



**INNOVATIONS IN THE
GLOBAL FIGHT AGAINST TB:**

Field Research from
Management Sciences for Health: 2008-2019

**Innovations in the Global Fight Against TB:
Field Research from Management Sciences for Health (MSH)**

Peer-reviewed implementation research on TB programs
co-authored by MSH, 2008-2019

Management Sciences for Health (MSH)

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*GeneXpert machine
Photo by Samy Rakotoniaina*

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Dear Colleagues,

Tuberculosis (TB) continues to be a global epidemic and the world's deadliest single infectious agent. Last year, TB claimed the lives of 1.5 million people, and it affects the lives and livelihoods of millions more. While early diagnosis and treatment can cure and prevent the spread of TB, underreporting and underdiagnosis remain big issues.

The 2019 Global TB report found that globally, 7 million people were diagnosed and treated for TB—up from 6.4 million in 2017—enabling the world to meet one of the milestones toward the United Nations' political declaration targets on TB.

The number of new cases of TB has been declining steadily in recent years. However, the burden remains high among low-income and marginalized populations: around 10 million people developed TB in 2018.

Drug resistance remains another impediment to ending TB. In 2018, there were an estimated half a million new cases of drug-resistant TB. Only one in three of these people was enrolled in treatment.

Still, we can end TB if governments, donors, the private sector, affected communities, and civil society actors work together to fund and execute an accelerated response to end the TB epidemic.

Responding to these challenges, last month, September 2019, heads of state agreed on a political declaration on Universal Health Coverage at the United Nations in New York, and highlighted the importance of expanding service coverage and committing specifically to strengthen efforts to address communicable diseases such as HIV, TB, and malaria.

As MSH has shown, innovations in TB prevention and treatment are needed throughout health systems. Better health system performance begins with inspired and inspiring leadership; sound management; and consistent, transparent governance. Advances must take into consideration central, district, and local environments; community involvement with capacity building; and accessible technical expertise to ensure correct use and sustainability.

This updated volume of 78 peer-reviewed journal articles includes additional contributions to the research literature from MSH staff and our national (ministries of health, national TB programs, local non-governmental organizations, and universities) and international partners, as well as donors (principally the US Agency for International Development) in Africa, Asia, Latin America, and the Caribbean.



Photo by Health for All staff

With nearly two decades spent fighting TB, MSH has the solid background in health systems strengthening needed to approach next-wave innovation, whether that be training community health workers or programming electronic information systems. The papers presented highlight particularly effective innovations for controlling this disease in the following technical areas:

- Quality DOTS implementation
- TB in fragile states and volatile environments
- Urban DOTS
- MDR-TB care and treatment
- TB epidemiology, monitoring, and evaluation
- TB contact investigation
- TB diagnostics, including GeneXpert analysis and Digital X-Ray
- e-TB Manager
- Public-private Mix (PPM)
- Quality assurance in laboratory services
- Patient-centered care for vulnerable and special populations, including those with HIV and other diseases
- TB drug management and pharmacovigilance
- TB financing
- Capacity building and surveillance systems

These articles are important contributions to the evidence base of what works in TB, including systems strengthening innovations that improve access to both established and novel TB medicines, ensuring safety and quality and promoting effective detection and case management.

We are thankful for the deep engagement of our respected colleagues: MSH staff, numerous partners, and donors, among whom USAID has been the steadiest and most generous.

Joining with you in the hope of a world free of TB,

A handwritten signature in black ink, appearing to read 'Pedro G. Suarez', with a large, sweeping flourish underneath.

Pedro G. Suarez, M.D., TB Practice Area Lead,
Management Sciences for Health

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January 2008–August 2019

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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 ser-

vices 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 POPULATION 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 Afghan-

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

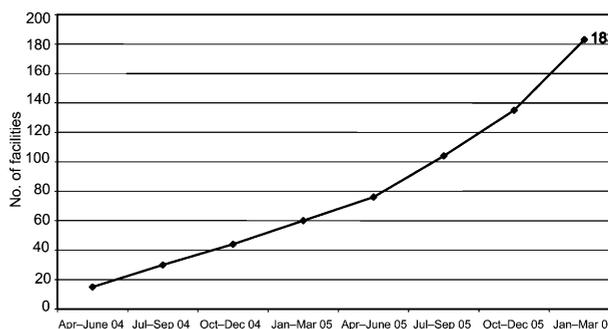


Figure 1 Number of REACH facilities (including basic health centers) that reported providing DOTS. REACH = Rural Expansion of Afghanistan’s Community-based Healthcare.

istan. 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

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

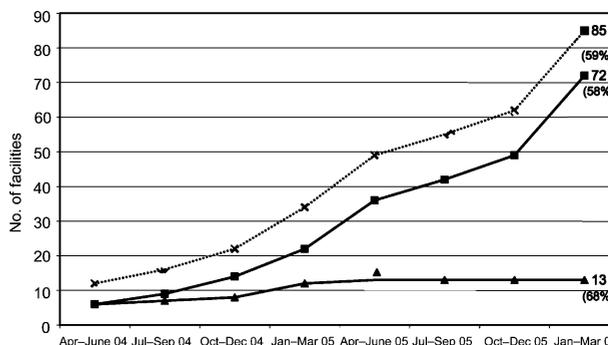


Figure 2 REACH-supported hospitals and comprehensive health centers offering active diagnosis and treatment of tuberculosis. Dotted line = total; line with squares = comprehensive health centers with active diagnosis and treatment services; line with triangles = district hospitals with active diagnosis 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 <i>n</i> (%)
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

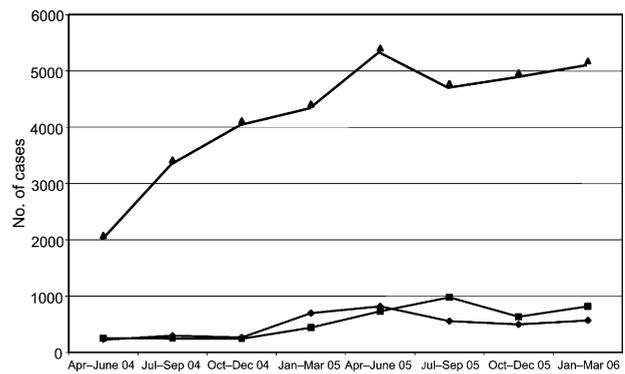
Source: NTP, 2005.¹¹

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

**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.

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

Year	TB sputum smear-positive cases			Outcomes, <i>n</i> (%)					
	Notified <i>n</i>	Analyzed in study cohort <i>n</i>	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 diagnos-

tic 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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R É S U M É

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.

R E S U M E N

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 cen-

tros 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.

Research article

Open Access

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; Kibaha 132,045; Kisarawe 95,614 and Mkuranga 187,428) [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 ran-

dom 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)	OR = 0.5 (95%CI 0.10-2.80) OR = 05 (95%CI 0.08-2.41)
18-40	49/79(62.03)	80/124 (64.52)	
> 40	28/79(35.44)	38/124 (30.65)	
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)‡ OR = 0.5; (95%CI 0.17- 1.38)
Private facility	16/78(20.51)	20/126 (15.87)	
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 NTL 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)	OR = 0.3(95%CI 0.03-2.25)
18-40	73/119 (61.3)	57/84 (67.8)	
> 40	40/119 (33.6)	26/84 (31.0)	
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 health 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 Disease 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 than 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].

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 health 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.

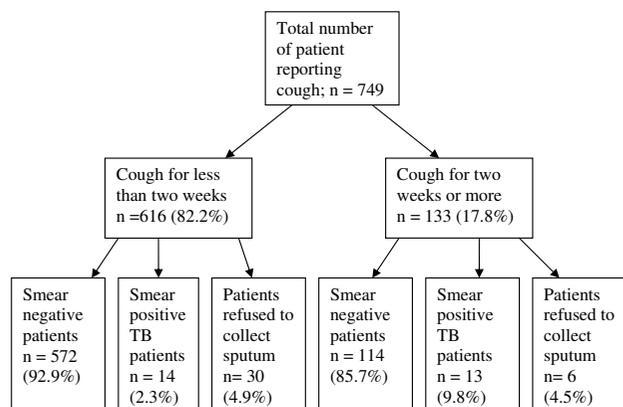


Figure 1 Comparison of smear results by cough duration.

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 roll-out. 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 for-

malized 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 trials⁴ 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 effort¹⁸ 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 world-

wide 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 study²¹ 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 <i>n</i> *	Respondents <i>n</i> *
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 ± 0.99 years for roll-out (mean \pm 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
	Delete 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	Delete 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 Positive factors affecting decision-making during past regimen changes

Decision factor during regimen change	Total respondents	
	<i>n</i>	Countries <i>n</i>
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 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 4 Negative factors during past regimen changes

Delay or difficulty during decision making or roll-out	Total respondents	
	<i>n</i>	Countries <i>n</i>
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.

'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

Table 5 Evidence required for future regimen change

Requirement*	Total respondents	
	<i>n</i>	Countries <i>n</i>
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.

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 targets²² 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 interviewees 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 reassignment 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).

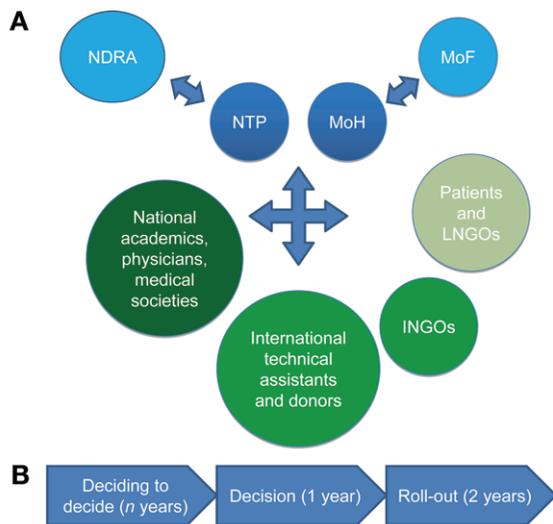


Figure Influence diagram for regimen decision making. **A.** The NTP and MoH are central to decision making, with the NTP providing guidance on priorities to the NDRA, and the MoF requiring a cost justification from the NTP and MoH. In an advisory capacity, national academics, physicians and medical 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/iatld/jitld/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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Conflict of interest statement: WAW, CC, HRI, EG and NRS

were or are employed by the Global Alliance for TB Drug Development, whose activities are aimed at developing and making available new therapies for TB. NK and DL are employed by Management Sciences for Health, which provides technical assistance with drug management in many of the high-burden countries.

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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'efficacité, 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 : À 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.



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 ≥ 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 reinfection 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 ≥ 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 (≥ 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	<p>Include at least four anti-TB drugs with either certain, or almost certain, effectiveness during the intensive phase of treatment</p> <p>Consider adding more drugs in patients with extensive disease or uncertain effectiveness</p> <p>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)</p> <p>Ethambutol may be considered effective and included in the regimen if DST shows susceptibility</p> <p>Treatment with Group 5 drugs is recommended only if additional drugs are needed to bring the total to four</p>	<p>Include at least four second-line anti-TB drugs likely to be effective, as well as pyrazinamide during the intensive phase of treatment</p> <p>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</p> <p>The regimen should include pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide) and cycloserine, or else PAS if cycloserine cannot be used</p> <p>Ethambutol may be used but is not included among the drugs making up the standard regimen</p> <p>Group 5 drugs may be used but are not included among the drugs making up the standard regimen</p>
Duration of treatment	<p>Use of a parenteral agent for a minimum of 6 months and ≥ 4 months after culture conversion</p> <p>A minimum total length of treatment of 18 months after culture conversion</p>	<p>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</p> <p>A total treatment duration of ≥ 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</p>
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, $\oplus\circ\circ\circ$ /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, $\oplus\circ\circ\circ$ /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	Ethionamide/prothionamide, 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 $\geq 90\%$ 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 indicators 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 $500/\text{mm}^3$ or less, regardless of symptoms
- Pregnant women after the first trimester who are symptomatic or have a CD4-lymphocyte count $< 500/\text{mm}^3$

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 $500 \text{ cells}/\text{mm}^3$ 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 over-emphasised, 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 from 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 man-

agement. 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 regimens¹ 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

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 described¹¹ (inquiries 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 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 Taskforce¹⁶ 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.

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

Table 3 Weight bands used for adult Category I regimens

Country	Rifampicin dosages in treatment guidelines?				Weight bands <i>n</i>
	300 mg	450 mg	600 mg	750 mg	
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.

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

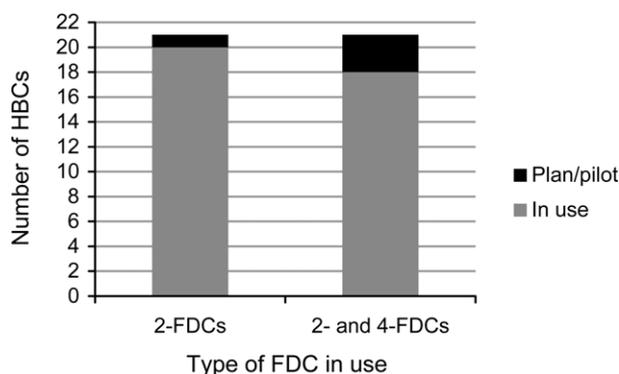


Figure Number of HBCs using 2- and 4-FDCs. HBC = high-burden country; FDC = fixed-dose combination.

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 Nam¹⁸), 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 options²⁰ 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 reports¹⁷), 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 previously²⁴ 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 surveillance²⁸ and regimen design²⁹ 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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R É S U M É

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 persistan-

tes 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.

R E S U M E N

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 pacien-

tes, 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.

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 ($p=0.15$) and 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 understanding of 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

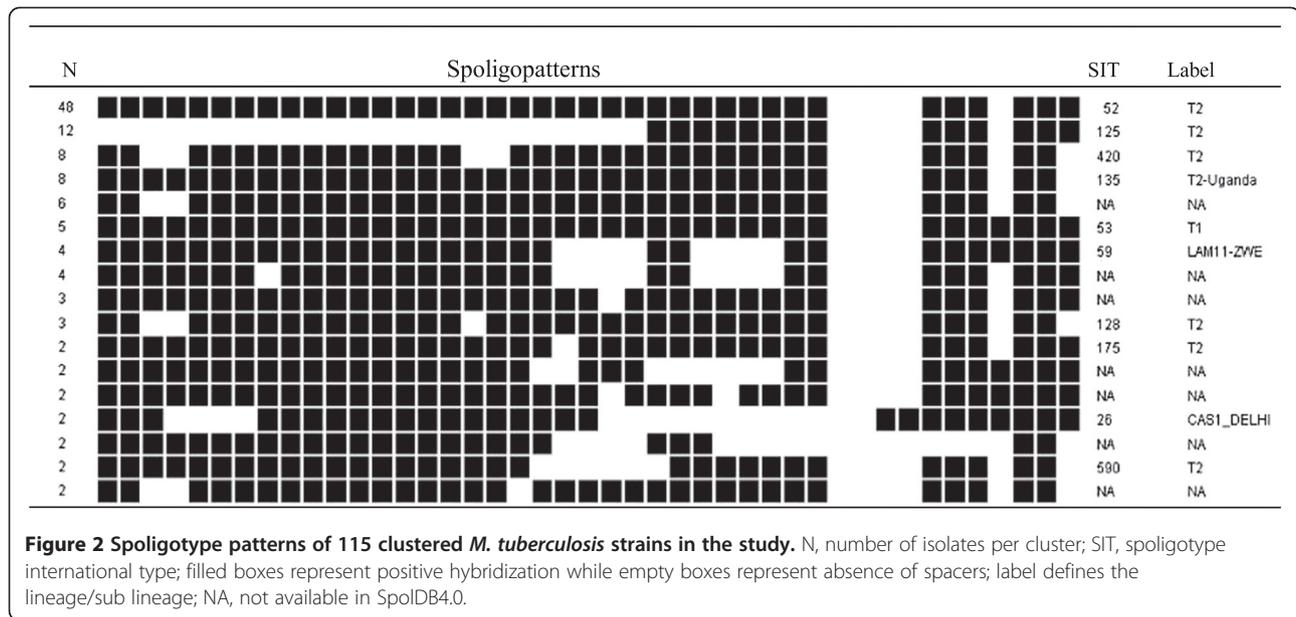
At the NRL, about 5mls of specimen were homogenized by digestion for 1 minute at room temperature with 1 ml of N-acetyl L-cysteine (NALC, 25mg/ml) in phosphate buffer (pH 6.8) and vortexed with several 4 mm glass beads for 30 seconds. A 5 ml aliquot was decontaminated using 1% NaOH [19] and concentrated 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-



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 isoniazid), 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 isoniazid 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 its 12 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%)
Treatment history	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

^aSensitive indicates isolates susceptible to both isoniazid and rifampicin; ^bResistance to isoniazid only, ^cresistance to rifampicin only, ^dresistance to both isoniazid 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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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

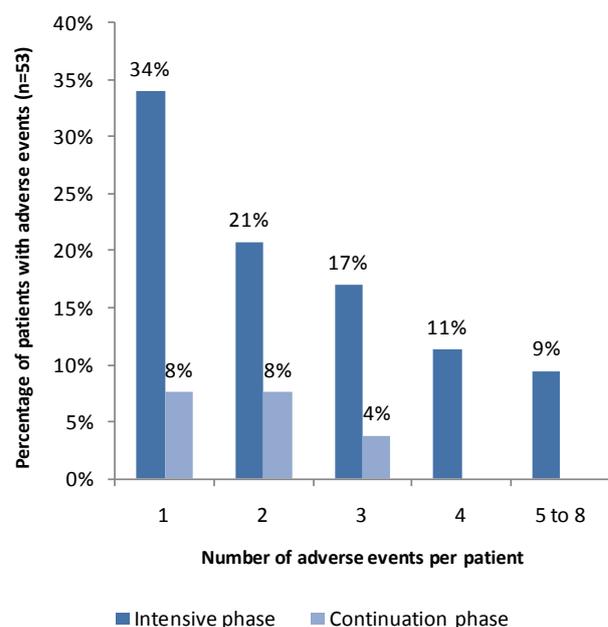
Characteristic	n (%)
Gender	
Male	38 (64%)
Female	20 (34%)
Missing	1 (2%)
Age (years), SD	
Male	36.9 ± 8.4
Female	31.0 ± 10.2
Weight (kg), SD	
Male	53.6 ± 7.8
Female	49.8 ± 16.4
Occupation	
Unemployed	18 (31%)
Employed	20 (34%)
Student	1 (2%)
Missing	20 (34%)
Type of TB	
PTB smear +	55 (93%)
PTB smear -	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*	
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).

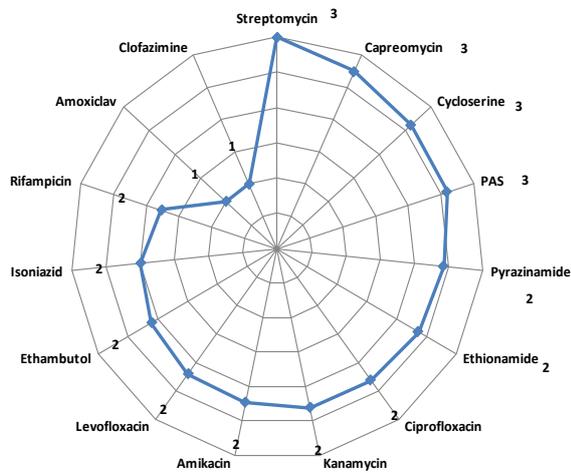
In total, there were fifteen different anti-tuberculosis medicines that were used by the patients included in this study (Table 3). Most of the patients were treated with DR-TB regimens containing pyrazinamide (93%) and ethionamide (92%). All patients were treated with an injectable anti-tuberculous 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 amoxicillin/ 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%	

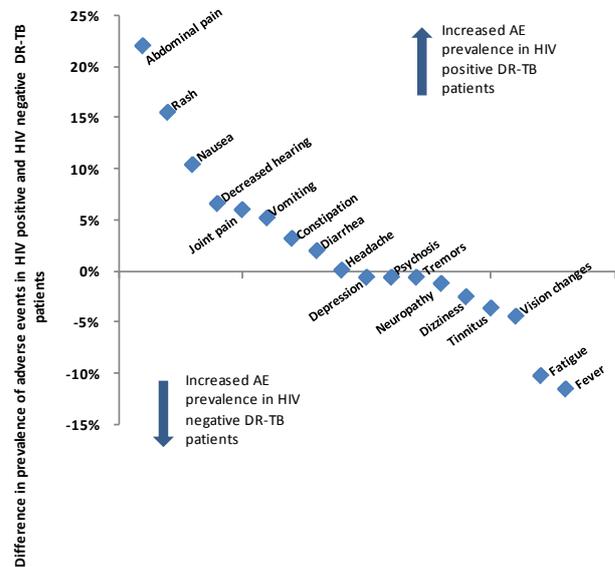
*53 of the 59 patients reported to have experienced at least one DR-TB treatment-related adverse event. All the 53 patients had either completed or were still in the intensive phase of treatment at the time of data collection. †49 of the patients had progressed into the continuation phase of treatment 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	
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

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

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 disease⁶ 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,

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.

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

	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 $P < 0.05$.

DEBATE

Open Access

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

Andre Gemal¹, Joel Keravec², Alexandre Menezes³ and Anete Trajman^{4,5,6*}

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 anti-retroviral 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 Pharmaceutical 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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RESEARCH ARTICLE

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

Selamawit Hirpa^{1*}, Girmay Medhin², Belaineh Girma³, Muluken Melese³, Alemayehu Mekonen⁴, Pedro Suarez⁵ and Gobena Ameni¹

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, Rifampicin 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 Löwenstein-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 assess 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 Akililu 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 5 th –8 th grade	16	11.9	20	15
Completed 8 th –10 th grade	27	20.1	25	18.6
Above 10 th 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

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

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

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 (n = 134)		Controls (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 5 th -8 th grade	16	20	1.3 (0.5-3.2)	1.2 (0.3-5.1)
Completed 8 th -10 th grade	27	25	1.7 (0.7- 4.0)	1.4 (0.4-5.1)
Above 10 th 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)

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

Characteristics	Case Number	Control Number	Crude OR (95% CI)	Adjusted OR (95% CI)
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 living 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/ μ l 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 ($BMI < 18 \text{ kg/m}^2$), CD4 < 50 cell/ μ l, 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/ μ l 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 assess: 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/ μ l), 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 reported 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/ μ L. But half, 53.6% of patients in controls had CD4+ cell count less than 200 cells/ μ L. 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/ μ L were more likely to develop TB compared to patients who had ≥ 350 cell/ μ L 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 $\alpha = 0.05$.

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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 or IV	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)	\leq 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
	\geq 350	16(8.6)	74(18.9)	1		

*significant at $\alpha = 0.05$.

WHO = World Health Organization, INH = Isoniazid, CTX = Cotrimoxazole, ART = Antiretroviral Therapy, Hgb = Hemoglobin, 1a = Stavudine, lamivudine, nevirapine→d4t-3TC-NVP, 1b = Stavudine, lamivudine, efavirenz→d4t-3TC-EFV, 1c = Zidovudine, lamivudine, nevirapine→AZT-3TC-NVP, 1d = Zidovudine, lamivudine, efavirenz→AZT-3TC-EFV, 1e = TDF, lamivudine, efavirenz→TDF-3TC-EFV, 1f = TDF, lamivudine, nevirapine→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 \leq 10 mg/dl have 2.4 times higher risk of developing TB than those patients having hemoglobin level \geq 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 isoniazid (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 predictors 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

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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 addi-

tional 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

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, infor-

mation 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 = multi-drug-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 WHO²⁴ as $\geq 40\%$ 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

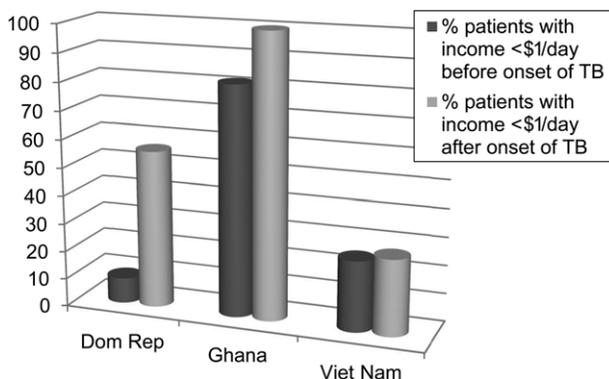


Figure Patients below US\$1/day poverty line before and after onset of TB. TB = tuberculosis.

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.

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 tool²¹ 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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R É S U M É

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.

SCHEMA : 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.

R E S U M E N

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.

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 notified³ 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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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 planners, 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 Referral 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".

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

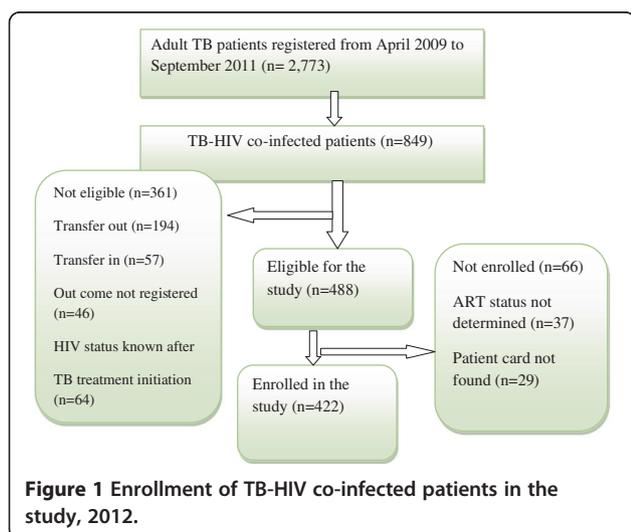
Ethical clearance for this study was obtained from the Review Ethics Committee of the School of Public Health at Addis Ababa University. To preserve patient confidentiality, nurses working in the ART clinics extracted the data from patients' medical records. Moreover, no personal identifiers were used 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%), ($\chi^2 = 21.721$; $df (1)$; $p = 0.000$). 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 ($\chi^2 = 10.434$; $df = 2$; $p = 0.005$). 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)	χ^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 \pm SD	32.58 \pm 9.123	31.98 \pm 9.837	0.753 \blacklozenge	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%)		

\blacklozenge = 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 $\alpha = 0.05$, ♦ = 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/ μ l (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

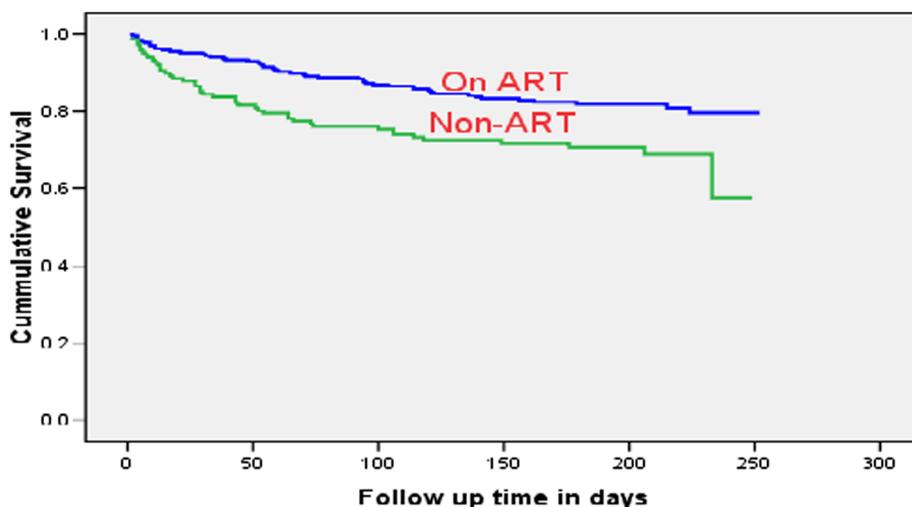


Figure 2 Kaplan-Meier estimate of survival among TB-HIV co-infected patients in Bahir Dar town, 2012.

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/ μ l, 75-150 cells/ μ l, and 150-250 cells/ μ l; 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/ μ l. This is similar with a study conducted in Zimbabwe where 84.6% of study participants had a CD4 count below 350 cells/ μ l [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 $\alpha = 0.05$. 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-infected 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

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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: Interquartile 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 km² 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

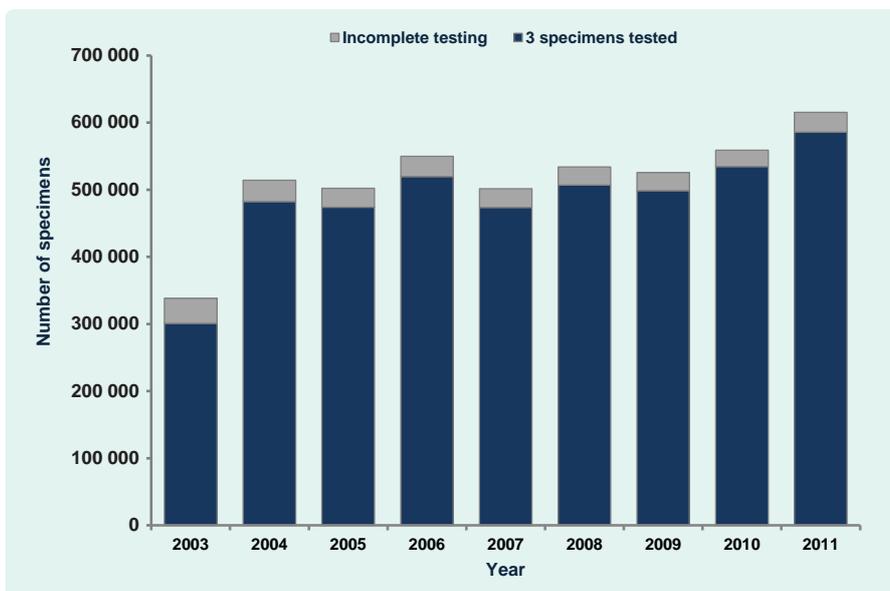
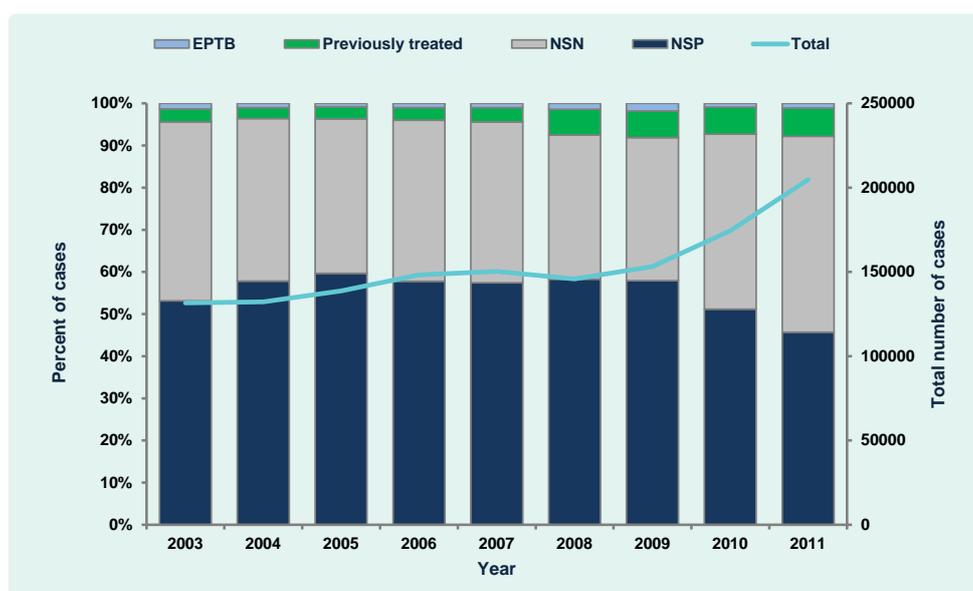


Figure 2. Total number of TB cases and the proportion by case classification, the Philippines, 2003 to 2011



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

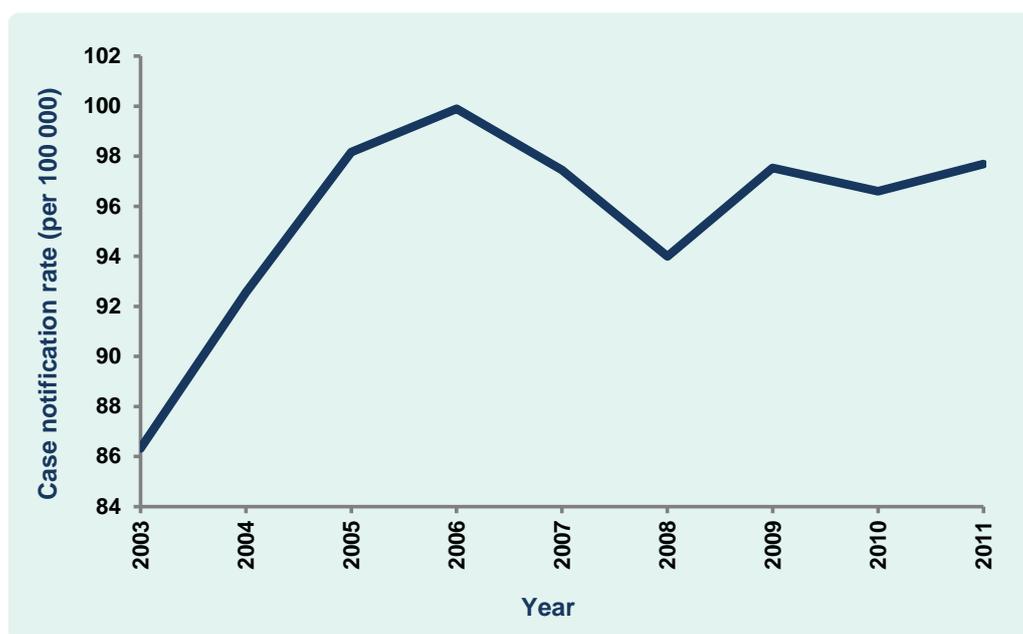
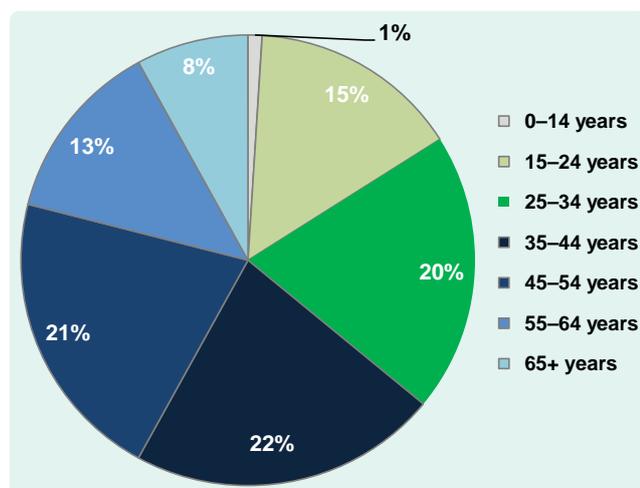


Figure 4. Proportion of all new smear-positive cases by age group, the Philippines, 2003 to 2011



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

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

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 rates¹¹ 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.

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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.

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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 countries⁴ 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. 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 $\pm 1\%$. 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 $\pm 2.0\%$.

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 test¹⁵ 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–Jensen 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

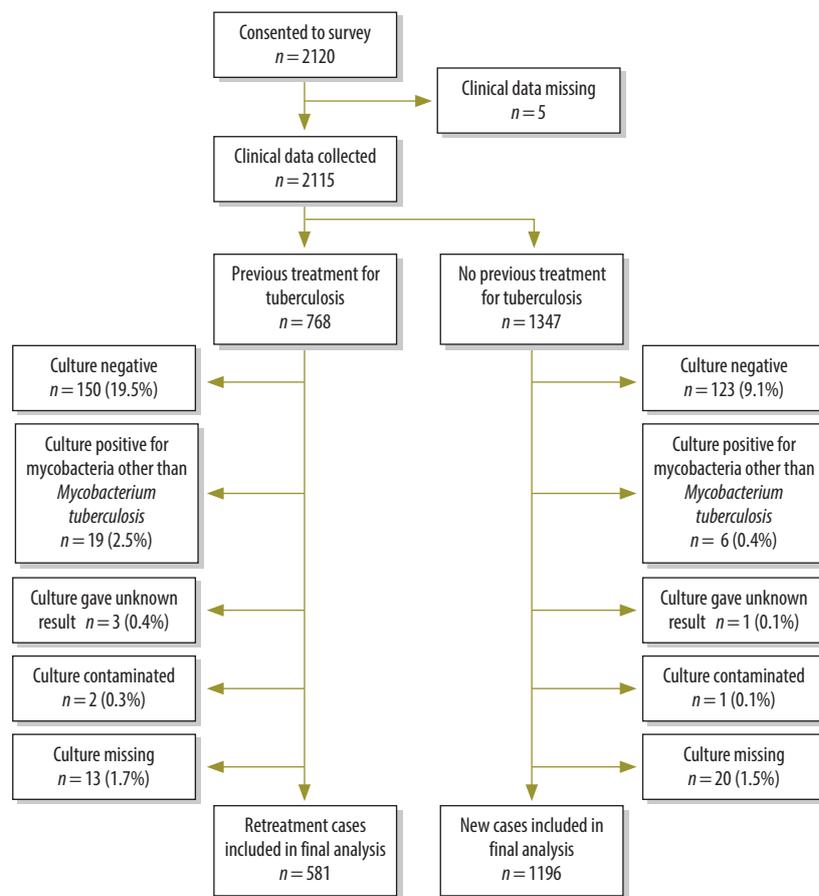
Ethical approval was granted by the Malawi National Health Sciences Research Committee in April 2009. This study commenced in 2009, before requirements for review of all WHO-supported research by the WHO research ethics review committee were fully implemented. Written informed consent was obtained from 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.

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-

Fig. 1. Flowchart to determine multidrug resistance in people diagnosed with tuberculosis in Malawi, 2010–2011



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

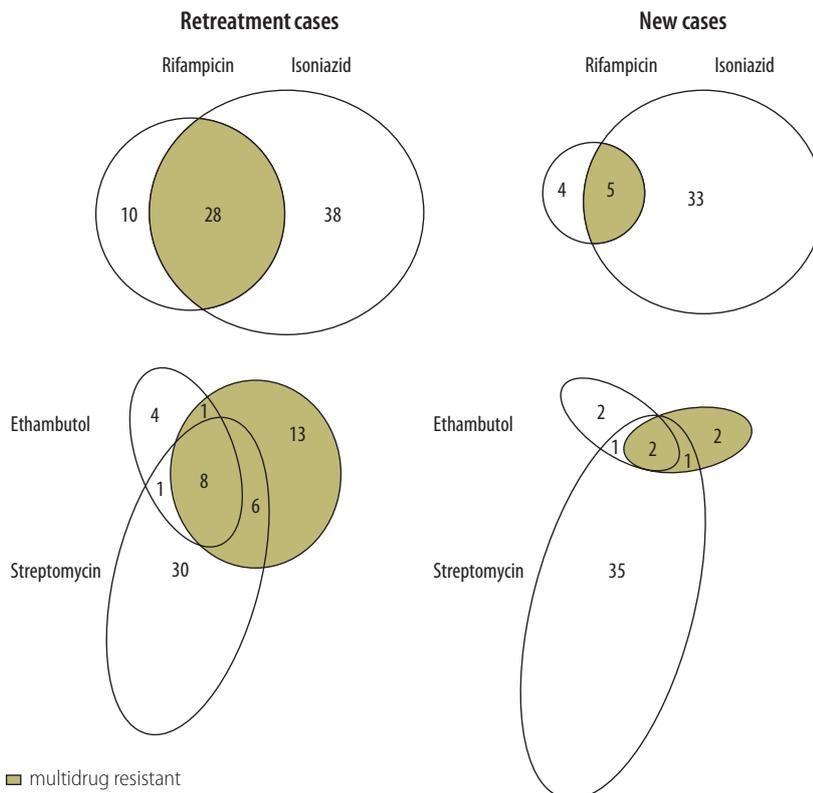


Table 3. Comparison of anti-tuberculosis drug susceptibility testing of Malawian *Mycobacterium tuberculosis* isolates, 2010–2011

Malawian result	South African result ^a			MDR
	Sensitive to all drugs	Resistant to rifampicin only	Resistant to isoniazid only	
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 tuberculosis²⁴ – 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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ملخص

مقاومة الأدوية للبكتريا المتفطرة السلية في ملاوي: دراسة استقصائية متعددة القطاعات

(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 للسلسل الشديد المقاوم للأدوية. وتبين من اختبار فيروس العوز المناعي البشري للأشخاص الذين تم الحصول على مستفرديات البكتريا المتفطرة السلية 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 بالسلسل الذين سجلوا نتائج إيجابية لاختبار اللطاخة منخفضاً في أفريقيا جنوب الصحراء الكبرى - بما يوضح على نحو محتمل قوة برنامج مكافحة السلسل 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 بالسلسل.

الغرض توثيق انتشار مقاومة الأدوية المتعددة بين الأشخاص الذين جرى تشخيص إصابتهم حديثاً بالسلسل - والذين تكرر علاجهم من السلسل - في ملاوي.

الطريقة أجرينا دراسة استقصائية تمثيلية على الصعيد الوطني للأشخاص المصابين بالسلسل وسجلوا نتائج إيجابية لاختبار لطاخة البلغم بين 2010 و2011. وقمنا بجمع البيانات الديمغرافية والسريرية وعييتين 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 مستفرديات البكتريا المتفطرة السلية التي تبين مقاومتها للأدوية المتعددة من أجل تحديد مقاومتها لأدوية الخط الأول - واختبارها من أجل تحديد مقاومتها لأدوية الخط الثاني - في مختبر مرجعي للسلسل على الصعيد فوق الوطني في جنوب أفريقيا.

النتائج بشكل عام، تم استفراد البكتريا المتفطرة السلية من 1777 (83.8%) مريضاً من أصل 2120 مريضاً بالسلسل سجلوا نتائج إيجابية لاختبار اللطاخة. وتم تحديد مقاومة الأدوية المتعددة في خمس (0.4%) من أصل 1196 مستفردة من حالات جديدة و28

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. 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. 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 Задokumentировать 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. 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. 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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Poor symptomatic tuberculosis screening practices in a quarter of health centres in Amhara Region, Ethiopia

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**SUPPLEMENT: THE ETHIOPIAN OR INITIATIVE****Poor symptomatic tuberculosis screening practices in a quarter of health centres in Amhara Region, Ethiopia**G. B. Gebregergs,^{1,2} M. Alemneh,³ D. N. Koye,⁴ Y. Kassie,⁵ M. Assefa,⁶ W. Ayalew,⁷ C. Temesgen,⁸ E. Klinkenberg,^{9,10} T. Tadesse⁴<http://dx.doi.org/10.5588/pha.14.0053>

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 1.23–30.80) 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 immuno-

deficiency 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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case finding; implementation; out-patients

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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 <i>woreda</i> health office: at least monthly supervision visits to health centres by <i>woreda</i> health officers
Review meeting: a quarterly meeting conducted to evaluate performance against quarterly plan and recommendations made by health centres, <i>woreda</i> 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 $\geq 80\%$ 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
<i>Woreda</i> officers: health professionals assigned at <i>woreda</i> (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 ($\geq 80\%$ 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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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 <i>woreda</i> 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 $\geq 80\%$ 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 $\geq 80\%$ 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 $\geq 80\%$ 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 $\geq 80\%$ 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

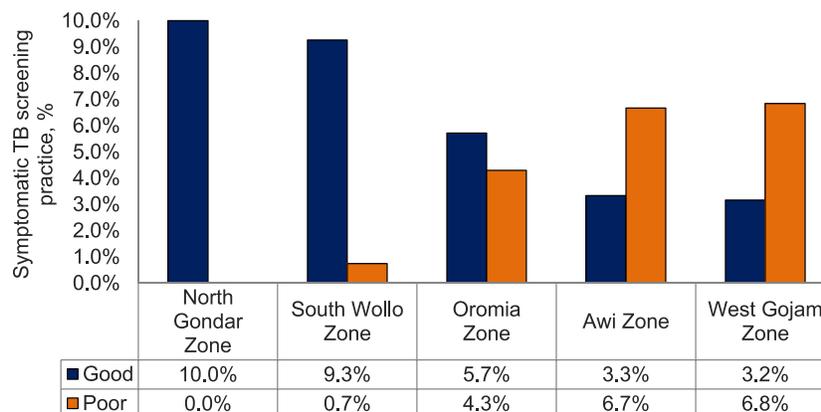


FIGURE Symptomatic TB screening practice at health centre out-patient departments by zone in the Amhara Region, Ethiopia, 2013. TB = tuberculosis.

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 ($\geq 80\%$)	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 <i>woreda</i> 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'Éthiopie 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 : Évaluer 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, Éthiopie.

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 Éthiopie.

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 diagnóstico 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.

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 36 states 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 formula 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 Wasu 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

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

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

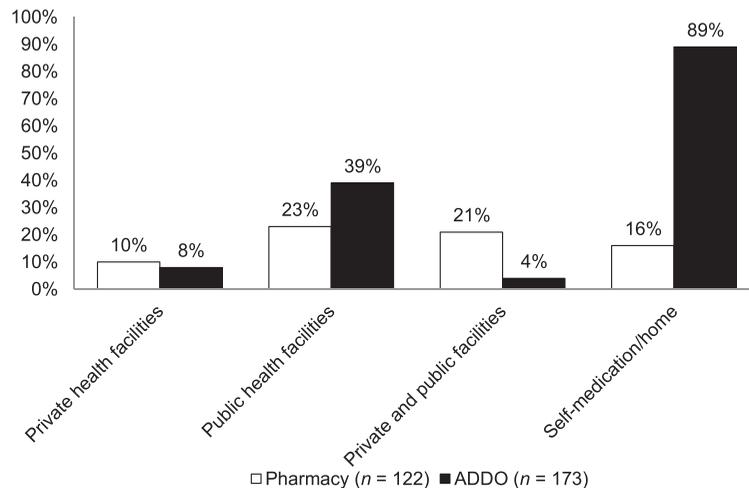


Figure Retail outlets' sources of clients (multiple responses allowed).

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 ≥ 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		Total (<i>n</i> = 295) <i>n</i> (%)
	Pharmacy (<i>n</i> = 122) <i>n</i> (%)	ADDO (<i>n</i> = 173) <i>n</i> (%)	
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 NTLF 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		Total (<i>n</i> = 295) <i>n</i> (%)
	Pharmacy (<i>n</i> = 122) <i>n</i> (%)	ADDO (<i>n</i> = 173) <i>n</i> (%)	
Anti-tuberculosis drugs stocked			
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 NTLTP 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 NTLTP, 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 NTLTP 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.

SCHEMA : 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 commodas 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.

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, $\chi^2 = 8.8$, $P = 0.01$). 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, $\chi^2 = 5.4$, $P = 0.02$) 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 tuberculosis 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 achievement 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 vulnerable 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/mm³ or < 20%, 36–59 months: < 350 cells/mm³ or < 20%, 5 years or older - same as adults: < 200 cells/mm³ 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 approval 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/mm³.

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

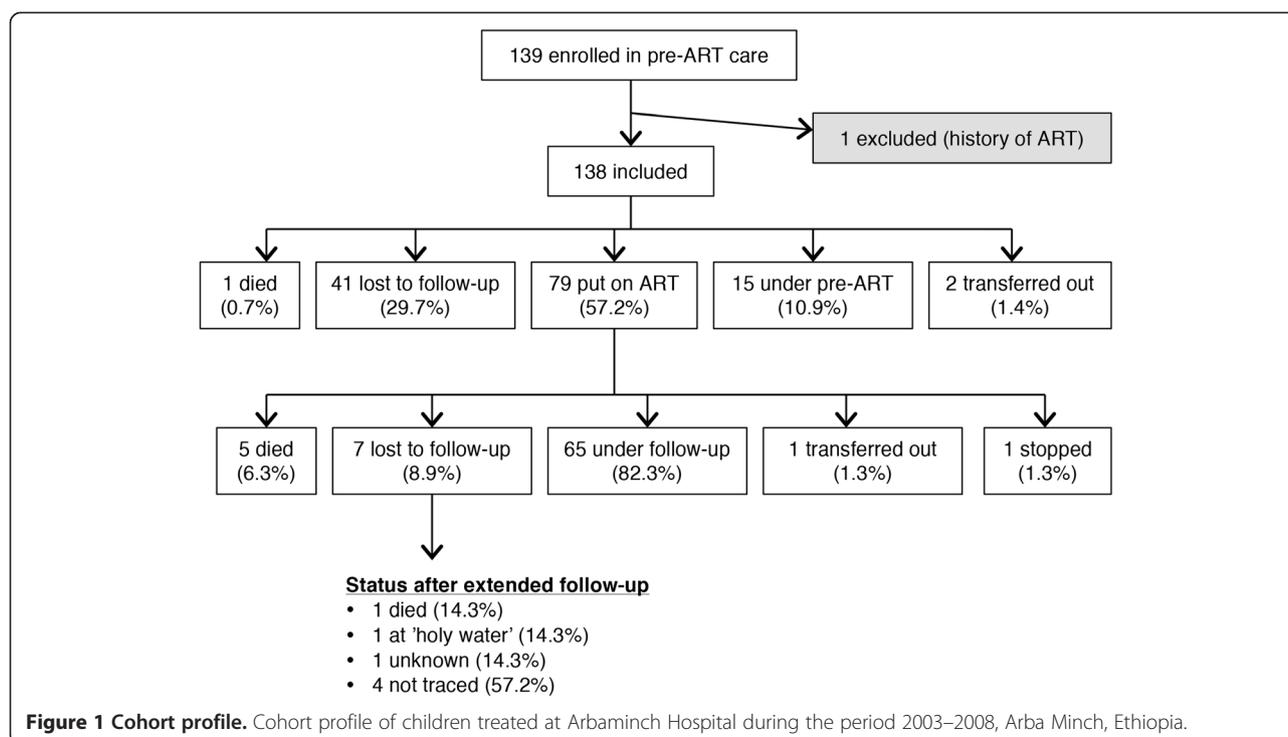


Table 1 Presenting characteristics of children, Arba Minch Hospital, Ethiopia

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].

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

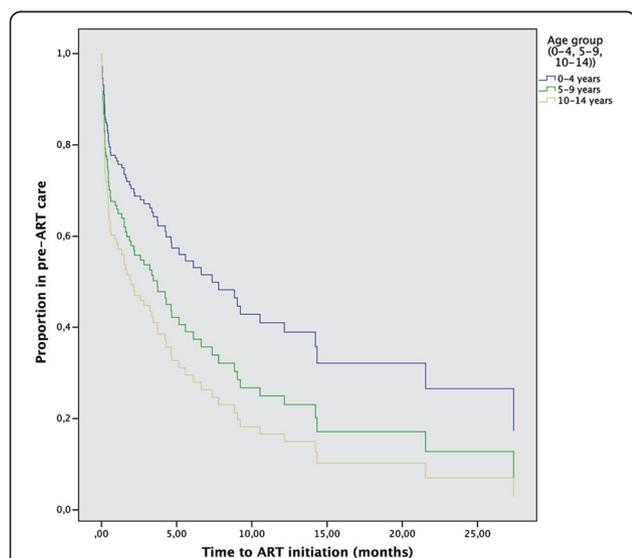


Figure 2 Time to ART for different age groups. Survival curves according to Cox regression analysis showing time to ART initiation for different age groups controlling for sex, place of residence, enrolment phase and WHO clinical stage upon presentation. Survival times for patients not reaching the event during the time of their observation (censored data) are also accounted for in the figure.

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	

^aChi-square significance test.

^bFisher'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.

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.

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.

Abbreviations

AIDS: Acquired Immunodeficiency Syndrome; ART: Antiretroviral therapy; ARV: Antiretroviral drug; CI: Confidence interval; HIV: Human immunodeficiency 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 tuberculosis 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}

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 ≥ 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 ≥ 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).

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

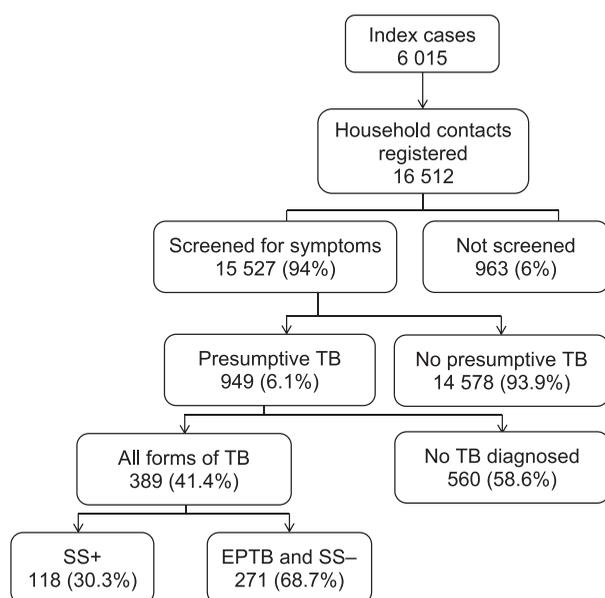


Figure Profile of contacts registered, screened and evaluated, Ethiopia, September 2014. TB = tuberculosis; SS = sputum smear; + = positive; EPTB = extra-pulmonary TB; – = negative.

Table 2 Variations in the yield of household contact investigations by administrative region, Ethiopia, April 2013–March 2014

Characteristic	Amhara <i>n</i> (%)	Oromia <i>n</i> (%)	Total <i>n</i> (%)	<i>P</i> 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, <i>n</i> (95%CI)	26 (25–26)	12 (11–12)	16 (16–17)	<0.0001
All forms of TB cases diagnosed, <i>n</i> (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, <i>n</i> (95%CI)	181 (177–185)	102 (99–104)	132 (130–134)	<0.01
NNT, <i>n</i> (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		Total % (95%CI)	<i>P</i> value
	≥5 years % (95%CI)	<5 years % (95%CI)		
Contacts screened, <i>n</i>				
Total	13 779	1 748	15 527	
Presumptive TB cases				
Total, <i>n</i>	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, <i>n</i> (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, <i>n</i>	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, <i>n</i> (95%CI)	42.4 (41.7–43.1)	27.3 (26.1–28.6)	39.9 (39.3–40.5)	<0.0001
NNT, <i>n</i> (95%CI)	2.2 (2–2.3)	3.9 (3.4–4.4)	2.4 (2.3–2.6)	<0.0001
SS+ TB				
Total, <i>n</i>	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, <i>n</i> (95%CI)	121.9 (119.9–124)	349.6 (333.4–366.4)	131.6 (129.5–133.7)	<0.0001
NNT, <i>n</i> (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.

SCHEMA : 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.

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.

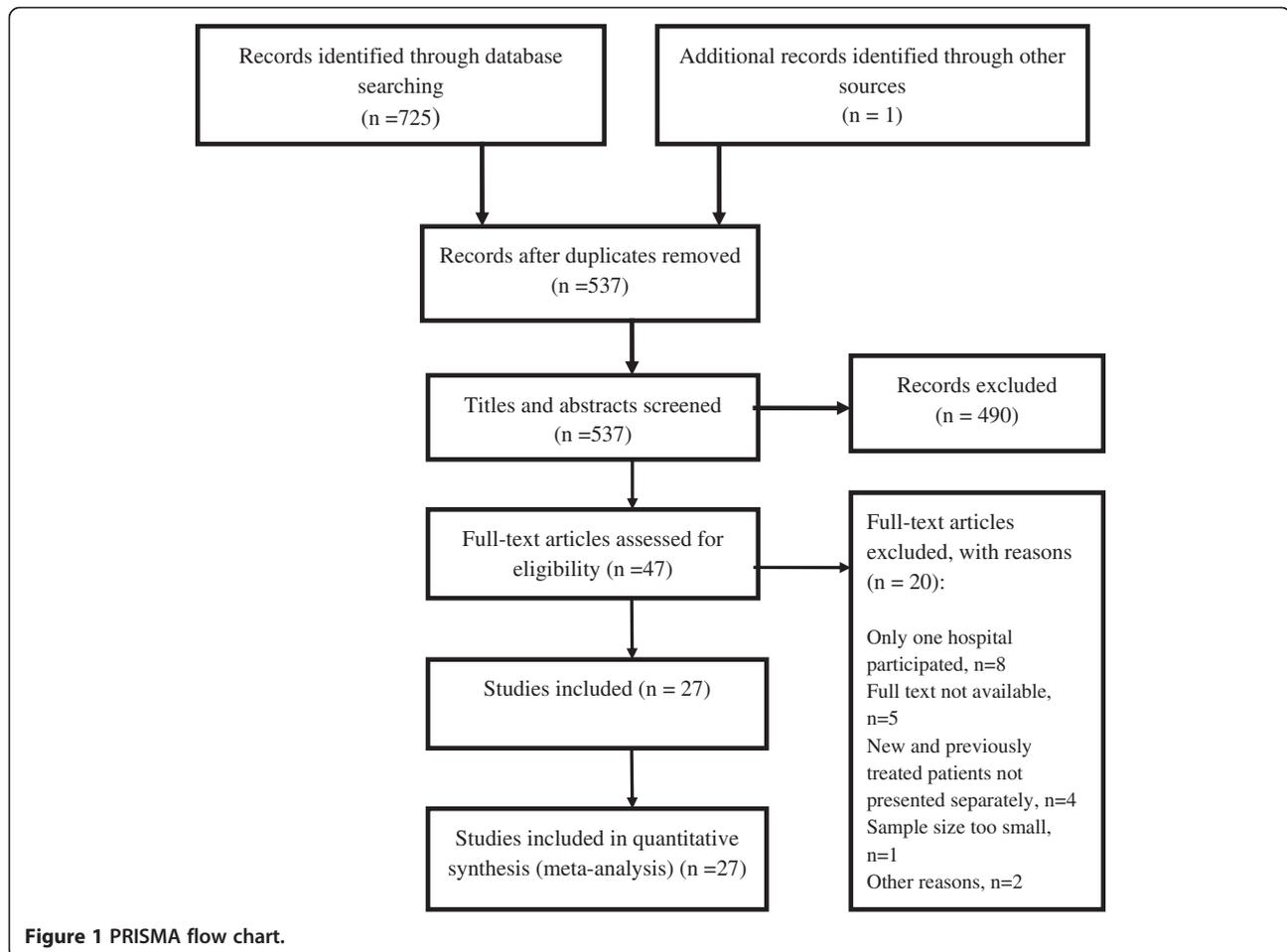
DR-TB data was reported for a total of 15,462 sputum smear-positive TB patients in the 27 articles included from 2003 to 2013. Of these, 13,645 (88.4%) and 1,776 (11.6%) were new and previously treated patients, respectively. All reported estimates for any resistance and MDR-TB among new and previously 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,



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 <i>et al.</i> [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. <i>et al.</i> [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. <i>et al.</i> [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. <i>et al.</i> [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. <i>et al.</i> [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. <i>et al.</i> [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. <i>et al.</i> [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. <i>et al.</i> (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. <i>et al.</i> [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. <i>et al.</i> (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. <i>et al.</i> [31]	2004-2005	Rwanda	National survey.	New and PT patients	701	N/A	3.3	LJ	INH, RMP, SM, EMB
Irenious S. <i>et al.</i> [15]	2011	Somalia	National survey.	New and PT patients	946	N/A	N/A	Hain	INH, RMP only
Chonde TM <i>et al.</i> [32]	2006-2007	Tanzania	National survey.	New and PT patients	1,167	N/A	5.8	LJ	INH, RMP, SM, EMB
Tessema B. <i>et al.</i> [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. <i>et al.</i> [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. <i>et al.</i> [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. <i>et al.</i> [36]	2002	Botswana	National survey.	New and PT patients	2,425	60	25.7	LJ	INH, RMP, SM, EMB
Ramarokoto H. <i>et al.</i> [37]	2005-2007	Madagascar	National survey.	New and PT patients	1,275	N/A	0.6	LJ	INH, RMP, SM, EMB
Samo Gudo P. <i>et al.</i> [38]	2007-2008	Mozambique	National survey.	New and PT patients	1,200	N/A	11.5	LJ	INH, RMP, SM, EMB
Sanchez-Padilla E. <i>et al.</i>	2009	Swaziland	National survey	New and PT patients	633	79.9	25.8	MGIT or LJ	INH, RMP, SM, EMB
Edgbola R.A. <i>et al.</i> [39]	1999	Gambia	National survey.	New and PT patients	225	N/A	2.1	LJ	INH, RMP, SM, EMB
Affolabi D. <i>et al.</i> [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. <i>et al.</i> [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. <i>et al.</i> [42]	2005	Ivory Coast	National survey.	New patients	320	N/A	4.9	LJ	INH, RMP, SM, EMB
Sangare L. <i>et al.</i> [43]	2010	Bukina Furso	National survey.	New and PT patients	416	28.7	1.3	LJ	INH, RMP, SM, EMB
Ellis Awusu-Dabo <i>et al.</i> [44]	2001-2004	Ghana	National survey.	New and PT patients	216	25.9	4.7		INH, RMP, SM, EMB, Thiacetazone
Jurgen Noesk <i>et al.</i> [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. <i>et al.</i> 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.

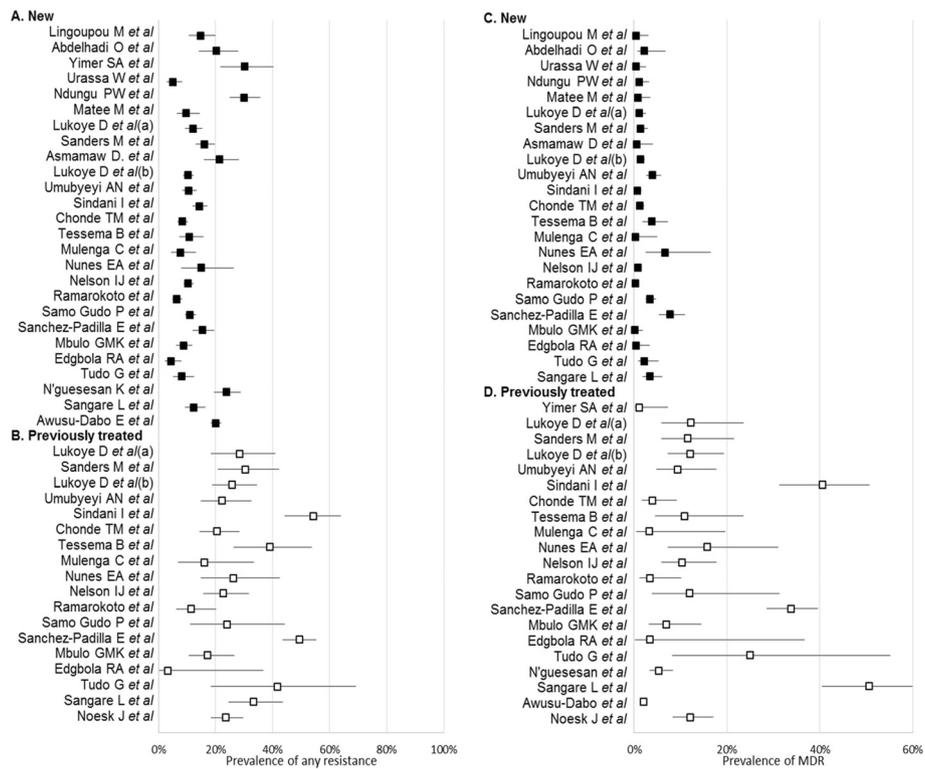


Figure 2 Forest plot of prevalence of any resistance and MDR among new and previously treated patients.

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

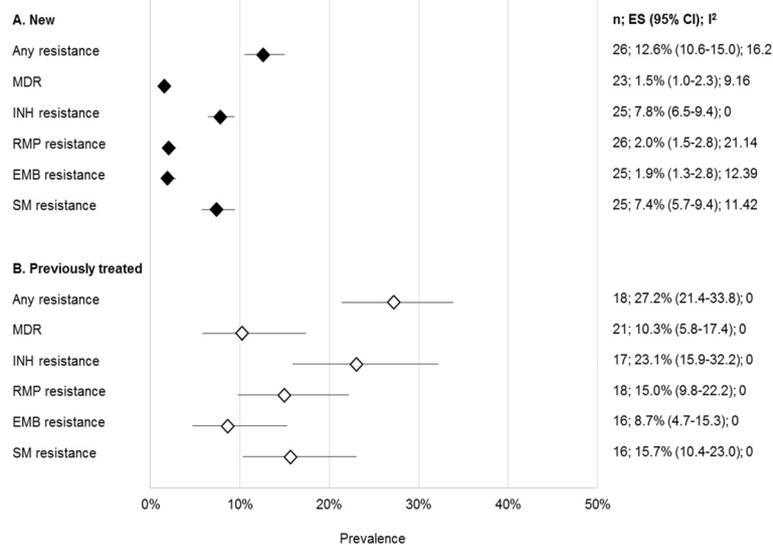


Figure 3 Pooled estimates for all resistance patterns among new and previously treated patients. Abbreviations: n, number of studies; ES, estimate; INH, isoniazid; RMP, rifampicin; EMB, ethambutol; SM, streptomycin.

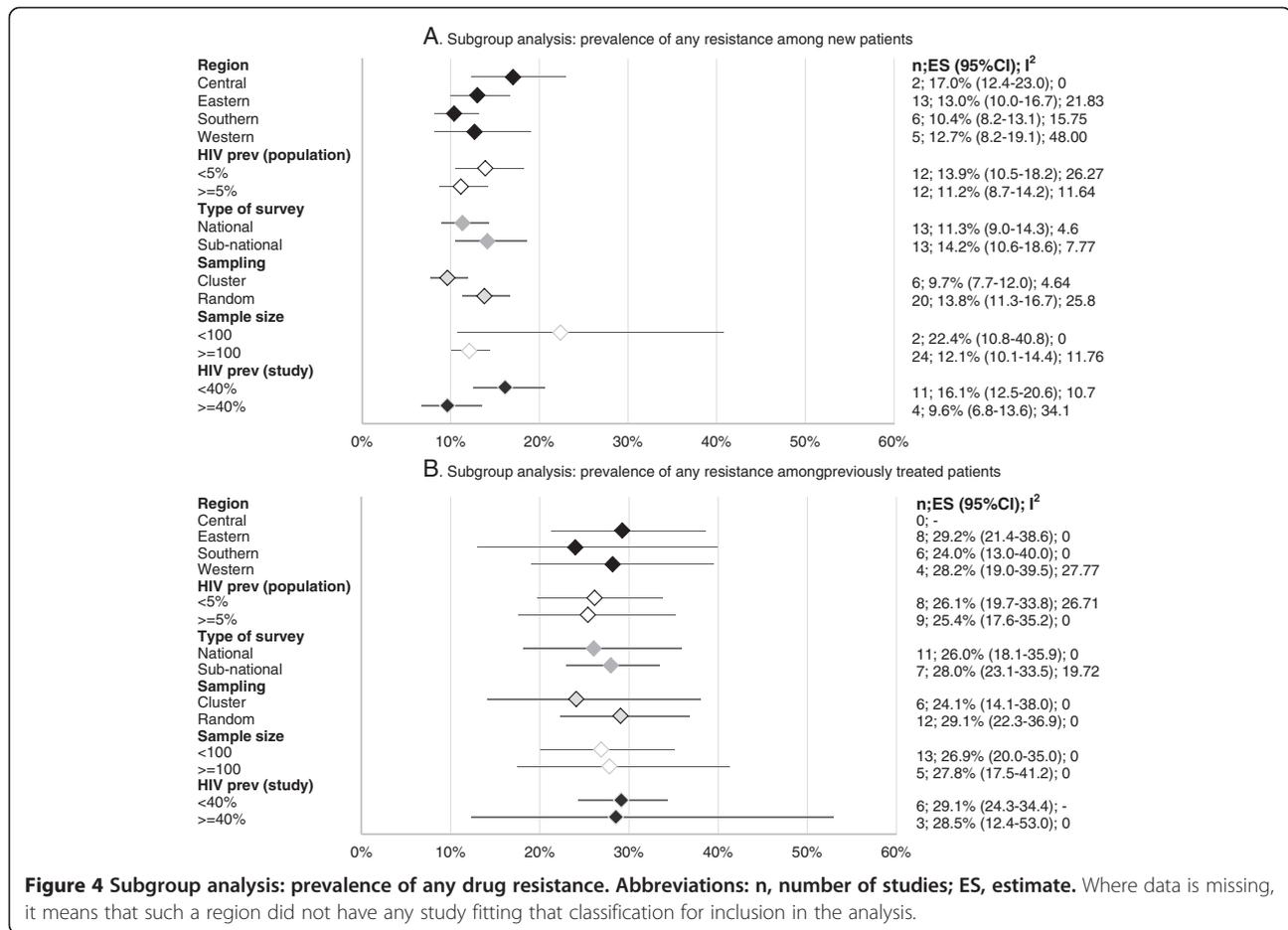


Figure 4 Subgroup analysis: prevalence of any drug resistance. Abbreviations: n, number of studies; ES, estimate. Where data is missing, it means that such a region did not have any study fitting that classification for inclusion in the analysis.

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).

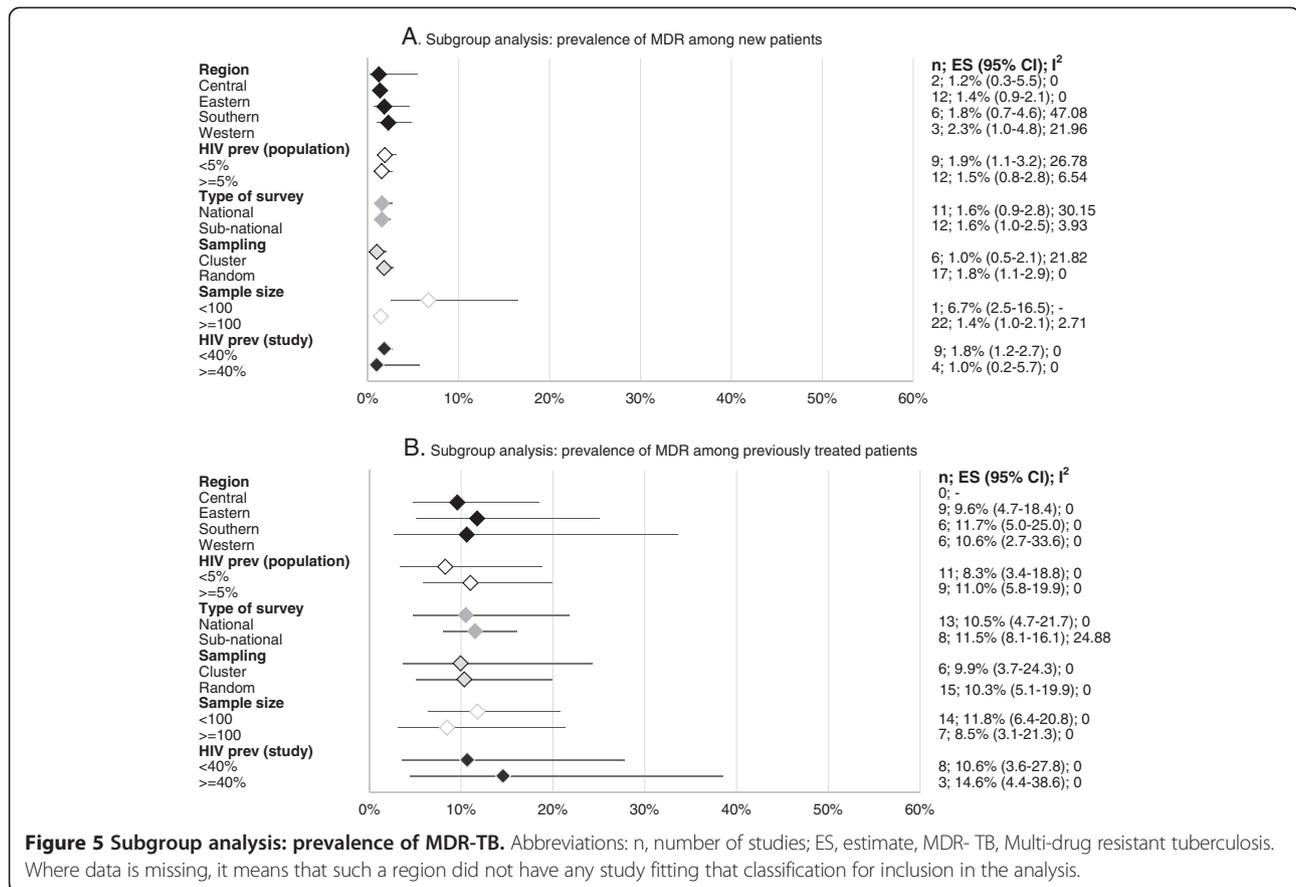
Sampling design

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)



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).

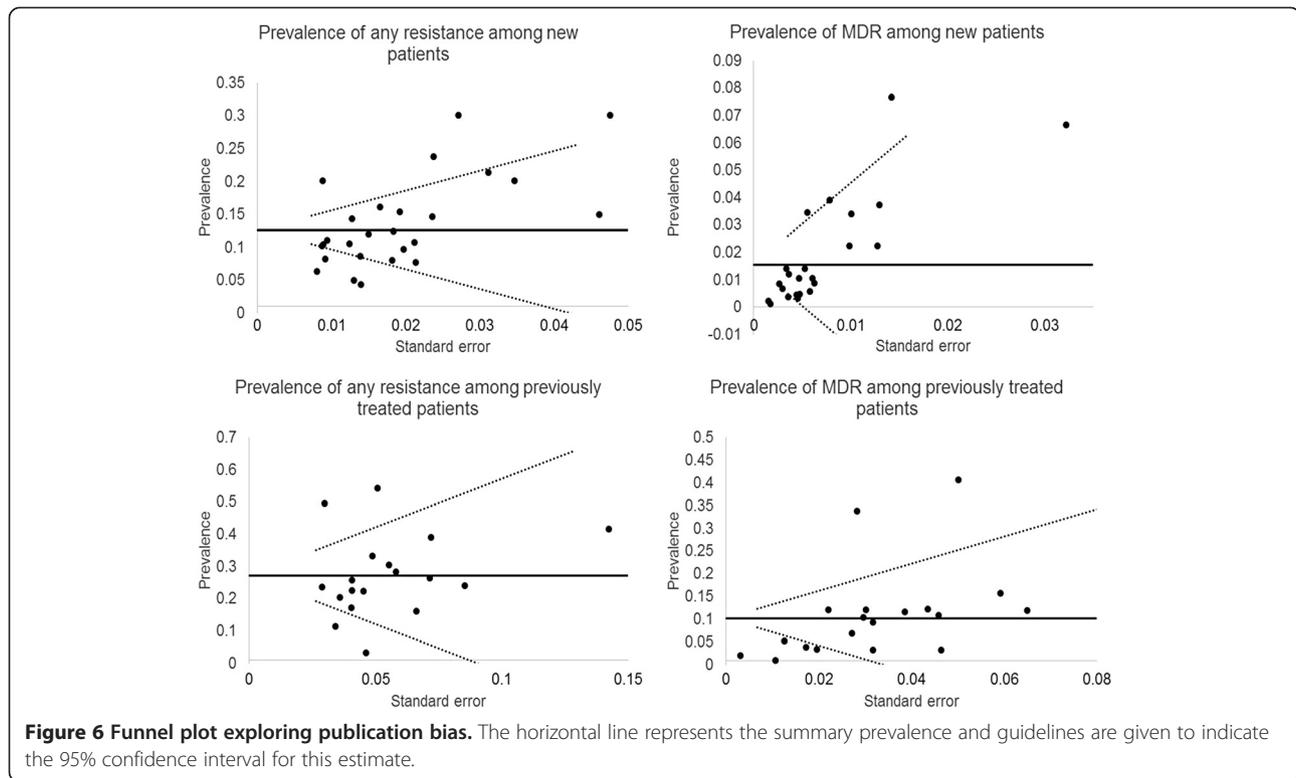
Publication bias

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



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

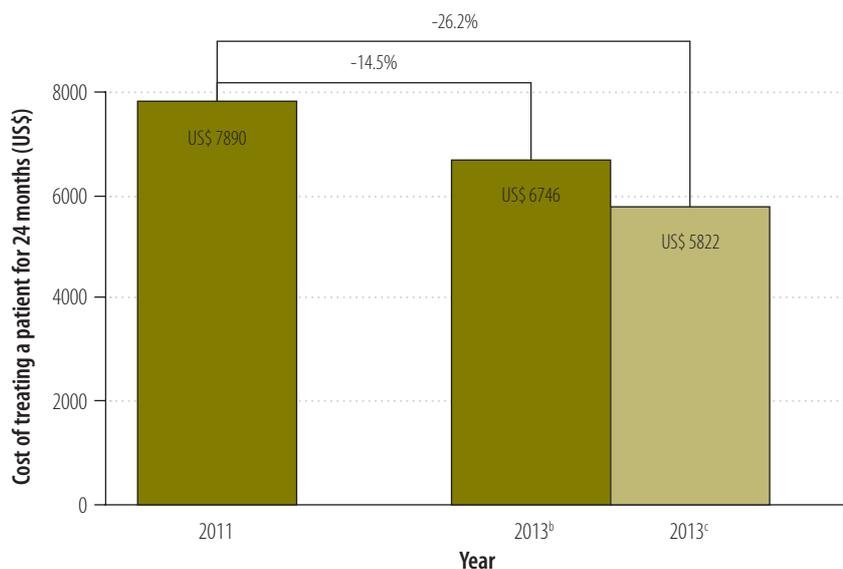
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Fig. 1. **Cost of selected treatment^a for multidrug-resistant tuberculosis from the Global Drug Facility, 2011–2013**



US\$, United States dollars.

^a The selected treatment was the longest and most expensive regimen for multidrug-resistant tuberculosis: 12 months of capreomycin, prothionamide, cycloserine, moxifloxacin and *para*-aminosalicylic acid sodium salt, followed by 12 months of prothionamide, 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

في تحسين الوصول على الصعيد العالمي إلى الأدوية المضادة للسل وتقنيات التشخيص التي تليها 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

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

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.

ضخمة. ويزيد دمج السوق بهذه الطريقة الحوافز لموردي الأدوية مضمونة الجودة.

التغيرات 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 وأهبط ثمناً للمريض بمقدار 26٪ - أي من 7890 دولاراً أمريكياً في عام 2011 إلى 5822 دولاراً أمريكياً في عام 2013.

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 grands 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» предназначен 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

Table 1 Interview affiliations

Country	Organization							Total
	NTP	Health Ministry	Procurement	Regulatory	WHO	Expert	NGO	
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*											Total number of 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†
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.

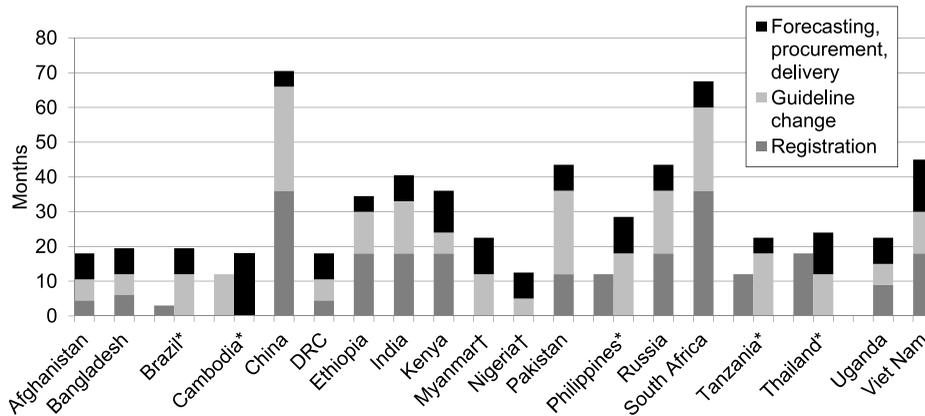


Figure 1 Estimated median time for key steps toward product availability. *Indicates that more than one of these processes may occur in parallel. †Stakeholders report that registration is not required as a condition for introduction of new anti-tuberculosis drugs. DRC = Democratic Republic of Congo.

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

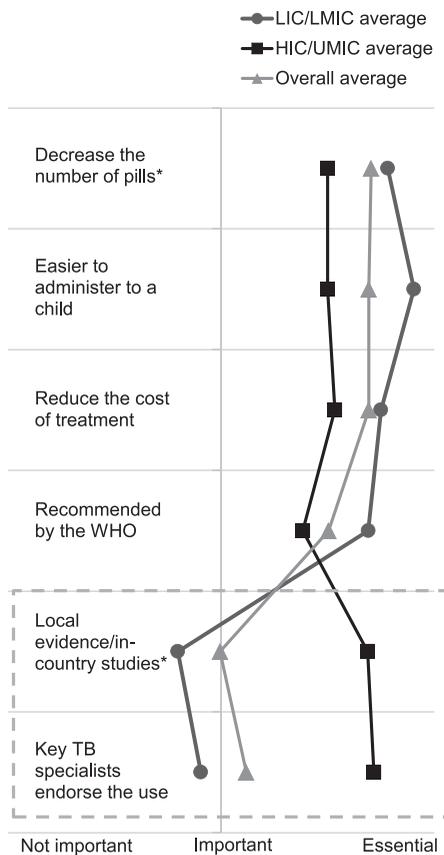


Figure 2 Key criteria for treatment adoption. *Myanmar data on the number of pills and Brazil data on local evidence not available. WHO = World Health Organization; LIC = low-income country; LMIC = low-middle-income country; HIC = high-income country; UMIC = upper-middle-income country.

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.

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-

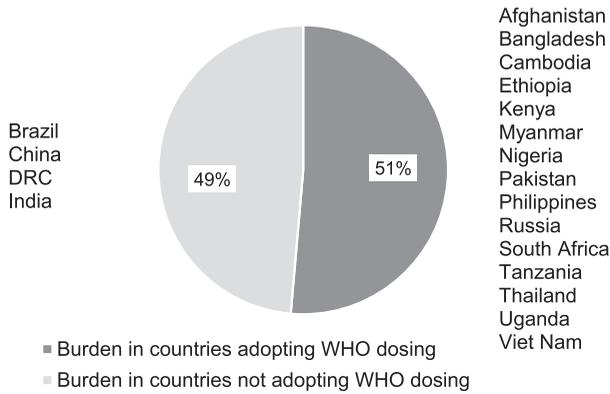


Figure 3 Burden in countries per WHO guideline adoption status. WHO = World Health Organization; DRC = Democratic Republic of Congo.

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-

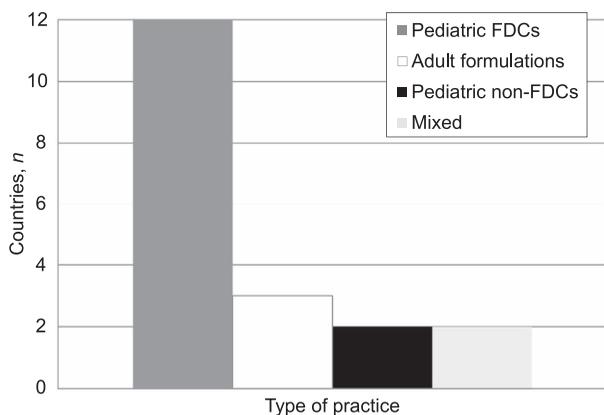


Figure 4 Formulation practices. FDC = fixed-dose combination.

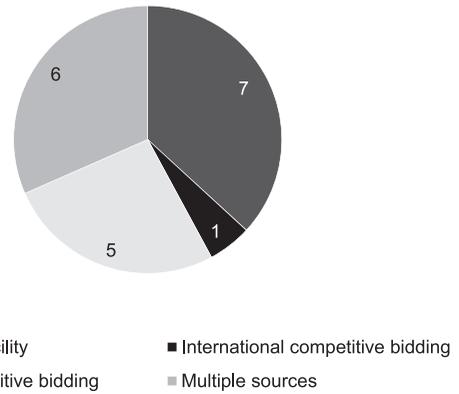


Figure 5 Source of country first line drug supply.

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.

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APPENDIX

World Bank Country and Lending Group Classifications, 2015¹

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

Reference

¹ World Bank. Country and lending groups. Washington DC, USA: World Bank, 2015. data.worldbank.org/about/country-and-lending-groups. Accessed September 2015.

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.

RESEARCH ARTICLE

Open Access



Multidrug resistant tuberculosis: prevalence and risk factors in districts of metema and west armachiho, Northwest Ethiopia

Feleke Mekonnen¹, Belay Tessema², Feleke Moges², Aschalew Gelaw², Setegn Eshetie^{2*} and Gemechu Kumera³

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 February 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 health 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 from 16–75 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 from 10 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 north-western 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

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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 to 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

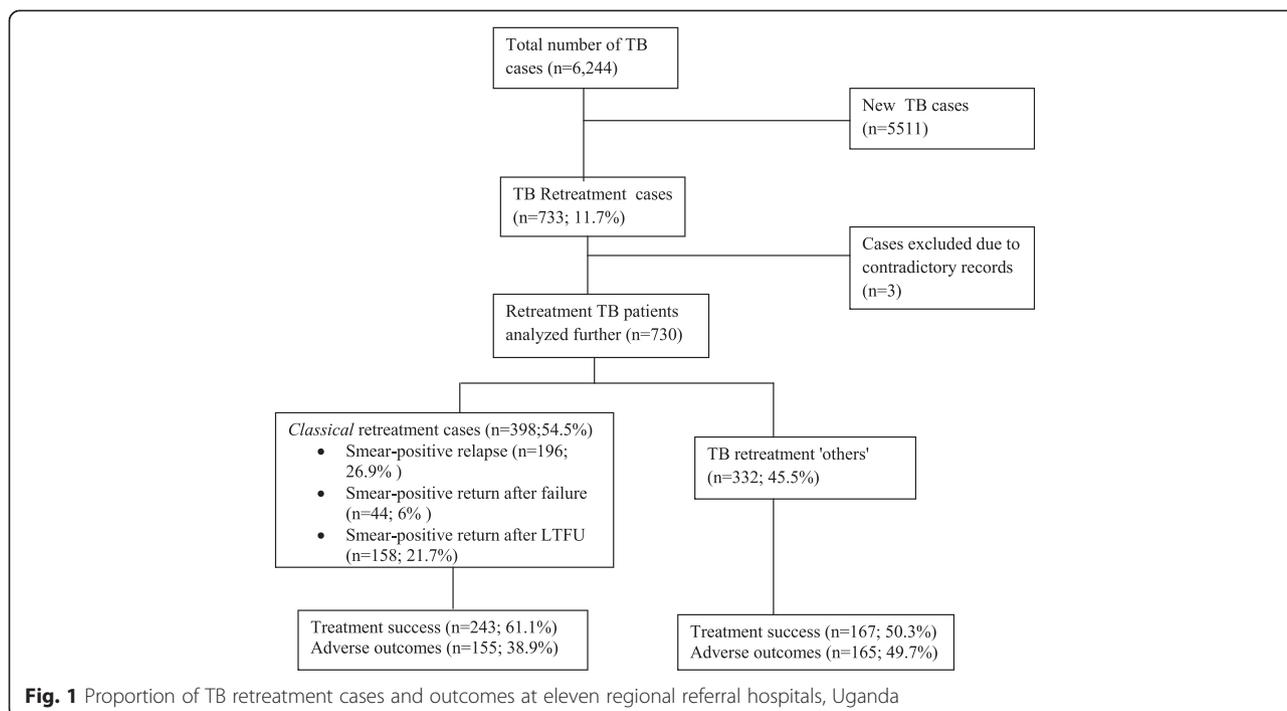
In Uganda, a TB retreatment case is defined as a person previously treated with anti-TB drugs for a month or more and is being treated again, in line with WHO definitions [1, 8]. The retreatment category is further classified either as 'relapse', 'treatment after failure', 'return after LTFU' or 'others'. 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



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 DTLs 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 n (%)	Type of retreatment cases		P-value*
		Classical TB retreatment cases; n = 398 (%)	TB retreatment 'others'; 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

^a1 patient had missing data

^bOther 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 anti-retroviral 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 n (%)		HIV Positive n (%)		HIV Positive 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

^a1 patient had missing data on this variable

^bCotrimoxazole 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 $P = 0.05$ ^a1 patient had missing data^bAdjusted 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; NTL: 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 Landis 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 homogeneously 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]

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 100,000—more 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.

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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 for 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

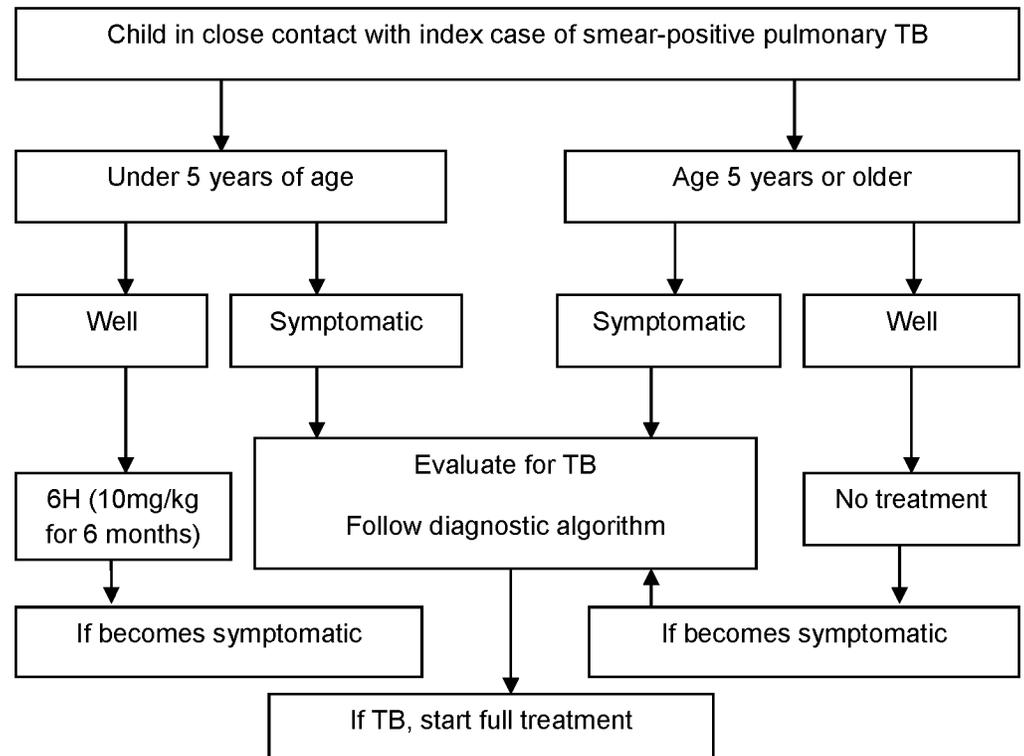


Fig 1. Algorithm for screening children in contact with an index case.

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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 facilities—at 52% at 2010, 89% in 2014, and 80% in 2015—as 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 notification							
Outpatient attendance	232,367	340,394	374,866	412,352	474,205	545,536	627,136
Presumptive TB patients identified/ 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 notified (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 notified	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 notification rate per 100,000 population (all forms)	59	77	71	81	87	118	125
Case notification rate 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 notified among 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 = confidence 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).

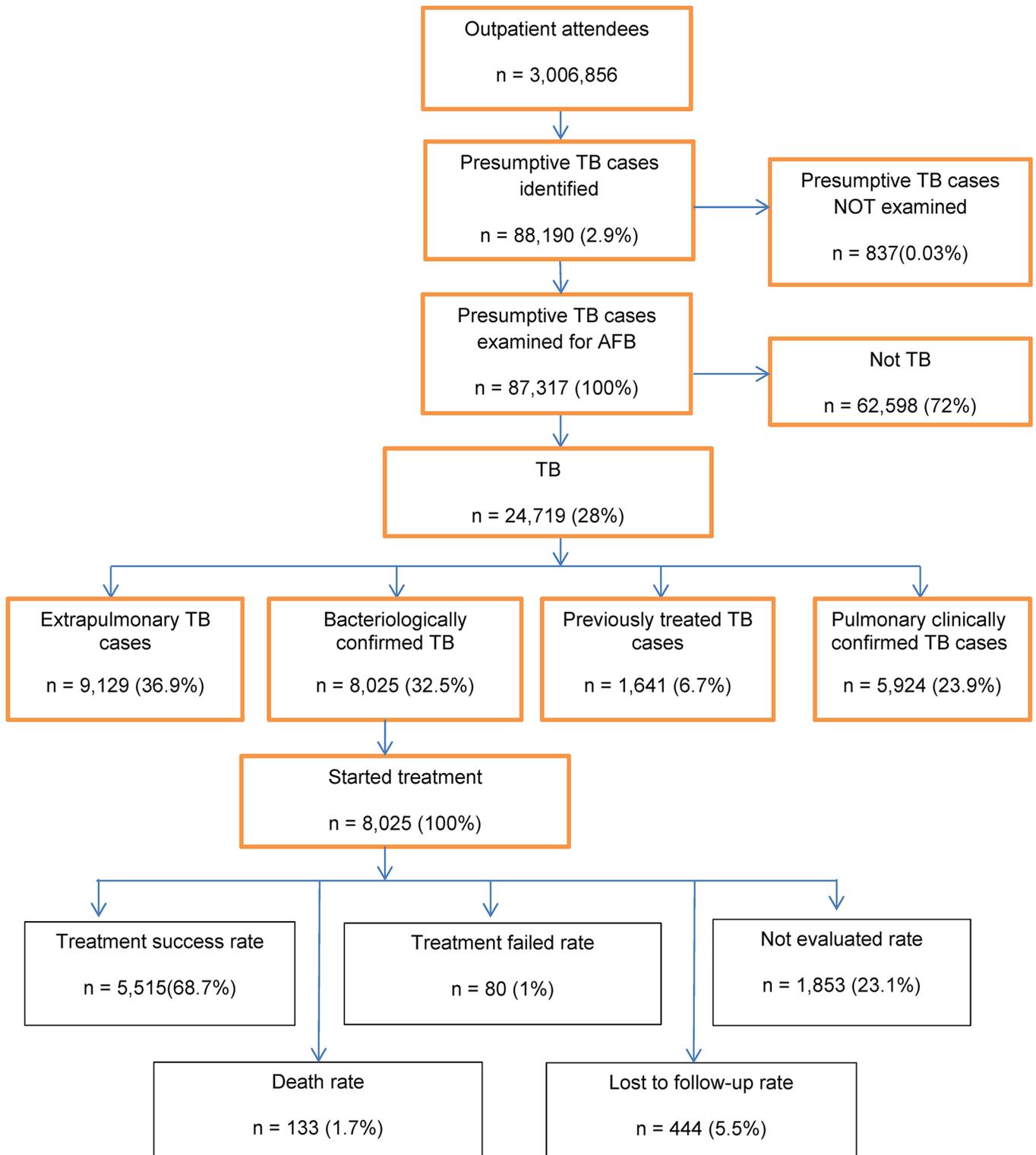


Fig 2. Flow chart of TB case notification and treatment outcomes in Kabul, 2009–2015.

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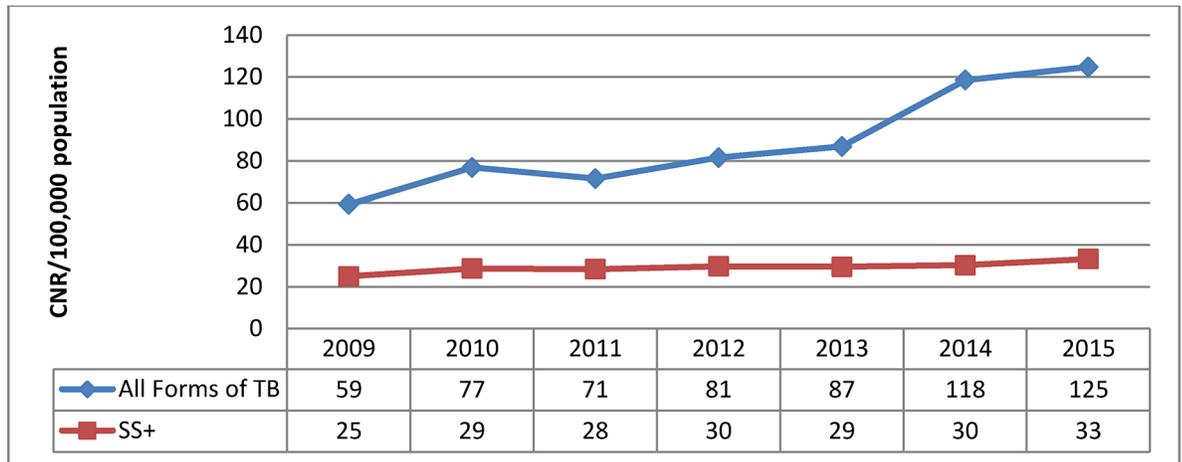


Fig 3. Case notification rate per 100,000 population in Kabul, 2009–2015.

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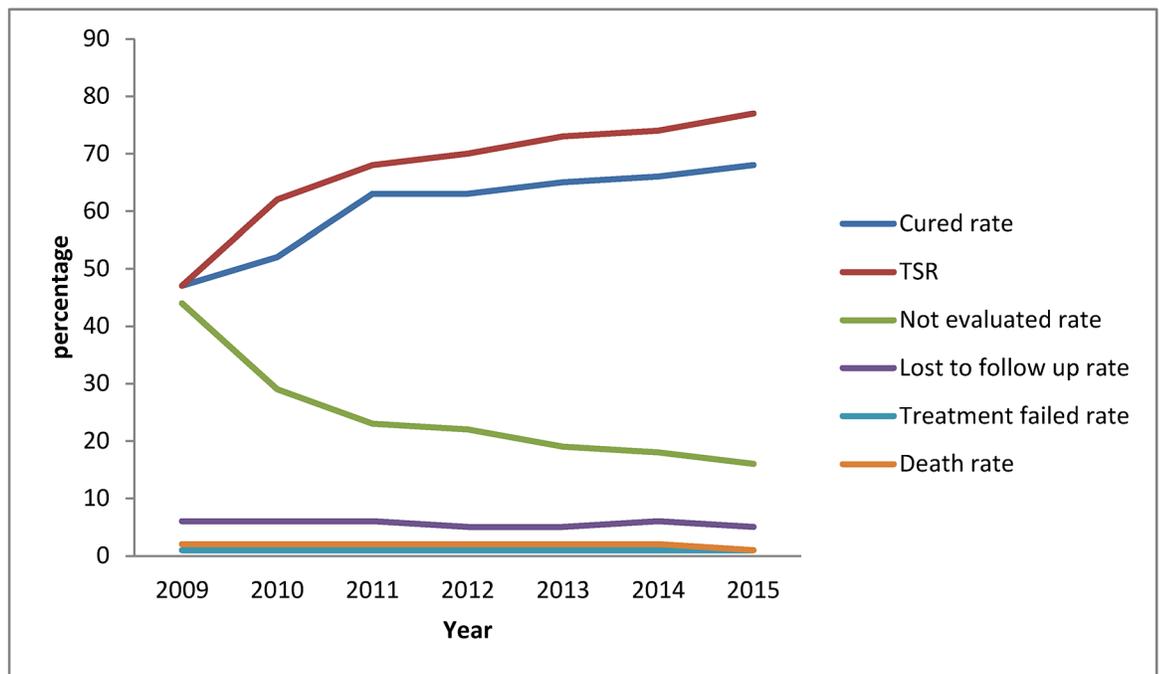


Fig 4. Treatment outcomes for SS+ TB, Kabul, 2009–2015.

<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 notified	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 components—including other government agencies and the private sector—have 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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RESEARCH ARTICLE

Open Access



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 rifampicin) 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 outcome, 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).

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).

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

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 variate 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 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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RESEARCH ARTICLE

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Epidemiology of tuberculosis in children in Kampala district, Uganda, 2009–2010; a retrospective cross-sectional study

Eric Wobudeya^{1,2*}, Deus Lukoye³, Irene R. Lubega^{1,2}, Frank Mugabe⁴, Moorine Sekadde⁴ and Philippa Musoke^{2,5}

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 NTLTP 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
	5–9	246
	10–14	292
District	Kampala	685
	Wakiso	238
	Others	244
Division	Kawempe	172
	Makindye	139
	Central	38
	Nakawa	120
	Rubaga	216
Sex	Female	548
	Male	619
TB type	PTB	1041
	EPTB	126
Sputum collected	Yes	456
	No	711

Seventy five percent (874/1167) had HIV test counseling, 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		P value
		Positive n (%)	Negative n (%)	
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

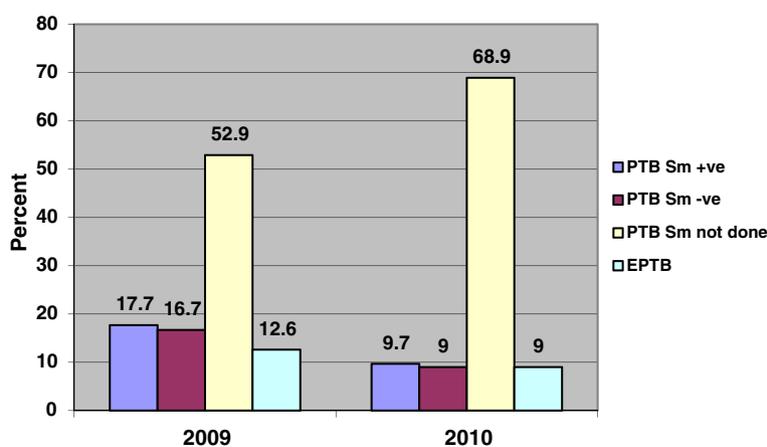


Fig. 1 Distribution of TB types in children in Kampala district, Uganda 2009, 2010 (N = 1167)

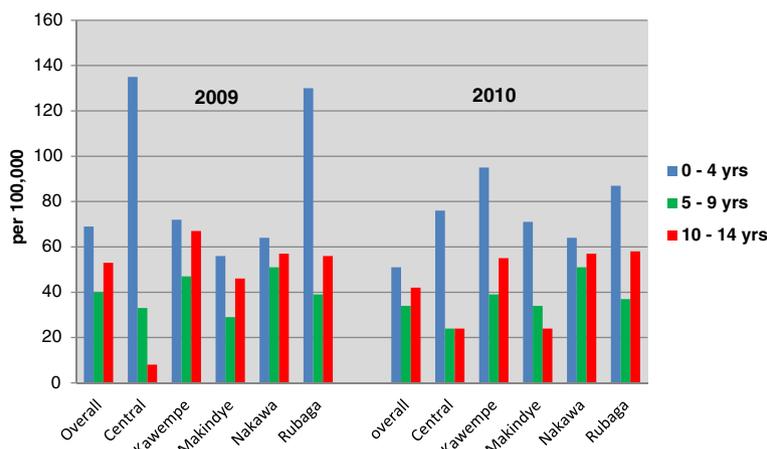


Fig. 2 Childhood TB incidence by age group and division in Kampala district, Uganda 2009, 2010

[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

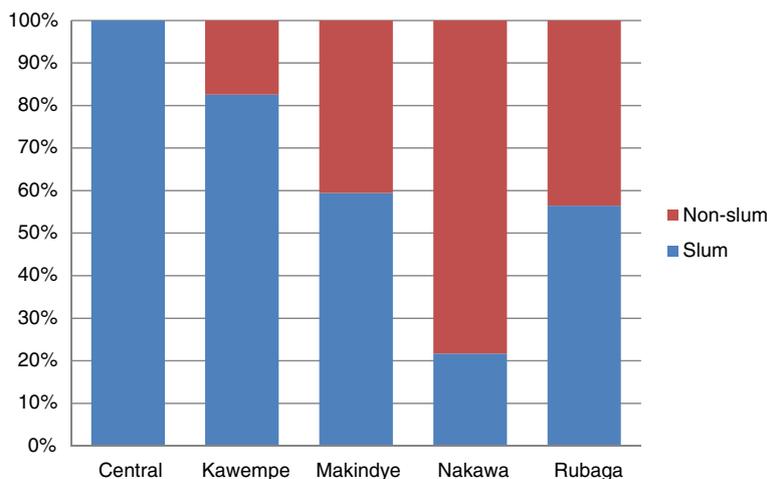


Fig. 3 Distribution of residence of TB cases residing in Kampala District, Uganda 2009–2010 (N = 685)

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 anti-retroviral 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

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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, USA¹) or monitor treatment for the human immunodeficiency virus (HIV) (e.g., Alere Pima[™] CD4, Alere, Waltham, MA, USA²) 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 tools⁷ 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 hamstringing 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 burden¹¹ 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 accessibles, 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.

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 Jerene² and Wakgari Deressa³

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 6EH 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 rifampicin 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 Immunodeficiency 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 Epiinfo 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 (χ^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/4RH regimens 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 4RH (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 vs 387 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 Anti-retroviral 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)	

^aStandard deviation, ^bCPT Cotrimoxazole prophylactic therapy, ^cART antiretroviral therapy

TB cases, 78.6 % had undergone sputum follow up examination at least once after the diagnosis (76.3 % among 6EH and 80.9 % among 4RH, $p = 0.3$). Thus sputum smear results at the end of second, fifth and sixth/seventh months of treatment were available for 274 (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			P value
		6EH (n = 395) n (%)	4RH (n = 395) n (%)	Total N (%)	
Weight at 2 nd month	Mean ± SD	49.9 ± 8.9	50.8 ± 8.2	50.4 ± 8.6	0.2
Weight at 5 th month	Mean ± SD	51.4 ± 8.6	51.3 ± 7.3	51.3 ± 7.9	0.9
Weight at 6/7 th month	Mean ± SD	51.1 ± 8.9	52.5 ± 6.5	51.7 ± 7.9	0.3
Change in weight at 2 nd 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 2 nd 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 5 th 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 6/7 th 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 2 nd 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)

^aConfidence interval, ^bExtra pulmonary Tuberculosis, bold figures indicate statistically 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 rifampicin 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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Priority digital health products will be profiled and developed to support the scale-up of WHO's End TB Strategy <http://ow.ly/4mRRjR>

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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.

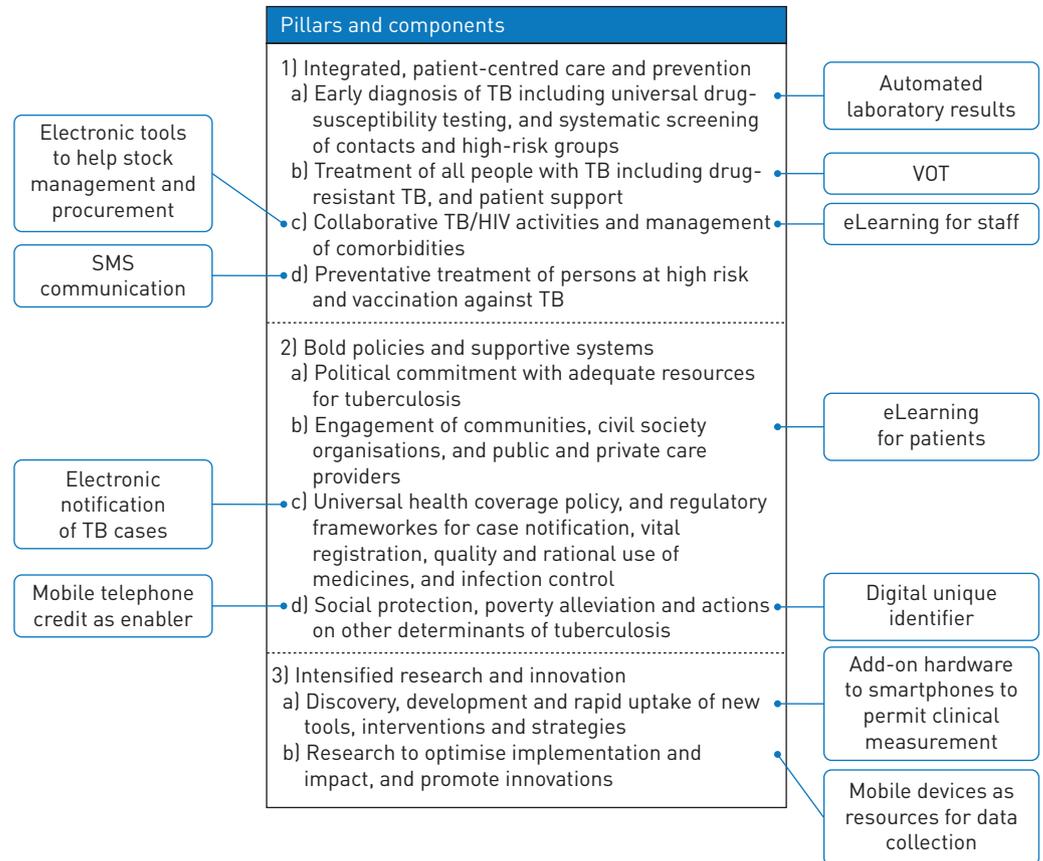


FIGURE 1 Examples of common digital health products and their potential contribution to different components of the End TB Strategy. TB: tuberculosis; VOT: video (virtually) observed therapy; eLearning: electronic learning; SMS: Short Message Service.

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 <i>via</i> 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

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.

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

junction 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

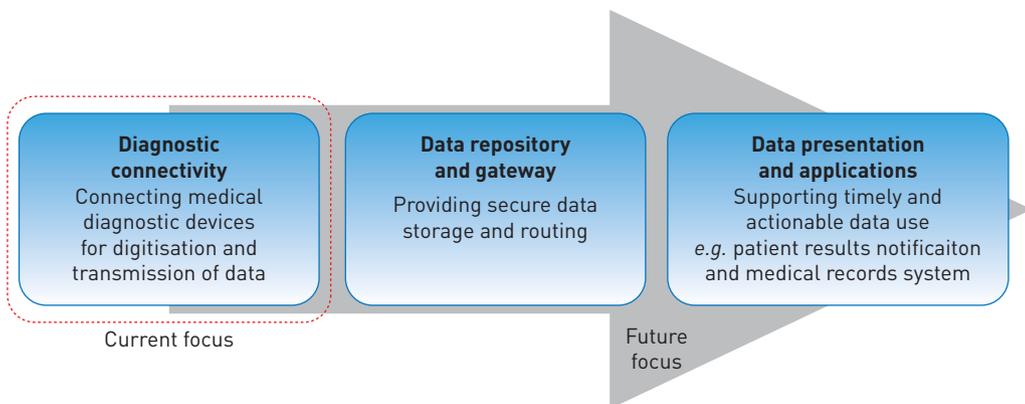


FIGURE 2 Schematic representation of the position of “diagnostic device connectivity” alongside other elements of a comprehensive laboratory information system for tuberculosis.

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

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.

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 95% CI 1.13–2.68), having index cases who registered for treatment within <12 months (AOR:

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Formal analysis: ZG DH NH.
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Visualization: ZG DJ DH MM NH.
Writing - original draft: ZG.
Writing - review & editing: ZG DJ DH MM NH.

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-variables, 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).

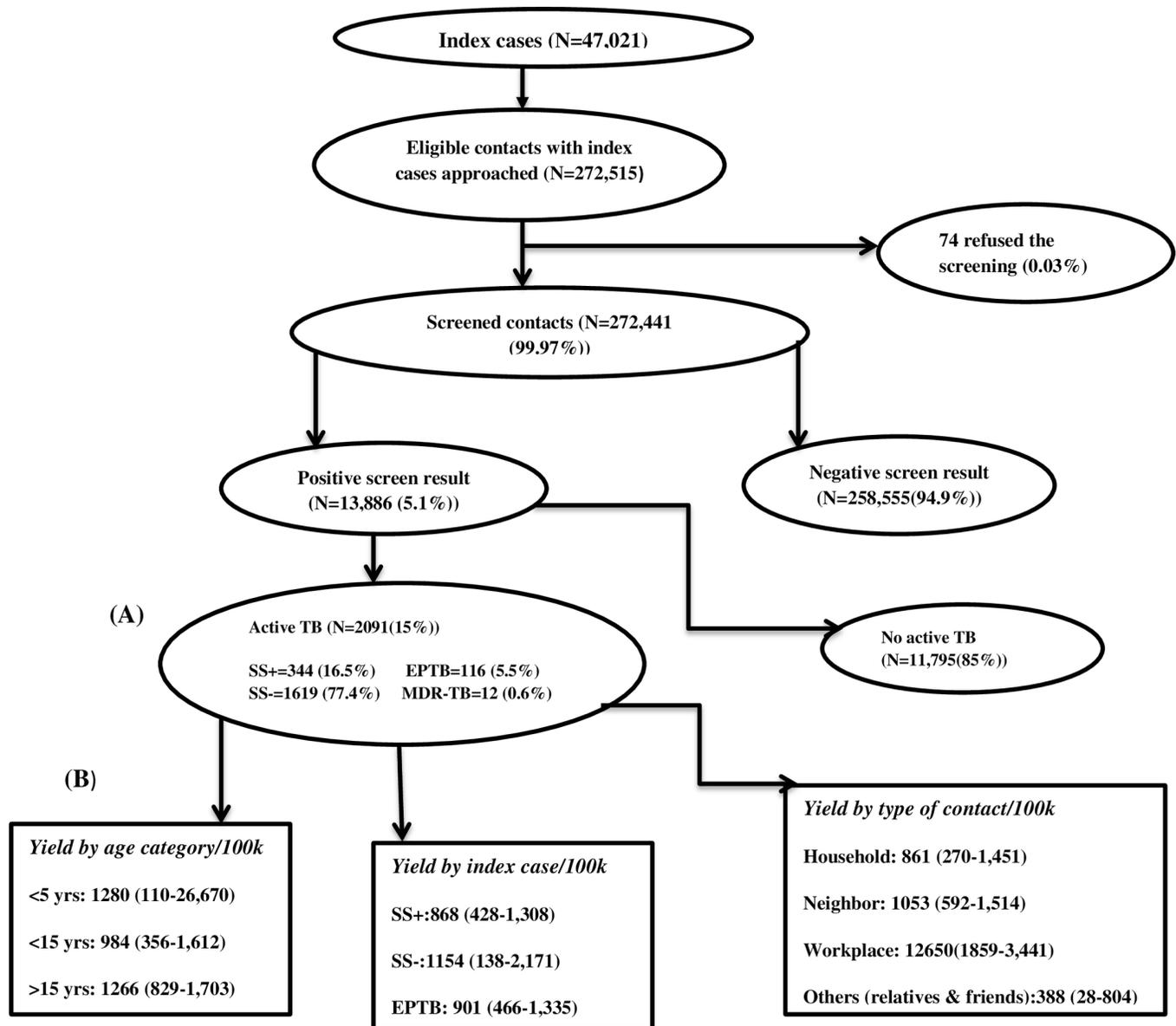
Being contact of SS- index cases (AOR: 1.74 95% CI 1.13–2.68), having index cases who registered for treatment within <12 months (AOR: 2.41 95% CI 1.51–3.84), and being household contact (AOR: 0.072 95% CI 0.01–0.52) were factors that were significantly associated with the occurrence of active TB in 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.

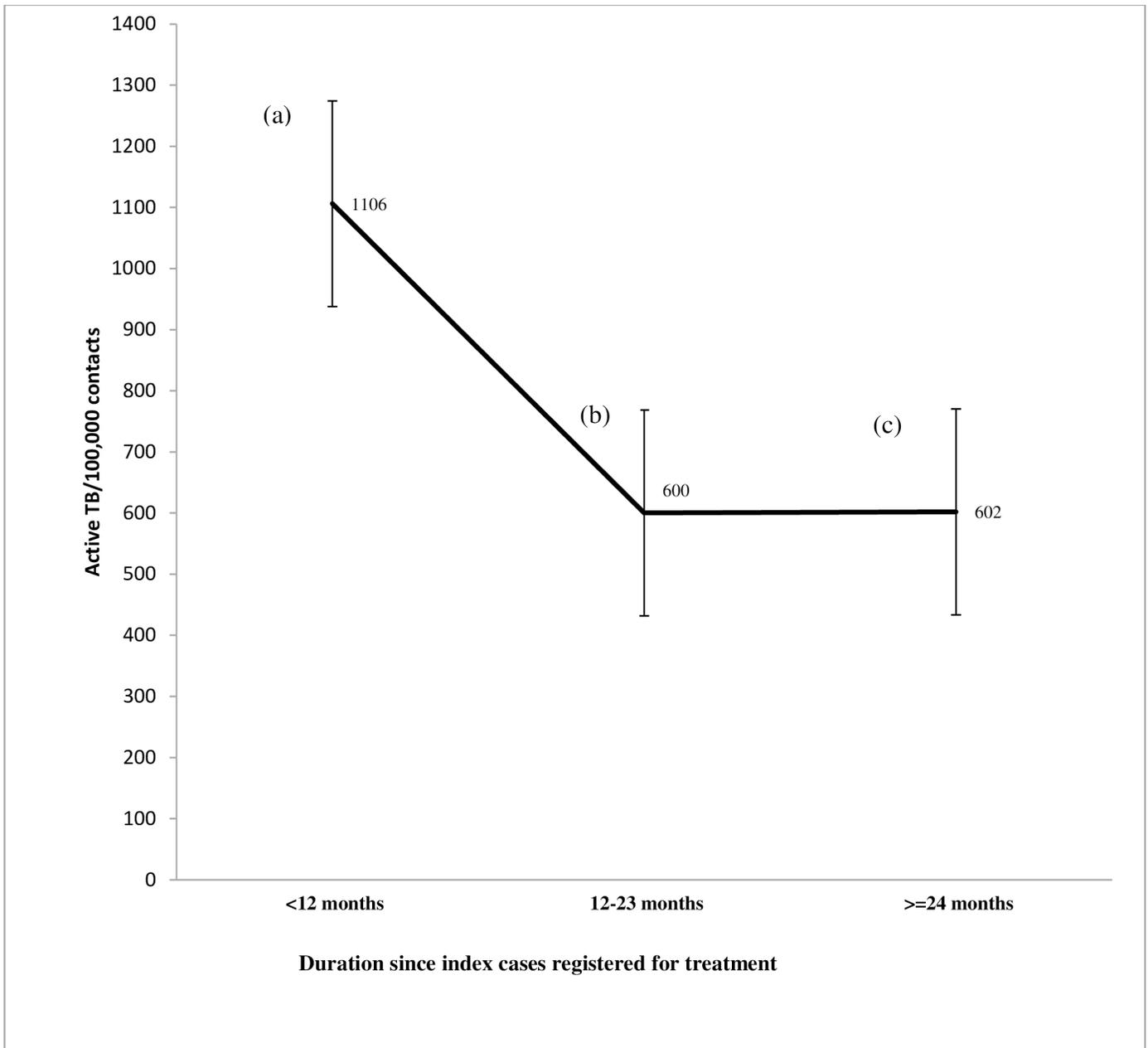
The 2.5% SS+ cases among the presumptive TB cases in this study might be underestimate but still relatively higher than the corresponding rate of 1.2% in the Ethiopian National TB prevalence survey [32]. However, the 106/100,000 prevalence of SS+ among the adult contacts is much higher than the result 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)	<u>2.04</u>	<u>1.64–2.54</u>	<u>1.77</u>	<u>1.42–2.21</u>
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 Category of contacts					
Children (<15 years)	581 (0.7)	<u>0.68</u>	<u>0.54–0.84</u>	<u>0.55</u>	<u>0.44–0.69</u>
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	<u>1.35</u>	<u>1.02–1.78</u>
Workplace	78(4.8)	<u>4.5</u>	<u>2.55–7.94</u>	<u>3.95</u>	<u>2.21–7.03</u>
Other	34(0.2)	<u>0.14</u>	<u>0.09–0.22</u>	<u>0.13</u>	<u>0.08–0.20</u>

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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)	<u>1.85</u>	<u>1.20–2.84</u>	<u>1.78</u>	<u>1.16–2.75</u>
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)	<u>2.69</u>	<u>1.69–4.27</u>	<u>2.4</u>	<u>1.50–3.82</u>
12 months—23months	131 (0.6)	1.4	0.78–2.51	1.31	0.73–2.36
> = 24 months	137 (0.4)	<u>1</u>			
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	<u>0.03–0.51</u>	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

doi:10.1371/journal.pone.0160514.t003

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. © 2016 The Authors. Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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 undetected¹. The cases that remained undetected continue to suffer from TB disease and also transmit the disease to their contacts². The regions that contributed for most of the undetected all-forms incident TB cases are south-east Asia and Africa³. 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 contacts⁸. 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 cases¹¹. 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 TB¹¹.

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 age¹². 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 episode⁹. 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 TB⁸. 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 recommendations¹¹. Rifampicin resistant results by GeneXpert test were immediately communicated to each health centers for proper management of patients as per the national tuberculosis program recommendations¹¹.

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.

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

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)

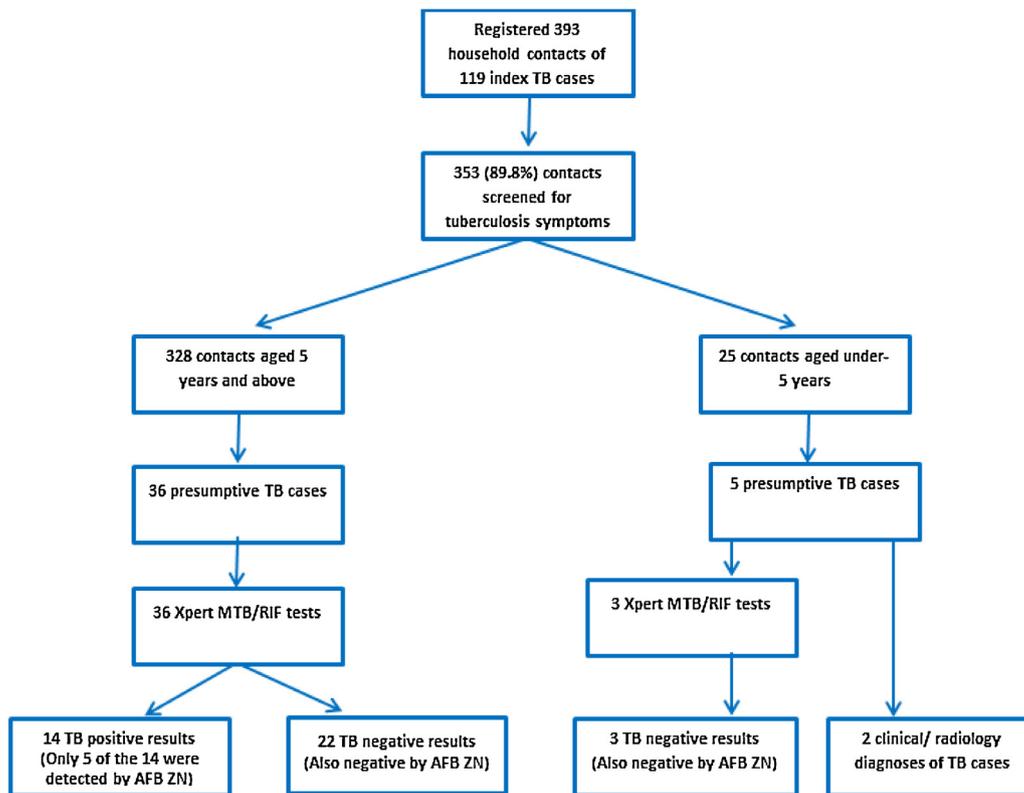


Fig. 1. Active case finding among household contacts of smear positive index TB cases.

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 survey²⁰. 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 study²¹.

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 microscopy²². 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 level¹⁶.

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 TB¹. 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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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.

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

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

^athese are primary outcomes for those who were first-time ART initiations (N = 820367)

The data are taken and modified from reference 4

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/mm³ 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/mm³ 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] 2013 WHO Consolidated Guidelines [47]	None

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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Availability of data and materials

No original data were used in the study. Aggregate data were taken from the Ministry of Health, Government of Malawi, Integrated HIV Program Report April to June 2015. Lilongwe, Malawi. This report is available at: <http://www.hiv.health.gov.mw/index.php/our-documents>.

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 identify 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 \leq 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 (HNPSPP) (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. MDR 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 \leq 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 \geq 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)				
\leq 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%

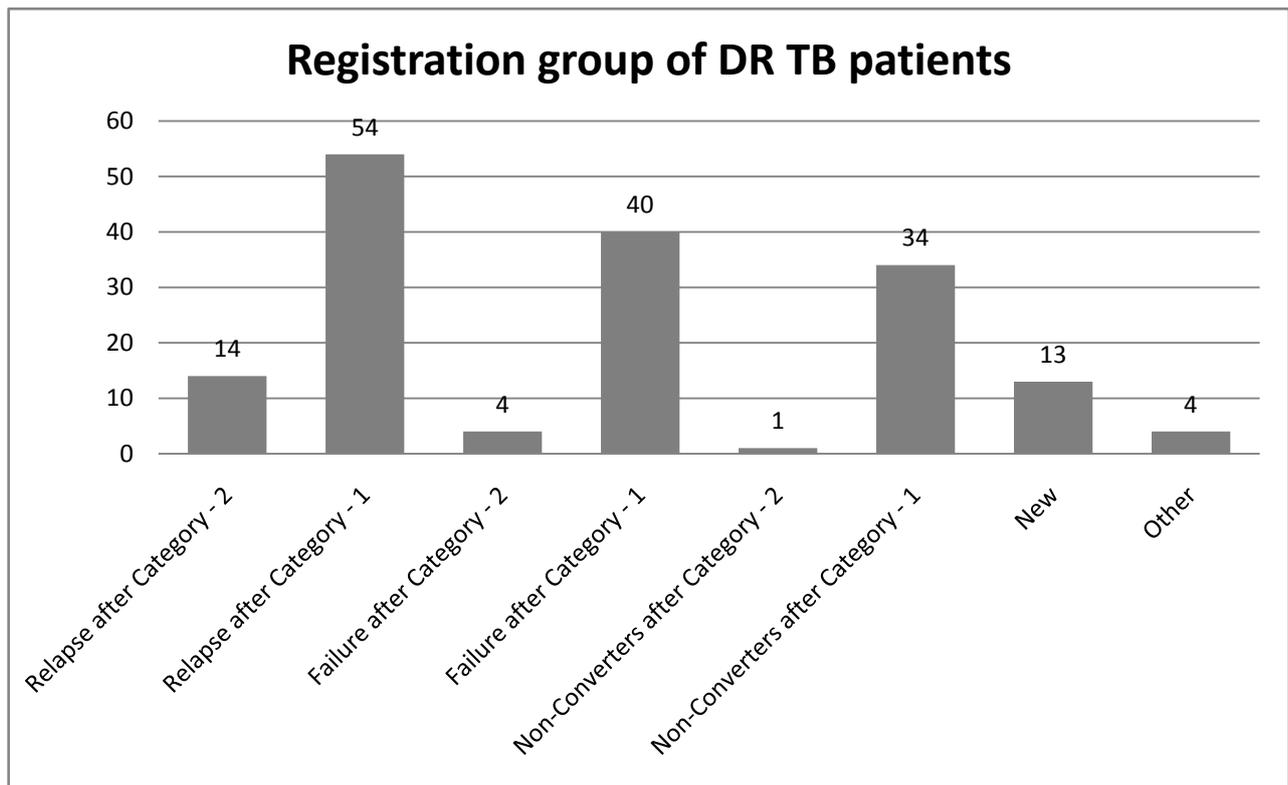


Figure 1. Registration group of the respondents

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
	Smoking	51	67
	Smoking + Ganja	7	9
Among Male	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=Ofloxacin, K = Kenamycin, 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, essentially 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 Kanamycin, b) Tablet Levofloxacin, c) Tablet Cycloserine, d) Tablet Prothionamide 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 Ahmedabad 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 underlying 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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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.

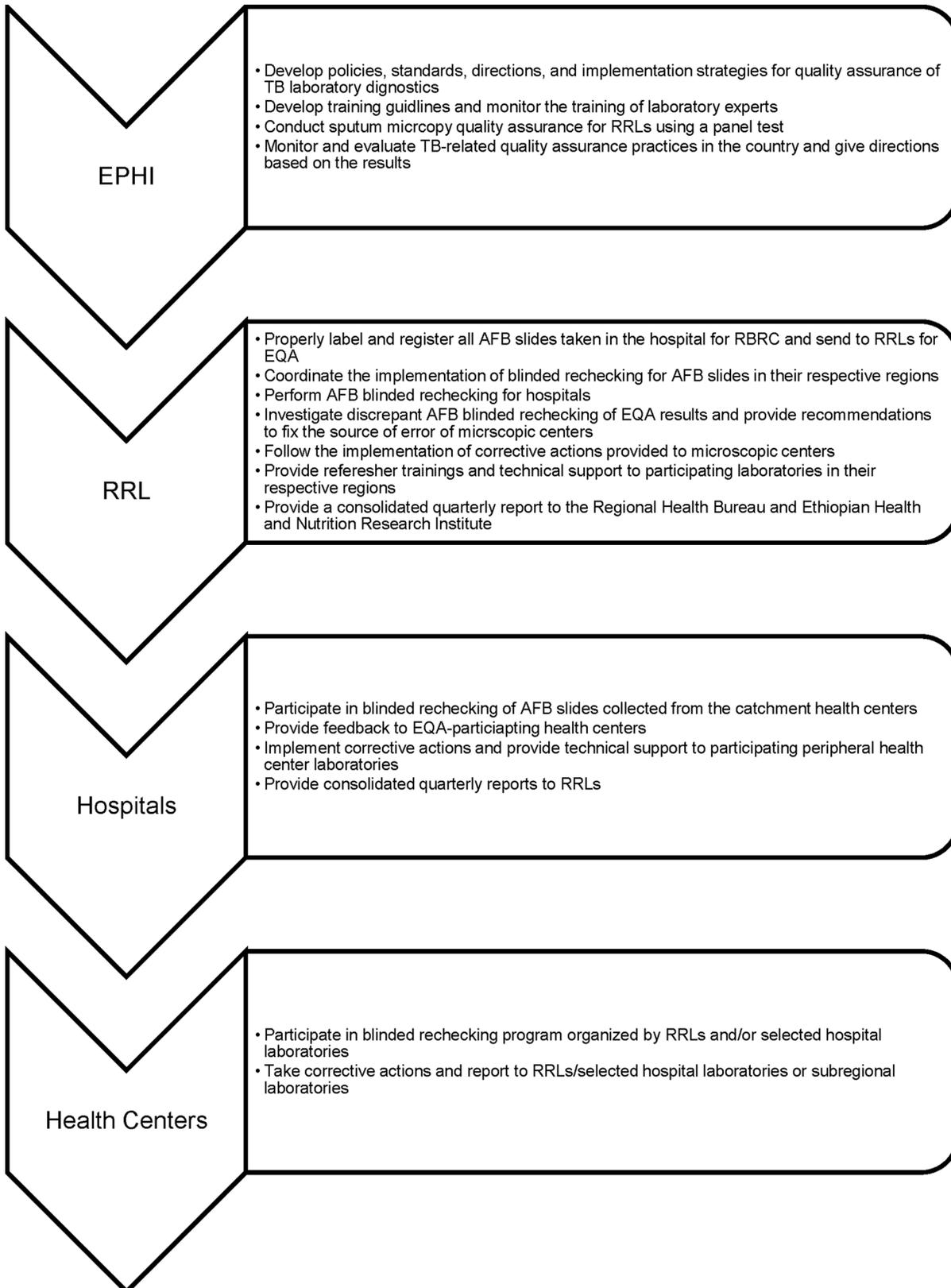


Fig 1. Model for decentralized AFB random blinded rechecking in Ethiopia.

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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

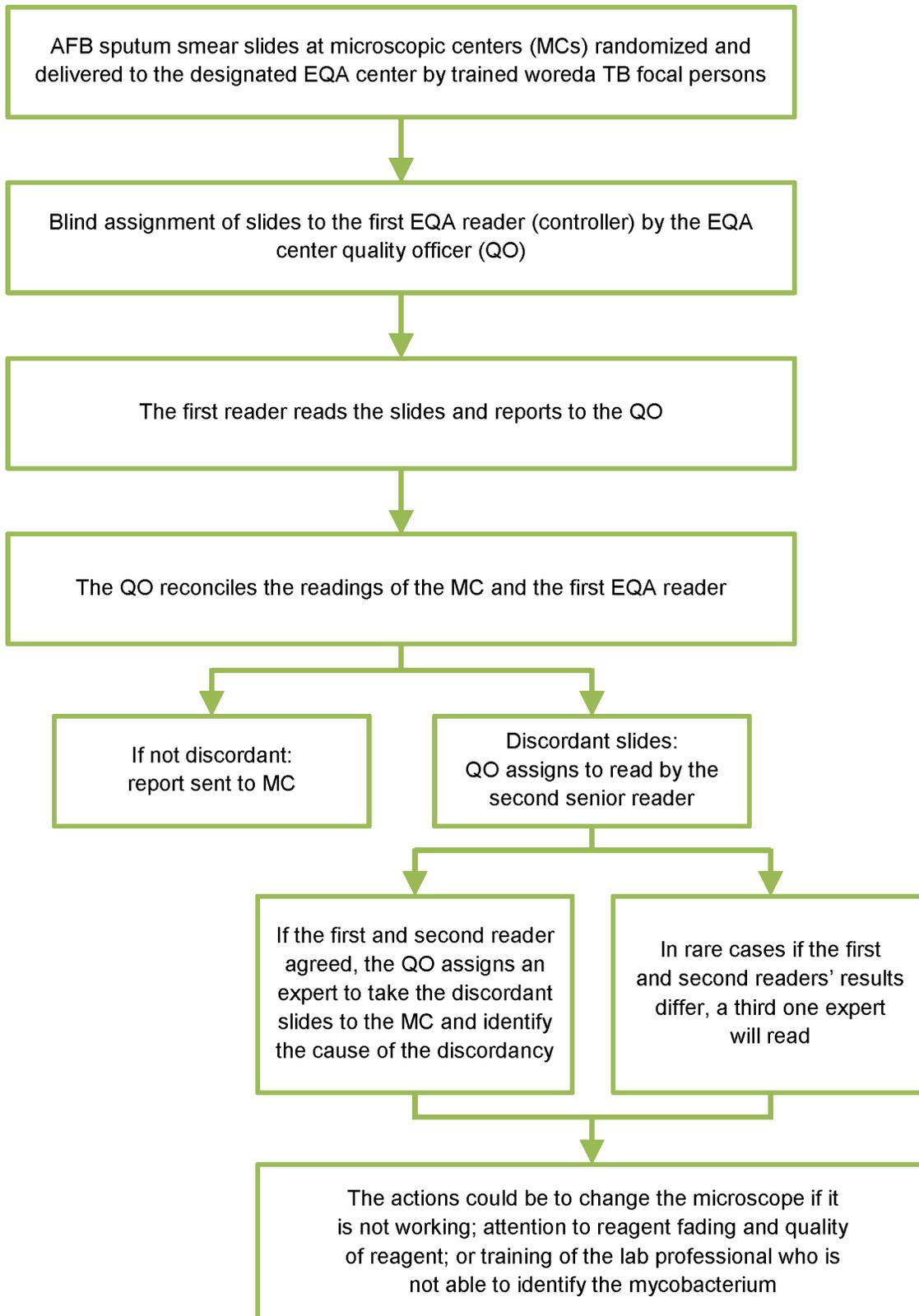


Fig 2. Flow chart of procedures for blinded random rechecking.

doi:10.1371/journal.pone.0151366.g002

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]
Quarter-Year	Phase II: Implementation Zones			
	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]
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 HF's participated in RBRC. It takes approximately 6–9 months to prepare the HF's for RBRC, but in Phase II, 335 HF's enrolled in EQA, which was faster than expected because of the experience gained during Phase I implementation.

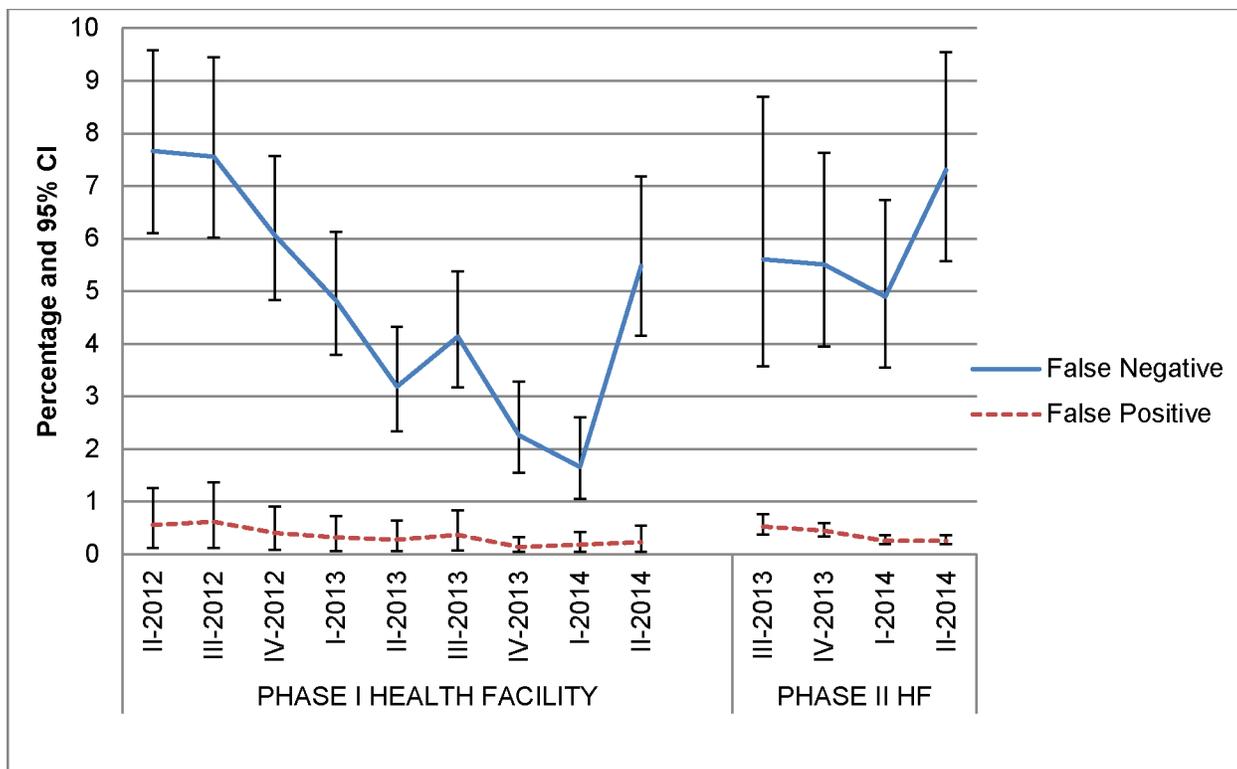


Fig 3. Health facilities' reported false-negative and false-positive error rates per quarter, April 2012-June 2014.

doi:10.1371/journal.pone.0151366.g003

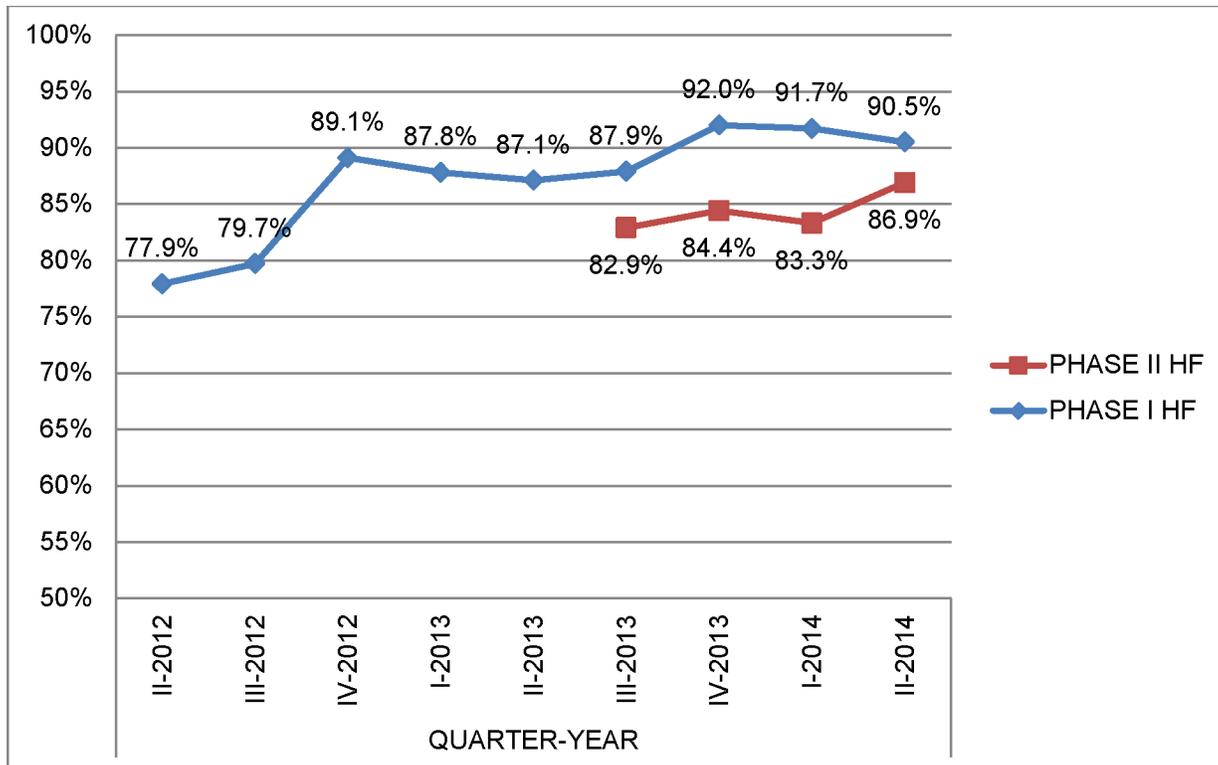


Fig 4. Percentage of health facilities without any error per quarter, April 2012–June 2014.

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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
<i>Total</i>		<i>201,334</i>					
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
<i>Total</i>		<i>47,498</i>					

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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

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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 performing 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 Biotec, 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 cannot 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.

Sensitivity 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 sensitivity 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)

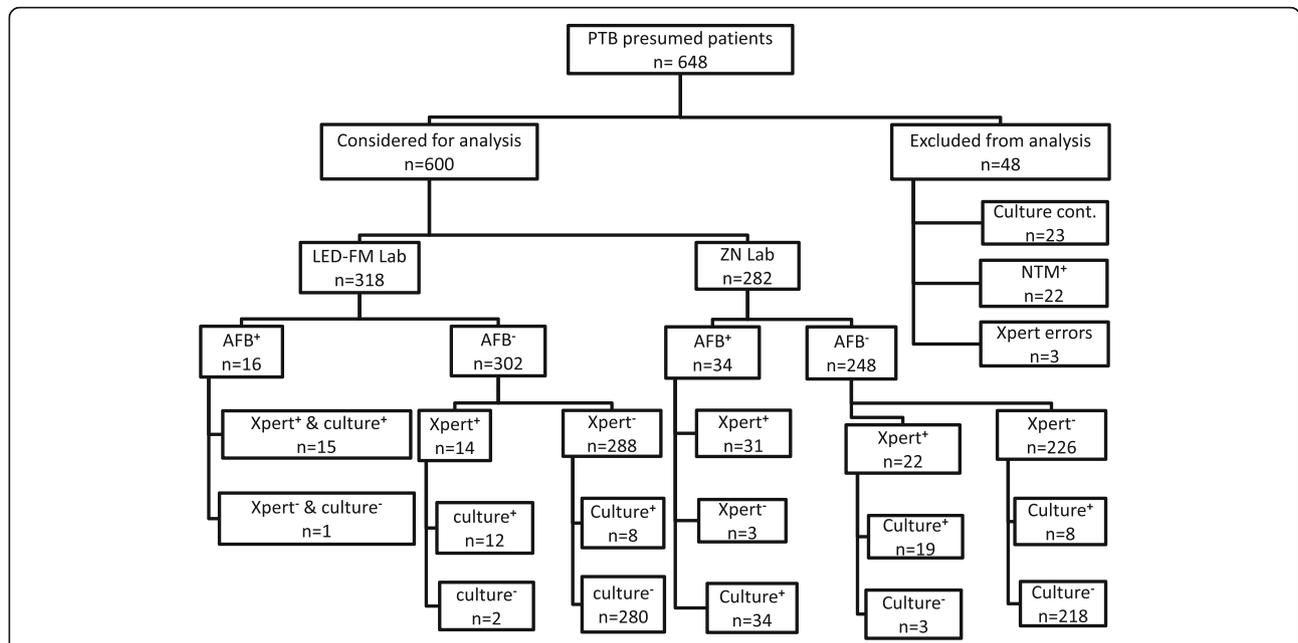


Fig. 1 Flow chart showing series of participants' recruitment and the outcome of different tuberculosis testing methods used. +: Positive, -: Negative, AFB: Acid Fast Bacilli, PTB: Pulmonary tuberculosis, ZN Lab: Ziehl Nelsen health facility laboratories-, LED-FM Lab: Light emitting diode-fluorescence 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 health 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 sensitivity of LED-FM was higher than that of ZN microscopy, indicating differences in skills requirements among microscopy methods. This study revealed a significant 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 HIV/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/mm³).¹³ A systematic review of treatment of HIV-1 and helminthic co-infections found reductions in viral load following deworming, ranging from 0.17 log₁₀ to 2.10 log₁₀ 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 log₁₀ and 0.77 log₁₀ reduction in viral load, respectively, noting that a 1.0 log₁₀ 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.^{5,21,22} 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.

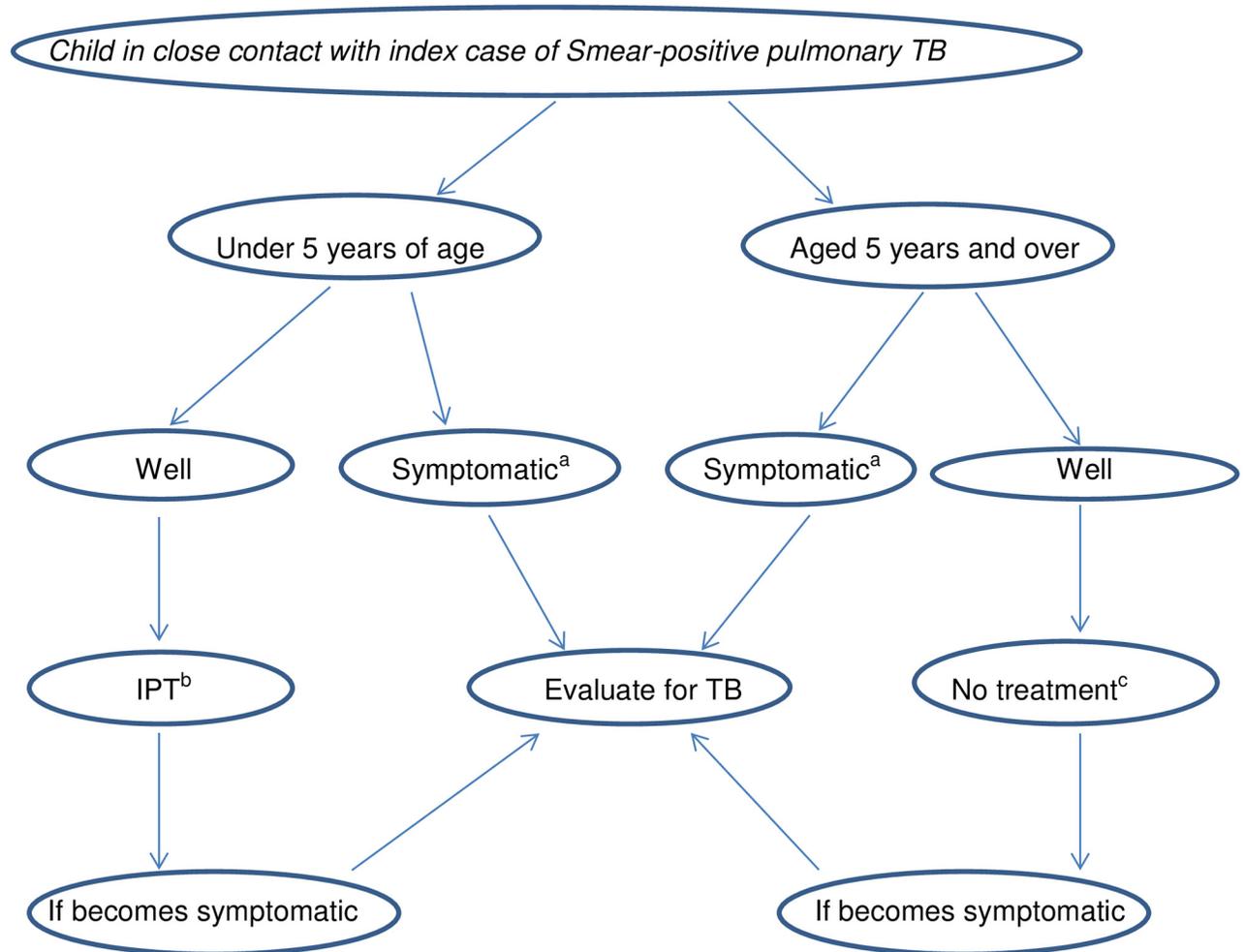
Data Analysis

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



^a Work up for active TB

^b Start INH preventive therapy with monthly TB screening

^c Monitor Clinically for possible development of active disease

Source: National comprehensive TB-Leprosy guideline, 2013

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

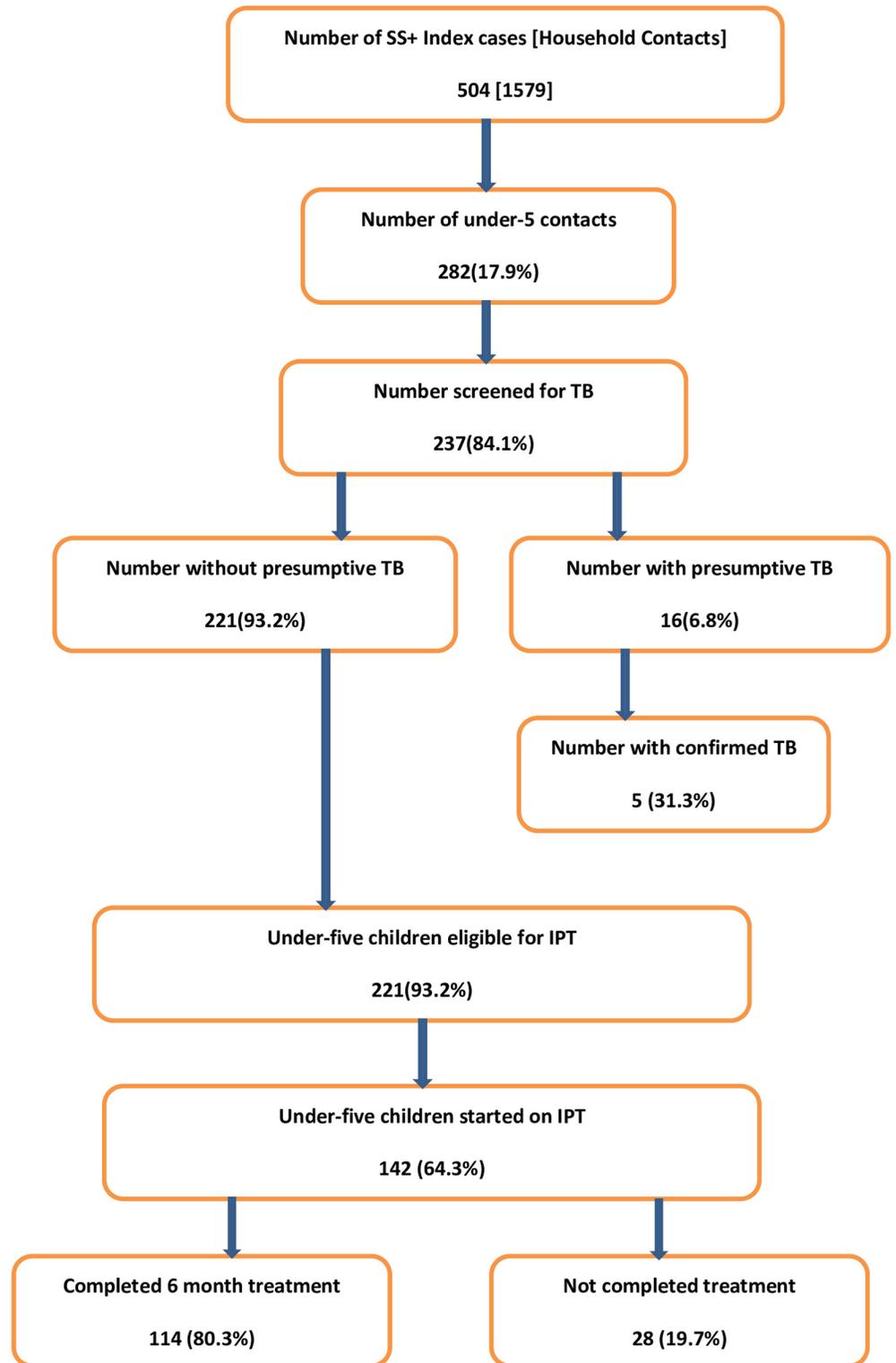


Fig 2. Contact screening and IPT among under-five children, Oct. 2013-June 2014, Ethiopia.

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(N=142)

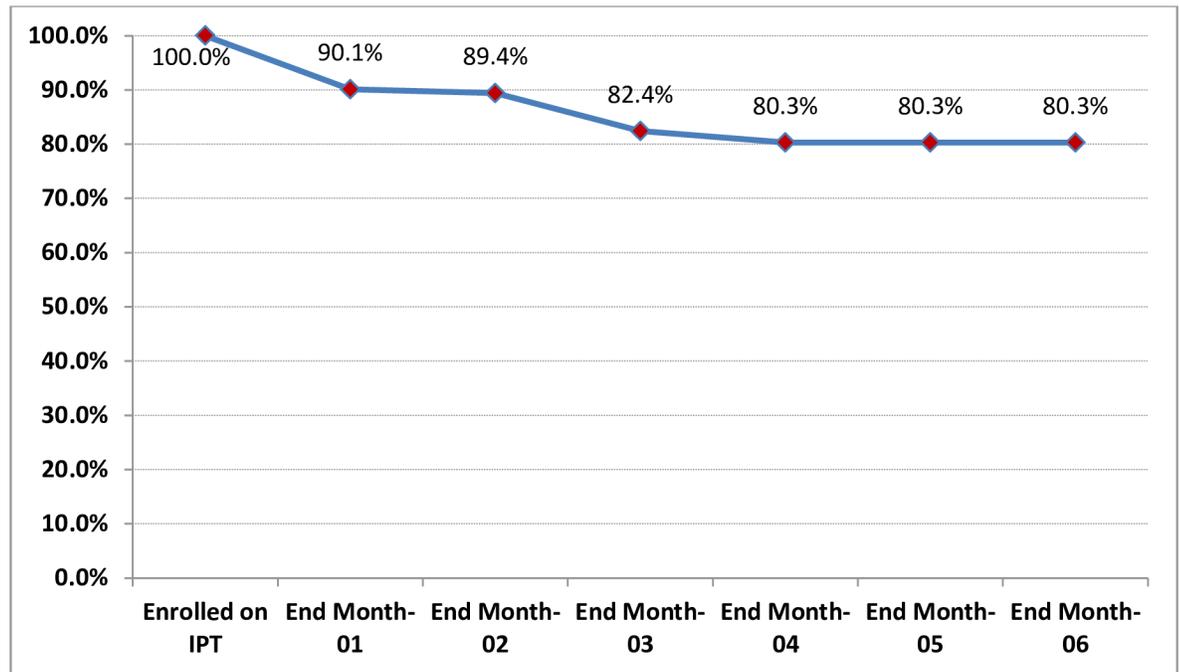


Fig 3. Percentage of under-five children retained on IPT during six-month follow-up.

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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		P- value ^a
	Health center	Hospital	
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 tuberculosis 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 colleagues³ 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

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%	\$4963 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 abuse¹¹ 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 study²⁰ 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

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 Sudan¹²

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, Tanzania¹³

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, Rwanda¹⁴

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, Zambia¹⁵

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 Sudan¹²

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, Rwanda¹⁴

"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, Uganda¹¹

ARVs=antiretrovirals.

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 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, 2011.⁴⁷

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 clinic³¹ 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 screen⁷⁴ 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 review⁷⁵ 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 Zambia²⁰ and South Africa⁶⁷ 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-naïve 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 study⁶⁰ 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 Nigeria⁸⁸ and Kenya.⁸⁹ In a South African study⁹⁰ 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 training⁹⁵ to provide HIV and tuberculosis treatment and other services⁹⁵ 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

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.

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

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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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 docu-

mented 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.

RESEARCH ARTICLE

Open Access



The socioeconomic impact of multidrug resistant tuberculosis on patients: results from Ethiopia, Indonesia and Kazakhstan

Susan van den Hof^{1,2*}, David Collins³, Firdaus Hafidz⁴, Demissew Beyene⁵, Aigul Tursynbayeva⁶ and Edine Tiemersma^{1,2}

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 Ak-mola 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; Epi-Data (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

^aAssuming that all costs for these elements had been made before the time of the interview (hence, costs were not extrapolated to the treatment phase)

^bSummed direct costs over last month x internationally defined duration of treatment phase

^cIn 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 were 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	
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)
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

^aSums are based on adding up medians from different groups of patients, and therefore must be interpreted with caution

^bNot 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 (<i>for those reporting an income change</i>)	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 %

^aFor those patients in hospitalized at time of interview, assuming hospitalization for patients during standard duration of intensive phase

^bNot available as this question was taken out of the locally used questionnaire

^cFor Ethiopia and Kazakhstan, this includes the value of vouchers; for Indonesia it only includes cash assistance

^dIn 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

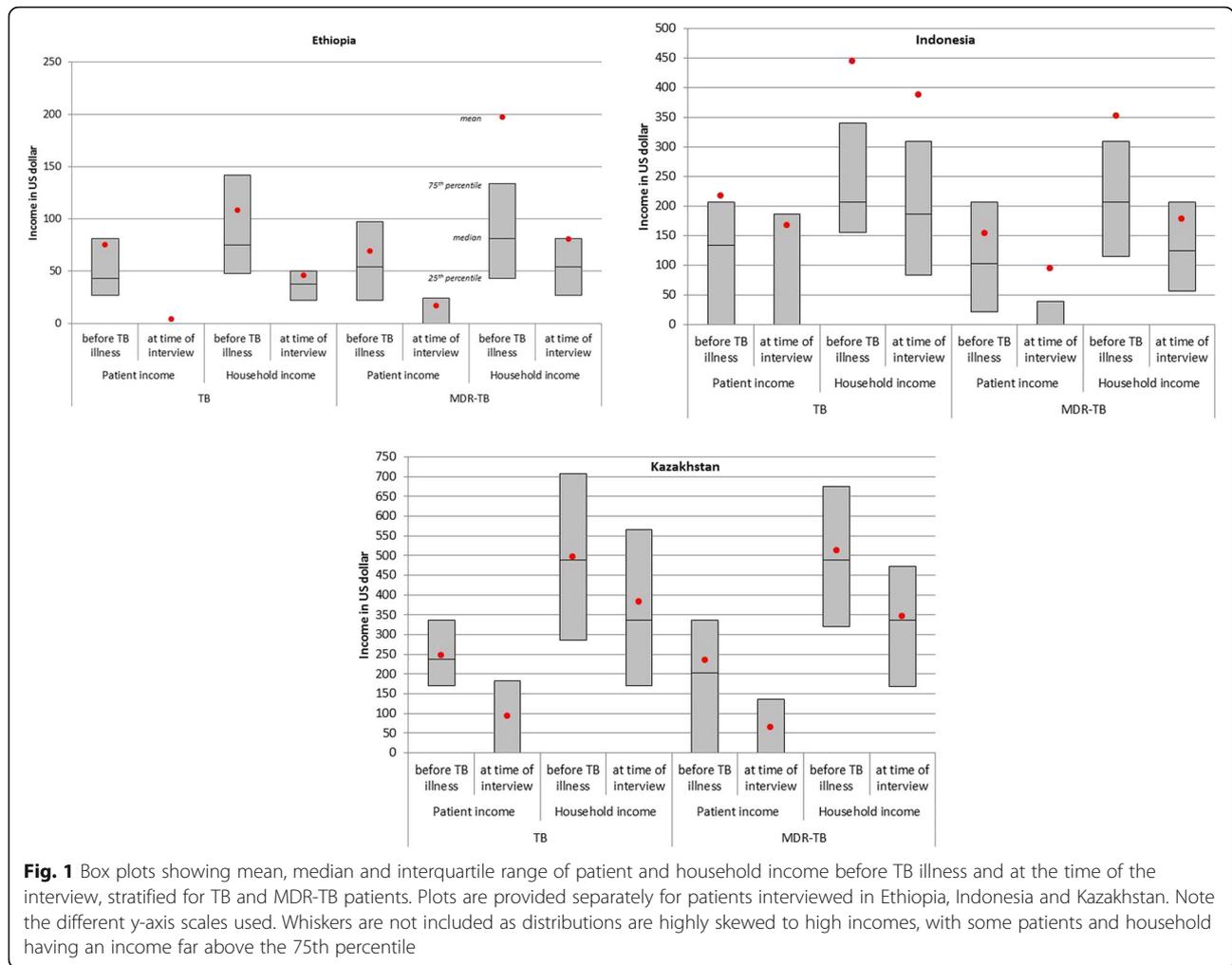
Policy options for mitigating patient costs due to (MDR) TB were listed during national workshops with participants representing different Ministries, Universities, hospitals, non-governmental organizations (NGOs), civil society organizations (CSOs), and patients. Options related to TB service improvements 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



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 USD 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 sub-committee 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
<i>TB service improvements</i>			
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	
<i>Social protection improvements</i>			
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
<i>TB service improvements</i>			
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., IS6110 based PCR for detection of <i>Mycobacterium tuberculosis</i>) 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	
<i>Social protection improvements</i>			
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 Akmla 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.

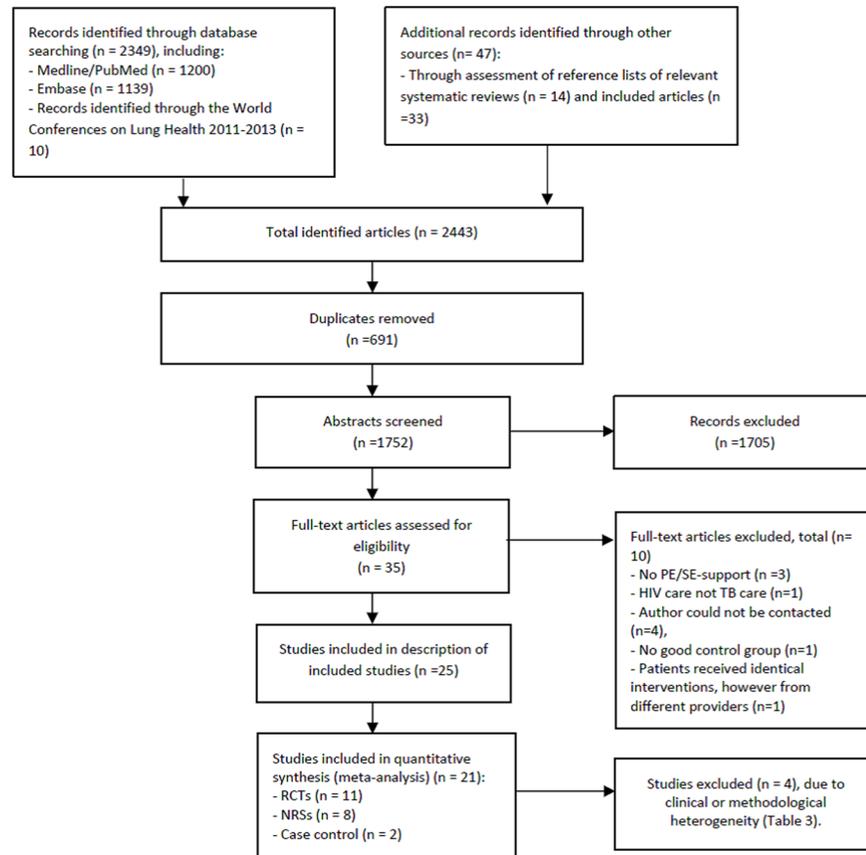


Fig 1. Flow diagram for review and meta-analysis.

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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												
<i>Non-Randomized Studies</i>												
Bock et al. 2001 [20]											X	X
Cantalice Filho 2009 [45]								X			X	X
Davidson et al. 2000 [56]											X	X
Farmer et al. 1991 [57]						X				X		X
Finlay et al. 2012 [53]	X											X
Garden et al. 2013 [54]								X	X			X
Geimanova et al. 2011 [66]						X	X		X			X
Jakubowiak et al. 2007 [44]								X	X	X		X
Lu et al. 2013 [48]										X		X
Maccq et al. 2008 [59]		X	X		X							X
Soares et al. 2013 [68]						X		X	X			X
Sripad et al. 2014 [62]										X		X
Wei et al. 2012 [63]										X		X
Zou et al. 2013 [64]										X		X
<i>Randomized Controlled Trials</i>												
Alvarez et al. 2008 [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
Liefoghe et al. 1999 [46]	X										X	X
Lufge et al. 2013 [47]											X	X
Martins et al. 2009 [60]								X			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

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Table 2. Summary table for all studies included in the qualitative analysis.

Study	Country income*	Study type	Enrollment period	N*	Population	Comparison	Intervention(s)	Funding source and organization	Outcome(s)	Other
Alvarez Gordillo et al. 2003 [50]	Chiapas, Mexico, LMIC.	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 (I: 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) Counseling 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 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 enrollment. 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, LMIC.	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	Enrollment 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	Enrollment period	N*	Population	Comparison	Intervention(s)	Funding source and organization	Outcome(s)	Other
Jahnvi & Sudha 2010 [53]	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 grains 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 receive 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	Enrollment period	N*	Population	Comparison	Intervention(s)	Funding source and organization	Outcome(s)	Other
Liefooghe et al. 1999 [45]	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 counselors 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 ombudsman between the hospital/paramedical team and the patient. Two male and two female paramedics 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, C: 961, 2010; 734, C: 2006, C: 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 where 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 administrator 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.

(Continued)

Table 2. (Continued)

Study	Country income*	Study type	Enrollment 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 counselling 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.
Scores et al. 2013 [63]	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). 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 CHWs 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.	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 CHWs 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	Enrollment 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 24 months. 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	Enrollment 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 (I: 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 assessment 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 χ^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.

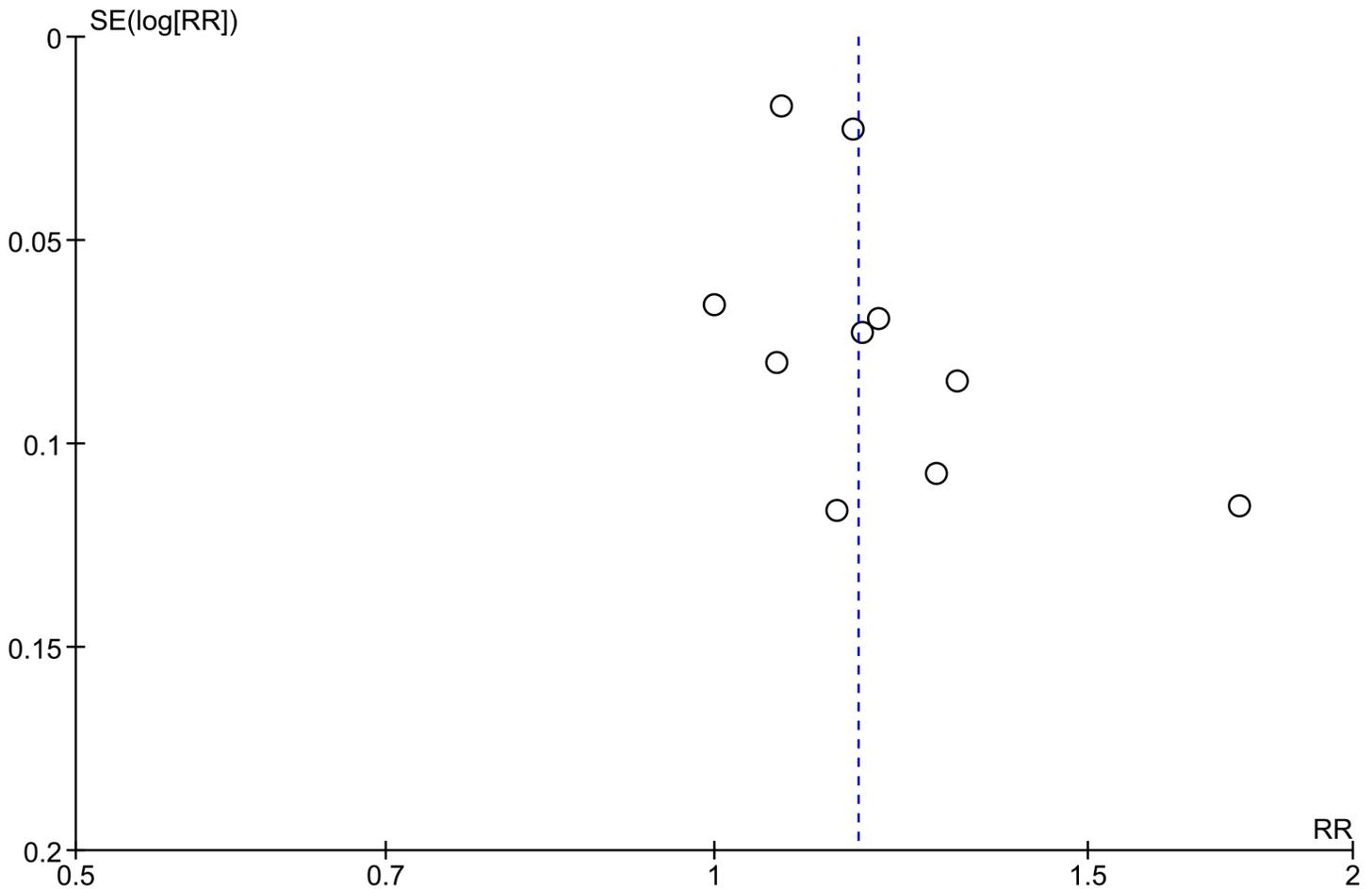


Fig 2. Funnel plot to evaluate publication bias in Randomized Controlled Trials on the effects of social support interventions on treatment outcomes.

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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 heterogeneous (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–

The effects of patient support on treatment success by type of intervention

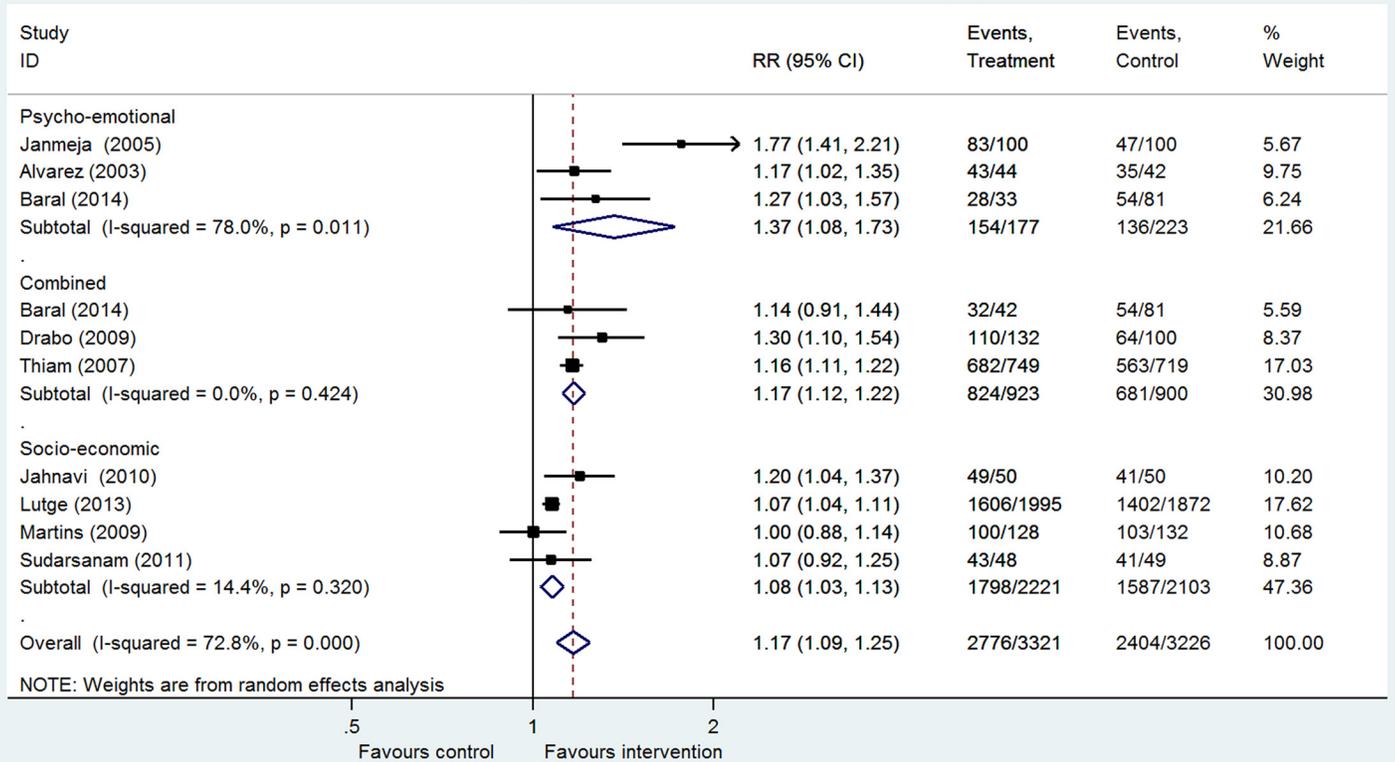


Fig 3. The effects of social support on treatment success by type of intervention in Randomized Controlled Trials.

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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

The effects of patient support on unsuccessful treatment outcomes by type of intervention

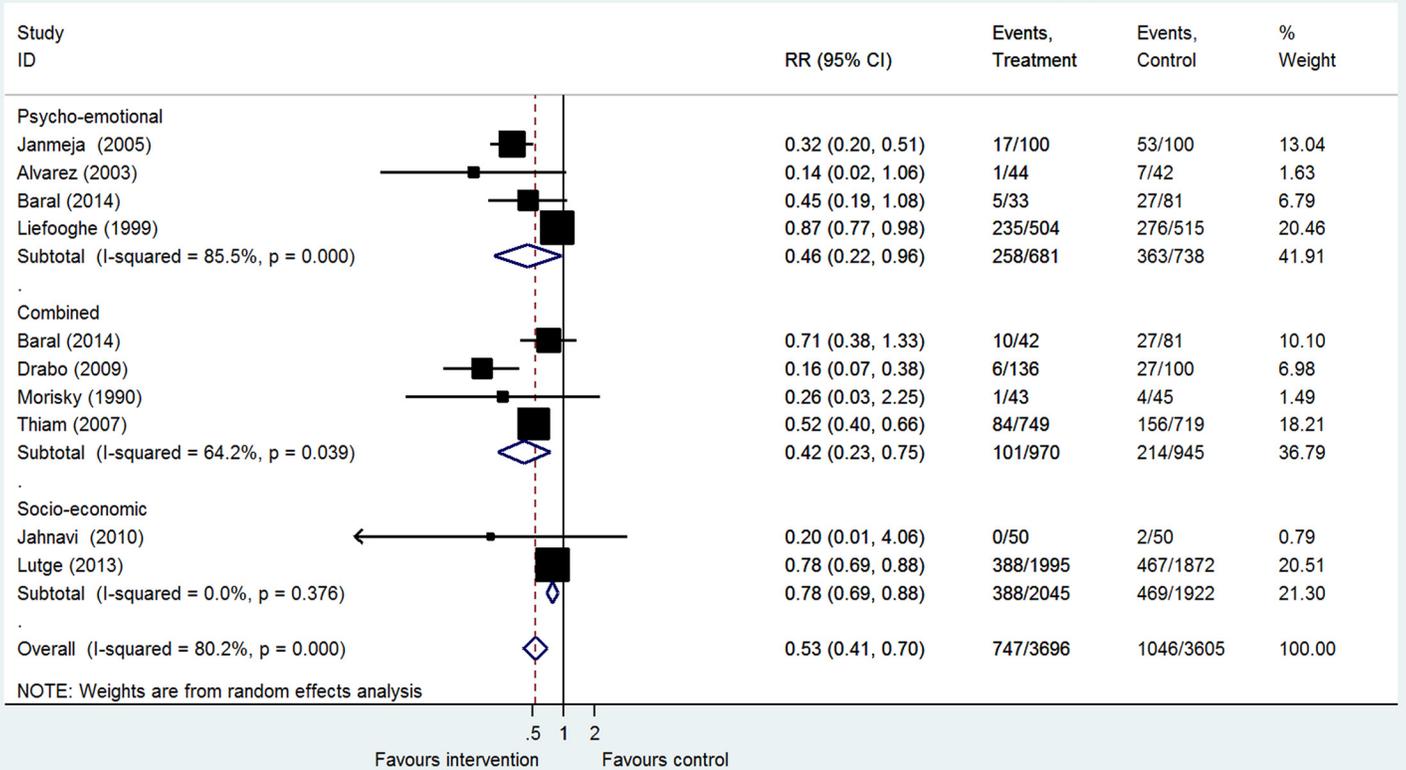


Fig 4. The effects of social support on unsuccessful treatment outcomes by type of intervention in Randomized Controlled Trials.

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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 unsuccessful treatment outcomes. Both studies showed significant beneficial effects (RR 0.51 (CI 0.37–0.70) 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 km².¹¹ 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 times 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 study²⁵ 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	<i>n</i>	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

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	<i>n</i> (%)
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, <i>n</i>	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.

SCHEMA : 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 de decisión, 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 sería 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.

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/ μ l (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;

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. \geq 350 cells/ μ l for the pre-ART cohort and <200 vs. \geq 200 cells/ μ l 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/ μ l, 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/ μ l. 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/ μ l 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/ μ l*					
\geq 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/ μ l					
\geq 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/ μ l 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

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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 multi-stage 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 non-prescription 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.

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

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 (<i>no specific data for pharmacies</i>). 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 (<i>no specific data for pharmacies</i>).
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.

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

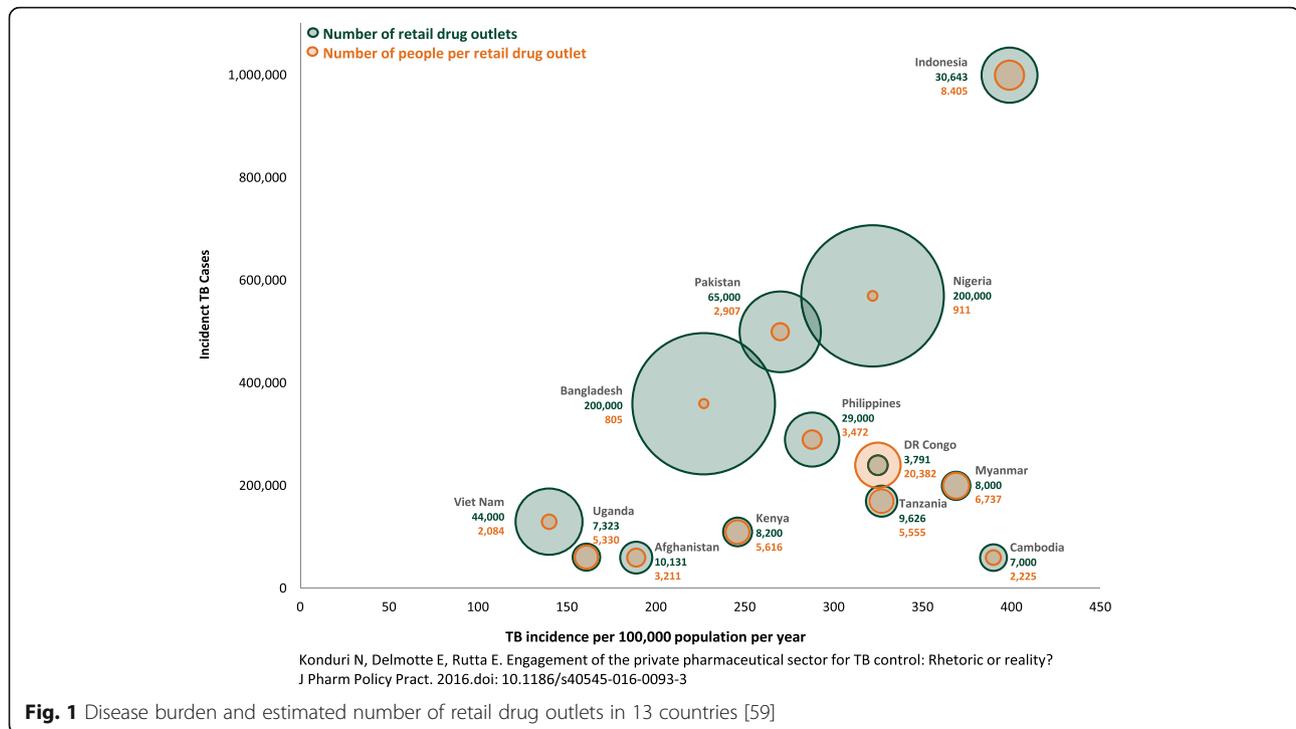
of articles and abstracts in varying geographic locations have demonstrated that retail drug outlets are willing and able to contribute to TB control efforts, as shown by the number of referrals (Table 4). However, given the diversity of the private sector in high-TB-burden countries and the reality 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		

^aPrivate expenditure on health as a percentage of total expenditure on health. WHO (2013) [18]

^bOnly if ‘pharmacy association’ was explicitly mentioned in the strategy instead of the generic term ‘professional association’



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

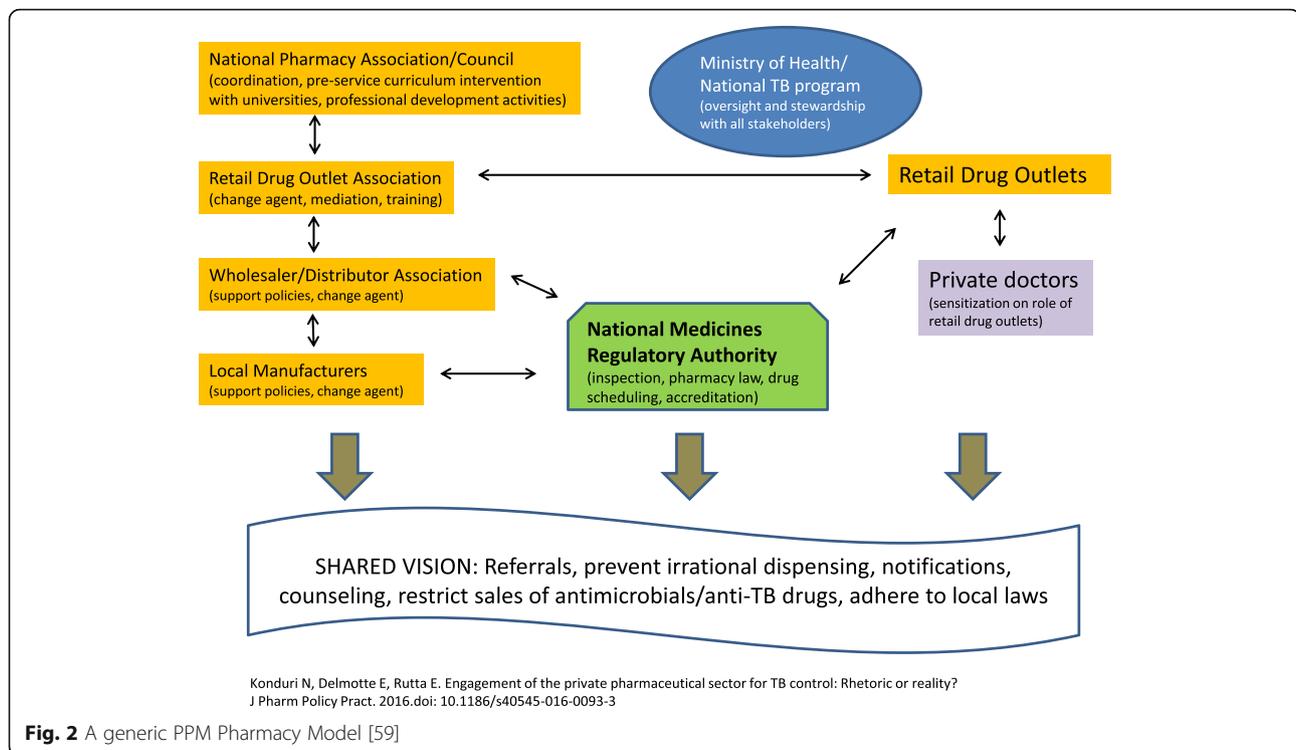


Fig. 2 A generic PPM Pharmacy Model [59]

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.

Competing interests

The authors declare that they have no competing interests.

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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 10000 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 (27110), followed by Kiev city (19037). 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, $p<0.05$, $\eta^2=.01$	Main effect for years working in TB programme: F (3, 274)=5.07, $p<0.01$, $\eta^2=.05$
Q3: I do not need more training on the national TB registry	No two-way interaction was significant	No two-way interaction was significant
Q4: I am happy with the available support and infrastructure for the national TB registry	Two-way interaction for years using registry*location: F (1, 279)=4.98, $p<0.05$, $\eta^2=.02$	
Q6: The national TB registry helps me to improve case management	Main effect for age: F (3, 279)=2.74, $p=0.04$, $\eta^2=.03$	Main effect for years working in TB programme: F (3, 265)=4.78, $p<0.01$, $\eta^2=.05$
Q8: The information needed for case management is available in the national TB registry	Two-way interaction for age*location: F (3, 279)=2.75, $p<0.05$, $\eta^2=.03$	No two-way interaction was significant
Q9: Generating reports from the paper system is faster than the national TB registry[#]	Main effect for age: F (3, 279)=3.39, $p<0.05$, $\eta^2=.03$	
Q10: The national TB registry does not help me identify errors or inaccuracies in patient files[#]	Two-way interaction for age*location: F (3, 279)=3.87, $p<0.05$, $\eta^2=.04$	Main effect for location: F (2, 265)=3.58, $p=0.02$, $\eta^2=.02$
Q11: My workplace productivity has improved because of the national TB registry	Main effect for location: F (2, 279)=4.85, $p<0.01$, $\eta^2=.03$	Two-way interaction for age*years in TB programme: F (8, 265)=2.74, $p<0.01$, $\eta^2=.08$
Q12: The national TB registry is reliable	Three-way interaction for years using registry*age*location: F (3, 279)=4.35, $p<0.01$, $\eta^2=.04$	Main effect for age: F (3, 265)=3.03, $p=0.03$, $\eta^2=.03$
	Main effect for age: F (3, 279)=2.86, $p<0.05$, $\eta^2=.03$	Main effect for location: F (2, 265)=4.48, $p<0.01$, $\eta^2=.03$
	Main effect for location: F (2, 279)=5.50, $p<0.01$, $\eta^2=.04$	No two-way interaction was significant
	Two-way interaction for age*location: F (3, 279)=2.97, $p<0.05$, $\eta^2=.03$	
	Main effect for age: F (3, 279)=3.61, $p<0.01$, $\eta^2=.03$	
	Two-way interaction for age*location: F (3, 279)=4.72, $p<0.01$, $\eta^2=.04$	
	Two-way interaction for age*location: F (3, 279)=3.28, $p<0.05$, $\eta^2=.03$	

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

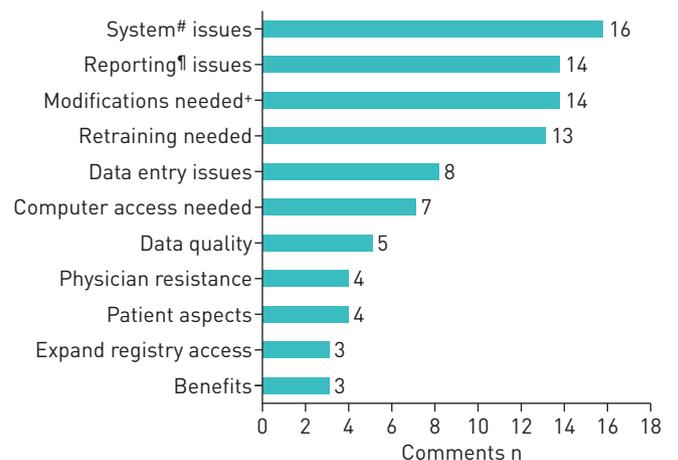


FIGURE 2 Major themes from the user comments. Comments from 74 users were coded into 11 major themes. #: server or registry platform; ¶: paper-based reports and registry data fields; *: suggestions on registry structure.

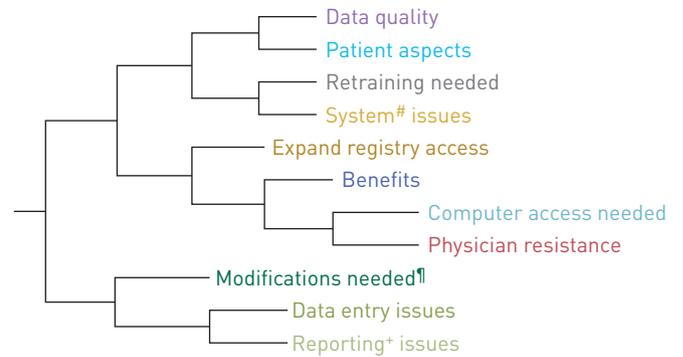


FIGURE 3 Dendrogram: themes clustered by word similarity. Themes clustered by word similarity: the dendrogram is the result of a cluster analysis of user comments that clustered selected themes together if they have many words in common. Similar items are clustered together on the same branch and different 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.

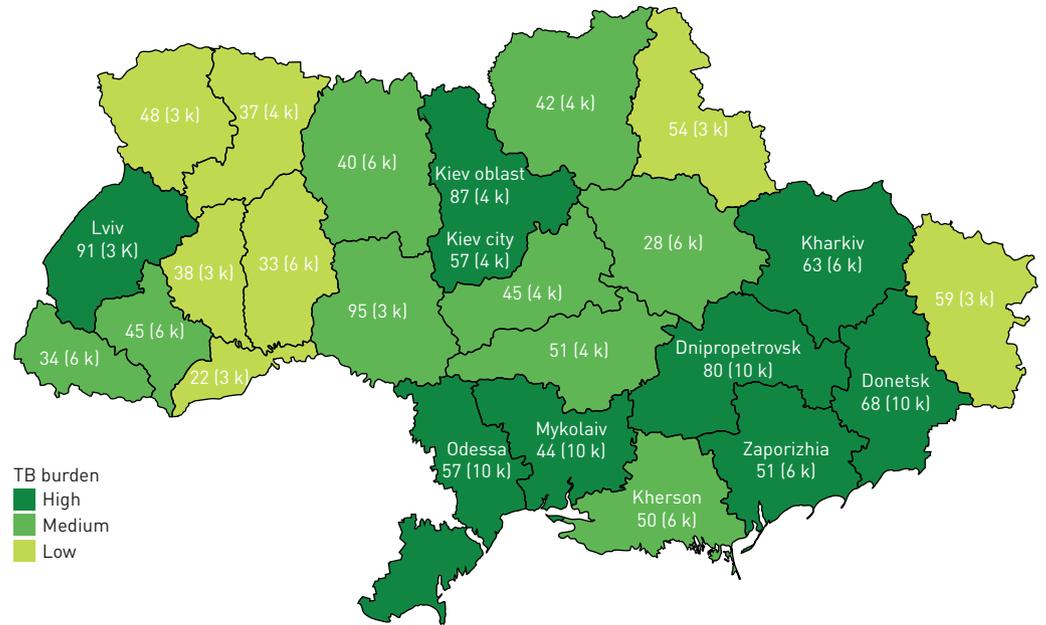


FIGURE 4 Usability statistics among active users of the national tuberculosis (TB) registry by TB burden. Each oblast (region) lists the number of active registry users in June 2016. Numbers in parentheses indicate average transactions per user in thousands (k). For example, the Kherson oblast with a 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.

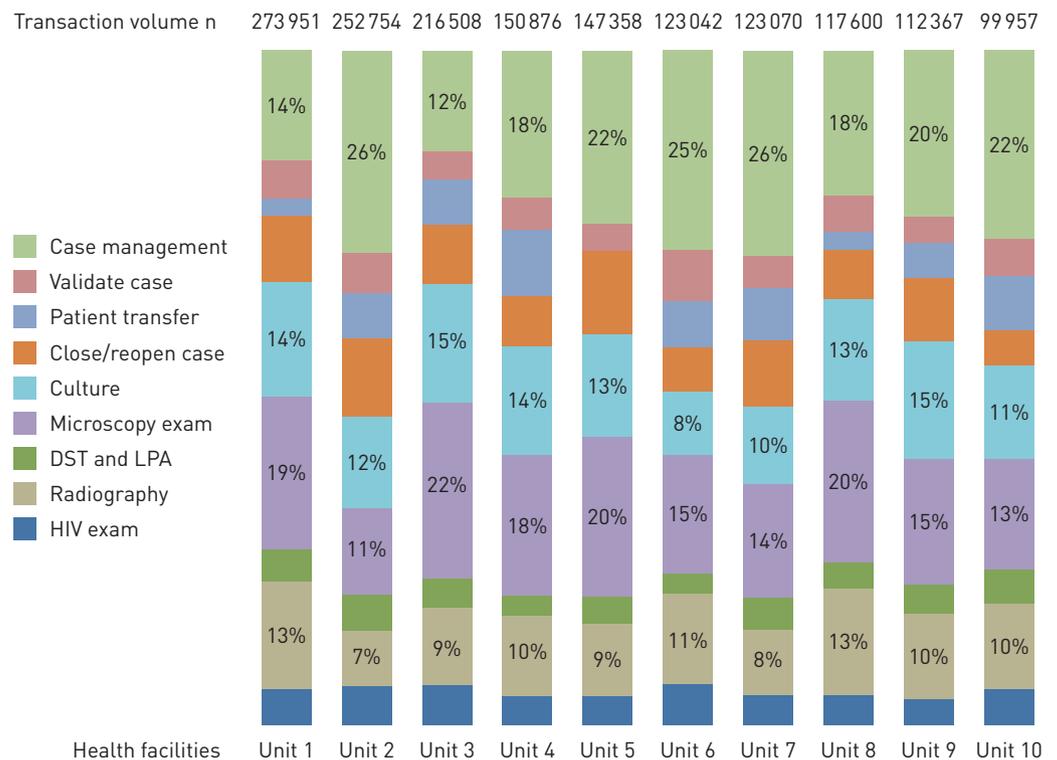


FIGURE 5 Usability statistics among top 10 tuberculosis (TB) units by transaction type for key data fields. This figure presents anonymous cumulative transaction statistics for selected data fields from the registry's case module from January 2012 to May 2016. The top 10 out of 647 active TB health units, 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.

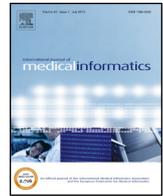
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User experience analysis of an eHealth system for tuberculosis in resource-constrained settings: A nine-country comparison



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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
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 = 0.000 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.

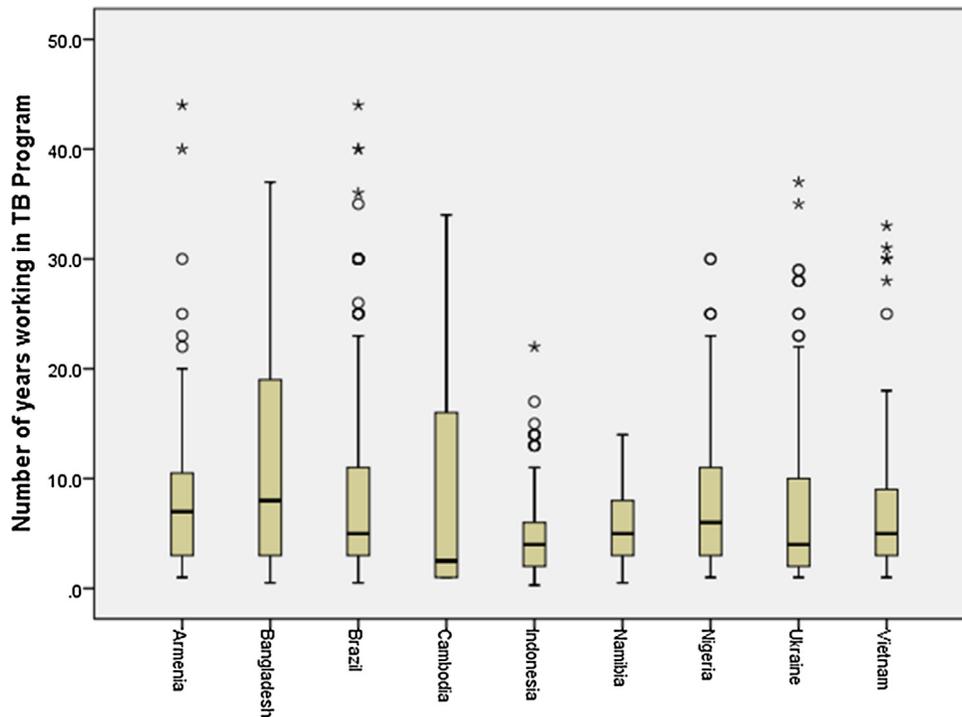


Fig. 1. Number of years working in TB program.

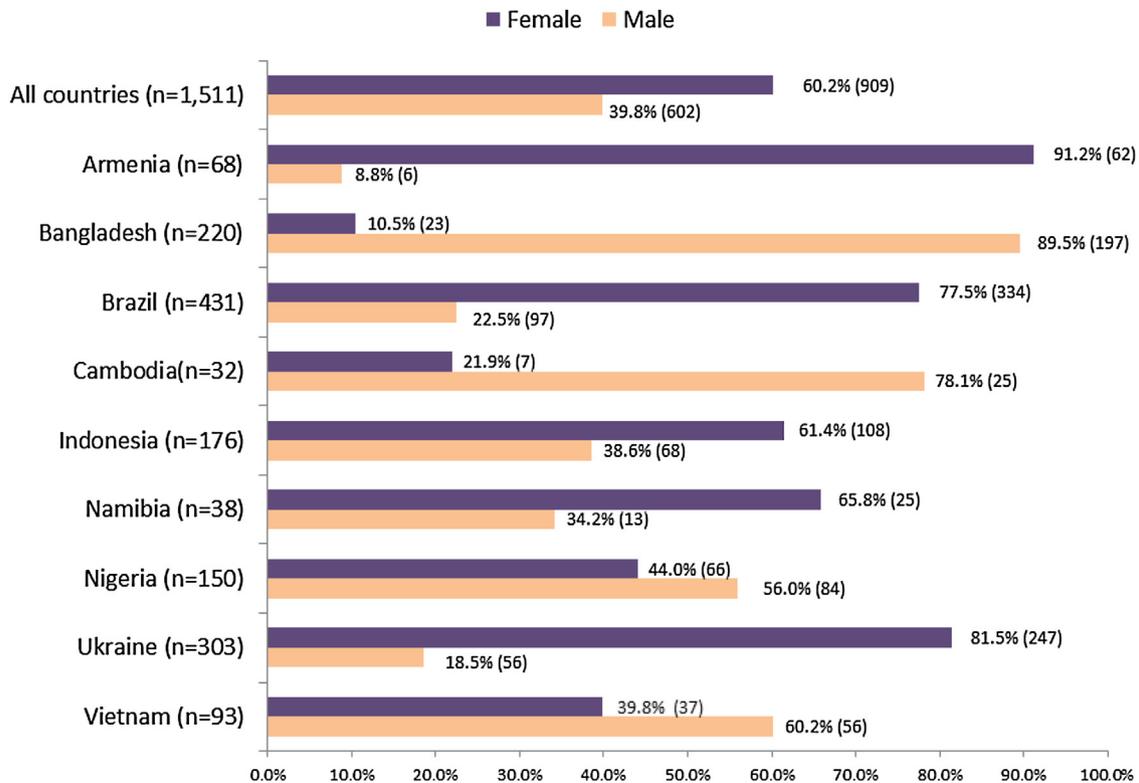


Fig. 2. Gender of e-TB Manager users.

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

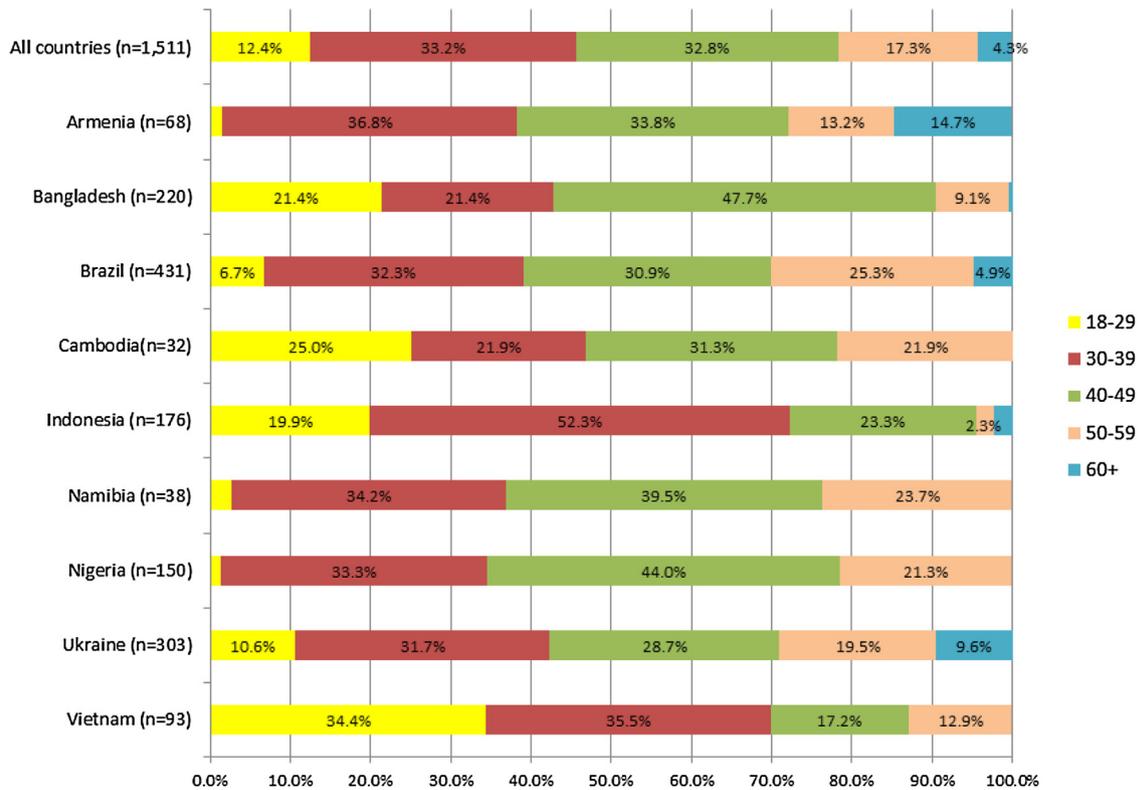


Fig. 3. Age of e-TB Manager users.

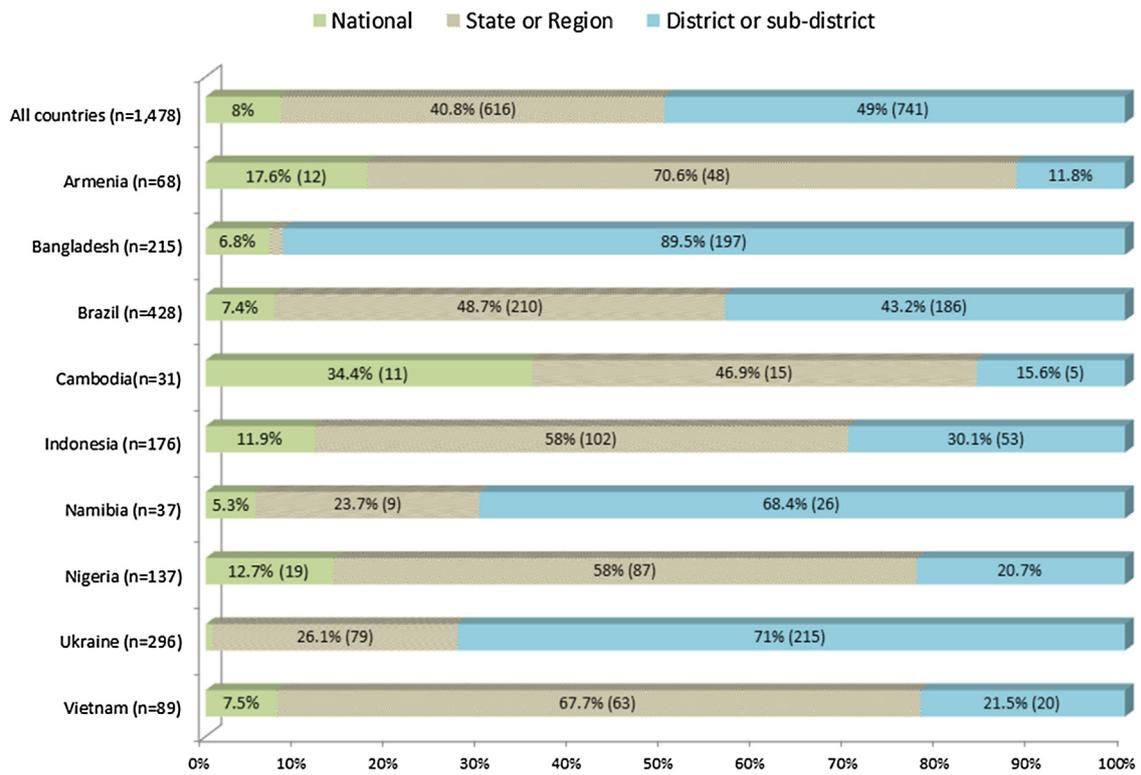


Fig. 4. Location of e-TB Manager users.

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, η ² =0.01 age*location: F (6, 1454) = 2.41, p < 0.05, η ² =0.01 location*e-TB Manager: F (2, 1454) = 4.38, p < 0.05, η ² =0.01	age*location: F (6, 1433) = 2.19, p < 0.05, η ² =0.01 age*NTP: F (9, 1433) = 2.11, p < 0.05, η ² =0.01 age*location*NTP: F (15, 1433) = 1.68, p < 0.05, η ² =0.02
Q2: Have capacity	Main effect for years using e-TB Manager F (1, 1454) = 45.57, p < 0.00, η ² =0.03	Main effect for years working in NTP F (3, 1433) = 4.29, p < 0.01, η ² =0.01
Q3: Do not need more training	Main effect for location: F (2, 1454) = 6.22, p < 0.01, η ² =0.01 Main effect for years using e-TB Manager: F (1, 1454) = 20.99, p < 0.00, η ² =0.01 location*e-TB Manager: F (2, 1454) = 5.95, p < 0.01, η ² =0.01	Main effect for location: F (2, 1433) = 8.15, p < 0.00, η ² =0.01
Q4: Support and infrastructure	Main effect for location F (2, 1454) = 5.93, p < 0.01, η ² =0.01	Main effect for location: F (2, 1433) = 3.95, p < 0.05, η ² =0.01
Q5: enter or find information	Main effect for location: F (2, 1454) = 5.35, p < 0.01, η ² =0.01 Main effect for years using e-TB Manager: F (1, 1454) = 7.85, p < 0.01, η ² =0.01 location*e-TB Manager: F (2, 1454) = 4.46, p < 0.05, η ² =0.01	Main effect for location F (2, 1433) = 5.12, p < 0.01, η ² =0.01
Q6: Case management	Main effect for years using e-TB Manager: F (1, 1454) = 12.75, p < 0.00, η ² =0.01 age*location: F (6, 1454) = 2.17, p < 0.05, η ² =0.01 location*e-TB Manager: F (2, 1454) = 4.52, p < 0.05, η ² =0.01	Main effect for years working in NTP: F (3, 1433) = 3.11, p < 0.05, η ² =0.01
Q7: Training is adequate	Main effect for location: F (2, 1454) = 3.89, p < 0.05, η ² =0.01 Main effect for years using e-TB Manager: F (1, 1454) = 30.55, p < 0.00, η ² =0.02	Main effect for years working in NTP: F (3, 1433) = 5.90, p < 0.01, η ² =0.01
Q8: Information is available	Main effect for location: F (2, 1454) = 5.90, p < 0.01, η ² =0.01 Main effect for years using e-TB Manager: F (1, 1454) = 10.64, p < 0.01, η ² =0.01	Main effect for location: F (2, 1433) = 7.90, p < 0.00, η ² =0.01 age*NTP: F (9, 1433) = 2.87, p < 0.01, η ² =0.02 age*location*NTP: F (15, 1433) = 1.67, p < 0.05, η ² =0.02
Q9: Paper system is faster ^a	age*location*e-TB Manager: F (6, 1454) = 5.10, p < 0.00, η ² =0.02	age*location*NTP: F (15, 1433) = 1.69, p < 0.05, η ² =0.02
Q10: Errors or inaccuracies ^a	Main effect for location: F (2, 1454) = 4.42, p < 0.05, η ² =0.01 age*location: F (6, 1454) = 2.10, p < 0.05, η ² =0.01	Main effect for location: F (2, 1433) = 3.02, p < 0.05, η ² =0.00
Q11: Workplace productivity	Main effect for years using e-TB Manager F (1, 1454) = 8.79, p < 0.01, η ² =0.01	age*NTP F (9, 1433) = 2.87, p < 0.01, η ² =0.02
Q12: Reliable	Main effect for location: F (2, 1454) = 3.85, p < 0.05, η ² =0.01 Main effect for years using e-TB Manager: F (1, 1454) = 7.48, p < 0.01, η ² =0.00 Age*location: F (6, 1454) = 2.36, p < 0.05, η ² =0.01	Main effect for location F (2, 1433) = 5.23, p < 0.01, η 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, Q10) and one negatively worded question (Q3) may have caught users off guard and affected their response.

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.

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.

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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>.

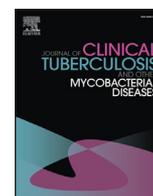
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The experience of scaling up a decentralized, ambulatory model of care for management of multidrug-resistant tuberculosis in two regions of Ethiopia



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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].

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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

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 as 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 pro-

vided 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-Cm₆-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-

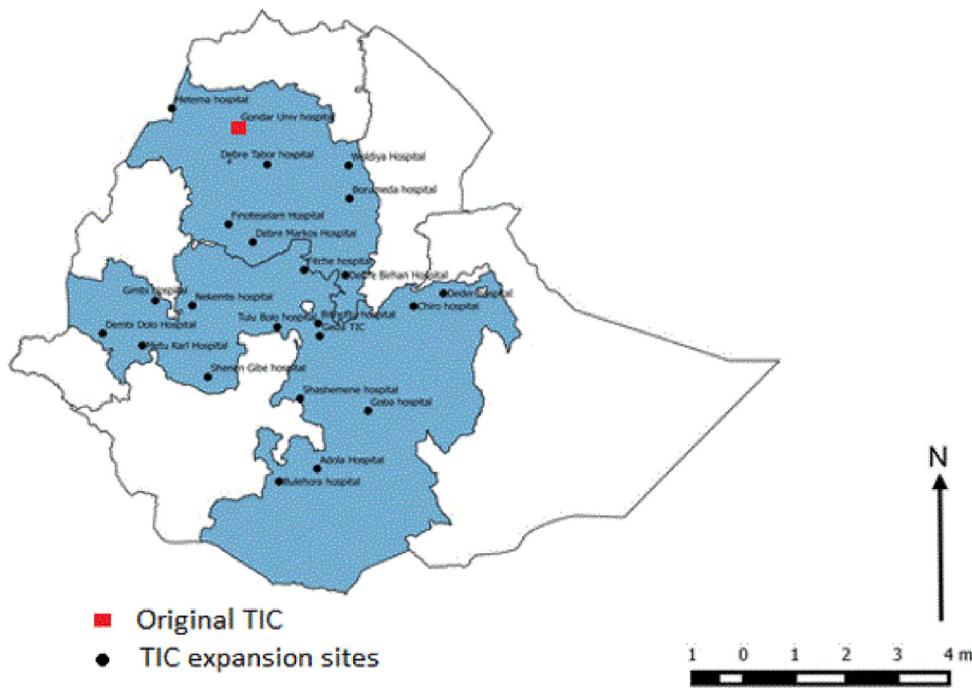


Fig 1. Map of Ethiopia showing the location of TICs in Amhara and Oromia Regions, Ethiopia, as of August 2015.

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%

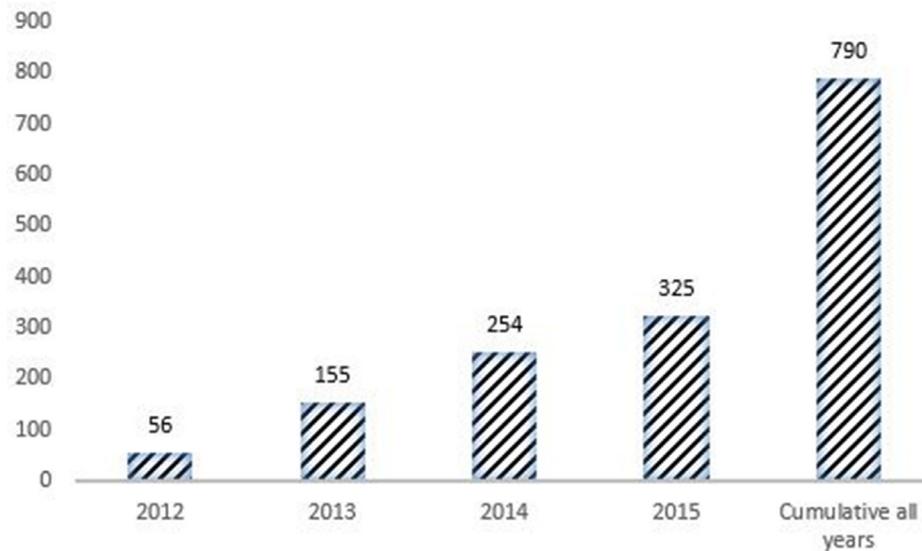


Fig. 2. Cumulative and new MDR TB patients enrolled per year, 2012–2015, Amhara and Oromia Regions, Ethiopia.

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).

Discussion

This is the first large scale implementation experience of the ambulatory MDR TB treatment model in Ethiopia, through which

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)

it was possible to achieve rapid expansion of MDR-TB services. Between 2012 and 2015, patient enrollment rate increased twelve-fold 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 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 (Biomérieux, Marcy l'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 1.9–9.6; $p < 0.001$) 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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RESEARCH ARTICLE

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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 benchmarks 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 \times EXP (growth rate \times 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 $\leq 5\%$ 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 NTL, 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 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	<i>p</i> 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 ^{****}

^bnotification per 100,000**P* ≤ 0.05, ***P* ≤ 0.01, ****P* ≤ 0.001, *****P* ≤ 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	<i>p</i> 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

^anotification per 100,000**P* ≤ 0.05, ***P* ≤ 0.01, ****P* ≤ 0.001, *****P* ≤ 0.0001^bbacteriologically 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	<i>P</i> value for trend
Overall	Notified cases	568	417	401	507	433	
	Tested for HIV	333	264	387	508	433	
	% 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**
0–4 years	Tested for HIV	180	135	197	280	207	
	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
5–9 years	Tested for HIV	54	71	81	97	93	
	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****
10–14 years	Tested for HIV	99	58	109	131	133	
	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* ≤ 0.05, *P* ≤ 0.01, ****P* ≤ 0.001, *****P* ≤ 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 NTLT 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 NTLT 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: Millennium development goal; MoH: Ministry of Health; MREC: Mulago Research and Ethics Committee; NTLT: 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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RESEARCH ARTICLE

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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

Abyot Asres^{1,3*}, Degu Jerene² and Wakgari Deressa³

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 6.1 million 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 15.7 million 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 1.8 million 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 microscopy 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 extra-pulmonary 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 delay computed 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 (\pm SD) of 3.6(\pm 2.4) visits to an average (\pm SD) of 2.2(\pm 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 bacteriologically 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).

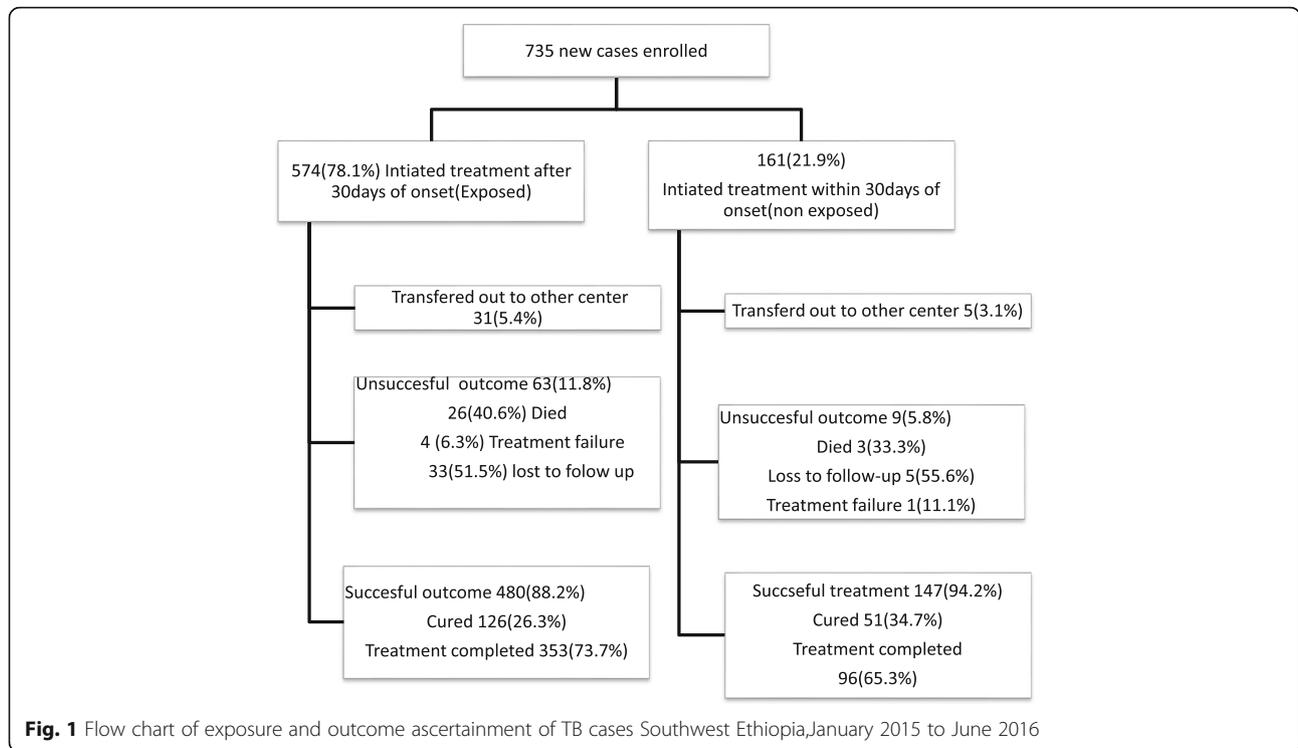


Table 1 Socidemographic characteristics and delays to treatment in southwest Ethiopia January to December 2015

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)

^ahousemaid, daily laborer, ^bstudents, housewife

Table 2 Patient characteristics and time delays to treatment 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(%)		
Type of TB	Pulmonary positive	277(48.3)	96(59.6)	0.02	373(50.7)
	Pulmonary negative	167(29.1)	46(28.6)		
	Extra pulmonary	130(22.6)	19(11.8)		
HIV status	Positive	57(9.9)	11(6.8)	0.4	68(9.3)
	Negative	517(90.1)	150(93.2)		
Mode of TB diagnosis	Bacteriological	277(48.3)	96(59.6)	0.04	373(50.6)
	Clinical	297(51.7)	65(40.4)		
Treatment center	Hospital	206(35.9)	60(37.3)	0.02	266(36.2)
	Health center	368(64.1)	101(62.7)		
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)		
Place TB diagnosis made	Public	493(85.9)	143(88.8)	0.09	636(86.5)
	Private	81(14.1)	18(11.2)		
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)		
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)		
Initial weight	Mean(±SD) Kg	49.0(8.6)	47.7(8.5)	0.9	48.7(± 8.6)

^aHealthcare Facility, ^bself 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 bacteriologically 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)		P value	Total n(%)
		> 30(exposed) N = 574 n(%)	<=30 (non exposed) N = 161 n(%)		
Sputum smear end of 2 nd month(n = 373)	Positive	3(1.1)	3(3.0)	0.5	6(1.6)
	Negative	158(57.9)	67(67.0)		
	Not available	112(41.0)	30(30.0)		
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)		
	Not available	132(48.4)	41(41.0)		
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)		
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)		
Weight end of 2 nd month	Mean(SD)	51.2(8.6)	50.2(8.6)	0.9	51.3(8.6)
Weight change end of 2 nd month	Unchanged/lost	93(16.2)	30(18.6)	0.2	123(16.7)
	Gained	298(52.0)	80(49.7)		
	Unknown	183(31.8)	51(31.7)		
Weight end of 5 th month	Mean(SD)	54.2(8.7)	51.8(9.5)	0.5	53.6(8.9)
Weight end of 6 th 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)		
	Loss to follow-up	33(5.7)	5(3.1)		
	Died	26(4.5)	3(1.9)		
	Treatment failure	4(0.7)	1(0.6)		
	Not evaluated ^a	31(5.4)	5(3.1)		
Treatment success (n = 699)	Unsuccessful	63(11.6)	9(5.8)	0.01	72(10.3)
	Successful	480(88.4)	147(94.2)		

^acases 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\$93.7 vs 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% Vs 46.3%, $p = 0.02$), 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 coinfecting 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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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 Jerene² and Wakgari Deressa³

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), pyrazinamide (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

^aHousemaid, daily laborer^bStudents, housewife^cFather/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) n(%)	End line (n = 627) n(%)	P value
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

^aSelf-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)

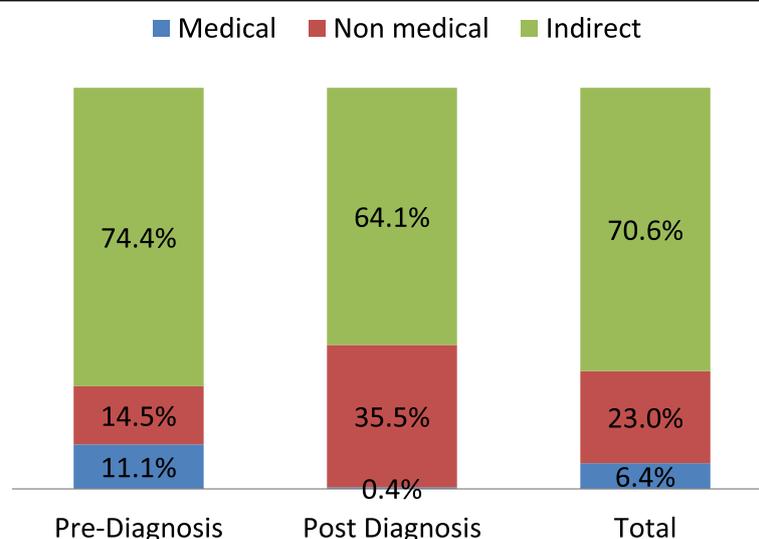


Fig. 1 Distribution of TB patient costs across pre and post diagnosis periods in districts of southwestern Ethiopia January 2015 to June 2016

(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)	<i>P</i> value	Adjusted exp. ^b coefficient (95% CI)	<i>P</i> 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 $p < 0.05$

^aExponent to the power of 10

^bAdjusted for all the variables listed in the table

^cVariable treated as continuous

^dSelf-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 $p < 0.05$ ^aExponent to the power of 10^bAdjusted for variables in the table^cVariable treated as continuous^dSelf-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 take 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

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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	<i>P</i> < 0.001
Cough triage	19.3	63.0	<i>P</i> < 0.001
IP/TB IC committee	29.1	61.1	<i>P</i> < 0.001
TB IC Plan	4.7	56.1	<i>P</i> < 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 HF 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. JJ 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 treat-

ment 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 *birr* and were converted into US dollars using the average daily midpoint exchange rate for March 2013 (18.60 Ethiopian *birr* = 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 <i>n</i>	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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R É S U M É

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.

SCHEMA : 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.



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](#)).

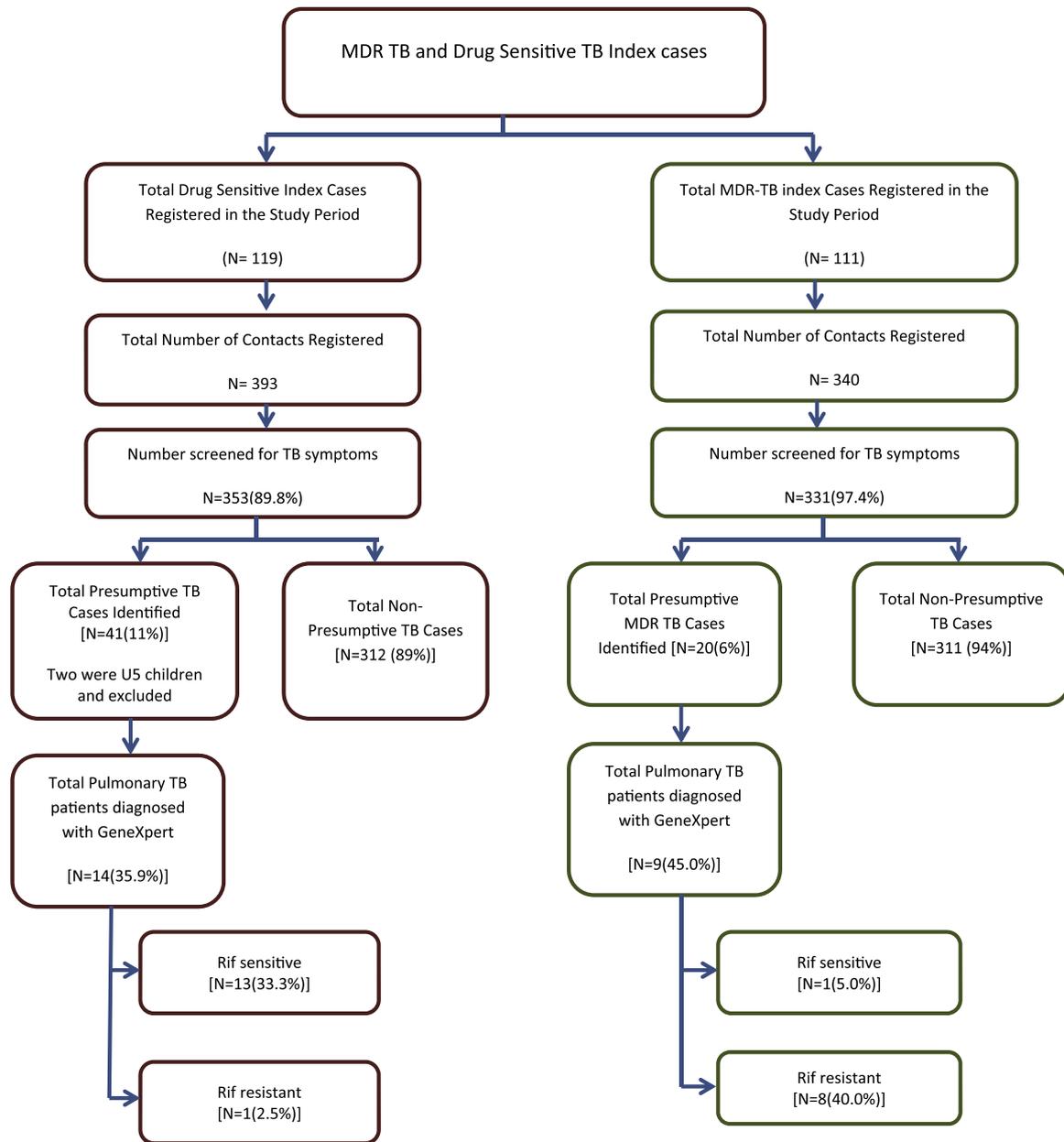


Figure 1. The procedures followed in screening and diagnosis among contacts of drug sensitive and MDR-TB index cases.

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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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 significant 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.

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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 (\pm SD 7.5 years), among males and females it was 67.1 years (\pm SD 7.9 years) and 68.2 years (\pm 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 X².

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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

^aUnfavorable 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.

Age	Total Died	Documented Date of Death	Month of Death during Treatment								
			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 health 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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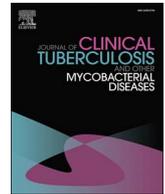
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Use of indicators of standards of care to improve tuberculosis program management in Ethiopia

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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 $\geq 95\%$ 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	TB register	<table border="1"> <tr> <td>< 80</td> <td>80-85</td> <td>> 85</td> </tr> </table>	< 80	80-85	> 85
			< 80			80-85	> 85	
	Total no. of smear-positive patients in registered cohort (evaluated during the last quarter)							
C9	Cure rate (re-treatment)	No. of retreatment TB patients cured in the reporting period	TB register	<table border="1"> <tr> <td>< 80</td> <td>80-85</td> <td>> 85</td> </tr> </table>	< 80	80-85	> 85	
< 80	80-85	> 85						
C10	Sputum conversion 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 <u>previous quarter</u> that were smear-negative at the end of the intensive phase of Rx	TB register	<table border="1"> <tr> <td>< 85</td> <td>85-90</td> <td>> 90</td> </tr> </table>	< 85	85-90	> 90	
		< 85			85-90	> 90		
Total no. of new smear-positive TB cases registered for Rx in the <u>previous quarter</u>								
C11	Proportion of smear-positive TB cases that were not examined at the	No. of new smear-positive TB cases registered in the <u>previous quarter</u> that were	TB register	<table border="1"> <tr> <td>0</td> <td>1-4</td> <td>0</td> </tr> </table>	0	1-4	0	
0	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 managers 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

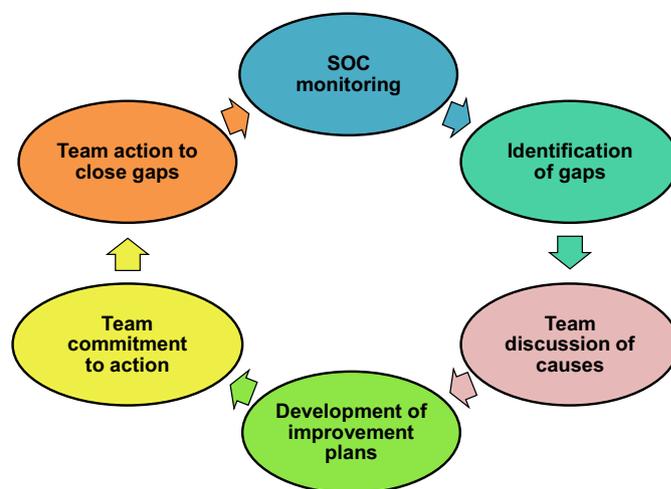


Fig. 1. The cycle of standards of care at the health facility, woreda, zonal, and regional levels.

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 health 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).

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 $\geq 95\%$ 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

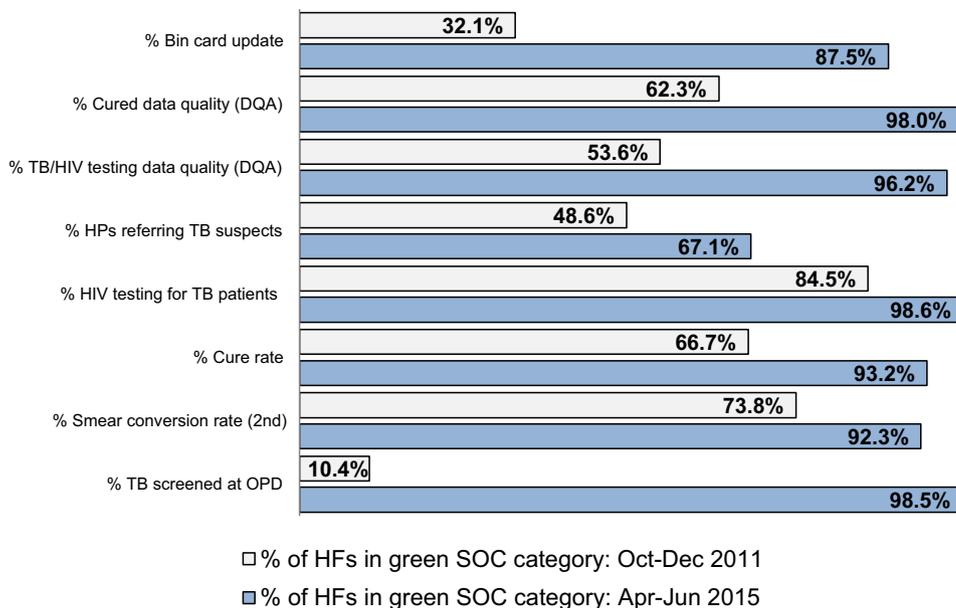


Fig. 2. Progress in the performance of selected indicators of standards of care, 2011–2015.

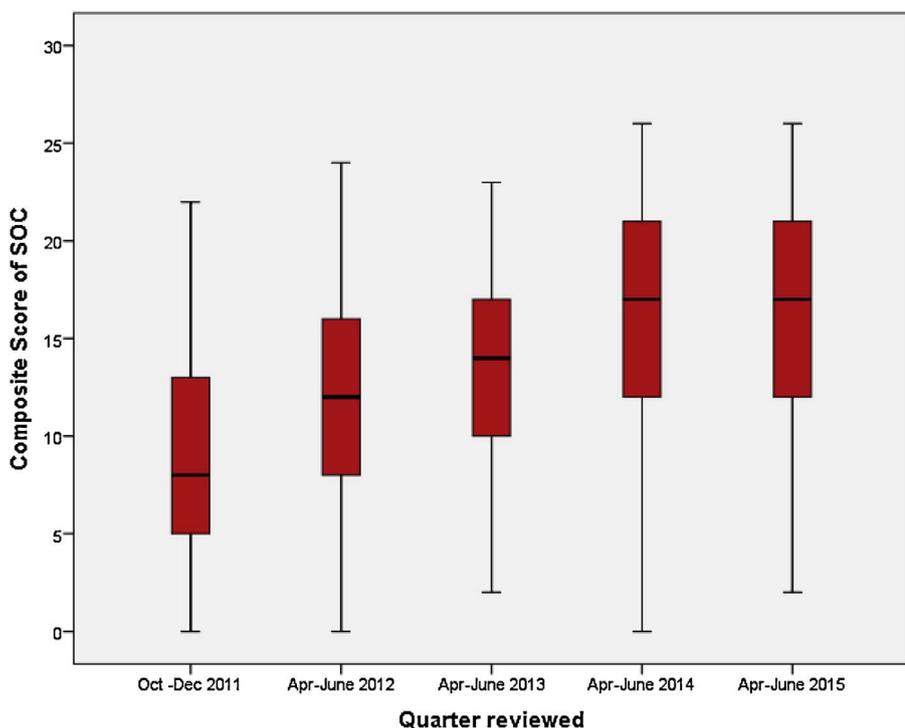


Fig. 3. Improvement in the composite score of 13 standard of care indicators in 10 zones, 2011–2015.

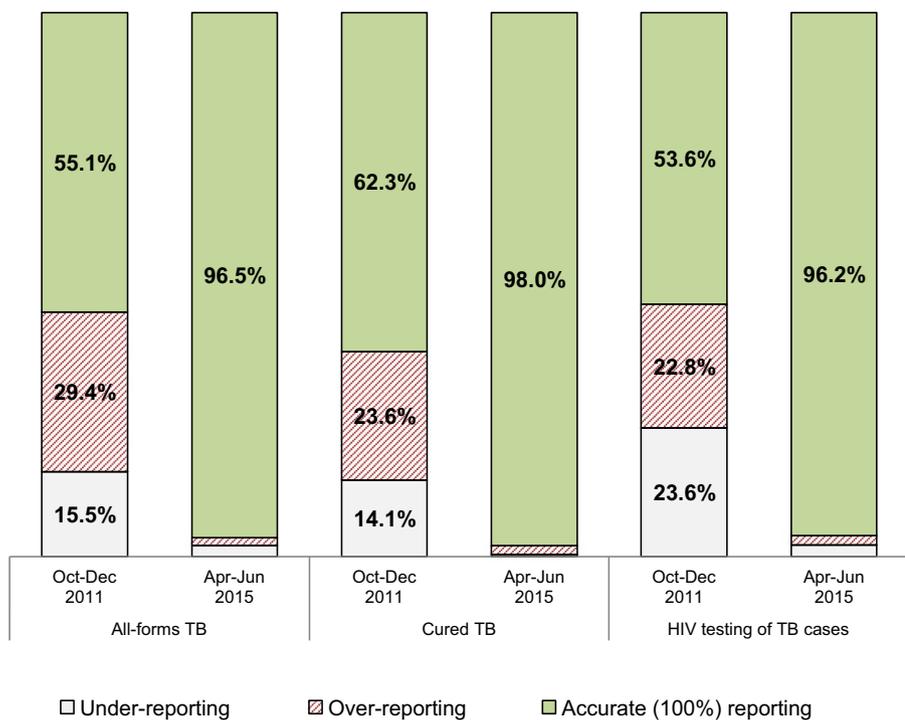


Fig. 4. Percentage improvement in the accuracy of reporting of selected TB program indicators in Ethiopia, 2011–2015.

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-

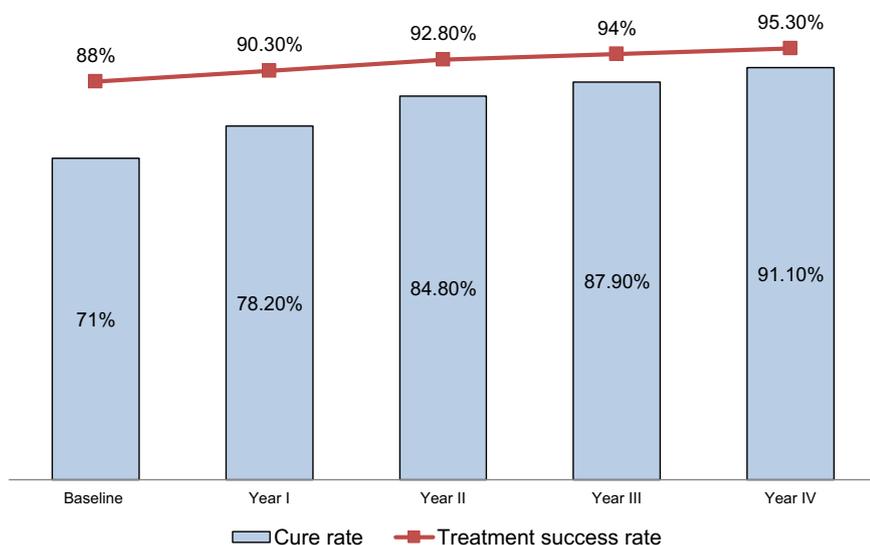


Fig. 5. Trend in treatment success and cure rates, 2011–2015.

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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Correspondence

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 conjunctiva. 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 sputum² 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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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/ μ l, 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



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	
<i>Demographics</i>				
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
<i>Presentation and medical history</i>				
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.

^aFisher'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. (%) [†]	χ^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 (0.2–16.2)	.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.

^aORs adjusted for age group 0-4 years.

^bORs 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 coinfecting 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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RESEARCH ARTICLE

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Delays to anti-tuberculosis treatment initiation among cases on directly observed treatment short course in districts of southwestern Ethiopia: a cross sectional study

Abyot Asres^{1,3*}, Degu Jerene² and Wakgari Deressa³

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 occurred [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 1.3 million 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 new TB 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 Kruskal 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	

^aStandard deviation ^bhousemaid, 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
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)	

^aneck swelling, head ache, joint pain, back pain, wound, ^bHCF closed, mistrust health care provider, bad previous experience at HCF, fear of HIV test and fear of TB diagnosis, ^cHEW = Health Extension worker (trained females those provide household package of health care to household), ^ddrug shop (13), holy water (14), traditional healer (4)

an average (\pm 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)	

^aAntiretroviral therapy ^b Cotrimoxazole Prophylactic 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 beyond 25 days. 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 from 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](mailto: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 multi-stage 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

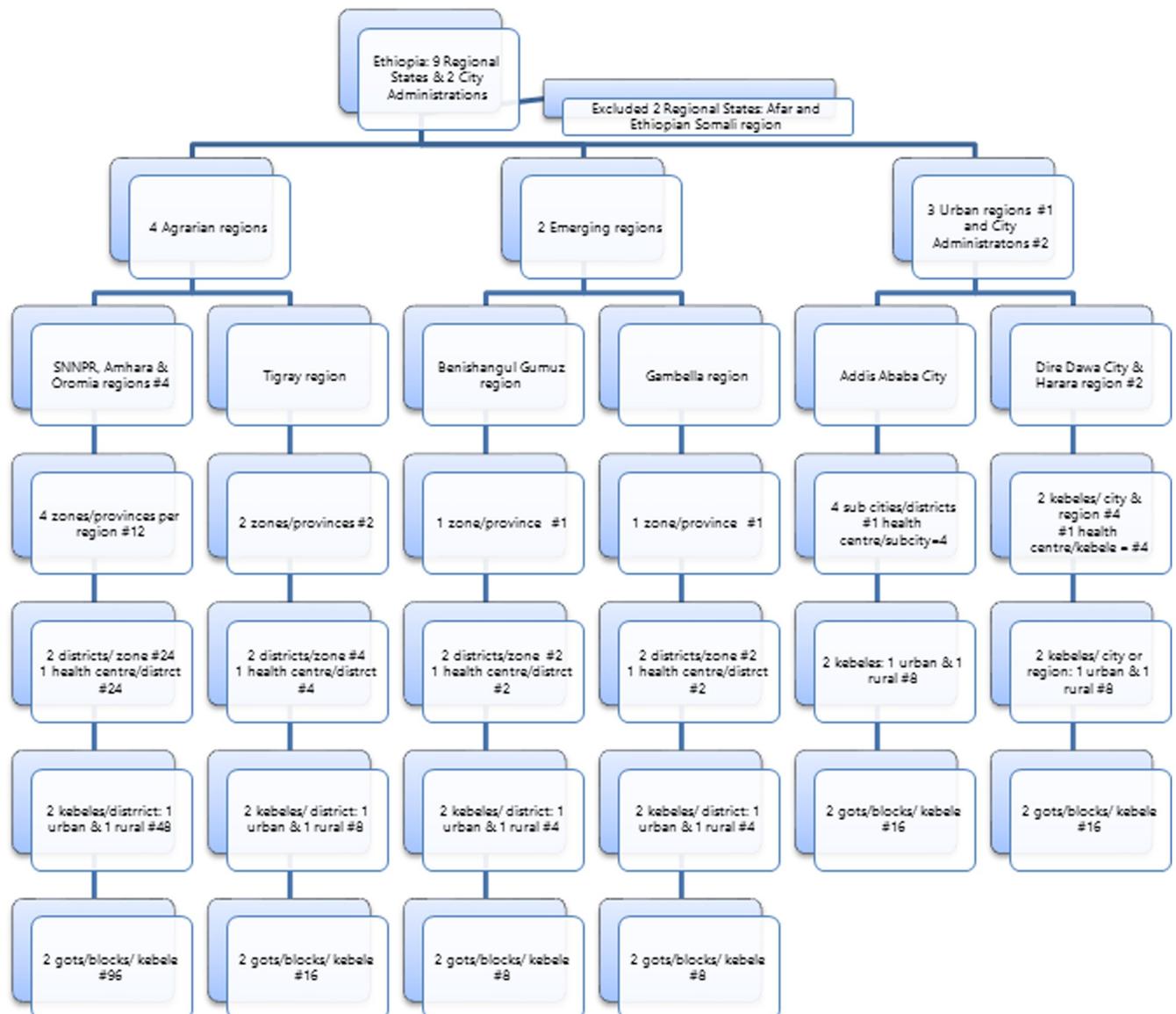


Fig 1. Study sites for the knowledge attitude and practice related to tuberculosis in Ethiopia.

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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 ± 12.9 years for both sexes, 34.9 ± 13.2 for men and 33.8 ± 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

¹Evil 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

³Only 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
	Tigray	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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RESEARCH ARTICLE

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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 PBC 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 documented classification of TB in the register.

The PBC TB patients had a mean age of 31.92 (SD \pm 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+

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 \pm 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

(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).

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

^aStatistically 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.

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

^aStatistically Significant Variable

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 hospital 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 NTL'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 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

^aStatistically 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 patients. 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

^aStatistically 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

^aStatistically 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 classes 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

^aStatistically 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; NTL: 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, DK and DL 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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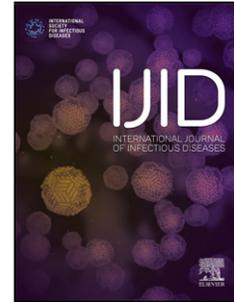
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Prevalence of tuberculosis among mentally ill patients in conflict-stricken Afghanistan: a cross-sectional study

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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.

- 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

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).

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.

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

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

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.

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.

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

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.

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).

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

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

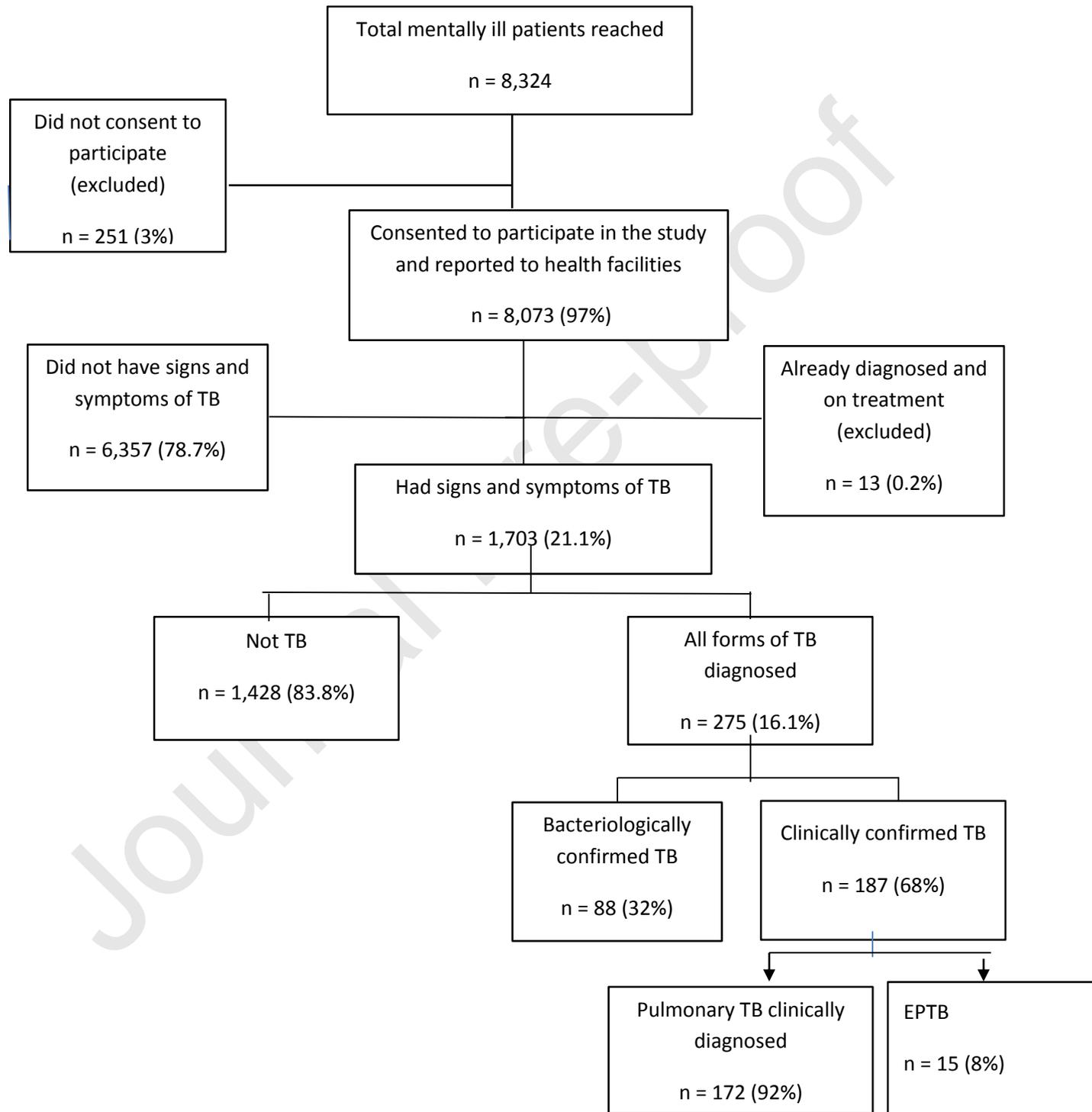


Table 1. Sociodemographic characteristics of psychiatric patients screened for TB

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%)

	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
Negative		6,212 (76.9%)
Unknown/not disclosed		1,853 (23.0%)

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)		

	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)	

DRUG DELIVERY

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- μ m-thick Eudragit RS 100 polymer coating to prevent

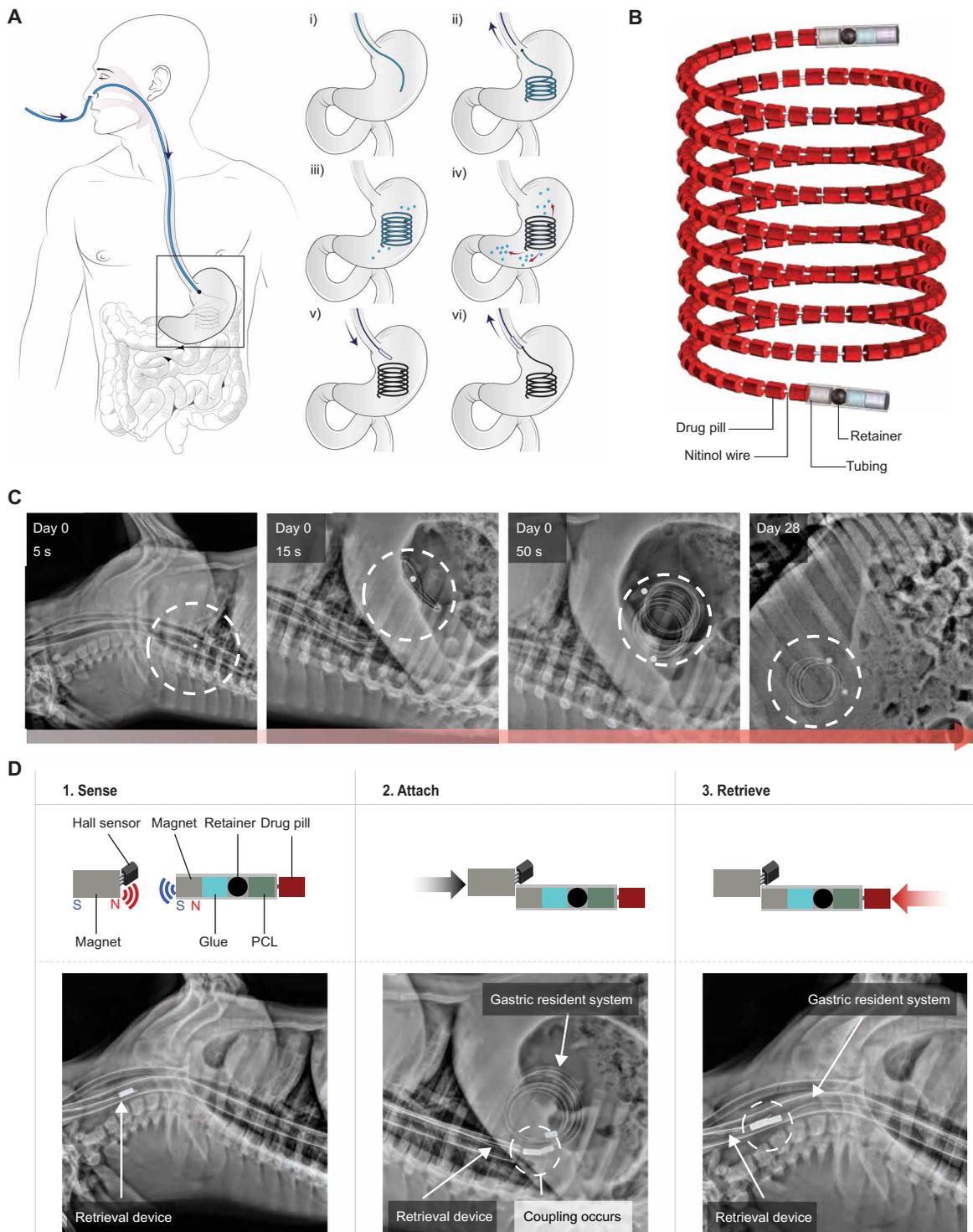


Fig. 1. Design and in vivo evaluation of a large-dose GRS for drug delivery. (A) (i-ii) An NG tube is first placed as a conduit for the large-dose GRS to be non-surgically administered, and then the NG tube is removed from the patient. (iii-iv) The GRS resides in the gastric cavity while releasing drugs. (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(ϵ -caprolactone) (PCL) plug] are also shown.

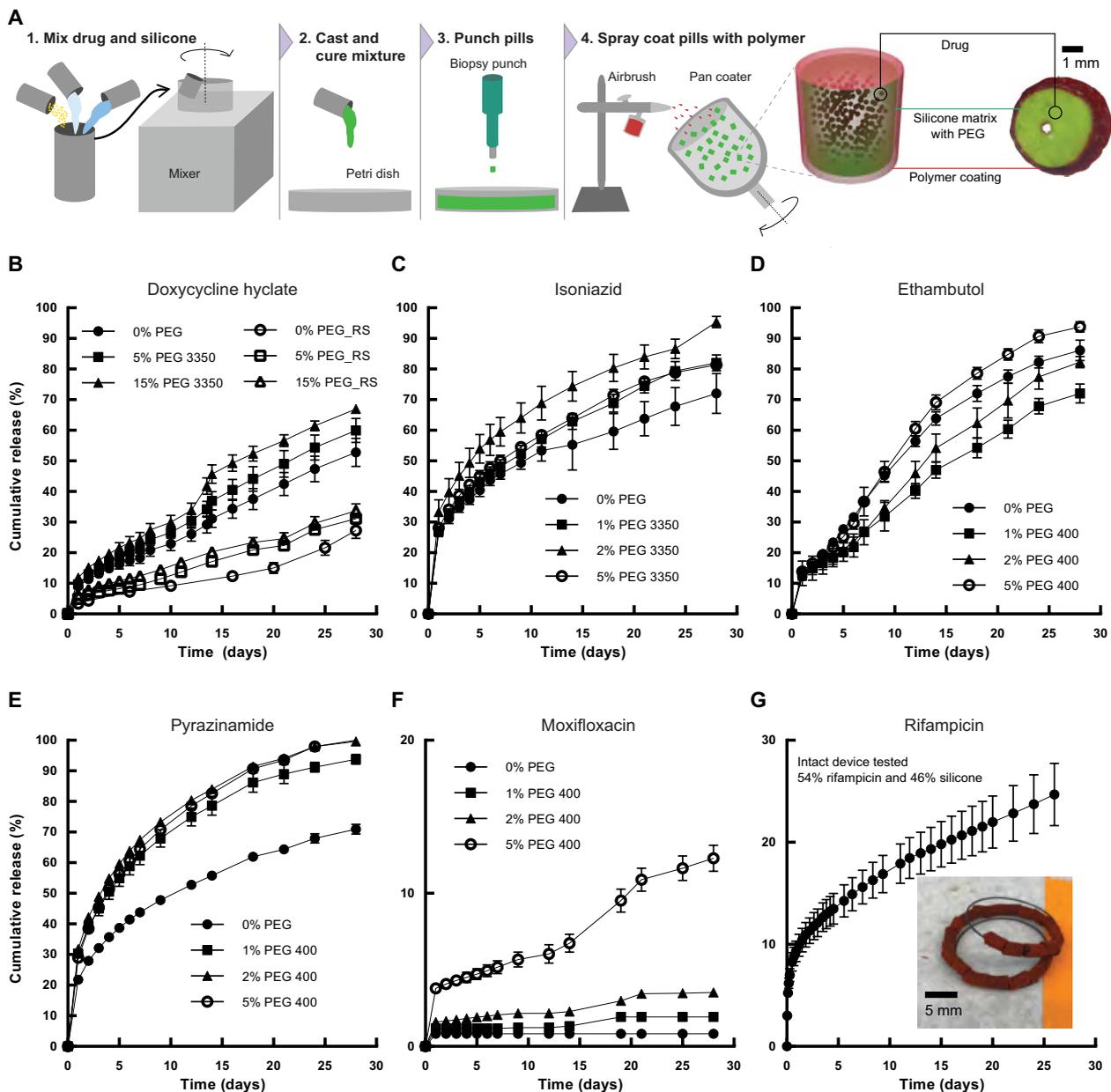


Fig. 2. Fabrication and in vitro release of TB antibiotics from individual drug pills. (A) Coated drug pills are made by mixing drug with silicones and extracting individual pills from the homogeneous matrix using a biopsy punch before spray-coating pills in a pan coater. A schematic visualization and 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).

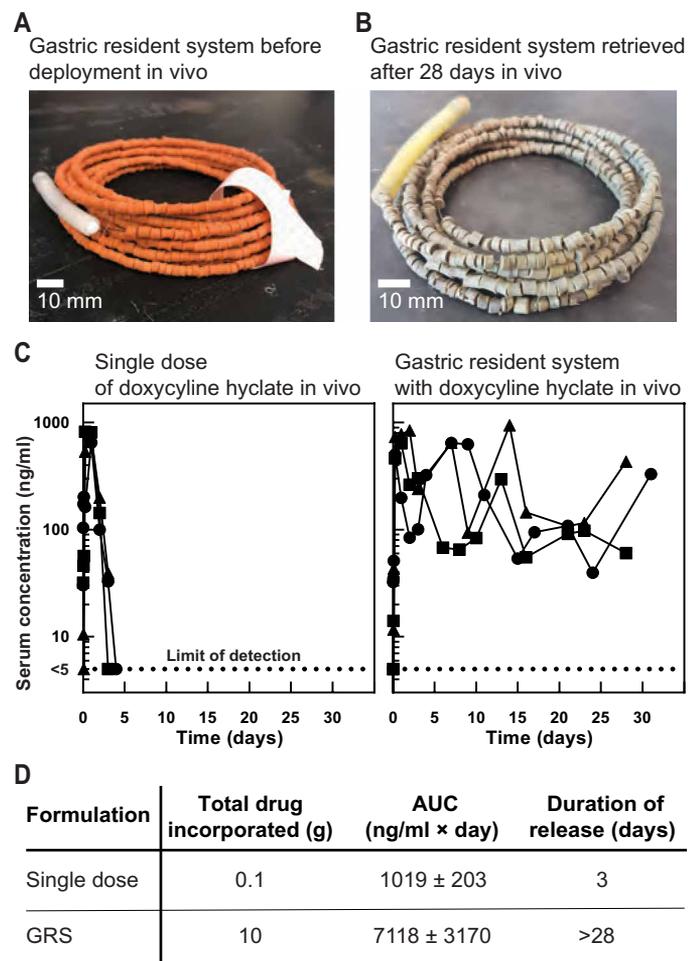


Fig. 3. In vivo release of doxycycline hyclate from the GRS in a swine model. (A) Representative photograph of a GRS after assembly of drug pills along a nitinol wire before deployment in vivo. (B) Representative photo of a retrieved GRS after 28 days in vivo in a swine model. (C) Left: Concentration-time 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.
- References (60–68)

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