121 (30.0)	134 (33.8)	0.72
	Continuation	312 (70.0)	263 (66.2)	

SNNP = Southern Nations, Nationalities, and Peoples.

TABLE 3. Mean medical, non-medical, and indirect costs of the two surveys (US$).

Type of cost	Baseline	Follow-up	Z-score	P-value
Average annual household income	715.5	690.1	4.63	0.732
Mean medical cost	117.9	41.8	4.86	< 0.0001
Mean non-medical cost	213.0	50.4	8.38	< 0.0001
Mean indirect cost	41.2	45.7	1.83	0.76
Mean total cost	372.1	137.8	7.10	<0.001

*Exchange rate of US$1 = ETB44.3 for the baseline and US$1 = ETB52.8 for the follow-up survey. ETB = Ethiopian birr.

0.001). Significant reduction in the proportion of households experiencing TB-related catastrophic costs was observed in the Amhara, Oromia, and SNNP Regions ($P < 0.05$), but no change was observed in Sidama Region (Table 4). The share of direct non-medical cost reduced by 57.6 percentage points (from 76.2% to 18.6%) between the two surveys, while the share of direct medical cost and indirect costs increased by 18.4 and 39.2 percentage points (Table 5).

DISCUSSION

The proportion of households experiencing TB-related catastrophic costs showed a 21.0 % point reduction in the follow-up surveys conducted after 2 years of implementing the interventions. This is expected given the wide range of interventions implemented following the baseline survey in the regions. Despite this encouraging achievement, the current proportion of catastrophic costs (44%) in

TABLE 4. Proportion of patients who incurred TB-related catastrophic costs in the baseline survey and the follow-up survey, by region.

	Participants		Catastrophic cost		Difference, %	
Region	Baseline *n*	Follow-up *n*	Baseline *n* (%)	Follow-up *n* (%)	*Z*-score	*P*-value
Amhara	107	87	89 (83.2)	51 (58.6)	3.8	<0.0001
Oromia	159	161	108 (67.9)	65 (40.4)	4.9	<0.0001
Sidama	24	40	14 (58.3)	20 (50.0)	1.2	0.26
SNNP	143	109	69 (48.3)	38 (34.8)	1.3	0.02
Total	433	397	280 (64.7)	174 (43.8)	6.2	<0.000 1

SNNP = Southern Nations, Nationalities, and Peoples.

TABLE 5. Proportion of the different costs categories in the two TB cost surveys.

Type of cost	Baseline %	Follow-up %	*Z*-score	*P*-value
Direct medical cost	11.6	30.0	8.6	<0.0001
Direct non-medical cost	76.2	18.6	21.8	<0.0001
Indirect cost	12.2	51.4	16.0	<0.0001

the four regions is unacceptably high. This implies addressing the determinants of catastrophic cost; therefore, achieving the national target 'zero catastrophic cost by 2025' might require a commitment of high-level leadership and coordinated multisectoral actions.

The major reduction was related to direct non-medical costs, including transport and food and drink costs. This could be mainly associated with the additional TB diagnostic equipment allocated in health facilities nearest to the community, improvement of the sample transportation system by non-health workers, rather than patient referral for diagnosis, as well as decentralisation of TB treatment follow-up to health posts—all of which reduce the frequency and distance to visit health facilities.

In contrast, while the mean cost shows a slight reduction, the share of medical and indirect costs, out of the total cost, shows an increase in the follow-up survey. This could be due to the significant reduction in direct non-medical costs. However, inflation in the costs of transport, accommodation, and food items, which we did not consider in the calculation, could also contribute to the difference. It also indicates that patients are still visiting many health facilities before diagnosis and continue to experience delays, implying the need to improve the quality of TB diagnosis and treatment.

However, given the interventions implemented, continuing high out-of-pocket (OOP) spending to receive medical care is concerning. This is mainly because of the policy that exempts 'TB diagnosis and treatment' only, but the costs incurred before diagnosis, when patients must visit different health institutes before TB disease confirmation,[20] diagnosis of extrapulmonary TB, and diagnosis and treatment for illness other than TB, developed due to TB disease or side effects of TB drugs, are not covered by the exemption policy.[21]

The proportion of catastrophic events has shown a significant reduction in all regions, except in Sidama Region. However, there remains a wide difference among regions, despite the same health system and policy. The Amhara Region has higher TB-related catastrophic costs. This could be due to the higher proportion of extrapulmonary TB (EPTB) cases in the region.[3] EPTB is known to have a delay in diagnosis[4] and is not exempted in Ethiopia,[21] which contributes to higher OOPs.

Limitations

The two TB catastrophic surveys in Ethiopia were undertaken when the country was in two different contexts, and factors such as the COVID-19 epidemic and the conflict in northern Ethiopia and the Oromia Region could affect the estimation of catastrophic cost. In addition, the surveys were conducted mainly in rural agrarian regions, excluding cities and pastoral regions, indicating caution for generalizability. The effect of inflation rate, which is not considered in the calculations, is another limitation that could affect the estimation.

CONCLUSIONS

Although there was a 21% reduction between the two surveys over the 2 years, the proportion of households experiencing TB and TB-related catastrophic costs remains unacceptably high. The health sector should consider revising the policy 'TB services exemption', to 'TB patient exemption', to cover the costs of diagnosis and treatment for illnesses other than TB, including pre-diagnosis costs and diagnosis of EPTB, as well as further decentralisation of improving access to and quality of TB diagnosis and treatment services. Undertaking future studies in Ethiopia, including a national TB cost survey, by applying a stronger prospective cohort study design with all relevant determinants is essential to understand the detailed factors associated with catastrophic cost in the country.

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OBJECTIFS : Mesurer les progrès accomplis dans la réduction des coûts catastrophiques liés à la TB dans 19 zones des régions d'Amhara, d'Oromia, de SNNP (Région des nations, nationalités et peuples du Sud) et de Sidama en Éthiopie.

MÉTHODES : Une enquête de base a été menée dans des établissements de santé sélectionnés au hasard dans tous les districts des 19 zones de novembre 2020 à février 2021. Des interventions ciblant les principaux facteurs de coûts catastrophiques identifiés dans l'enquête de référence, telles que l'installation de 126 machines GeneXpert et 13 Truenat, la sécurisation de la connectivité de 372 GeneXpert, la mise en place de systèmes alternatifs d'orientation des échantillons et le renforcement des capacités des agents de santé, ont été mises en œuvre. Une enquête de suivi a été menée d'octobre à décembre 2022. L'outil générique de l'OMS a été utilisé pour recueillir des données fondées sur une probabilité proportionnelle à la taille. Les données ont été saisies dans le logiciel STATA, et la proportion des coûts catastrophiques a été calculée et comparée entre les deux enquêtes.

RÉSULTATS : Au total, 433 et 397 patients ont participé respectivement à l'enquête de base et à l'enquête de suivi. La proportion des coûts catastrophiques est passée de 64,7% à 43,8% ($P < 0,0001$). La part des coûts non médicaux directs a diminué, passant de 76,2% à 19,2%, tandis que les coûts médicaux et indirects sont passés de 11,6% et 12,3% à 30,4% et 52,4%.

CONCLUSION : La proportion de ménages confrontés à des coûts catastrophiques liés à la tuberculose a considérablement diminué au cours de la période de 2 ans. Cependant, il reste inacceptable et varie selon les régions. Pour réduire davantage les coûts catastrophiques, il faut une réponse multisectorielle, une révision de la politique d'exemption des services de lutte contre la TB, une décentralisation plus poussée et une amélioration de la qualité des services de lutte contre la TB.

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ORIGINAL RESEARCH

Survival Rate and Predictors of Mortality Among TB-HIV Co-Infected Patients During Tuberculosis Treatment at Public Health Facilities in Bahir Dar City, Northwest Ethiopia

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Background: Tuberculosis and human immunodeficiency virus co-infection pose a major public health concern, particularly in developing countries. The survival and predictors of mortality were not sufficiently studied among TB-HIV co-infected patients in Ethiopia.

Objective: This study aimed to investigate the survival rate and predictors of mortality among TB-HIV co-infected patients during TB treatment at public health facilities in Bahir Dar, Northwest Ethiopia.

Methods: A retrospective follow-up study was conducted among 401 TB-HIV co-infected patients who were treated for tuberculosis between July 2018 and June 2022 at public health facilities in Bahir Dar city, Ethiopia. Data were collected using a structured checklist from patient charts. Data entry and analysis were done using EpiData 3.1 and Stata version 15, respectively. A Cox proportional Hazard regression model was used to identify predictors of mortality. Predictors with $P < 0.05$ in the multivariable regression were considered statistically significant.

Results: Among the 401 TB-HIV co-infected patients, 59 (14.7%) died during the follow-up period. Predictors like lower BMI (AHR = 3.00, 95% CI = 1.44, 6.28), extrapulmonary TB infection (AHR = 3.30, 95% CI = 1.50, 7.29), presence of opportunistic infection (AHR = 5.07, 95% CI = 2.55, 10.08), functional status (bedridden: AHR = 4.49, 95% CI = 1.63, 12.33), and adherence to TB treatment (fair = AHR = 2.74, 95% CI = 1.41, 7.20, and poor = AHR = 3.75, 95% CI = 1.52, 9.23) were associated with mortality.

Conclusion: Mortality among TB and HIV coinfected people was high at public health facilities in Bahir Dar city. This result suggested that in order to increase patient survival, it would be necessary to enhance nutritional status, increase adherence to TB treatment, and prevent opportunistic infections.

Keywords: TB, HIV, mortality, predictors, retrospective, survival, Ethiopia

Introduction

Tuberculosis (TB) and the Human Immunodeficiency Virus (HIV) are among the leading public health problems globally. Tuberculosis is one of the most common illnesses and causes of death among people living with HIV (PLWHIV). HIV positive individuals have a 20–30 times greater risk of contracting TB than HIV negative individuals due to lowered immunity. Reports also indicated that PLWHIV are more likely to develop active TB than HIV negative.[1,2] The global TB report 2021 stated that out of ten million people infected with TB, 8% were PLHIV. The proportion of TB episodes coinfected with HIV was highest in the African region, exceeding 50% in parts of Southern Africa.[2]

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TB and HIV form a lethal combination, each speeding the other's progress. As a result, individuals with co-infections of TB and HIV have a significant risk of increased mortality. Without proper treatment, 60% of HIV-negative people with TB on average and nearly all HIV-positive people with TB will die.[3] Globally, 1.6 million people died from TB and 1 million from HIV in 2017 and accounting for one in every 300,000 deaths from both diseases.[1] Most recently, about one-third of all AIDS-related deaths worldwide are caused by TB, which is the leading cause of death among HIV-positive individuals. An estimated 167,000 people died from TB-HIV coinfection in 2022.[3] The syndromic interaction between TB and HIV has played a ruinous role, with Africans bearing a disproportionate share of the burden. In 2019, people in Africa accounted for 73% of TB-HIV co-infection cases and 81% of all TB-HIV deaths. At the country level, South Africa and Nigeria rank among the worst affected in sub-Saharan Africa and globally for both diseases.[4,5] In addition to TB disease, PLHIV bears a high burden of drug-resistant TB strains; thus, if diagnosis is delayed, there is an increased risk of mortality from multidrug-resistant and extensively drug-resistant TB in this population.[6]

With an estimated TB incidence rate of 164 per 100,000 people and 112 cases per 100,000 TB cases among PLWHIV, Ethiopia is one of the twenty nations in the world with the highest burdens of TB and TB-HIV.[7,8] According to a nationwide retrospective cohort study, 9% of HIV patients receiving treatment also had TB.[9] About 13% of all new TB cases are also HIV coinfected. Moreover, Ethiopia is one of the high TB-HIV and multidrug resistant TB (MDR TB) burden countries. Among TB patients with known HIV status, about 11% were HIV co-infected.[10] According to the global report, 3600 people in Ethiopia who had TB and HIV co-infections died while receiving TB treatment in 2017 alone.[11] Despite the availability of free ART and anti-TB medications in the country, the survival rate for those with TB and HIV co-infection has not increased.[12,13]

Studies conducted worldwide indicated that the survival of TB-HIV infected patients was determined by different predictors. Socio-demographic and personal factors like age, sex, residency, education, occupation and body mass index play a key role in predicting the mortality of people co-infected with HIV and TB in countries around the world.[14–18] Studies showed that patients with TB-HIV without ART tend to have poorer TB outcomes compared to those who are on ART, and TB infection with late presentation and HIV diagnosis are further risk factors for unsuccessful TB treatment outcomes among patients with TB-HIV.[19,20] Previous research has also shown a significant correlation between TB-HIV-related mortalities and baseline CD4 cell count, WHO clinical stage, use of co-trimoxazole preventive therapy, the presence of opportunistic infections and baseline functional level.[9,21,22] Although, co-infection with TB and HIV is bidirectional and a dual public health burden worldwide, TB-HIV co-infected patients have not received enough attention.[23,24]

A few studies conducted in Ethiopia found that factors such as ART status, baseline CD4 cell count, baseline functional level, WHO clinical stage, cotrimoxazole preventive therapy, type of TB diagnosis, and coexistence of other opportunistic infections (OIs) were predictive of survival among TB-HIV co-infected patients.[21,25] However, previous studies are not sufficient to estimate the survival status of the patients. In addition, the results of earlier studies may no longer be applicable to use as an intervention tool to improve patient survival because there are recurring or ongoing changes in the characteristics of the diseases, in the ART and TB treatment regimens, in population migration, and in the drug resistance of the disease. As a result, up-to-date studies are required that take all these changes into consideration. Therefore, this study was conducted to identify the survival status and predictors of mortality among TB-HIV-coinfected patients who were on TB treatment between 2018 and 2022 at public health facilities in Bahir Dar City.

Methods and Materials

Study Setting and Period

This study was conducted at public health facilities located in Bahir Dar City by reviewing medical records of patients recorded from July 2018 to June 2022. Bahir Dar is the capital city of Amhara Regional State, which is located 560 km northwest of Addis Ababa, the capital of Ethiopia. There are eleven HCs and three public hospitals administered by the Bahir Dar city health department. These facilities are expected to serve about 422,580 people around Bahir Dar and other nearby areas.

Study Design: An institution-based retrospective follow-up study was conducted among TB-HIV co-infected patients treated at public health facilities in Bahir Dar city.

Source and Study Populations

The source population was all TB-HIV-coinfected patients being treated for TB at public health facilities in Bahir Dar city, while the study population was all TB-HIV-coinfected patients being treated for TB at public health facilities in Bahir Dar city from July 2018 to June 2022.

Inclusion and Exclusion Criteria

All TB-HIV co-infected patients who were treated for TB at public health facilities in Bahir Dar city from July 2018 to June 2022 were included. And those patient charts that lacked complete disease documentation, an incomplete base line, and follow-up data were excluded from the study.

Study Variables

Dependent Variable

The dependent variable for this study was survival time to death of TB-HIV co-infected patients from the time of initiation of TB treatment to end of follow-up period.

Independent Variables

Socio demographic factors: age, sex, marital status, educational status, occupation, residence.
Clinical characteristics: WHO clinical stage, CD4 count/mm^3, hemoglobin level, nutritional status (Weight, Height), site of TB, functional status, comorbidities (DM, HTN, Asthma) and opportunistic infection (OI).
Treatment-related factors: TB regimen, ART regimen, adherence to TB and HIV, and CPT.

Operational Definition

Survival time: The time in days between diagnosis of TB-HIV co-infection and occurrence of outcome (event or censored).
Time to death: The time from TB-HIV co-infection to the occurrence of the event (death) during the follow-up period.
Events: The event of this study is death of a TB-HIV co-infected patients.
Censored: Represents patients lost to follow-up, treatment completed, recovered and treatment failure.
Loss to follow-up: A TB-HIV co-infected patient whose treatment was interrupted for 2 consecutive months or more.
Transferred out: Those TB-HIV patients who were transferred-out to another health facilities for TB treatment.
Adherence: A patient was following the recommended course of treatment by taking all prescribed medications and coming for scheduled exams and tests.

Sampling Techniques and Procedures

All patients co-infected with TB and HIV who were registered and receiving follow-up care from July 2018 to June 2022 were included in the current study. During the study period, a total of 2675 HIV-positive clients and 3192 TB patients were notified. Among these patients, 472 were TB-HIV co-infected. Each TB-HIV co-infection patient in the cohort was retrospectively studied, starting from the initiation of TB treatment to the occurrence of the outcome (event or censored) or the end of the follow-up period. Seventy-one charts were rejected due to incompleteness, and 401 TB-HIV-coinfected patients who were treated during the study period were included in the study.

Data Collection Methods and Procedures

The data were collected using a structured checklist prepared in English. The data extraction tool was adapted from existing studies and adopted from patients' charts, registrations, and ART and TB intake forms. The tool consisted of predictors related to socio-demographic characteristics, clinical characteristics of the patient, laboratory investigations, treatment, and adherence to treatment. Four nurses who have training in ART and TB participated in the data collection process.

Data Quality Assurance

Prior to actual work, data collectors and supervisors were given a one-day orientation on data collection tools. During orientation, emphasis was given on the purpose of the study, how to use data extraction tools and their content, and how to address possible problems. In each facility, a card room porter was recruited for card delivery from the card room. The principal investigator and the supervisors closely monitored the whole data collection process on a regular basis. The collected data were cleaned before the analysis.

Data Processing and Analysis

Data were entered using EpiData version 3.1 and analyzed using STATA version 15. Before analysis, the data were cleaned and checked for consistency by using simple frequencies and cross tabulation; re-categorization of categorical variables and categorization of continuous variables was done to make it suitable for analysis. Descriptive statistics were used to present the demographic and background clinical characteristics of the patients. The Kaplan–Meier survival curve was used to estimate the median survival time and cumulative probability of survival, while the Log rank test was used to assess overall survival differences between group predictors. Cox proportional hazard regression analysis was used to identify the potential predictors of mortality. Multicollinearity between predictors was checked. A bivariable Cox-proportional hazard regression model was fitted for each explanatory variable, and those variables having a p-value ≤0.25 were selected for multivariable analysis. The adjusted hazard ratio (AHR) with 95% confidence intervals was computed, and statistical significance was declared at $p < 0.05$. Finally, results were presented using tables, graphs, and text.

Results

Socio-Demographic Characteristics

The data used for this study was obtained from the medical records of 401 TB-HIV-coinfected patients. The median age of the patient was 35, with an interquartile range of 13 years (28 to 41). Slightly more than half, 227 (56.6%) were male in sex, and most, 340 (84.79%) of them were urban regarding their residency. A total of 164 (40.9%) individuals were married, and nearly one-third (30.43%) of participants had no formal education (Table 1).

Table 1 Socio-Demographic Characteristics of TB-HIV Co-Infected Patients at PHFs in Bahir Dar City, Northwest Ethiopia, August 2023 (n = 401)

Variables	Category	Frequency	Percent
Age	<15	15	3.74
	15–24	38	9.48
	25–34	147	36.66
	35–44	126	31.42
	≥45	75	18.70
Sex	Male	227	56.61
	Female	174	43.39
Residence	Urban	340	84.79
	Rural	61	15.21

(*Continued*)

Table 1 (Continued).

Variables	Category	Frequency	Percent
Educational level	No formal education	122	30.43
	Primary	111	27.68
	Secondary	110	27.43
	Diploma and above	58	14.46
Occupation	Employed (private and govt)	103	25.68
	Farmer	104	25.94
	Merchant	49	12.22
	Not working (student)	46	11.47
	Daily laborer	82	20.45
	Others	17	4.24
Marital status	Currently married	164	40.90
	Single	123	30.67
	Divorced	77	19.20
	Widowed	37	9.23

Background Clinical Characteristics

The findings of this study showed that among participants majority, 358 (89.28%) were in advanced WHO stages (stage III and IV). In addition, 20 (4.99%), 10 (2.49%) and 24 (5.99%) had asthma, diabetic mellitus, and hypertension, respectively. Among individuals who have one or more comorbidities 23 (42.59%) died during the follow-up period. Regarding the functional status of participants, 291 (72.57%), 96 (23.94%), and 14 (3.49%) were working, ambulatory, and bedridden, respectively. More than half (55.86%) of patients were diagnosed with pulmonary TB, while the rest, 177 (44.14%), were extra-pulmonary. Among 83 (20.7%) patients who had opportunistic infections, 38 (45.78%) died during the follow-up period. In addition, from 97 (24.19%) patients with a CD4 count <200 cells/mm^3, 17 (17.5%) died during the TB treatment period. Of the study's participants, 168 (41.90%) had their ART treatment regimen changed after enrolling, and 25 (14.88%) of them passed away while receiving TB treatment. Among those patients who were co-infected, 19 (4.74%) and 20 (4.99%) exhibited poor adherence to ART and TB treatment, respectively. There were 283 (70.57%) patients who received cotrimoxazole preventive therapy, of whom 7.77% died during TB treatment and the follow-up period (Table 2).

Mortality and Survival Status of TB-HIV Co-infected Patients

Among the 401 patients who were included in this study, there were 310 (73.3%) treatment successes, 59 (14.7%) deaths, 18 (4.5%) did not get evaluated, 8 (2.0%) lost follow-ups, and 6 (1.5%) treatment failures. High mortality in TB and HIV co-infected patients was observed in the earlier months of the treatment period. Twelve (27%), twenty-two (64%), and fifty-four (95%) of deaths among co-infected patients occurred in the second, third, and sixth-months following anti-TB treatment initiation, respectively. The incidence rate of mortality among TB-HIV coinfected patients was 7.47 per 10,000-person day (95%: CI = 5.79, 9.64) or 242 per 10,000-person month. The survival rates were also 96%, 90%, and 85% at 2, 3, and 6 months, respectively, after the initiation of TB treatment.

Table 2 Base Line Clinical Characteristics of TB and HIV Co-Infected Patients During TB Treatment at PHFs in Bahir Dar City, Northwest Ethiopia, August 2023 (n = 401)

Variable	Category	Frequency	Percentage
WHO clinical stage	I	24	5.98
	II	19	4.74
	III	180	44.89
	IV	178	44.39
Body Mass Index	<18.5	161	40.15
	18.5–24.5	191	47.63
	>24.5	49	12.22
Site of tuberculosis	Pulmonary	224	55.86
	Extra Pulmonary	177	44.14
History of opportunistic infection	Yes	83	20.70
	No	318	79.30
Functional status	Working	291	72.57
	Ambulance	96	23.94
	Bedridden	14	3.49
CD4 count	<200	97	24.19
	>200	304	75.81
Hemoglobin level	Abnormal	144	35.91
	Normal	257	64.09
Regimen change	Yes	168	41.90
	No	233	58.10
ART Adherence	Good	354	88.28
	Fair	28	6.98
	Poor	19	4.74
Tuberculosis Adherence	Good	332	82.79
	Fair	33	8.23
	Poor	36	8.98
CPT	Started	283	70.57
	Not started	118	29.43

Abbreviations: CD4, clusters of differentiation 4; ART, antiretroviral therapy; OI opportunistic infection, CPT, co-trimoxazole preventives therapy.

Overall Survival and Survival Comparison Between Group Predictors

The Kaplan–Meier technique was employed to plot the survival graph. Even though there was no abrupt decline, the Kaplan–Meier survival curve showed that overall survival was gradually declining until about three months (the 200 days) of the follow-up period. However, in the subsequent follow-up period, the graph flattened out, showing nearly

constant survival time until the end of the follow-up period (Figure 1). The Log rank test and the KM graphical curve were used to evaluate survival differences for categorical predictors. Therefore, a separate Kaplan–Meier graph was drawn for each predictor. Accordingly, there were differences in the survival times for predictors such as the site of the TB, the presence of OI, the body mass index, the patient's functional level, TB adherence, status of DM, CD4 count, and CPT. For other group predictors such as sex, residency, or age, there were, however, no clear differences in survival time.

Predictors of Mortality Among TB-HIV Coinfected Patients

In this study, the Cox proportional hazard analysis was used to identify significant predictors of mortality. Variables that meet the basic requirements of the Cox proportional hazard assumptions and that had a p-value of ≤0.25 in the bi-variable Cox proportional analysis were included in the final model. Accordingly, marital status, the presence of asthma, the presence of DM, BMI, WHO clinical stages, sites of TB, the presence of OI, the functional status of the patients, adherence to the ART treatment, adherence to TB treatment, and cotrimoxazole preventive therapy were variables fitted into the final model. In multi-variable Cox-Proportional Hazard model, BMI, the site of TB infection, the presence of OI, functional status of the patient, and adherence to TB treatment were remain significant predictors of mortality.

Patients who had a BMI of lower than normal were 3.00 times higher risks of dying as a compared to those who had normal BMI (AHR = 3.00, 95% CI = 1.44, 6.28). Patients with Extrapulmonary TB had 3.30 times more risk of death than patients with pulmonary TB (AHR = 3.30, 95% CI = 1.49, 7.29). The risk of dying was 5.07 times higher for those patients with OIs as compared to their counterparts (AHR = 5.07; 95% CI = 2.55, 10.09). Bedridden patients had a mortality risk that was 4.49 times higher than those with working functional status (AHR = 4.49; 95% CI = 1.63, 12.33). Furthermore, this study found that patients who had fair and poor adherence to their TB treatment had 2.74 times (AHR = 2.74, 95% CI = 1.41, 7.20) and 3.75 times (AHR = 3.75, 95% CI, 1.52, 9.23) a higher risk of dying during TB treatment compared to patients who had good adherence to their treatment, respectively (Table 3).

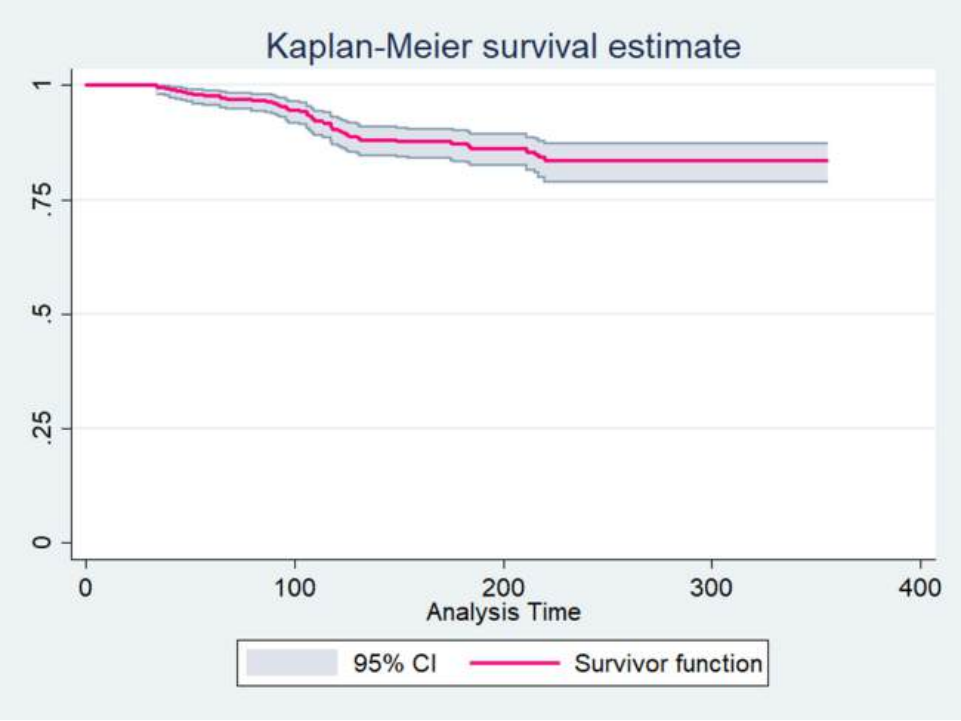

Figure 1 Overall Kaplan-Meier survival probability curve among TB-HIV coinfected patients, during TB treatment at PHFs in Bahir Dar City, Northwest Ethiopia, August 2023 (n = 401).

Table 3 Multivariable Cox Regression Analysis Among TB-HIV Co-Infected Patients Being Treated for TB at PHFs in Bahir Dar City, Northwest Ethiopia, August 2023 (n = 401)

Variables	Category	Outcome			CHR 95% CI	AHR (95% CI)	P-value
		Censored	Event	Total			
Asthma	No	333 (87.40)	48 (12.60)	381(100)	1	1	0.37
	Yes	9 (45.00)	11 (55.00)	20 (100)	4.82 (2.50, 9.29)	1.49 (0.63, 3.60)	
Diabetics	No	335 (85.68)	56 (14.32)	391(100)	1	1	0.38
	Yes	7 (70.00)	3 (30.00)	10 (100)	2.26 (0.71, 7.22)	1.53 (0.48, 6.51)	
BMI	<18.5	130 (80.75)	31 (19.25)	161 (100)	1	3.00 (1.44, 6.28)	
	18.5–24.5	177 (92.67)	14 (7.33)	191 (100)		1	0.01*
	>24.5	35 (71.43)	14 (28.57)	49 (100)	1.44 (0.76, 2.71)	0.56 (0.98, 5.66)	0.66
WHO stage	I	23 (95.83)	1 (4.17)	24 (100)	1	1	
	II	16 (84.21)	3 (15.79)	19 (100)	0.24 (0.025, 2.30)	7.84 (0.75, 8.50)	0.09
	III	159(88.33)	21 (11.67)	180 (100)	0.68 (0.20, 2.27)	2.82 (0.34, 23.53)	0.34
	IV	144(80.90)	34 (19.10)	178 (100)	1.14 (0.35, 3.71)	1.77 (0.21, 14.63)	0.60
OI	No	297 (93.40	21 (6.60)	318(100)	1	1	<0.001*
	Yes	45 (54.22)	38 (45.78)	83 (100)	9.48 (5.55, 16.20)	5.07 (2.55, 10.08)	
Functional Status	Working	250(85.91)	41 (14.09)	291(100)	1	1	
	Ambulance	85 (88.54)	11 (11.46)	96 (100)	1.22 (0.63, 2.38)	0.52 (0.25, 1.09)	0.08
	Bedridden	7 (50.00)	7 (50.00)	14 (100)	5.66 (2.19, 14.63)	4.49 (1.63, 12.33)	0.004*
Adherence (ART)	Good	326 (92.09)	28 (7.91)	354 (100)	1	1	
	Fair	9(32.14)	19 (67.86)	28 (100)	0.08 (0.45, 0.15)	0.98 (0.72, 4.90)	0.20
	Poor	7 (36.84)	12 (63.16)	19 (100)	0.81 (0.39, 1.67)	1.30 (0.44, 3.83)	0.06
Adherence (TB)	Good	308 (92.8)	24 (7.2)	333 (100)	1	1	
	Fair	15 (45.5)	18 (54.5)	33(100)	0.05 (0.03, 0.10)	2.74 (1.41, 7.20)	0.04*
	Poor	19(52.8)	17(47.2)	36(100)	1.11 (0.57, 2.16)	3.75 (1.52, 9.23)	0.004*
Marital status	Married	154 (93.90)	10 (6.10)	164 (100)	1	1	
	Single	106 (86.18)	17 (13.82)	123 (100)	2.42 (1.11, 5.29)	1.37 (0.55, 3.37)	0.50
	Divorced	61 (79.22)	16 (20.78)	77 (100)	3.72 (1.69, 8.20)	1.10 (0.39, 3.08)	0.85
	Widowed	21 (56.76)	16 (43.24)	37 (100)	8.29 (3.76, 18.27)	1.31 (0.49, 3.44)	0.59
CPT	No started	81 (68.64)	37 (31.36)	118 (100)	1		0.21
	Started	261(92.23)	22 (7.77)	283 (100)	0.22 (0.13, 0.38)	0.68 (0.29, 1.31)	
Site of TB	Pulmonary	210 (93.75)	14 (6.25)	224 (100)	1	1	0.003*
	Extra Pulmonary	132 (74.58)	45 (25.42)	177 (100)	(2.46, 8.16)	3.30(1.50, 7.29)	

Note: *Indicated significant predictors with a p-value of <0.05.
Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CPT, co-trimoxazole preventive therapy; OI, opportunistic infection; TB, tuberculosis.

Discussion

This study was conducted to determine the survival time and predictors of mortality among TB-HIV co-infected patients during tuberculosis treatment at public health facilities in Bahir Dar. The finding indicated that the median follow-up period was 212 days with a minimum and maximum days of 34 and 355 days.

This study revealed that the cumulative incidence of mortality was 14.7% (95% CI = 11.4%, 18.6%) among TB-HIV co-infected patients during TB treatment and follow-up period. The finding was consistent with a study in Myanmar, 13.7%[26] and Ethiopian studies reported from, Somali, 11.1%[27] and Bahir Dar, 18%.[28] But it was lower than studies in Almaty, Kazakhstan 27.4%,[29] Metu Karl Hospital 20.9%,[30] Mizan Tepi University Hospital 21.8%,[31] and Mekelle, 23.0%.[24] However, this finding significantly higher than the study conducted in Harar town 7.7%.[32] The overall incidence rate was 2.42 per 100 person months (95% CI = 1.88, 3.12), which was higher than studies conducted in

Metu Karl Referral Hospital and Mizan Tepi teaching Hospital which reported 1.21 per 100 person month and 0.52 per 100 person month, respectively.[4,30] However, the finding was lower than a study conducted in Bahir Dar[28] which reported 4.1 per 100 Person-Month. The differences might be having been due to differences in the study's design and period, differences in the quality of care in the treatment center and changes in the treatment protocol.

TB-HIV co-infected patients whose BMI was lower than normal (BMI < 18.5 kg/m2) had more than three times higher risk of death as compared to those with normal BMI. The finding was in line with a study in Lesotho[18] and an Ethiopian study conducted in Mekelle.[33] The possible justification might be that those with a lower BMI are supposed to suffer from malnutrition, which is one of the causes of immunocompromising diseases that result in death.

Site of TB was also a predictor of mortality, and hence, Extra Pulmonary TB (EPTB) had 3.3 times more risk of mortality than pulmonary TB. The finding was consistent with studies conducted in Ethiopia, Mekelle[24] and Bahir Dar.[28] Possible justification for the similarities might be that EPTB cases have a greater chance of being disseminated to different body organs, which may result in treatment failure, and, finally lead to multi-drug resistance and mortality.[24] Unlikely, the result of this study were different from a study conducted in Ambo Referral Hospital, Ethiopia, indicated PTB patients were 2.3 times more likely to die than EPTB.[21] The differences might be due to differences in study period, setting and design of the study.

Those patients with opportunistic infections had 5.07 times higher risk of dying compared with those without opportunistic infections. The finding was consistent with other studies conducted in Botswana[34] and Cameron[35] and at teaching hospitals in Harar Ethiopia.[32] The possible reason could be that those patients with opportunistic infection less likely to resist TB and recover from their illness.

The functional status of the patient was another predictor of mortality among TB-HIV coinfected patients. Those bed ridden patients were 4.49 times more at risk of death compared to those with working status. The finding was in line with studies conducted at Mizan Tepi, Bahir Dar, Metu Karl and Jimma Referral hospitals.[4,28,30,36] This might be because bedridden patients have a worse prognosis for health because of a relentless immunity-lowering cycle, which can result in patients contracting opportunistic infections and dying.[30]

According to this study, participants with poor adherence to TB treatment had 3.75 times an increased risk of mortality as compared to good adherence. This agreed with a study done in Mizan-Tepi southwest Ethiopia.[31] The similarities could be those people who were unable to take TB drugs adherently had come up with many problems such as treatment failure, a resistant strain which resulted in death of their outcome.

Limitations of the Study

The data were extracted from secondary sources, and as a result, some important variables related to behavioral factors like smoking, drug use, and others like income were missed, which might be potential predictors of mortality in TB-HIV co-infected patients.

Conclusion

The findings of this study indicated that there was high mortality among TB-HIV coinfected patients during the follow-up period, and specifically, low survival was observed in the earlier months of initiation of TB treatment. Since the number of deaths was significantly high, efforts must be made to reduce it. Low BMI (<18 gm/m2) at baseline, presence of OI, EPTB, bedridden functional status, and inability to adhere to anti-TB treatment were independent predictors affecting the survival of TB-HIV co-infected patients. Therefore, to increase the survival of the patient, health care providers in the study area should work to improve the nutrition status of the patient, improve their adherence, and prevent and treat opportunistic infections.

Abbreviations

AIDS, acquired immune deficiency syndrome; ART, antiretroviral therapy; BMI, body mass index; CD4, cluster differentiation-4; EPTB, extra pulmonary TB; HIV, human immunodeficiency virus; OI, opportunistic infection; PHFs, public health facilities; TB, tuberculosis; WHO, World Health Organization.

Data Sharing Statement

The corresponding author will provide the datasets used and/or analyzed for this study upon reasonable request.

Ethics Approval

The study was conducted after getting ethical clearance from the Amhara Public Health Institute research directorate ethical review committee. The study utilized the five-year secondary data collected retrospectively from individual patient medical records. Therefore, the ethical committee approved that there was no patient consent as there was no direct patient contact during data collection, provided that the data would be used only for the sole purpose of the study. The letter of cooperation written by the ethical committee on January 27, 2023, with a reference number of 1888/APHI, was presented to each health facility in Bahir Dar city. The research committee in each health facility gave a grant to conduct the research in their respective facilities. Confidentiality of the information was secured throughout the study by excluding names and patient medical record numbers on the data extraction form, and the data were used only for the proposed study. This study adhered to the Declaration of Helsinki's ethical standards.

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Author Contributions

All authors made a significant contribution to this work, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors declare no competing interests in this work.

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LETTER

A survey of the effectiveness of centralized consilia in providing advice on drug-resistant TB

Dear Editor,

Annually, approximately 410,000 people globally acquire multidrug-resistant TB (MDR-TB) and rifampicin-resistant TB (RR-TB).[1] However, in 2021, only 161,746 people were enrolled in MDR/RR-TB treatment, with most of the enrollees being adults.[2] The biggest barrier to care is failure to diagnose drug-resistant TB (DR-TB), but once it is diagnosed, access to treatment and lack of provider experience are important additional barriers.[1] To expand treatment capacity, centralized hubs of expertise have been set up in many countries to provide either advice and/or direction in selecting treatment regimens and monitoring for tolerability and effectiveness. However, centralization of care may also be a barrier to prompt treatment initiation, especially when centralized decision-making is required before drugs are released. These systems, called 'consilia', evolved when MDR/RR-TB treatment was first introduced, and control was prioritized over access.[3] Currently, WHO provides guidelines on the duration and composition of treatment, but consilia may still be important in some settings for translating these guidelines into individual patient decisions.[4] In 2000, the first forum for advice on MDR/RR-TB treatment, the 'Green Light Committee (GLC)' was created to improve access to quality-assured second-line anti-TB drugs.[3] In 2014, because many care providers had limited experience in devising and monitoring treatment for DR-TB, WHO recommended that MDR-TB and extensively drug-resistant TB (XDR-TB) case management be overseen by centralized teams at regional levels. These are meant to help with the discussion of difficult cases and serve as the 'gateway to accessing second-line drugs and/or the new drugs'.[4] A typical TB consilium is made up of clinicians, public health officers, microbiologists, pharmacologists and other relevant roles. Although consilia aim to improve care for MDR-TB and XDR TB, there are both advantages and disadvantages. Advantages include the ability to receive expert advice, collaboration amongst TB experts, peer quality assurance and potential teaching opportunities. Disadvantages include a slower response rate (potentially leading to delays in initiating treatment) and a limited number of cases that can be discussed.[5] RESIST-TB and the Union's DR-TB Working Group sought to examine the role of centralized decision-making as perceived by its users and to determine how it might be improved. We therefore performed a survey examining MDR/RR-TB decision-making and recommendations within different countries.

A questionnaire with 17 questions was sent by e-mail to approximately 1,500 members of the Tuberculosis Section of the International Union Against Tuberculosis and Lung Disease (The Union) – see Supplementary Data for the questionnaire. Members of The Union were also encouraged to share the survey with non-members. The survey was open from March to June 2023. We excluded responses that answered which country they were responding from but did not complete any subsequent questions. Responses were stratified by country. In addition, we grouped the 38 free-response recommendations by categories based on keywords to gain insight into needs and potential improvements in MDR/RR-TB care support.

We received 175 survey responses from 46 countries, but 70 respondents did not initiate the questionnaire, leaving 105 responses from 46 countries for analysis. Of the 46 countries, 13 (28%) were in the WHO African region, 5 (11%) in the Eastern Mediterranean, 11 (24%) in the European, 6 (13%) in the Americas, 2 (4%) in Southeast Asian and 9 (20%) in the Western Pacific. Of the 46 countries represented in this analysis, 38 (84.4%) had a consilium (or several consilia) that gave advice on MDR/RR-TB treatment regimens and 8 (21.1%) did not. Of the 38 countries with a consilium, 29 (76.3%) had circumstances requiring their advice, whereas 9 (23.7%) did not. Of these 29 countries, 8 were in Africa, 3 in the Eastern Mediterranean, 7 in Europe, 4 in the Americas, 2 in Southeast Asia and 5 in the Western Pacific. There was variability in the circumstances in which consilium advice was required (Figure). Of the consilia in the 29 countries where advice was mandatory, 23 (79%), provided advice within 2 weeks, 4 (14%) within 2–3 weeks and 2 (7%) in four or more weeks. In the open response field, our respondents observed that consilia were often understaffed and lacked adequate financial and social support for patients. They also identified challenges that may have been outside the remit of the consilium that adversely affected patient treatment decisions, such as lack of drug availability and limited access to second-line susceptibility testing. Specifically, in 27% of the countries, respondents identified the lack of access to susceptibility testing for drugs used in MDR/RR-TB treatment as an important barrier. In addition, lack of access to bedaquiline, pretomanid and or delamanid was cited in 12%, and the high cost of treatment to the patient was cited in 7%.

These results show substantial variability in the circumstances where consilium input must be sought (per local TB Program guidelines) and considerable

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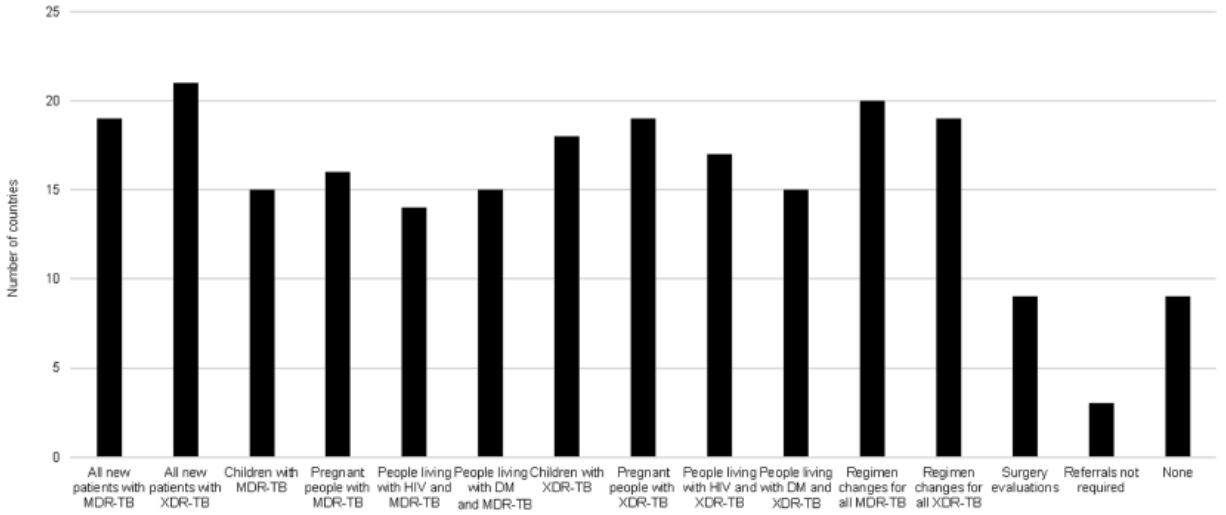

Figure. Circumstances when advice from consilium must be sought according to national guidelines. MDR-TB = multidrug-resistant TB; XDR-TB = extensively drug-resistant TB; DM = diabetes mellitus.

differences in the time taken to respond with treatment advice. The results of our survey on consilia are similar to challenges reported in the literature: other studies have reported that shortages of expert staff to manage high caseloads can slow response times;[5] and a French consilium (comprised of a small number of experts) also noted average response time of one month.[6,7] In comparison, the European Respiratory Society/WHO consilium (comprised of 54 experts) reported an average response time of 48 hours, and five other countries (four of them in Europe) reported responses in 1–5 days.[7] The French consilium saw an increase in the availability of the new drugs over time, whereas access and availability remain challenging in the countries responding to our survey. In countries with small numbers of patients with MDR/RR-TB and where clinical expertise is limited, consilia can function to ensure quality of care. An alternative is to set up special treatment centers rather than overseeing inexperienced clinicians treating occasional patients. In countries where the burden is substantial, consilia may need to focus on training providers of MDR/RR-TB care so they can function without oversight. Moreover, where there are substantial numbers of children with MDR/RR-TB, there may be a need for specialized support.

These results demonstrate a substantial degree of variability between countries and the need to improve responsiveness for treatment guidance. The availability of Group A second-line drugs and susceptibility testing to these drugs continues to be suboptimal.[8] The functions of consilia may need to be more closely matched to the local conditions to reflect the levels of MDR/RR-TB in the population.

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KEY WORDS: tuberculosis, multi-drug resistant tuberculosis; MDR-TB; rifampicin-resistant TB; RR-TB; consilia

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