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On the Front Lines of the Global Fight against TB: Eight Years of Field Research from MSH

Peer-reviewed implementation research on TB programs co-authored by MSH health experts, 2008-16

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Management Sciences for Health

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Dear Colleagues,

Last year, tuberculosis (TB) killed more people than did HIV/AIDS—becoming the world's deadliest single infectious agent. More than 95 percent of TB deaths occur in low- and middle-income countries, especially those with weak health systems.

We know that TB is both preventable and curable, and we have the technical tools and expertise to end the global TB epidemic by 2035. Stopping the epidemic requires more than medical expertise: it requires bold policies—such as universal health coverage—political commitment; funding; education of and authentic engagement with communities and all providers, public and private; social protection of TB patients and families; stronger regulatory frameworks; and research for better medical tools as well as to hasten implementation and impact.

In other words, vanquishing this disease requires stronger health systems, backed by political support in each country, and robust TB control programs, plus continuing research to improve the effectiveness and reach of interventions.

The four dozen peer-reviewed journal articles in this volume—plus a few not included here—are contributions to the research literature from MSH staff and our national partners (ministries of health, national TB programs, local NGOs, and universities) and international partners, as well as donors (principally the US Agency for International Development) in Africa, Asia, Latin America, and the Caribbean.

They draw on MSH's more than 15 years of experience on the front lines of combatting the TB epidemic. The papers present what works not in theory, but in the field; how successful approaches can be adapted in new settings; and cautionary lessons for the practitioner.

A unique compilation of lessons from programs around the world, these studies highlight particularly effective innovations for controlling this disease in the following technical areas:

- Quality DOTS implementation
- TB in fragile states and volatile environments
- MDR-TB care and treatment
- TB epidemiology, monitoring, and evaluation
- TB and gender
- TB contact investigation,
- TB diagnostics, including GeneXpert analysis

- Quality assurance in laboratory services
- Patient-centered care for vulnerable and special populations, including children; residents of crowded cities, refugee camps, or isolated rural communities; prisoners; and those with HIV and other diseases
- TB drug management and pharmacovigilance
- TB financing
- Capacity building and surveillance systems.

I believe that together these papers make an important contribution to the evidence base of what works in TB programming for vulnerable populations, and in complex environments and fragile states. It is my greatest hope that these lessons will be widely applied and continue to be refined in many settings where TB services are desperately needed.

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

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

Pedro G. Suarez, M.D.
Senior Director
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Management Sciences for Health
Arlington, VA, USA

Bibliography
Peer-Reviewed Publications on TB

Authored or co-authored by MSH technical experts

January 2008 – September 2016

Note: Primary author listed first; MSH contributors listed thereafter. *Primary author is MSH contributor. **Publications without open access, thus not included in this volume.

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Peer-Reviewed Publications on Tuberculosis

Authored or co-authored by MSH technical experts

(Listed by year of publication)

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Drug resistance of *Mycobacterium tuberculosis* in Malawi: a cross-sectional survey

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Objective To document the prevalence of multidrug resistance among people newly diagnosed with – and those retreated for – tuberculosis in Malawi.

Methods We conducted a nationally representative survey of people with sputum-smear-positive tuberculosis between 2010 and 2011. For all consenting participants, we collected demographic and clinical data, two sputum samples and tested for human immunodeficiency virus (HIV).The samples underwent resistance testing at the Central Reference Laboratory in Lilongwe, Malawi. All *Mycobacterium tuberculosis* isolates found to be multidrug-resistant were retested for resistance to first-line drugs – and tested for resistance to second-line drugs – at a Supranational Tuberculosis Reference Laboratory in South Africa.

Findings Overall, *M. tuberculosis* was isolated from 1777 (83.8%) of the 2120 smear-positive tuberculosis patients. Multidrug resistance was identified in five (0.4%) of 1196 isolates from new cases and 28 (4.8%) of 581 isolates from people undergoing retreatment. Of the 31 isolates from retreatment cases who had previously failed treatment, nine (29.0%) showed multidrug resistance. Although resistance to second-line drugs was found, no cases of extensive drug-resistant tuberculosis were detected. HIV testing of people from whom *M. tuberculosis* isolates were obtained showed that 577 (48.2%) of people newly diagnosed and 386 (66.4%) of people undergoing retreatment were positive.

Conclusion The prevalence of multidrug resistance among people with smear-positive tuberculosis was low for sub-Saharan Africa – probably reflecting the strength of Malawi's tuberculosis control programme. The relatively high prevalence of such resistance observed among those with previous treatment failure may highlight a need for a change in the national policy for retreating this subgroup of people with tuberculosis.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

Although the World Health Organization (WHO) has monitored the emergence of drug resistance of *Mycobacterium tuberculosis* since 1994,[1] there have been few national surveys of such resistance in sub-Saharan Africa.[2]

In 2012, it was estimated that about 1.9% of people newly diagnosed and 9.4% of those undergoing retreatment in Africa had multidrug-resistant (MDR) tuberculosis.[3] The prevalence of MDR tuberculosis in Africa varies between countries[4] and might be generally increasing.[3,5]

Over several years, attempts have been made – at the Central Reference Laboratory in Lilongwe – to isolate *M. tuberculosis* from all smear-positive patients undergoing retreatment in Malawi to investigate drug susceptibility. In 2008, about 8% of people investigated in this manner were found to have MDR tuberculosis (James Mpunga, Malawi National Tuberculosis Control Programme, personal communication, 2008) – although most of the samples came from urban centres and the laboratory's attempts to isolate *M. tuberculosisM. tuberculosis* often failed.[6] The only published data on MDR tuberculosis in Malawi indicated that just 0.5% of people newly diagnosed with tuberculosis and 0.9% of people being retreated in Karonga district had MDR tuberculosis in 1996–1998.[7]

In 2007, the nationally recommended treatment regimen for people newly diagnosed with tuberculosis in Malawi changed. The initial supervised treatment remained the same – i.e. daily isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months – but the unsupervised continuation phase changed from 6 months of isoniazid and ethambutol to 4 months of isoniazid and rifampicin.[8,9] There are four problems since this change that need monitoring. The first is that poor adherence during this currently-recommended continuation phase could lead to the emergence of MDR tuberculosis. Another problem is that nothing is known about the resistance of Malawian isolates of *M. tuberculosis* to the second-line drugs that began to be used routinely in Malawi in 2007. A third problem is the high prevalence of human immunodeficiency virus (HIV) infection among people with tuberculosis.[10] In 2010, 63% of Malawian tuberculosis patients tested for HIV were found positive.[4] Finally, the national prevalence of drug-resistant tuberculosis may be affected by migration of people from neighbouring countries, where such outbreaks have occurred.[11] Given these issues, we conducted a national survey of resistance to anti-tuberculosis drugs in Malawi.

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Methods

Study setting and design

We engaged all of Malawi's 48 tuberculosis registration centres to conduct a prospective, cross-sectional survey. The centres were grouped into three zones – northern, central and southern – for phased sample collection.

Data collection and management

Health workers in each registration centre formed a recruitment team and attended a three-day training course about the survey protocol. They subsequently collected data on each consenting smear-positive tuberculosis patient, including the patient's age, sex, level of education, occupation, marital status and HIV status – if known – and details of any previous tuberculosis treatment. After each patient was asked if they had received tuberculosis treatment, the patient's medical records at the health facility of recruitment were checked for evidence of such treatment.

Following national policy in Malawi,[8] each participant in the survey was offered HIV testing and counselling. At the time of the survey, two rapid blood tests – Uni-Gold Recombigen HIV-1/2 (Trinity Biotech, Bray, Ireland) and Determine HIV-1/2 (Alere, Waltham, United States of America) were used in the registration centres. Any samples giving inconclusive results were sent to the Central Reference Laboratory for retesting.

Data were collected on piloted forms and double-entered into an Epi Info (Centers for Disease Control and Prevention, Atlanta, United States of America) spreadsheet.

Participants and case definitions

Using the definitions recommended by WHO,[12] new cases were defined as people who had never been treated for tuberculosis – or had previously received anti-tuberculosis medications for less than one month – and retreatment cases were defined as those who had previously received tuberculosis treatment for at least one month. Retreatment cases were grouped according to the outcome of previous treatment: cured, completed, defaulted or failed. A patient was defined as cured when the person was smear-negative at, or one month before, treatment completion and on at least one previous occasion. A completed treatment was defined as a patient who completed treatment but without smear microscopy proof of cure. Persons who had treatment interruption for two consecutive months or more were grouped as defaulted. Those who remained smear-positive when tested five or six months after initiation of their previous treatment were defined as treatment failures.

For our survey, sputum samples were collected from each newly-diagnosed person with sputum-smear-positive tuberculosis seen at a registration centre in the northern, central and southern zones in May–July 2010, August–October 2010 and November 2010–January 2011, respectively. Sputum samples were also collected from each person with smear-positive tuberculosis undergoing retreatment at any registration centre between February 2010 and March 2011.

Drug resistance definition

Isolates of *M. tuberculosis* were defined as MDR if they were at least resistant to isoniazid and rifampicin, and extremely drug resistant (XDR) if they were also resistant to an injectable drug and a quinolone of the second-line medications.

Sample size projections

Assuming that 1.8% and 20% of the people newly diagnosed would have MDR tuberculosis and be lost to follow-up, respectively, we estimated that we needed to enrol 1260 new cases to estimate the prevalence of MDR tuberculosis among such cases with a precision of ± 1%. Similarly, assuming that 5.0% and 20% of our retreatment sample would have MDR tuberculosis and be lost to follow-up, respectively, we estimated that we would have to enrol 770 people undergoing retreatment to estimate the prevalence of MDR tuberculosis with a precision of ± 2.0%.

Laboratory procedures

Prior to enrolment, each participant had been found positive for tuberculosis by the microscopic examination of three smears of sputum.[12,13] Each month, a random selection of sputum smears from the registration centres – five from each health centre and 25 from each district hospital – was re-examined by a visiting laboratory supervisor. Concordance between the registration centres' results and the supervisor's remained above 96% during our survey.

For our survey, two additional sputum samples were collected – under supervision and approximately one hour apart – from each enrolled patient and stored at 2–8 °C in the registration centre. Efforts were made to ensure that these samples were collected before anti-tuberculosis treatment was commenced. The samples were transported to the Central Reference Laboratory, in cooler boxes, by bus or in a district health vehicle or study team vehicle.

Once a sample had reached the laboratory, it was decontaminated and further homogenized.[14] Part of the pellet produced by centrifuging the sample was smeared, stained with auramine phenol stain and then checked for acid-fast bacilli. Another part was inoculated into two tubes of Lowenstein–Jensen medium – one containing glycerol and the other containing sodium pyruvate – which were examined for growth weekly for up to 8 weeks. Each contaminated culture was discarded and replaced with a new culture that was set up using another part of the relevant pellet – which had been kept in a refrigerator. The Capilia tuberculosis test[15] was used to identify isolates belonging to the *M. tuberculosis* complex. Indirect susceptibility testing to isoniazid, rifampicin, ethambutol and streptomycin was performed, on one isolate per participant, using the proportion method on Lowenstein–Jenson medium.[16]

All isolates defined as MDR tuberculosis were sent to the South African Medical Research Council's Supranational Reference Laboratory in Pretoria. There, they were retested for their susceptibility to first-line drugs – using a line probe assay and automated liquid culture[17,18] – and tested for their susceptibility to the second-line drugs amikacin, kanamycin, capreomycin, ofloxacin and ethionamide – using automated liquid culture.

Statistical analysis

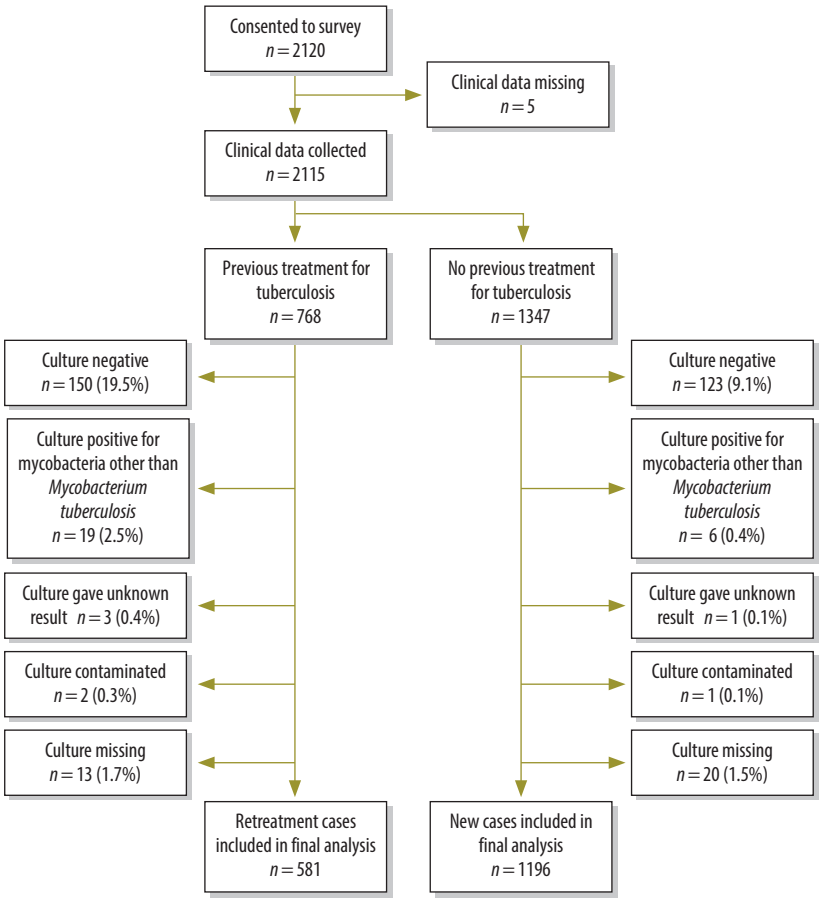
For our final analysis, we excluded those cases from which *M. tuberculosis* was not isolated in culture. Categorical and

non-parametric continuous variables were compared using χ^2 and Wilcoxon rank-sum tests, respectively. Data on new tuberculosis cases were analysed independently from retreatment cases. Associations between MDR tuberculosis and patient age, sex, HIV status, year of previous tuberculosis treatment and outcome of previous tuberculosis treatment were compared using Poisson logistic regression analysis. Unadjusted and adjusted incidence rate ratios (IRRs) were calculated in univariate and multivariate analyses, respectively. Stata 10.0 (StataCorp. LP, College Station, United States of America) was used for the statistical analysis.

Ethical considerations

Ethical approval was granted by the Malawi National Health Sciences Research Committee in April 2009. This study commenced in 2009, before requirements for review of all WHO-supported research by the WHO research ethics review committee were fully implemented. Written informed consent was obtained from adult participants and the caregivers of child participants. As recommended by the relevant national guidelines,[8] all cases of MDR tuberculosis were given six months of capreomycin, levofloxacin, ethionamide, cycloserine and pyrazinamide followed by 18 months of levofloxacin, ethionamide and cycloserine.

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



Results

During the study period, 2120 smear-positive individuals consented to participate. Five were excluded as their baseline data were missing, another 1347 were classified as newly diagnosed with tuberculosis and the remaining 768 were classified as retreatment cases (Fig. 1). *M. tuberculosis* was isolated from 1196 (88.8%) of the new cases. There was no difference in the distribution of age, sex, region or HIV status between these and new cases from which *M. tuberculosis* was not isolated. *M. tuberculosis* was isolated from 581 (75.7%) of people undergoing retreatment. Those in whom *M. tuberculosis* was not isolated were older than the other retreatment cases, with mean ages of 40.7 and 36.4 years, respectively.

Compared with the new cases, people undergoing retreatment were more frequently found to be culture-negative or to be culture-positive for mycobacteria other than *M. tuberculosis*.

Of 86 treatment failures, 31 samples were culture-positive for *M. tuberculosis*, six were culture-positive for other mycobacteria and 49 were culture-negative.

The median transit time of all samples, from collection to arrival at the Central Reference Laboratory was 4 days (interquartile range, IQR: 2–7 days). Transit time had no apparent effect on the probability that a sample would be found culture-positive for *M. tuberculosis* ($P = 0.71$).

Culture-positive tuberculosis

Culture-positive individuals in both new and retreatment groups were similar in terms of their sociodemographic characteristics (Table 1).

Overall, 66.4% (386) of the retreatment cases and 48.2% (577) of the new cases were known or found to be infected with HIV, demonstrating a significantly higher HIV prevalence among people retreated ($P < 0.01$). The retreatment cases reported that they had received tuberculosis treatment between 1978 and 2010 with a median of 2.4 years (IQR: 1.1–5.9 years) before their enrolment. Just 31 (5.3%) of the culture-positive retreatment cases had failed their previous treatment (Table 1).

Among the 1196 *M. tuberculosis* isolates from new cases, ethambutol, isoniazid, rifampicin and streptomycin resistance was present in 0.5%, 3.2%, 0.8% and 4.2%, respectively (Table 2). The corresponding values for the 581 isolates from the retreatment cases were all higher (Table 2).

Five (0.4%) of the 1196 new cases had MDR tuberculosis (Table 2 and Fig. 2). Other types of resistance (mono-resistance or any combination of drug resistance excluding MDR tuberculosis) were identified in 75 (6.3%) of the new cases but the remaining 1116 (93.3%) *M. tuberculosis* isolates from new cases were found to be sensitive to all four first-line drugs.

Table 1. **Characteristics of people newly-diagnosed with, and retreated for, tuberculosis, Malawi, 2010–2011**

Characteristic	New cases ($n = 1196$)		Retreatment cases ($n = 581$)	
	No.	% (95% CI)	No.	% (95% CI)
Mean age (years)	1196	35.6 (34.8–36.4)	581	36.4 (35.5–37.4)
Sex (% male)	1196	53.7 (50.8–56.5)	581	60.6 (56.6–64.6)
Marital status (%)				
Married	750	63.2 (60.5–66.0)	346	60.3 (56.3–64.3)
Single	232	19.6 (17.3–21.8)	106	18.5 (15.3–21.7)
Divorced	103	8.7 (7.1–10.3)	70	12.2 (9.5–14.9)
Widowed	101	8.5 (6.9–10.1)	52	9.1 (6.7–11.4)
Occupation (%)				
Business	226	19.5 (17.2–21.8)	120	21.1 (17.8–24.5)
Formal employment	195	16.8 (14.7–19.0)	126	22.2 (18.8–25.6)
Subsistence farmer	330	28.4 (25.8–31.0)	148	26.1 (22.4–29.7)
Unemployed	409	35.3 (32.5–38.0)	174	30.6 (26.8–34.4)
Educational level achieved (%)				
Tertiary	23	2.0 (1.2–2.8)	13	2.3 (1.0–3.5)
Secondary	262	22.5 (20.1–24.9)	171	29.9 (26.1–33.7)
Primary	729	62.6 (59.8–65.4)	319	55.8 (51.7–59.9)
None	151	13.0 (11.0–14.9)	69	12.1 (9.4–14.7)
HIV status (%)				
Positive	577	48.2 (45.4–51.1)	386	66.4 (62.6–70.3)
Negative	474	39.6 (36.9–42.4)	165	28.4 (24.7–32.1)
Unknown	145	12.1 (9.4–14.8)	30	5.2 (2.6–7.7)
Region of residence (%)				
Northern	115	9.6 (7.9–11.3)	85	14.6 (11.8–17.5)
Central west	283	23.7 (21.3–26.1)	108	18.6 (15.4–21.8)
Central east	135	11.3 (9.5–13.1)	46	7.9 (5.7–10.1)
South-west	359	30.0 (27.4–32.6)	207	35.6 (31.7–39.5)
South-east	304	25.4 (22.9–27.9)	135	23.2 (19.8–26.7)
Outcome of previous treatment (%)				
Cured[a]	NA	NA	389	67.0 (63.1–70.8)
Completed[b]	NA	NA	104	17.9 (14.8–21.0)
Defaulted[c]	NA	NA	49	8.4 (6.2–10.7)
Failed[d]	NA	NA	31	5.3 (3.5–7.2)
Unknown	NA	NA	8	1.4 (0.4–2.3)
Smear score (%)[e]				
Scanty	101	8.6 (7.0–10.2)	66	11.6 (8.9–14.2)
1+	135	11.5 (9.6–13.3)	66	11.6 (8.9–14.2)
2+	295	25.0 (22.6–27.5)	115	20.1 (16.8–23.4)
3+	647	54.9 (52.1–57.8)	324	56.7 (52.7–60.8)

CI: confidence interval; HIV: human immunodeficiency virus; NA: not applicable.

[a] Cured defined as a smear-positive patient who was smear-negative at, or one month before, treatment completion and on at least one previous occasion.[12]

[b] Treatment completed defined as a patient who completed treatment but without smear microscopy proof of cure.[12]

[c] Defaulted defined as treatment interruption for two consecutive months or more.[12]

[d] Failed defined as remaining smear-positive when tested five or six months after initiation of previous treatment.[12]

[e] Smear scores indicate the density of acid-fast bacilli seen on a sputum smear.[13]

Note: Data are missing for some characteristics. The sum of the percentages for some characteristics may not equal 100 due to rounding.

Twenty-eight (4.8%) of the 581 *M. tuberculosis* isolates from retreatment cases showed multidrug resistance (Table 2). Other types of resistance were identified in 83 (14.3%) of the retreatment cases but the remaining 470 (80.9%) *M. tuberculosis* isolates from retreatment cases were found to be sensitive to all four first-line drugs (Table 2 and Fig. 2).

In the multivariate analysis, sex, age and HIV status were not found to be significantly associated with MDR tuberculosis among new or retreatment cases. There was also no evidence of a significant association between region of residence and MDR tuberculosis. All of the 28 retreatment cases with MDR tuberculosis had received treatment in the previous five years – 23 (82%) within the previous two years. MDR tuberculosis in people undergoing retreatment was found to be significantly and inversely associated with time since previous treatment (adjusted IRR: 0.7, 95% confidence interval, CI: 0.5–0.9). Previous treatment failure – but no other previous treatment outcome – was strongly associated with MDR tuberculosis (adjusted IRR: 3.7, 95% CI: 1.6–8.4). Of the 31 treatment failures, nine (29.0%) cultured multi-drug resistant *M. tuberculosis*.

Of the 33 isolates of *M. tuberculosis* found to be multidrug-resistant in Malawi, 30 successfully underwent retesting in South Africa, and 11 of these were sensitive to either isoniazid or rifampicin or both of these drugs. If the results from South Africa are used as the gold standard, this indicates a 36.7% false-positive rate (11/30 in Table 3). When a random sample of 106 isolates of *M. tuberculosis* found not to be multidrug-resistant in Malawi were retested in South Africa, one was identified as MDR tuberculosis – giving a 0.9% false-negative rate (1/106 in Table 3).

The 20 isolates found to show multidrug resistance in South Africa were re-cultured in South Africa and tested for resistance to several second-line drugs. Although 18 of these isolates were successfully re-cultured and tested, none showed extensive drug resistance (Table 4).

Discussion

This is the first national survey of anti-tuberculosis drug resistance done in Malawi. We found the prevalence of MDR tuberculosis among people

Table 2. **Resistance to first-line anti-tuberculosis drugs among *Mycobacterium tuberculosis* isolates, Malawi, 2010–2011**

Resistance	Isolates from new cases ($n = 1196$)		Isolates from retreatment cases ($n = 581$)	
	No.	% (95% CI)	No.	% (95% CI)
Fully sensitive	1116	93.3 (91.7–94.7)	470	80.9 (77.5–84.0)
Any resistance[a]				
R	9	0.8 (0.4–1.4)	38	6.5 (4.7–8.9)
H	38	3.2 (2.3–4.3)	66	11.4 (8.9–14.2)
E	6	0.5 (0.2–1.1)	18	3.1 (1.9–4.9)
S	50	4.2 (3.1–5.5)	49	8.4 (6.3–11.0)
Multidrug resistance	5	0.4 (0.1–1.0)	28	4.8 (3.2–6.9)
RH	2	0.2 (0.0–0.6)	13	2.2 (1.2–3.8)
RHE	0	0.0 (0.0–0.3)	1	0.2 (0.0–1.0)
RHS	1	0.1 (0.0–0.5)	6	1.0 (0.4–2.2)
RHES	2	0.2 (0.0–0.6)	8	1.4 (0.6–2.7)
Other forms of resistance	75	6.3 (5.0–7.8)	83	14.3 (11.5–17.4)
R only	3	0.3 (0.1–0.7)	9	1.5 (0.7–2.9)
H only	22	1.8 (1.2–2.8)	32	5.5 (3.8–7.7)
E only	2	0.2 (0.0–0.6)	4	0.7 (0.2–1.8)
S only	35	2.9 (2.1–4.1)	30	5.2 (3.5–7.3)
RS	1	0.1 (0.0–0.5)	0	0.0 (0.0–0.6)
RE	0	0.0 (0.0–0.3)	1	0.2 (0.0–1.0)
HE	1	0.1 (0.0–0.5)	2	0.3 (0.0–1.2)
HS	10	0.8 (0.4–1.5)	3	0.5 (0.1–1.5)
ES	1	0.1 (0.0–0.5)	1	0.2 (0.0–1.0)
HES	0	0.0 (0.0–0.3)	1	0.2 (0.0–1.0)

CI: confidence interval; E: ethambutol; H: isoniazid; R: rifampicin; S: streptomycin.
[a] Any resistance indicates resistance to the anti-tuberculosis medication tested, independent of resistance results to the other medications.

newly diagnosed to be low, at 0.4%. As about 7200 new cases of smear-positive tuberculosis have occurred annually in Malawi over recent years,[4] we can expect there to be 29 cases of primary MDR tuberculosis in Malawi annually. Although we found the prevalence of MDR tuberculosis among retreatment cases to be significantly higher, as generally observed,[19] this could be expected to produce only 27 secondary cases of MDR tuberculosis annually.

The rates described here represent the lowest values reported in sub-Saharan Africa up to 2011.[3] Neighbouring Mozambique identified multidrug resistance in 3.5% of new tuberculosis cases and 11.2% of retreatment cases in 2007. In 2009, Swaziland reported corresponding values of 7.7% and 33.9%, respectively.[5] During our survey, the Central Reference Laboratory successfully isolated *M. tuberculosis* from the sputum samples from 88.8% of new cases and 75.7% of retreatment cases. Although the sample transit times recorded during our survey were disappointing, long transit times were not associated with isolation failures. Mycobacteria could not be grown from 49 of 86 samples from treatment failures, probably because the bacilli in the 49 samples were dead. Mycobacteria other than *M. tuberculosis* were cultured from six treatment failures. The proportion of sputum samples from retreatment cases that were found culture-positive for *M. tuberculosis* was significantly lower than the corresponding value for the new cases. This difference is partly explained by (i) the low isolation rate from treatment failures; (ii) the fact that samples from retreatment cases were relatively more likely to grow mycobacteria other than *M. tuberculosis*; and (iii) the fact that sputum samples from retreatment cases are relatively more likely to be collected from patients who have already begun treatment for their current episode of tuberculosis.

Since the results recorded by Malawi's Central Reference Laboratory were associated with a 36.7% false-positivity rate and a 0.9% false-negativity rate, the prevalences of MDR tuberculosis that we recorded in Malawi – although low – could overestimate the true values. Given the laboratory's limited capacity and the observation that resistance patterns probably do not vary between smear-positive and smear-negative cases of tuberculosis,[20] we did not investigate the drug resistance of any *M. tuberculosis* isolates from smear-negative tuberculosis patients.

We found HIV prevalence among new smear-positive cases of pulmonary tuberculosis to be 48.2%. The HIV prevalences reported among all tuberculosis cases by Malawi's National Tuberculosis Programme in 2010 and 2011 were higher, at 63% and 60%, respectively.[21] The programme's observations indicate that HIV prevalence among smear-negative cases of pulmonary tuberculosis exceeded 65% in 2010–2011. By focusing on smear-positive cases, we probably limited the extent to which we could explore associations between HIV and MDR tuberculosis. Although we found no association between HIV and MDR tuberculosis, it is possible that such an association exists in the overall population of people with tuberculosis. The existence of such a link remains a matter of controversy[3,5,22,23] but concomitant HIV infection certainly poses some unique challenges in the management of tuberculosis.[10]

Although we collected samples from different areas of Malawi at different times of the year, a retrospective analysis of new tuberculosis case notifications between 1999 and 2007 suggested that there was little variation in the number of new cases occurring in each quarter of the year (James Mpunga, Malawi National Tuberculosis Control Programme, personal communication, 2010).

The low prevalence of MDR tuberculosis that we recorded may be attributable to the success of Malawi's tuberculosis control programme. The frequencies of success in the treatment of tuberculosis in Malawi – 88% for new cases and 85% for retreatment cases – are among the highest recorded in sub-Saharan Africa.[4] We recorded higher prevalences of streptomycin resistance than of rifampicin or isoniazid resistance, perhaps because streptomycin was included in the recommended first-line treatment for tuberculosis in Malawi until 1992.

Fig. 2. **Resistance patterns of *Mycobacterium tuberculosis* to anti-tuberculosis drugs, Malawi, 2010–2011**

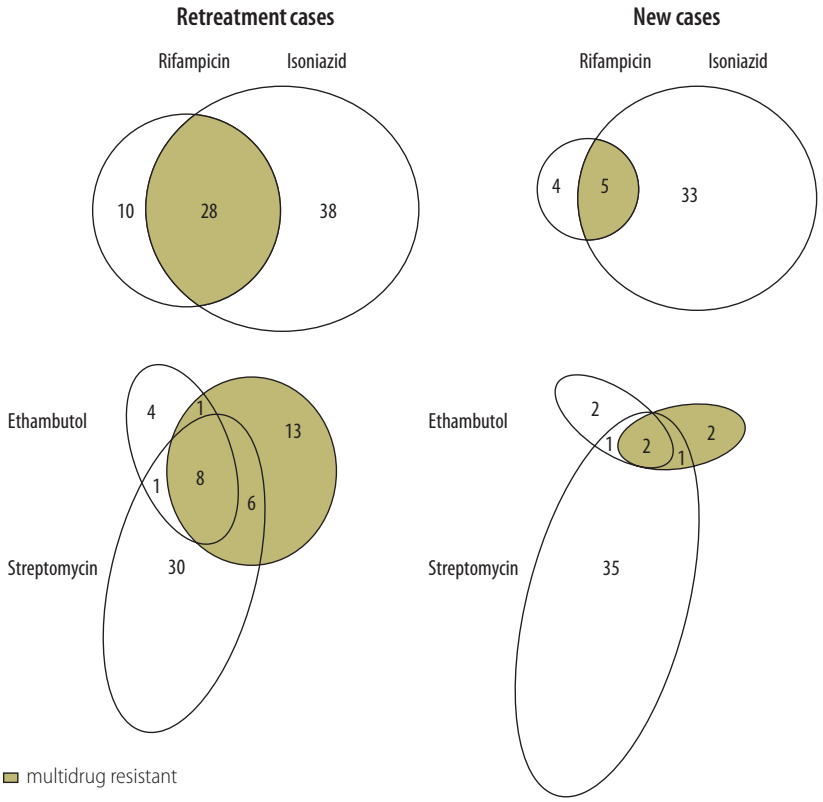


Table 3. **Comparison of anti-tuberculosis drug susceptibility testing of Malawian *Mycobacterium tuberculosis* isolates, 2010–2011**

Malawian result	South African result[a]			
	Sensitive to all drugs	Resistant to rifampicin only	Resistant to isoniazid only	MDR
Sensitive to all drugs	87	1	2	0
Resistant to rifampicin only	2	0	0	0
Resistant to isoniazid only	6	0	7	1
MDR	4	2	5	19

MDR: multidrug-resistant.

[a] The table shows the numbers of *M. tuberculosis* isolates, from Malawian cases of smear-positive pulmonary tuberculosis, that were tested for resistance to isoniazid, rifampicin, ethambutol and streptomycin in both the Central Reference Laboratory (Lilongwe, Malawi) and the South African Medical Research Council's Supranational Reference Laboratory (Pretoria, South Africa).

Table 4. **Resistance to second-line anti-tuberculosis drugs among 18 multidrug-resistant *Mycobacterium tuberculosis* isolates, Malawi, 2010–2011**

Isolate	Resistance[a]				
	Amikacin	Kanamycin	Capreomycin	Ofloxacin	Ethionamide
1–14	susceptible	susceptible	susceptible	susceptible	resistant
15	susceptible	resistant	susceptible	susceptible	resistant
16	susceptible	susceptible	resistant	susceptible	resistant
17	resistant	resistant	resistant	susceptible	resistant
18	resistant	susceptible	resistant	susceptible	resistant

[a] Amikacin, kanamycin, capreomycin, ofloxacin and ethionamide were tested at concentrations up to 1.0, 5.0, 2.5, 2.0 and 5.0 µg/mL, respectively.

We detected no XDR tuberculosis but did observe some resistance to second-line drugs. Since all of our isolates tested for resistance to ethionamide were found positive, the currently recommended 24-month regimen for the treatment of MDR tuberculosis in Malawi needs to be revised. Resistance to the second-line injectables was detected but not resistance to ofloxacin. At the time of the survey, Malawi's Central Reference Laboratory relied entirely upon the South African Supranational Reference Laboratory for the identification of Malawian cases of XDR tuberculosis.[8]

Treatment failure – frequently a forewarning for the development of drug-resistant tuberculosis[24] – was associated with a 29.0% risk of MDR tuberculosis in our survey. The initiation of a standard retreatment regimen while awaiting the results of drug susceptibility testing may amplify resistance in cases with pre-existing MDR tuberculosis.[25,26] Although use of an empirical MDR treatment regimen has been suggested as a replacement for the standard retreatment regimen for all treatment failures,[24,27,28] such a change in Malawi would expose most treatment failures – i.e. those who do not have MDR tuberculosis – to a more toxic and less effective therapy. During our survey, all patients with MDR tuberculosis who were diagnosed by phenotypic testing at the Central Reference Laboratory – including the 11 cases classified as drug sensitive when their sputum samples were investigated in South Africa – were managed with the nationally recommended second-line regimen. This was because (i) the phenotypic results were seen as more predictive of clinical response; (ii) the South African results became available several months after the patients had started second-line therapy; and (iii) it was felt that any changes to treatment made after the South African results became available would be confusing to patients.

Conclusion

The prevalence of MDR tuberculosis is currently low in Malawi – probably as the result of a strong tuberculosis control programme – whereas HIV-coinfection, which has been associated with high mortality in the presence of drug-resistant tuberculosis, is common. Almost a third of the treatment

failures we investigated had MDR tuberculosis. Given the discovery of ethionamide resistance in all 18 of the MDR tuberculosis isolates investigated for such resistance, ethionamide should be replaced with an alternative drug in Malawi's current MDR tuberculosis treatment regimen. Given an increasing prevalence of drug resistance in some neighbouring countries and the recent introduction of unsupervised rifampicin into tuberculosis treatment regimens in Malawi, we recommend repeating this survey within three years. ■

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ملخص

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

الغرض توثيق انتشار مقاومة الأدوية المتعددة بين الأشخاص الذين جرى تشخيص إصابتهم حديثاً بالسل – والذين تكرر علاجهم من السل – في ملاوي.

الطريقة أجرينا دراسة استقصائية تمثيلية على الصعيد الوطني للأشخاص المصابين بالسل وسجلوا نتائج إيجابية لاختبار لطاخة البلغم بين 2010 و2011. وقمنا بجمع البيانات الديمغرافية والسريرية وعينتين من البلغم واختبارهما لتحديد الإصابة بفيروس العوز المناعي البشري من جميع المشاركين الذين أبدوا موافقتهم. وتم إجراء اختبار المقاومة للعينات في المختبر المرجعي المركزي في ليلونغوي، بملاوي. وتم تكرار اختبار جميع مستفردات البكتريا المتفطرة السليّة التي تبين مقاومتها للأدوية المتعددة من أجل تحديد مقاومتها لأدوية الخط الأول – واختبارها من أجل تحديد مقاومتها لأدوية الخط الثاني – في مختبر مرجعي للسل على الصعيد فوق الوطني في جنوب أفريقيا.

النتائج بشكل عام، تم استفراد البكتريا المتفطرة السليّة من 1777 (83.8٪) مريضاً من أصل 2120 مريضاً بالسل سجلوا نتائج إيجابية لاختبار اللطاخة. وتم تحديد مقاومة الأدوية المتعددة في خمس (0.4٪) من أصل 1196 مستفردة من حالات جديدة و28 (4.8٪) من أصل 581 مستفردة من الأشخاص الذين تكرر علاجهم. وأظهرت تسع (29.0٪) من أصل 31 مستفردة من الحالات التي تكرر علاجها بعد فشل علاجها في السابق مقاومة للأدوية المتعددة. وعلى الرغم مما تبين من مقاومة لأدوية الخط الثاني، لم يتم اكتشاف حالات للسل الشديد المقاوم للأدوية. وتبين من اختبار فيروس العوز المناعي البشري للأشخاص الذين تم الحصول على مستفردات البكتريا المتفطرة السليّة منهم أن 577 (48.2٪) من الأشخاص الذين جرى تشخيصهم حديثاً و386 (66.4٪) من الأشخاص الذين تكرر علاجهم سجلوا نتائج إيجابية.

الاستنتاج كان انتشار مقاومة الأدوية المتعددة بين الأشخاص المصابين بالسل الذين سجلوا نتائج إيجابية لاختبار اللطاخة منخفضاً في أفريقيا جنوب الصحراء الكبرى – بما يوضح على نحو محتمل قوة برنامج مكافحة السل في ملاوي. من المحتمل أن يؤكد الارتفاع النسبي لانتشار هذه المقاومة التي لوحظت بين الأشخاص الذين فشل علاجهم في السابق على الحاجة للتغيير في السياسة الوطنية من أجل تكرار علاج هذه الفئة الفرعية من الأشخاص المصابين بالسل.

摘要

马拉维分枝杆菌肺结核耐药性：横断面调查

目的 记录马拉维肺结核新诊以及复治人群多耐药性流行率。

方法 我们针对 2010 年和 2011 年之间痰涂片阳性肺结核患者进行了具有全国代表性的调查。对于所有的参与者，我们都收集了人口和临床数据、两份唾液样本并进行艾滋病毒（HIV）检测。这些样本在马拉维隆圭中央参考实验室接受耐药性检测。在南非超国家结核病参考实验室对发现具有多耐药性的所有分枝杆菌肺结核分离菌再次进行一线药物的耐药性检测，然后进行二线药物耐药性检测。

结果 总的来说，在 2120 名痰涂片阳性肺结核患者中，从 1777 名（83.8%）患者中分离出肺结核分枝杆菌。从新患者的 1196 个分离菌中确定了 5 个（0.4%）有多耐药性，从复治患者的 581 个分离菌中确定了 28 个（4.8%）有多耐药性。在曾经治疗失败的复治病例中获得的 31 个分离菌中，9 个（29.0%）显示出多耐药性。尽管发现二线药物耐药性，但未发现广泛耐药性的肺结核病例。对获得肺结核分枝杆菌分离菌人群的艾滋病毒检测显示，新患者中有 577 例（48.2%）为阳性，复治患者中有 386 例（66.4%）为阳性。

结论 撒哈拉以南非洲痰涂片阳性肺结核患者多耐药性的流行率较低——可能反映了马拉维的肺结核病控制规划的效力。在先前治疗失败的人群中观察这种耐药性的流行率相对较高，这可能凸显了对这个肺结核患者子群的全国性复治政策作出改变的需求。

Résumé

Pharmacorésistance du *Mycobacterium tuberculosis* au Malawi: une enquête transversale

Objectif Documenter la prévalence de la résistance polymédicamenteuse de la tuberculose parmi les personnes nouvellement diagnostiquées et les personnes traitées à nouveau au Malawi.

Méthodes Nous avons mené une enquête nationale représentative des personnes atteintes de tuberculose à frottis d'expectoration positif entre 2010 et 2011. Pour tous les participants consentants, nous avons recueilli les données démographiques et cliniques, deux échantillons d'expectoration et effectué le dépistage du virus de l'immunodéficience humaine (VIH). Les échantillons ont subi des tests de résistance au Laboratoire central de référence de Lilongwe, au Malawi. Tous les isolats de *Mycobacterium tuberculosis* qui ont présenté une résistance polymédicamenteuse ont été retestés pour la résistance aux médicaments de première intention - et testés pour la résistance aux médicaments de deuxième intention – dans un laboratoire de référence supranational pour la tuberculose en Afrique du Sud.

Résultats Dans l'ensemble, *M. tuberculosisM. tuberculosis* a été isolé chez 1777 (83,8%) des 2120 patients atteints de tuberculose à frottis positif. La résistance polymédicamenteuse a été identifiée dans 5 (0,4%) des 1196 isolats obtenus à partir des nouveaux cas et dans 28 (4,8%) des 581 isolats obtenus à partir des personnes qui recevaient à nouveau un traitement. Parmi les 31 isolats issus des cas retraités qui ont connu un échec de traitement, 9 (29%) isolats ont présenté une résistance polymédicamenteuse . Bien que la résistance aux médicaments donnés en deuxième intention ait été identifiée, aucun cas de tuberculose ultrarésistante aux médicaments n'a été détecté. Les dépistages du VIH des personnes à partir desquelles les isolats de *M. tuberculosisM. tuberculosis* ont été obtenus ont montré que 577 (48,2%) des personnes nouvellement diagnostiquées et 386 (66,4%) des personnes recevant à nouveau le traitement étaient séropositives.

Conclusion La prévalence de la résistance polymédicamenteuse chez les personnes atteintes de tuberculose à frottis positif était faible en Afrique subsaharienne – reflétant probablement la force du programme de contrôle de la tuberculose du Malawi. La prévalence relativement élevée de cette résistance observée chez les personnes pour lesquelles le traitement précédent a échoué peut mettre en évidence un besoin de changement dans la politique nationale en matière de retraitement de ce sous-groupe de personnes atteintes de tuberculose.

Резюме

Лекарственная устойчивость *микобактерий туберкулеза* в Малави: перекрестное исследование

Цель Задокументировать распространенность множественной лекарственной устойчивости при первичном и повторном лечении больных туберкулезом в Малави.

Методы В 2010-2011 гг. было проведено национальное репрезентативное исследование больных туберкулезом легких с бактериовыделением. У всех согласившихся принять участие в исследовании были собраны демографические и клинические данные и взяты два образца мокроты; кроме того, они прошли тестирование на вирус иммунодефицита человека (ВИЧ). Лекарственная устойчивость полученных образцов была проверена в Центральной референс-лаборатории г. Лилонгве, Малави. Все изоляты микобактерий туберкулеза с выявленной множественной лекарственной устойчивостью были подвергнуты дополнительному тестированию на устойчивость к лекарственным препаратам первой и второй линии в наднациональной туберкулезной референс-лаборатории в Южной Африке.

Результаты В итоге, наличие *микобактерий туберкулеза* было выявлено у 1777 (83,8%) из 2120 больных туберкулезом легких с бактериовыделением. Множественная лекарственная устойчивость была обнаружена у пяти (0,4%) из 1196 изолятов, взятых у лиц, получавших первичное лечение туберкулеза, и у 28 (4,8%) из 581 изолятов, взятых у лиц, получавших повторное лечение. Из изолятов, взятых у лиц, получавших повторное лечение после неудачного первичного, множественная лекарственная устойчивость была выявлена в девяти (29%) случаях из 31. Притом, что устойчивость к лекарствам второй линии была обнаружена, случаев туберкулеза с широкой лекарственной устойчивостью выявлено не было. Тестирование на ВИЧ лиц, у которых были выделены изоляты микобактерий туберкулеза, показало наличие вируса у 577 (48,2%) больных, у которых туберкулез был выявлен впервые, и у 386 (66,4%) больных, получавших повторное лечение.

Вывод Распространенность лекарственной устойчивости среди больных туберкулезом легких с бактериовыделением в странах Африки южнее Сахары невелика, что, по-видимому, свидетельствует об эффективности противотуберкулезной программы Малави. В то же время, довольно высокая распространенность таких случаев среди лиц, лечение которых в прошлом не принесло результата, может указывать на необходимость изменения национального подхода к повторному лечению этой подкатегории больных туберкулезом.

Resumen

Resistencia medicamentosa a la *Mycobacterium tuberculosis* en Malawi: una encuesta transversal

Objetivo Documentar la prevalencia de la resistencia a medicamentos múltiples entre pacientes a quienes se ha diagnosticado recientemente o han vuelto a recibir tratamiento para la tuberculosis en Malawi.

Métodos Llevamos a cabo una encuesta representativa a nivel nacional de pacientes con tuberculosis que dieron positivo en el análisis de esputo entre 2010 y 2011. Para todos los participantes adultos, se recogieron datos demográficos y clínicos, dos muestras de esputo y realizamos pruebas del virus de inmunodeficiencia humana (VIH). Las muestras se sometieron a pruebas de resistencia en el Laboratorio Central de Referencia en Lilongwe (Malawi). Se volvieron a examinar todas las cepas de *Mycobacterium tuberculosis* multirresistentes para probar la resistencia a los medicamentos de primera línea y se probó su resistencia a los medicamentos de segunda línea en un laboratorio de referencia supranacional para la tuberculosis en Sudáfrica.

Resultados En general, la *M. tuberculosisM. tuberculosis* se aisló en 1777 (83,8%) de los 2120 pacientes de tuberculosis con baciloscopia positiva. Se detectó multirresistencia a medicamentos en cinco (0,4%) de las 1196 cepas de casos nuevos y en 28 (4,8%) de las 581 cepas de pacientes que se volvieron a someter al tratamiento. De las 31 cepas de casos de repetición del tratamiento que no habían respondido

previamente al tratamiento, nueve (29,0%) mostraron multirresistencia a medicamentos. Pese a que se halló resistencia a los medicamentos de segunda línea, no se detectaron casos de tuberculosis con resistencia extendida a medicamentos. Las pruebas del VIH de quienes se obtuvieron cepas de *M. tuberculosisM. tuberculosis* mostraron que 577 (48,2%) de los pacientes con diagnóstico reciente y 386 (66,4%) de los pacientes que se volvieron a someter al tratamiento dieron positivo.
Conclusión La prevalencia de la multirresistencia a medicamentos entre los pacientes con tuberculosis que dieron positivo en la baciloscopia positiva fue baja en el África subsahariana, lo cual probablemente refleja la eficacia del programa de control de la tuberculosis de Malawi. La prevalencia relativamente alta de dicha resistencia observada entre los pacientes que no respondieron al tratamiento anterior puede poner de manifiesto la necesidad de un cambio en la política nacional para volver a tratar a este subgrupo de pacientes con tuberculosis.

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

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SUMMARY

SETTING: Afghanistan.

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

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

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

KEY WORDS: tuberculosis; community health services; Afghanistan

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

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

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

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

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

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

With the NTP and partners, REACH worked to:

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

STUDY POPULATON AND METHODS

Setting

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

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

The DOTS strategy

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

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

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

Main TB control activities

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

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

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

Data

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

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

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

RESULTS

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

DOTS coverage in the country

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

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

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

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

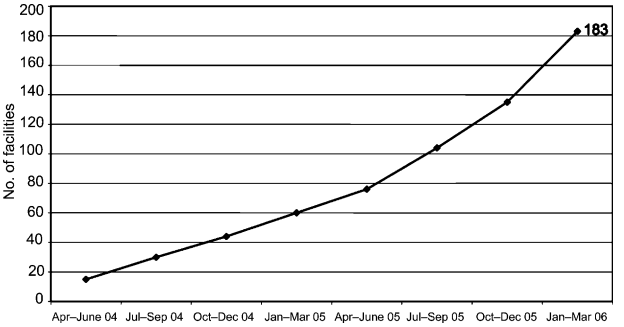

Figure 1 Number of REACH facilities (including basic health centers) that reported providing DOTS. REACH = Rural Expansion of Afghanistan's Community-based Healthcare.

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

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

Case detection and treatment

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

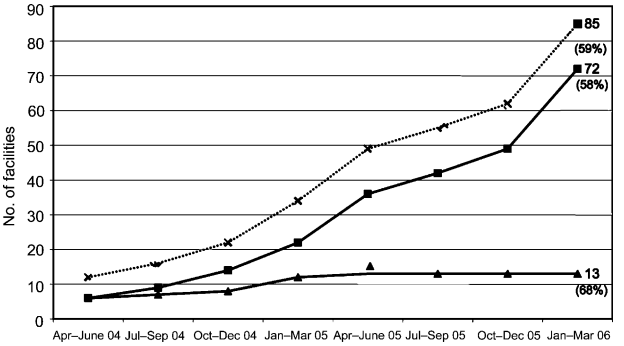

Figure 2 REACH-supported hospitals and comprehensive health centers offering active diagnosis and treatment of tuberculosis. Dotted line = total; line with squares = comprehensive health centers with active diagnosis and treatment services; line with triangles = district hospitals with active diagnosis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

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

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

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

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

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

Source: NTP, 2005.[11]

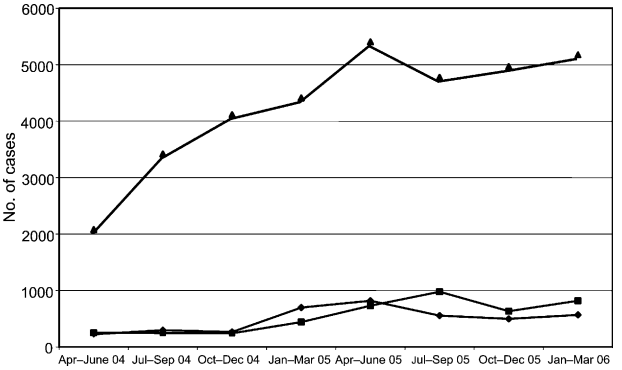

Figure 3 Suspected and newly diagnosed TB cases and treatment completion in REACH facilities (including provincial hospitals). Line with triangles = number of suspected TB cases; line with diamonds = number of new smear-positive TB cases; line with squares = number of TB cases who completed treatment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

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

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

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

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

DISCUSSION

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

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

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

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

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

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

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

CONCLUSIONS

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

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

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

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

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RÉSUMÉ

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

RESUMEN

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

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Connectivity of diagnostic technologies: improving surveillance and accelerating tuberculosis elimination

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SUMMARY

In regard to tuberculosis (TB) and other major global epidemics, the use of new diagnostic tests is increasing dramatically, including in resource-limited countries. Although there has never been as much digital information generated, this data source has not been exploited to its full potential. In this opinion paper, we discuss lessons learned from the global scale-up of these laboratory devices and the pathway to tapping the potential of laboratory-generated information in the field of TB by using connectivity. Responding to the demand for connectivity, innovative third-party players have proposed solutions that have been widely adopted by field users of the Xpert® MTB/RIF assay. The experience associated with the utilisation of these systems, which facilitate the monitoring of wide laboratory networks, stressed the need for a more global and comprehensive approach to diagnostic connectivity. In addition to facilitating the reporting of test results, the mobility of digital information allows the sharing of information generated in programme settings. When they become easily accessible, these data can be used to improve patient care, disease surveillance and drug discovery. They should therefore be considered as a public health good. We list several examples of concrete initiatives that should allow data sources to be combined to improve the understanding of the epidemic, support the operational response and, finally, accelerate TB elimination. With the many opportunities that the pooling of data associated with the TB epidemic can provide, pooling of this information at an international level has become an absolute priority.

KEY WORDS: laboratory; connectivity; tuberculosis; surveillance; data

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IN THE PAST DECADE, the use of new diagnostic tests has increased dramatically in the laboratories of developing countries and, more recently, in decentralised point-of-care facilities. Self-contained molecular diagnostic devices have been successfully deployed to detect tuberculosis (TB) (e.g., Xpert® MTB/RIF; Cepheid, Sunnyvale, CA, USA[1]) or monitor treatment for the human immunodeficiency virus (HIV) (e.g., Alere Pima™ CD4, Alere, Waltham, MA, USA[2]) in very basic clinical facilities. Despite the accumulating evidence that these tools can be successfully used in the most challenging environments[3,4] and the establishment of distribution and funding channels that should theoretically allow any country to access and scale up these new technologies, the majority of patients that could benefit from these technical evolutions still do not have access to them. It is clear that the introduction of an improved TB diagnostic tool is not sufficient to assure improved outcomes for patients, as the details of implementation within existing health delivery systems have a critical influence on impact.[5]

We suggest that the introduction of new tools such as Xpert offers an important opportunity to better understand, monitor and improve such delivery systems to assure greatest impact. If the scale-up of novel diagnostic devices can be accompanied by the simultaneous introduction of up-to-date quality indicators and technical connectivity solutions, the vast amount of data generated by this new generation of automates could both simplify and potentiate the global response to the TB epidemic.

On a national and global level, as the quantity of information produced following the introduction of new-generation laboratory instruments was not anticipated, no plans were in place on how to manage the information flow or orient it in such a way that it could generate an evolution in the organisation of the epidemic response. In the absence of adequate laboratory information technology infrastructure, complemented by standardised reporting solutions for screening activities and treatment follow-up, many low-resource countries have continued to use slow, error-prone paper-based recording systems. In such systems, editing and transmission of paper reports cause inherent delays and contribute to the cost, complexity and relative inaccuracy of data interpretation.

Diagnostic e-health solutions have the potential to help overcome some of these problems and maximise the patient and public health impact following the introduction of a particular technology. The combination of this unprecedented evolution of the laboratory landscape and the potential of e-health could be leveraged to generate the revolution in national and global health delivery systems that is needed to achieve TB elimination. Pragmatically, this requires device connectivity, whereby secure testing data and results are automatically sent to repositories, translated into useful information and channelled to appropriate parties. Although device connectivity within other industries has been routine for some time, within the health care community it is still largely in its infancy.[6]

In this paper, we discuss lessons learned from the global scale-up of the first generation of easy-to-connect diagnostic tools[7] and the pathway to tapping the potential of connectivity in the field of TB diagnostics.[8]

EXPERIENCE FROM FIRST-GENERATION CONNECTED DIAGNOSTICS: THE EXAMPLE OF XPERT

During the last decade, several diagnostic companies, such as Cepheid Inc and Alere Inc, have begun developing a new generation of tests essential to fight diseases of poverty such as TB and HIV, with significant support from public and philanthropic funders, including the National Institutes of Health (Bethesda, MD, USA) and the Bill & Melinda Gates Foundation (Seattle, WA, USA).

The Xpert assay, which is run on the GeneXpert platform, was the first truly game-changing test to come out of this research, and it has since been widely distributed in health facilities with limited human and infrastructure resources. The coverage of Xpert varies considerably between countries, with some countries still having only a limited number of machines based in reference laboratories, and others, such as South Africa, that realised the advantages of implementing this novel platform as a first-line test fairly rapidly.[9] In the last 5 years, more than 13 million Xpert tests have been procured worldwide. When GeneXpert was rolled out in 2010, the instrument had no built-in connectivity outside basic standards, and the TB community did not have the software tools to connect to GeneXpert machines and use the data being generated to its full capacity. Valuable information housed in the hard drives of local computers was thus never used to inform surveillance efforts or health care providers, and was largely lost.

In the light of this issue, national TB programmes (NTPs) called for tools to reduce loss to follow-up and improve device and laboratory management, including a better ability to maintain cartridge supplies and local redistribution, and evaluate and fulfil the training needs of device operators and laboratory technicians. Likewise, NTPs voiced a need for connectivity systems that could relieve the high overhead costs of data aggregation and analysis, which hamstring the process of collecting raw data and turning it into useful information.

In 2012, responding to this critical gap in the implementation landscape, innovative third-party players developed connectivity solutions. GxAlert

(ABT, Cambridge, MA, USA, and SystmOne, Horsforth, UK), XpertSMS (Interactive Research and Development, Karachi, Pakistan, and TB REACH, Geneva, Switzerland) and GenXchange (Université Catholique de Louvain, Louvain, Belgium, and the NTP, Kinshasa, Democratic Republic of Congo) were devised to respond to the needs of low-resource countries, where internet is often unavailable or unreliable and laboratory information systems or electronic medical records are not widely used. These tools offered immediate solutions and, in response to national requests, hundreds of local laboratories have since become interconnected on implementing these systems. The scaling of these connectivity solutions has been taken back by dedicated companies (Global Connectivity. Somerville, MA, USA. http://www.globalconnectivity.co/; and Savics. Brussels, Belgium. http://www.savics.org).

Cepheid, the manufacturer of GeneXpert, also worked to enable remote monitoring of their devices in response to expressed national needs and requests from the TB community. Like many developers, Cepheid lacked comprehensive information about what use-cases needed to be supported, and for ethical and regulatory reasons they prioritised data security and confidentiality. As a result, the company launched an initial software tool that was a step forward but was unable to fulfil all NTP needs.

In response, an alliance of key implementation partners, such as USAID (Washington DC, USA), MSF (Paris, France), Clinton Health Access Initiative (Boston, MA, USA) and Foundation for Innovative New Diagnostics (FIND) (Geneva, Switzerland) and donors, such as UNITAID (Geneva, Switzerland) and the Global Fund (Geneva, Switzerland), was formed, led by the World Health Organization (WHO), to work with Cepheid in ensuring secure, open access to critical data and finding a broader, holistic approach to connectivity and data management. An immediate solution was found, and both Cepheid and the alliance remain interested in the creation of a non-proprietary, long-term connectivity platform or a series of integrated and inter-operational platforms. This highlights how the global TB community can collectively define priority needs and work with manufacturers to negotiate and realise solutions for accessing and utilising key data.

Another important lesson from the implementation of first-generation connected diagnostics is the importance of a well-tailored delivery pathway for connectivity software that supports sustainable uptake in a given country. For example, Alere, the manufacturer of Pima™ CD4, devised a country-based public-private partnership model to ensure appropriate training and support for their connectivity software. Without this support and engagement of key stakeholders, many countries would have struggled to make use of the influx of data. While the tool itself has limited wider applicability because of the proprietary nature of the software, the partnership model offers a valuable example of how non-proprietary, interoperable systems could be disseminated and nurtured in the future.

CONNECTIVITY OF DIAGNOSTICS: A SHARED RESPONSIBILITY AND PUBLIC HEALTH NECESSITY

The WHO and research funding agencies have been advocating for, and implementing, data-sharing policies for some time. While these efforts have increased access to synthesised research data, efforts to make NTP data available are in their infancy. The use of new-generation diagnostic platforms has triggered thinking about the potential utility of real-time analysis of national data, and how diagnostic connectivity could further improve epidemiological surveillance and guide targeted public health responses. Accelerated TB elimination, for example, as called for in the WHO End TB strategy,[10] can only be realised if case detection, individual patient management and epidemiological surveillance are intensified simultaneously, and if these efforts are closely monitored and validated. Data generated by Xpert testing can be used both to improve patient management and treatment efforts and to provide important population-level information on average infectiousness as a predictor for TB burden[11] and spread of new mutations. This requires optimised programmatic data management, pooling, sharing, analysis and use. To realise improvements in surveillance and public health demands, the information generated by diagnostic technologies in programme conditions should be easily accessible and usable for national programmes. Ultimately, data access, enabled by diagnostic connectivity, should be seen as a public health good. Countries, international organisations, test developers and civil society organisations have a collective responsibility to work together to ensure sustainable use of information and communications technology to improve health care. In doing so, important questions regarding ethical obligations and data ownership and stakeholder interests, such as market competitiveness, need to be acknowledged and addressed. International collaborative efforts must furthermore address the issue of personal unique identifiers in a context of continuous human migration and data mobility.

THE WAY FORWARD: REALISING THE POTENTIAL OF CONNECTED DIAGNOSTICS

Built-in connectivity has become an evident prerequisite for upcoming diagnostic platforms.[12] Tests that until recently were un-connectable, such as rapid diagnostic tests for, for example, HIV and malaria,

can now be connected to digital readers, with collection of results, storage and transfer (e.g., Fio Corp, Toronto, ON, Canada).

In the field of TB diagnostics, a wide range of complementary laboratory tests are used. This includes rapid diagnostic tests and more conventional approaches such as microscopy, culture, drug susceptibility testing and sequencing.[13] Inter-connecting these diagnostic devices and further integrating this information with clinical indicators is the upcoming challenge for the TB community.

The Connected Diagnostics Initiative (CDx), coordinated by FIND, is an example of a potential solution for accelerating the connectivity and interoperability of diagnostic devices. CDx is providing an open-source software platform that allows centralised aggregation of data from diagnostics, regardless of the manufacturer. For this new effort to succeed, wide buy-in from implementers, policy makers and developers will be essential. In parallel, FIND is working with the WHO towards guidelines for standardised result reporting for diagnostic devices and assisting developers to be compliant with these standards. These efforts go hand in hand with further deployment of local laboratory information systems and electronic medical records.[14]

Alongside this initiative, various groups are creating global databases with the intention of enhancing research and development applications for data. For example, genTB (Harvard University, Cambridge, MA, USA) is an open-source platform that allows for the pooling, analysis and visualisation of genetic, epidemiological and clinical data. A global partnership, including the WHO, the US Centers for Disease Control and Prevention (Atlanta, GA, USA), the Center for Policy Analysis on Trade and Health (San Francisco, CA, USA), Stop TB (Geneva, Switzerland), the National Institute of Allergy and Infectious Diseases (Bethesda, MD, USA) and FIND, has been established to develop a data platform (ReSeqTB) to store, curate and provide access to globally representative TB data that can inform the development of new diagnostics, facilitate clinical decisions and improve surveillance of drug resistance. While opportunities for sharing information at an international scale must be promoted, countries must also be provided with technical solutions that can support them in efficiently managing with whom, and for what purposes, national data are shared, and to ensure that these database efforts ultimately benefit patients.

Consensus is forming around the central role that connected diagnostics and digitisation can play in tackling health systems weaknesses and diseases of poverty. However, the global health community must also address the complex question of how new tools and practices can be implemented effectively in health systems. Substantial programmatic changes will be required in the countries to absorb the innovation of connectivity and capture its benefits. This demands a holistic approach to cultivating effective development and adoption of new diagnostic tools. In this context, laboratory connectivity may also serve the need for more efficient post-marketing surveillance of newly rolled out diagnostics, for both national stakeholders and their global partners. As the amount of information collected will rapidly increase beyond our conventional capacities of analysis, the global health community will also need to initiate and intensify innovative collaboration to exploit the data collected using big data analysis and self-learning algorithms. Managing, visualising and analysing big data creates challenges beyond the capacities of standard statistical methods, and thus generates an increasing demand for data science and multidisciplinary efforts.

CONCLUSION

Our common goal of TB elimination is longer a dream: it is an achievable objective, with clear milestones.[15,16] The elimination effort will require strengthened collaboration between information technology and big data specialists, social medicine and private companies.[6]

In the future, all diagnostic technologies should be interconnected, allowing data generated by laboratories to be merged in a common repository while safeguarding patient confidentiality. The TB community could use such a repository to monitor progress and identify problems and potential solutions at both patient and global levels. Data pooling will open up opportunities to comprehend the rapid evolution of drug-resistant mutations, which will aid in selecting cost-effective treatment schemes and improving patient management. With the many solutions it can provide, data pooling at an international level is an absolute priority, as it will accelerate progress in critical sectors, including patient care, epidemiological surveillance and operational response. As an international health emergency, the TB epidemic requires optimal international collaboration and unambiguous political commitment for intensifying data-sharing efforts.

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RESUME

Dans le domaine de la tuberculose (TB) et d'autres épidémies majeures au niveau international, l'utilisation de nouvelles technologies pour le diagnostic s'est largement répandue, y compris dans les pays à faible ressources. Cependant, malgré la grande quantité de données générées par ces nouveaux outils, la majorité de cette source d'information reste aujourd'hui inexploitée. Dans cet article d'opinion, nous discutons les leçons tirées de l'utilisation de ces nouveaux outils diagnostics et la voie pour mieux mettre à profit les informations générées par les laboratoires TB en utilisant leur potentiel de connectivité. En réponse à l'absence de solutions permettant cette connectivité, des solutions innovantes ont été proposées par des acteurs tiers et ont été largement adoptée par les utilisateurs du test Xpert® MTB/RIF. L'utilisation croissante de ces solutions permettant la surveillance de larges réseaux de laboratoires a porté l'attention sur la nécessité de proposer une approche plus globale et intégrée par rapport à la connectivité des laboratoires diagnostiques. Ces solutions facilitent la transmission des résultats, mais permettent également le partage d'informations générées en situation réelle. Ces données, lorsqu'elles deviennent aisément accesibles, peuvent être utilisées pour améliorer la qualité des soins prodigués aux malades, la surveillance des maladies et la découverte de médicaments. Pour ces raisons, elles devraient être considérées comme un bien de santé publique. Nous dressons une liste d'exemples d'initiatives concrètes qui devraient permettre de faciliter le partage de données de laboratoire dans le but de renforcer notre compréhension de l'épidémie, soutenir les réponses opérationnelles, et accélérer l'élimination de la TB. En raison des nombreuses opportunités associées au partage d'information liées à l'épidémie de TB, la centralisation des données au niveau international est devenu une priorité absolue.

RESUMEN

En el contexto de la tuberculosis (TB), la utilización de nuevas pruebas diagnósticas está aumentando de manera espectacular, especialmente en los países en desarrollo. Pese a que nunca se ha generado tanta cantidad de datos, aún no se aprovechan todas las posibilidades que ofrece esta nueva fuente de información. En el presente artículo de opinión, se examinan las enseñanzas extraídas del uso en todo el mundo de estos nuevos instrumentos diagnósticos y se analiza la hoja de ruta hacia la explotación de las ventajas y el potencial de la conectividad para el diagnóstico de la TB. Respondiendo a la falta de conectividad incorporada a las herramientas de diagnóstico, se han creado soluciones de conectividad, que a su vez han sido adoptadas por usuarios en el terreno con el fin de monitorizar la utilización del test Xpert® MTB/RIF. El uso creciente de estas soluciones ha centrado la atención sobre la necesidad de explorar de manera más general y exhaustiva la conectividad destinada al diagnóstico. Además de facilitar a los laboratorios la tarea de comunicar los resultados, la información digital debería favorecer el intercambio y el acopio de la información recogida en el marco programático. Dado que estos datos pueden mejorar la atención al paciente, la vigilancia de enfermedades y el descubrimiento de nuevos medicamentos, es preciso considerarlos como un bien de salud pública. Aquí, enumeramos varios ejemplos de iniciativas concretas que deberían facilitar la combinación de diferentes fuentes de datos para mejorar la vigilancia de la TB y acelerar su eliminación. Habida cuenta de las múltiples soluciones que ofrece, la combinación de datos a escala internacional constituye una prioridad absoluta, pues agilizará el progreso en sectores primordiales como la atención al paciente, la vigilancia epidemiológica y la respuesta operativa.

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WHO GUIDELINES

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

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

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

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

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

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

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

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

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

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

MATERIAL AND METHODS

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

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

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

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

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

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

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

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

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

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

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

Reviewing the evidence

Data sources

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

Analysis

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

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

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

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

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

Developing the recommendations

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

TABLE 2 Quality of evidence and definitions

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

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

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

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

RECOMMENDATIONS

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

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

Remarks

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

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

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

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

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

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

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

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

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

Remarks

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

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

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

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

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

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

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

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

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

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

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

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

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

Remarks

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Remarks

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

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

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

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

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

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

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

Remarks

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

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

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

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

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

Remarks

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

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

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

PAS: *p*-aminosalicylic acid.

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

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

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

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

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

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

CONCLUSIONS

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

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

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

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

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

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Digital health for the End TB Strategy: developing priority products and making them work

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ABSTRACT In 2014, the World Health Organization (WHO) developed the End TB Strategy in response to a World Health Assembly Resolution requesting Member States to end the worldwide epidemic of tuberculosis (TB) by 2035. For the strategy's objectives to be realised, the next 20 years will need novel solutions to address the challenges posed by TB to health professionals, and to affected people and communities. Information and communication technology presents opportunities for innovative approaches to support TB efforts in patient care, surveillance, programme management and electronic learning. The effective application of digital health products at a large scale and their continued development need the engagement of TB patients and their caregivers, innovators, funders, policy-makers, advocacy groups, and affected communities.

In April 2015, WHO established its Global Task Force on Digital Health for TB to advocate and support the development of digital health innovations in global efforts to improve TB care and prevention. We outline the group's approach to stewarding this process in alignment with the three pillars of the End TB Strategy. The supplementary material of this article includes target product profiles, as developed by early 2016, defining nine priority digital health concepts and products that are strategically positioned to enhance TB action at the country level.

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Introduction

Tuberculosis (TB) remains an urgent public health threat and a leading infectious cause of death worldwide [1]. In 2014, the World Health Assembly resolved to end the global TB epidemic by 2035 [2]. This led to the elaboration of the End TB Strategy by the Global TB Programme of the World Health Organization (WHO) and its partners for the 20 years post-2015 [3, 4]. The End TB Strategy's vision is to make the world free of TB, with no deaths, disease and suffering due to the disease. For the global TB epidemic to be brought to an end by 2035, a drastic reduction in TB incidence and mortality will be needed. The strategy is structured around distinct components and achievement of its goals will depend on action on its three pillars, namely: 1) expanding the scope and reach of interventions for TB care and prevention, with a focus on efficient, high-impact and patient-centred approaches; 2) maximising the benefits of health and development policies and systems, by engaging a broader cross-section of actors across government, communities and the private sector; and 3) pursuing new scientific knowledge and innovations that can dramatically change TB prevention and care. The End TB Strategy is aligned to the broader post-2015 development framework mapped out by the United Nations Sustainable Development Goals (SDGs) [5]. The SDGs seek to build upon the actions catalysed by the Millennium Development Goals (MDGs) until 2015 and to complete what the MDGs did not achieve. The SDGs' vision is to improve the economic, social and environmental dimensions of development. A plan of action to strengthen universal peace and eradicate poverty by 2030 has been formulated, and the 17 SDGs and their 169 targets are geared towards this [6]. TB care and prevention fit primarily under SDG 3, which is devoted to health; however, activities needed to accomplish the End TB Strategy will need to engage other SDG domains, such as supporting infrastructure and innovation (SDG 9), reducing inequalities (SDG 10) and strengthening alliances with partners towards common ends (SDG 17).

Innovative approaches to care and prevention are needed to achieve the ambitious goals of the End TB Strategy and the SDGs. The operationalisation of the End TB Strategy requires that national TB programmes and other stakeholders re-examine how their respective objectives must evolve in order to align with the post-2015 trajectory.

Electronic health (eHealth) and mobile health (mHealth), collectively referred to as "digital health", occupy an increasingly important space in preventive and curative interventions in both affluent and resource-constrained settings. Digital health is destined to play a pivotal role in the implementation of key activities to achieve a number of SDGs and to end the global TB epidemic, be they old or new, or directed at patient care, surveillance, programme management, advocacy, staff development or the engagement of civil society (figure 1) [7]. These interventions will also be needed to implement most of the eight priority action areas to eliminate TB in low-incidence countries [8]. In recent years, TB programmes and technical partners worldwide have initiated several digital health projects in order to enhance the reach and effectiveness of their work. Some of these efforts have shown promise but many have lacked the scale, the end-user ownership and the coordination needed to achieve population-level impact.

The existing state of the art of information and communication technology (ICT) and its "next-generation" enhancements present opportunities to broaden the scale of action and to overcome barriers to programmatic interventions in TB, which appear insurmountable even today. Fresh thinking on how to adopt, implement, market and sustainably support these technologies would, however, be needed.

In April 2015, WHO established a Global Task Force on Digital Health for TB (referred to henceforth in this paper as the Task Force) to promote the integration of digital health into national operational plans to implement the End TB Strategy [9]. This paper expands upon the content of the WHO digital health Agenda for Action created by this enterprise and in collaboration with the European Respiratory Society (ERS) [10]. In addition, it describes the process by which the Task Force and other partners identified digital health products that are strategically positioned to address the challenges faced by TB patients and health professionals. A key outcome of this process is the development of a set of target product profiles (TPPs) by the Task Force: a detailed description of the TPPs can be found in the supplementary material.

Methods and rationale

Process

On February 25–26, 2015, WHO and the ERS held a joint technical consultation on the role of digital health for TB and tobacco control in Geneva, Switzerland [11, 12]. Ahead of this consultation, in early 2015, WHO surveyed public views on the priority products to be focused upon during the discussions using an online questionnaire. The consultation was attended by close to 100 participants and was organised into tracks of work devoted to each of the four functions identified by the WHO conceptual framework for digital health in the TB response, namely patient care, surveillance and monitoring, programme management, and electronic learning (eLearning) [13]. The programme management function was devoted to the strengthening of laboratory information systems, a critical priority for the TB manager. Each of the tracks focused on one or more digital health products selected by its members.

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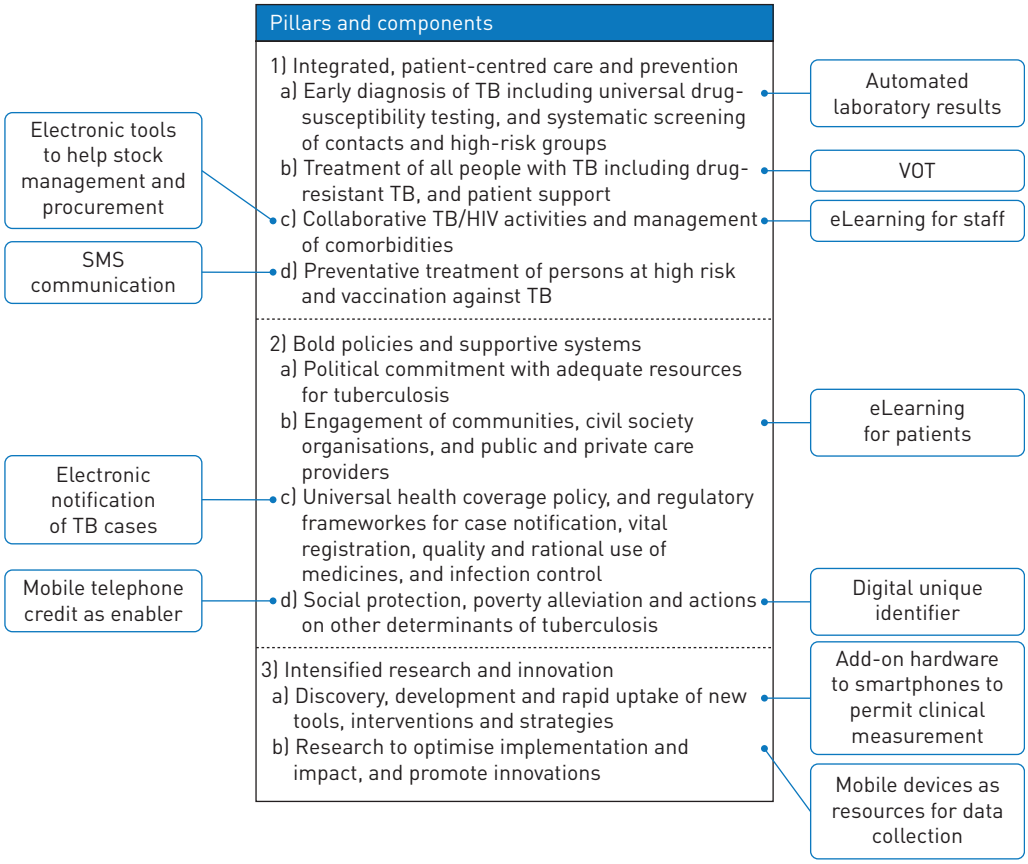

FIGURE 1 Examples of common digital health products and their potential contribution to different components of the End TB Strategy. TB: tuberculosis; VOT: video (virtually) observed therapy; eLearning: electronic learning; SMS: Short Message Service.

The characteristics of the digital health products were described using TPPs. TPPs define the features of the desired solutions in sufficient detail and transparency to stimulate more interest from potential developers [14]. They are dynamic discussion tools that are revised in the development process. Where they apply to the creation of software, the TPP approach shares many characteristics with behaviour-driven development [15]. The TPP approach has recently been used to focus the views of multiple stakeholders and developers on the priority diagnostics required for TB [16, 17]. One of the members of the Task Force was recently involved in finalising a detailed TPP for electronic medication monitors for use in patients on TB medication following positive findings from a trial of its use (Bruce V. Thomas, personal communication) [18]. This product is scheduled for large-scale roll out in high TB burden settings from 2016.

These recent developments motivated the Task Force and other partners who were involved in this initiative to follow a similar approach in their work. The digital health TPPs are expected to serve users at both national and global levels; they will guide developers to come up with solutions tailored to the problems faced by national TB programmes, and to steward the implementation of these new concepts, and ensure a more systematic method of collection and reporting of evidence.

This article presents the TPPs as they were developed until February 2016 as a result of an iterative consultative process, which started during the technical consultation and followed electronically thereafter (table 1 and supplementary material). The description of each of the TPPs is structured in nine identical sections, namely: 1) goals, scope and description; 2) target end-users; 3) value to the target end-user and other beneficiaries; 4) strategic fit; 5) rationale for prioritisation; 6) optimal requirements; 7) minimal requirements; 8) factors for success; and 9) key risks (threats) for its development. At this stage of development, the descriptions do not contain comprehensive details sufficient for a developer to create a product. The TPPs will eventually need to be refined by developers into technical specifications for the design of concrete products. Designing, building and rolling out a digital application needs to embrace a broad cross-section of representative users and policy-makers, one that engages with them and that supports their efforts [19]. This will require additional work to test concepts at the country level and study which processes need to happen alongside to ensure successful adoption, such as human resource

TABLE 1 Summary of target product profiles (TPPs) for the End TB Strategy (as of February 2016)

Function	TPPs
Patient care	1) Video treatment support (VOT) for TB patients *via* mobile telephones 2) eHealth portal to improve TB and tobacco care
Surveillance and monitoring	3) Digital dashboard for TB indicators and epidemiological trends 4) Digital notification of TB cases 5) Digital application for active TB drug safety monitoring
Programme management	6) Diagnostic device connectivity for TB
eLearning	7) Information resources platform for patients on TB and smoking cessation 8) Web-based training for health professionals on TB and smoking cessation 9) Clinical decision support systems for TB treatment and smoking cessation

eLearning: electronic learning; VOT: video (virtually) observed therapy; TB: tuberculosis; eHealth: electronic health.

development and changes to regulations. Moreover, the introduction of new technologies into a setting needs to complement others that are already in place, and to fit within the eHealth framework that a country may already have and within which these technologies are expected to function [20, 21].

TPPs for digital health for the End TB strategy: criteria for selection

The choice of products and associated activities were premised upon the pressing needs and realities of TB programmes, upon existing evidence and knowledge about the effectiveness of certain digital health interventions, and the rapid advances in technologies of which potential users may be unaware. Firstly, there is a need for an articulated and step-wise approach to develop comprehensive digital health solutions to support the End TB Strategy and other associated policies that exist (*e.g.* eliminating TB in low-incidence settings [8, 22, 23]), in particular, to limit fragmentation of efforts leading, for instance, to parallel systems, redundancy and waste of resources. The products and concepts defined by the TPPs were selected to complement each other in a given setting, which would be the desirable approach to implementation in contrast to the creation of independent standalones; they should thus be developed in parallel, ideally at comparable speeds towards completion [10]. Secondly, opportunities should be sought to integrate and seek synergies with promising ICT initiatives, both within healthcare and beyond, so as to increase the efficiency, scalability and sustainability of efforts. Thirdly, managers and other decision-makers may not be well informed about which digital health technologies could be most appropriate to match their needs in TB prevention and care work. Fourthly, on the practical side, the Task Force opted to keep the first batch of TPPs to a manageable set.

Based on these considerations, the members of the work groups selected one to three products deemed to be advantageously placed to secure gains to that particular function at a large scale, in the near future. This choice should not be construed as a recommendation for the immediate, large-scale implementation of these products, which at times represent emerging technologies with incomplete knowledge on their effectiveness. Moreover, the authors acknowledge that several promising concepts deserving of investment would not be captured in the initial wave of TPPs. These include telemedicine interventions, apart from video (virtually) observed therapy (VOT), which is described here, as well as electronic monitoring of the use of medication containers [18, 24–26]; computer-assisted diagnostic tools, particularly in connection with imaging techniques such as digital radiography [27]; aids to planning the supply of medicines and forecasting their consumption [28]; "clip-on" hardware that converts smartphones into clinical measurement devices [29–32]; and others. The Task Force encourages such initiatives and intends to stay abreast of similar developments led by technical or funding agencies to take forward additional TPPs to the nine included at this stage.

Justification for digital health in TB care and prevention

The pace with which ICT has developed and diversified over the years can only be described as revolutionary. By the end of 2015, half of the world's population had a mobile telephone subscription, representing more than a doubling in coverage within the space of 5 years (https://gsmaintelligence.com/). About 40% of the world's population can access the Internet, although coverage and broadband speed differ substantially between and within regions [33]. Smartphones are progressively replacing less sophisticated mobile phones all over the world, a trend primarily driven by uptake in developing countries. Developments such as these could present huge openings for health care, as users become better informed about lifestyles that pose a risk to health and about access to services, while health professionals enjoy

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more efficient means to keep their knowledge up to date and maintain contact with their patients to follow up on their healthcare needs.

New opportunities are created for public health researchers, health system managers, patients and practitioners to explore how the innovative use of these tools can strengthen health systems. Field experience with digital health interventions for TB is growing. The increased deployment of cutting-edge digital health concepts is destined to inject greater power, speed, flexibility and diversity into the same processes that have been helping public health practitioners, managers and clinicians to deliver better TB care to populations and patients for several decades. Improving the knowledge base on these experiences could increase opportunities for more of the successes and failures to be fed into a virtuous cycle of continuous quality improvement of digital interventions.

There is a need for better quality evidence for impact or efficiency from more rigorous studies that are directly relevant to TB programme implementation. Several digital health concepts still need to be tested under different conditions, including broader geographical spread, levels of decentralisation and models of care, and in a larger cross-section of patient subgroups. Certain digital activities are implemented on the basis of indirect evidence or experience imported from outside TB care, such as the monitoring of antiretroviral uptake [34–36] and smoking cessation programmes [37, 38]. Drawing parallels from outside the TB world can add value and is justified on the basis that the challenges of limited resources, such as the problems associated with stock management, supplies and logistics, cut across different disciplines. Inferences on behaviour change drawn from such analogies may, however, at times be obscured by imperfect comparison (such as the duration of treatment, safety profile of medicines used and stigma attached to TB). Conversely, there may be missed opportunities if the adoption and large-scale roll out of technological advances is put on hold until suitable studies have been devised and completed among TB patients. Given the imperative to link effectiveness with value for money, a sound "investment case" based on measured or modelled costs could build convincing arguments for specific interventions. This is particularly relevant for nascent technologies which have yet to attain the recognition needed to become integrated into mainstream activities or others that would need a significant outlay to take off.

One important question is: what type of evidence is required to support the operationalisation of digital health in TB programmes in future? And what kind of evidence would be recognised by implementers before a product is embedded in routine practice, including TB care and prevention [39]? Many trials are under way investigating different elements of mobile health [40]. Certain interventions lend themselves more easily to a prospective cohort study or randomised controlled trial (RCT) design than those for which impact is less straightforward to measure or is influenced by a number of external factors. These include interventions possessing parameters that can be fairly well standardised, for which the collection of quantitative data on both the intervention and the outcome is digitised and relatively discrete, which allow randomisation or where large numbers of study participants as well as comparison groups can be recruited. This may explain why initiatives involving mobile text messaging (Short Messaging Service (SMS)), medication monitors and VOT for adherence support have been studied more frequently under RCT conditions than others such as eLearning or laboratory information systems. Another closely related question relating to evidence is how much research will be needed before users are confident of the effectiveness or efficiency of an intervention? The ease with which data can nowadays be collected and stored during the operation of a digital tool paves the way for the prospect of continuous appraisal and validation, bringing processes such as routine surveillance based on electronic medical records within the reach of more users.

Patient care

Treatment of active TB requires daily administration of medicines for at least 6 months, and up to 2 years or more in the case of multidrug-resistant (MDR)-TB and extensively drug-resistant (XDR)-TB [41]. Erratic treatment adherence may lead to unfavourable outcomes with continued spread of infection, acquisition of drug resistance, disease chronicity, and death. Loss to follow-up could be alleviated if patients are better supported during their treatment [42, 43]. Improved communication between patients and healthcare providers could thus increase patient engagement to adhere to treatment; ICT could facilitate bidirectional exchange. An added advantage is that the same medium of communication for patient–caregiver interaction could address other health risks that predispose to poor patient outcomes, such as smoking [44, 45]. Action on social and behavioural risk factors is very much in line with the objects of pillar 2 (Bold policies and supporting systems) of the End TB Strategy [4]. The potential for digital health tools to deliver and monitor access to social support and, more specifically, social protection schemes like cash transfers, is largely untapped at the moment. The extensive global coverage of standardised TB programmes represents a unique opportunity to deliver other interventions at a time when patients may be particularly attuned to health messaging (*e.g.* smoking cessation to tobacco users). The long-term care of patients with MDR-TB and XDR-TB, some of whom are in need of palliative care,

others of concomitant management of comorbidities such as HIV and diabetes, could benefit from existing and emerging digital health products.

As global connectivity expands, and hardware becomes more widely available and affordable, digital health products are destined to become increasingly present in the daily life of TB patients and practitioners. The potential for mobile phones to influence patient outcomes has been the subject of recent reviews [46, 47], one of which has looked specifically at evidence for the impact of SMS on TB adherence. Both reviews concluded that the evidence for the effectiveness of SMS-based interventions was not always clear: at times, no impact was registered, such as when SMS was used as a reminder. This lack of effect indicates that the design of future studies may need to test digital interventions within a wider range of behaviour-change techniques. High-quality evidence from RCTs is rare in this area and more has been published based on work from observational studies [48–52]. However, results from RCTs of mHealth and TB treatment adherence (including latent TB infection) conducted in very contrasting settings and using different applications, ranging from simple SMS to smartphone and online applications, are expected in the next few years [53–57]. Video interventions using phones have the potential to save resources when used to observe treatment and support patients [58–62]. Their feasibility is set to increase as Internet-enabled phones increasingly come to dominate the mobile phone markets, with low-resource countries expected to drive the incremental trend into the future [63]. Two ongoing RCTs are now investigating the effectiveness of VOT in TB patients using smartphones or other mobile digital devices [64, 65]; more are planned for the near future, including for the treatment of latent TB infection [66].

As various digital health products start to be developed in support of different components of TB programmes, it will be important to optimise their uptake at large scale. Even at the country level, it is becoming difficult, at times, to keep track of all the different initiatives, leading to underuse or wasteful parallel development of tools with a similar purpose. A one-stop Internet hub that links up to different services of relevance to TB care could serve to channel health professionals, patients and the wider public to an appropriate service (*e.g.* http://e-sanatate.md/). The end-product will not replace the triage or counselling roles of healthcare workers but will help them to locate resources better. This product may overlap with other tools being proposed in this report under the eLearning track (see the "eLearning" section later in this report, and TPPs 4.1 and 4.2); however, the primary intent of the Internet portal will be to inform about access rather than to promote learning.

The discussion on the digital health products for the "patient care" function thus focused on two items that were of particular interest at this juncture, namely: 1) VOT using mobile electronic devices to support TB patients on treatment; and 2) a common eHealth portal to inform TB patients and professionals about resources.

Surveillance and monitoring

Public health surveillance involves the continuous and systematic collection, analysis and interpretation of health-related data for planning, implementation and evaluation of public health practices [67]. It is one of the principal pillars of any functional public health system and an important tool for health action [68]. Effective surveillance will be needed to support the End TB strategy in the coming years [3], particularly through: measuring and monitoring the burden of disease and death, and determinants of TB, including risks such as tobacco use; measuring and monitoring the effectiveness of efforts to tackle the TB burden; reducing delays in TB care; monitoring drug safety; detecting and responding to TB outbreaks, including identifying "hot spots" and drug resistance, and interrupting the chain of transmission; planning for and managing resources such as TB medicines; guiding the planning, implementation, and evaluation of programmes and public policy to prevent TB; identifying gaps in knowledge and devising questions for research.

Implementing the core activities for a functional TB surveillance system often remains challenging in many countries due to a variety of factors, including: underdiagnosis or misdiagnosis of TB either through lack of access to health services or through poor diagnostic skills; inaccurate reporting and/or under-reporting of TB cases and inconsistent follow-up by frontline healthcare workers; inadequate use of the WHO standardised TB case definitions and reporting parameters [69]; TB notification may not be mandatory or, if it is, may not be enforced, with little motivation for the individual clinician (public or private) to notify; no coordination between different sources in the management of data useful for surveillance, including public and private sectors, insurance systems, laboratories, and hospital and outpatient facilities (these may have multiple information systems that live in silos and are not interoperable); weak culture of making use of programme data to inform decisions and often few efforts being made to have good quality data (*e.g.* by providing user feedback, updating the information and correcting mistakes); fragile health systems with limited resources, technology, human resources, knowledge, skills and time of frontline health workers due to various factors including competing duties, mismatching of an individual's skills with their job profile, inadequate pay, inefficient and error-prone paper-based processes, lack of feedback on the utilisation of the data, and lack of logistical and expert support.

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While general surveillance of TB often faces challenges in accuracy and completeness, the monitoring of TB drug safety tends to be even less developed globally. Many countries lack a functional drug-safety monitoring framework, as a result of weak health systems and the absence of a culture for routine monitoring of drug toxicity in TB programmes (in contrast for instance to TB drug resistance surveillance, which has been a mainstay for over 20 years [70]). This aspect of surveillance is now gaining importance within TB programmes as new drugs and novel regimens that incorporate repurposed medicines start to become available globally, particularly for MDR-TB and XDR-TB. These new interventions carry fresh hope for improved outcomes for patients. However, the safety profile of new medicines such as bedaquiline and delamanid, which were released on the market ahead of the completion of phase III trials, remains incomplete [71, 72]. The WHO policy on the use of these medicines recommends active monitoring for possible harm related to their use is in place. In 2015, WHO and main technical and financial partners defined the parameters for different levels of active drug-safety monitoring and management as they apply to the particular context of TB programmes [73, 74]. Development of basic but effective digital tools to collect and consolidate TB drug-safety data are thus in high demand at this point in time as countries prepare to expand their programmatic management of drug-resistant TB and avail of initiatives to facilitate access to new drugs (*e.g.* [75, 76]).

For many of the problems related to the collection, management, safe storage and transmission of data, today's state-of-the-art in ICT can already offer transformative solutions [77–80]. However, information systems are tightly knitted to social, cultural, legal and working environments, and the introduction of new digital products may be perceived by people as a challenge and an intrusion into their work. The intended users are more likely to embrace change if they are convinced that it will bear tangible benefits. Thus, for instance, the flexibility for managers to access data securely from wherever they can get online could be an important selling point. As in any other areas of change management, introducing new digital products in surveillance and monitoring needs an enabling environment [81], which includes: support of senior management for change; sufficient resources for key functions such as training, software development, updates, testing and troubleshooting, and data storage; development of guidance and standard operating procedures; health policy changes (*e.g.* mandatory notification of infectious diseases to public health authorities); data policy, such as promotion of data standards and interoperability [82], the adoption of unique patient and provider identifiers to link data sets, and the adoption of standard data dictionaries; and a legal framework for data ownership and privacy to establish trust in information systems.

Streamlining the electronic health record and reducing tedious and time-consuming paperwork could support "eHealth readiness" [83]. The steady transition in the management of medical records and surveillance systems, from paper-based methods, through electronic systems installed on isolated computer terminals, to systems on local area networks and, now, Internet-accessible databases with storage of data on the cloud, is an evolution over a continuum that happened in the space of a few decades. Such processes are not easy to evaluate with efficacy trials. Nonetheless, basic principles that apply under comparable situations, such as how to protect patient confidentiality and ensure that data are valid, safely stored and not corrupted, need to be followed when implementing digital health interventions [19, 84]. There are various measures that can be put in place to achieve this, ranging from automating error logs and crash reports (*e.g.* for electronic surveillance systems), building in user feedback modules (*e.g.* in eLearning packages), and holding regular audit reviews with system users to analyse critical episodes. Users intent upon introducing digital health interventions to facilitate their work would benefit from the description of best practices and lessons learnt narratives [85–87]. The effects described in such experiences could be modelled to illustrate their potential to save resources or to render a process more efficient. Implementation research to document gaps, bottlenecks, workarounds and good practices will be important for continued advancement [88–90].

TPPs for three products were proposed following the discussion in the consultation, namely: 1) an electronic dashboard of indicators and epidemiological trends relevant to TB; 2) digital notification of TB cases detected outside national TB programmes; and 3) digital tools to monitor the safety of TB drugs.

Programme management

Measuring the impact of ICT on programme management and building an evidence base around it pose similar challenges to those encountered in other areas of TB systems, given that the determinants of successful coordination and management are multifactorial. Indicators can nonetheless be identified to characterise the performance of certain elements of management. One such example is the influence of digital laboratory information systems (LISs) on the accuracy and turnaround time of test results [91, 92].

Diagnostic tests are an integral part of many public health interventions, guiding the detection of markers of disease and response to therapy. They have an important role in ensuring proper treatment, and avoiding unnecessary treatment and waste. In selecting the representative target product within the "programme management" function, the technical consultation focused on the performance of TB diagnostics as a domain of particular importance in modern TB care and which is now at a crucial

juncture following the wide roll-out of self-contained systems that employ molecular methods functioning on digital platforms, such as GeneXpert (Cepheid, Sunnyvale, CA, USA) [93]. These units can work with a high accuracy even when operated by staff without formal laboratory training located in decentralised healthcare centres with basic facilities. However, inefficiencies in the management of data are being recognised as a bottleneck in the operation of these new diagnostics. In reaction, software that extracts and transmits data from GeneXpert machines has been developed and successfully implemented in recent years [94–97]. However, up to now, these software programmes have been narrowly focused on a single technology and work in isolation of other diagnostic equipment located at times within the same premises. They thus miss out on larger benefits to be gleaned from a more comprehensive system that manages information from various diagnostic processes and that can also handle rapid roll-out and decentralisation of the diagnostic capacity.

Reliable and timely information is of paramount importance for the proper functioning of several processes in the TB laboratory, ranging from the management of patient results data (*i.e.* emission to the requestor of the tests and their integration within electronic health records to facilitate clinical management), the quality assessment of testing, the monitoring of laboratory activity, and the generation of indicators for surveillance (by avoiding repeated enumeration of same samples from the same patient) [98]. Improving laboratory information also serves the "patient care" function, by reducing time for patients to receive results [99]. Projects aiming to implement LIS in low-resource settings have rarely advanced beyond the pilot or demonstration stages. One reason for this is that the chain of requirements necessary for its proper functioning at the scale of a country or a laboratory network often has weaknesses in one or more elements. The difficulty of sharing data between different diagnostic technologies has been one formidable hurdle, resulting from either insufficient knowledge or willingness by the manufacturers of equipment to render their machine software compliant with accepted standards that facilitate the interoperability of data without additional costs to the user (*e.g.* Health Level Seven (www.hl7.org) and LOINC (http://loinc.org)).

Figure 2 is a schematic representation of three critical stages in information management within a functional TB diagnostic facility. The first step represents the concept of "connected diagnostics", whereby data generated by different diagnostic equipment are routed through a single channel. This stage would be closely followed by the next two components, namely 1) the storage of data and 2) their transmission to the requesting clinician or to the electronic health record. The TPP described in this document relates only to the first step; once the concept has matured, it is planned to develop separate TPPs for the next two components in the logical sequence.

eLearning

eLearning is defined as "an approach to teaching and learning, representing all or part of the educational model applied, that is based on the use of electronic media and devices as tools for improving access to training, communication and interaction and that facilitates the adoption of new ways of understanding and developing learning" [100]. eLearning techniques range from support, to conventional learning (as a "blended" approach), to teaching that is delivered entirely online. Regardless of the technology applied, learning still remains its central element [101].

Innovations in eLearning, such as the application of game techniques to education (gamification), and technologies like augmented reality and three-dimensional learning environments, are challenging the time-honoured fundamentals of how new knowledge is acquired. For instance, some websites now promote

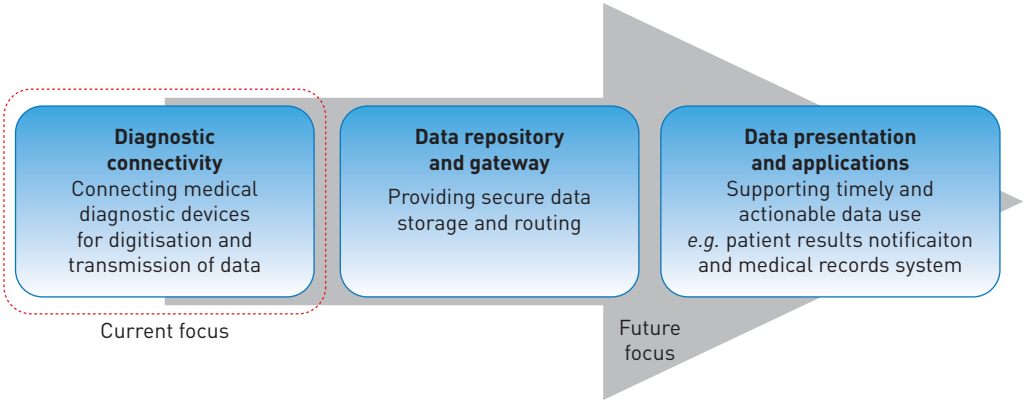

FIGURE 2 Schematic representation of the position of "diagnostic device connectivity" alongside other elements of a comprehensive laboratory information system for tuberculosis.

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the sharing of resources between frontline healthcare workers in peer-to-peer fashion (*e.g.* www.health-orb.org). Beyond eLearning as defined above, other resources, such as clinical decision support tools can assist health professionals to make a diagnosis or find the most suitable intervention in a particular patient interaction [102–104].

Both healthcare workers (formal or lay) and patients could benefit from new developments in learning techniques. In healthcare, the health needs of the population keep outpacing the health workforce availability and expertise, and eLearning presents many opportunities to close this gap. Reliable information about TB and other health risks could help patients and their relatives to cope better with the associated challenges. Clear and easy-to-understand messaging is expected to lead to a better informed decision when considering treatment options. Treatment of active TB involves the concomitant use of multiple medicines that often cause adverse effects that the patient should be aware of. Moreover, much of the evidence-based policy in TB care relies on low or very low quality data, which limits the strength of recommendations: in such a situation, aids would be of help for patients and professionals to make the most advantageous informed decision on care [105]. The combination of rapid access to a vast repertoire of online resources and the computational power of handheld devices now makes it possible to exploit more operational intelligence data when making a decision. This could ultimately improve a clinician's skills, just as eLearning delivers knowledge to a learner.

eLearning has the added advantage that it affords learners the luxury to work at their own pace and to follow their preferred educational pathways. When tutors are involved, these also stand to benefit from greater flexibility when compared to conventional training in organising their schedules and managing their time. eLearning is likely to reduce costs, improve the speed with which training and refresher courses are delivered, and permit access to a vast spread of resources, including novel curricula and experts. By virtue of their availability to a huge number of users across geographical space, eLearning products bear great promise as interventions that can be scaled up rapidly and efficiently.

Various sources for self-directed learning on TB management or smoking cessation are available online [106–114]. However, many such courses usually focus on one particular disease, and fail to capture a fuller spectrum of pulmonary conditions and other noncommunicable disease (NCD) risks that may be pertinent for the learner. The need for maintenance and updates of eLearning course material is often understated, and the quality and state of content of some sites may be poor. eLearning resources available today are still frequently text-heavy and not always customised for the virtual environment and for handheld devices in particular.

Published research comparing the outcomes of eLearning with more traditional methods of acquisition of knowledge in healthcare is still limited. However, there is a growing literature that supports the potential benefits for web-based training and use of multimedia techniques [115, 116], although there are only few reported studies that address synchronous eLearning programmes in medical education [117]. Online tobacco cessation courses have been reported by learners to improve ability and skills to counsel patients on tobacco cessation [118].

One of the risks of eLearning is the tendency for the depersonalisation of teaching and training. In some studies, dropout rates among eLearning students have been associated with feelings of isolation [119–124]. Greater interaction between eLearning participants may avert such situations [125].

Clinical decision support tools have been shown to influence the screening of patients at high risk of latent TB infection [126]. In another study, a clinical scoring system was found to be cost-effective for the diagnosis of smear-negative pulmonary TB [127]. Automating routines such as these could conceivably serve the practicing physician. Given the potential for such tools to improve the technical knowledge of the user, they have been included under the eLearning function.

Discussions during and after the WHO/ERS consultation identified three priority concepts for which TPPs could be usefully developed to support TB programmes. In the eLearning tools directed at both patients and professionals, antitobacco components feature prominently, given the impact that improved knowledge is expected to have on changing the behaviour of TB patients who smoke, alongside economic, environmental and organisational influences, and thus improving their treatment outcome. The TPPs were: 1) an online tool for patients and their relatives to learn about disease, treatment options, risk of transmission and associated health risks such as smoking (linked to TPP 1.2, which focuses on information on access rather than learning); 2) a comprehensive, web-based course on respiratory diseases, optimised for mobile devices and equipped with visual instruction aids aims to help building capacity and skills of health professionals in managing TB and reducing risks of negative outcomes (*e.g.* from smoking); and 3) a clinical decision-support tool to facilitate the daily work of practitioners and reduce the number of patients who receive suboptimal treatment.

Key steps in implementing digital health products for the End TB strategy

As discussed, the introduction of novel digital health technologies into a setting needs to fit within the digital health landscape that exists or is planned for the health services [20]. There needs to be agreement on the nature of the problem to be addressed, its relative priority compared with other pressing needs and the expectations made of the solution being envisaged. These discussions would need to be held through an iterative process with all interested parties.

Several digital health products may contribute to different functions of the digital health framework for TB [13]. Thus, for instance, eLearning is instrumental to staff development and would help caregivers acquire new skills in digital concepts, LISs will contribute not only to "programme management" but also to "patient care" and to "surveillance and monitoring", while digital applications for drug-safety monitoring will be important for "patient care". Likewise, many of the digital health products identified will contribute variably to the different components of the End TB strategy (table 2 and figure 1) [4].

"Thinking digital" needs to become a recurring motif in discussions on how to align national TB strategic plans [128], TB guidelines, budgets, grant proposals and other documents to the concepts of the End TB Strategy. These processes should keep abreast of ICT advances and, mindful of the fast pace with which ICT evolves, ensure that solutions do not lose their edge between the time that they are conceived to when they get deployed. A sequence of key steps is proposed for decision-makers to follow when digital health is operationalised at the country level.

At the country level, influential deciders in the TB programme who have the vision, knowledge, authority and drive will champion the "digital health" cause and steward in the necessary developments. To act as true "agents of change", they need to be willing to address critical issues in the adaptation and uptake of digital health interventions [129]. Different concepts are unified into a single vision for the local context. A group of key stakeholders, representing TB, public health, ICT, mobile and Internet network providers, technical agencies, private caregivers, patients and donors, is required to advise in different areas. Multidisciplinary "consortia" of developers and designers, users, and donors could be assigned to specific tasks, and to develop particular concepts, and ensure their sustainability and, at times, commercial viability.

Pillar 2 components of the End TB Strategy (on "bold policies and supportive systems"), which lie beyond the span of control of TB programmes or even ministries of health, are a particular challenge. Nonetheless, digital health can provide opportunities to make significant inroads in this domain and can have a profound impact on many of the upstream determinants of TB. These include broader issues in lung health and in prevention of NCD, money transfers *via* mobiles to reward health-promoting behaviour and alleviate poverty, universal health care (*e.g.* unique digital identifiers, such as the e-AADHAAR project in India (https://uidai.gov.in)), and other contributors to health system strengthening.

Critical points are identified on the pathway to the successful implementation of the End TB Strategy at the national level. These can then be mapped to complementary digital health interventions that are suited to the problems. The interventions would need to be prioritised based on the dual considerations of 1) knowledge of their effectiveness and 2) programmatic circumstances, including feasibility, time to implementation, resource use, potential benefit, associated opportunities, support structure for particular technologies and "eHealth readiness", *etc*. The TPPs described in this article were identified through a similar process and could be a starting point for similar country-level discussions. The documentation (*e.g.* national strategic plan [128]) and any regulatory instruments (*e.g.* eHealth strategy [20]) that need to be created or updated should be targeted for specific focus.

Resources will be needed for implementation. The interventions can be mapped to various likely sources of funding to create sound "investment cases" for specific interventions. Such investments will be expected to generate dividends beyond TB and health; this needs to be emphasised in messaging and is of particular relevance in the SDG era [130]. Products that are either open source or operated under a model of socially responsible licensing would be preferred [85, 131, 132]. Building capacity and developing human resources necessary for the implementation of the End TB Strategy needs to factor in the additional requirements for the workforce of tomorrow to be conversant with ICT and its uses. Looking for in-country expertise can stimulate innovation and cultivate partnerships that are more likely to be sustainable than those depending heavily on external support.

A realistic timeline for implementation should be developed and new interventions validated in the local setting ahead of scale-up. The notion of feasibility at scale is an important consideration when prioritising products: interventions should not remain stuck in the pilot stage [133].

Operational research should be planned in advance to measure the uptake, utilisation (type and extent) and impact of the intervention on performance, including costs. It is a means to ensure adherence to good

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TABLE 2 Relative importance of digital health products targeted by the target product profiles to individual components of the End TB strategy

End TB strategy pillars and components	1) Patient care		2) Surveillance and monitoring			3) Connected diagnostics for TB	4) eLearning		
	1.1) VOT	1.2) Digital health portal	2.1) Digital notification	2.2) Electronic dashboard	2.3) Drug safety data capture		4.1) Tools for patients	4.2) Tools for healthcare staff	4.3) Aids to decision-making
1) Integrated, patient-centred care and prevention									
a) Early diagnosis of TB including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups		++	++	++		++	++	++	++
b) Treatment of all people with TB including drug-resistant tuberculosis, and patient support	++	++	++	++	++	++	++	++	++
c) Collaborative TB/HIV activities and management of comorbidities	++	++	++	+	++	++	++	++	++
d) Preventive treatment of persons at high risk and vaccination against TB		++					++	++	++
2) Bold policies and supportive systems									
a) Political commitment with adequate resources for TB care and prevention		+	+						
b) Engagement of communities, civil society organisations, and public and private care providers	+	++	++				++	++	++
c) Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control	++		++	+	++		++	++	
d) Social protection, poverty alleviation and actions on other determinants of TB			++	+			++	+	

Continued

TABLE 2 Continued

End TB strategy pillars and components	1) Patient care		2) Surveillance and monitoring			3) Connected diagnostics for TB	4) eLearning		
	1.1) VOT	1.2) Digital health portal	2.1) Digital notification	2.2) Electronic dashboard	2.3) Drug safety data capture		4.1) Tools for patients	4.2) Tools for healthcare staff	4.3) Aids to decision-making
3) Intensified research and innovation									
a) Discovery, development and rapid uptake of new tools, interventions and strategies	+	+				++	++	++	++
b) Research to optimise implementation and impact, and promote innovations			+	++	++	+			

TB: tuberculosis; VOT: video (virtually) observed therapy; +: some relevance; ++: high relevance.

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practice, for instance, in data management and security during implementation [84]. Reporting of findings in a systematic manner would go some way to help strengthen the evidence base [90]. Lessons learnt would contribute to the third pillar of the End TB strategy ("intensified research and innovation"). Communication of findings would be of interest to both local and international workers.

Conclusion and next steps

Digital health interventions can strengthen health systems yet they remain underused [130]. In TB programmes, they need to be applied more consistently to improve patient care (*e.g.* support to adherence and efficient handling of medical records), surveillance and monitoring (*e.g.* improved notification, follow-up and drug-safety monitoring), programme management (*e.g.* laboratory management and drug procurement), and eLearning to enhance patient education and professional development [13]. In its diversity, ICT can contribute to all three pillars and 10 components of the End TB strategy [4]. This is particularly important in the first years of the post-2015 period, when TB programmes need to draw upon their creativity to optimise the effectiveness of currently available interventions to achieve the early targets slated for 2025 [2]. Digital health has far-reaching potential to help address more upstream determinants of TB, such as the large-scale assignment of truly unique personal identifiers (*e.g.* e-AADHAAR), which not only enhances medical record keeping but also facilitates access of vulnerable populations to their social entitlements. Similarly, schemes to reward healthy behaviours can be mediated more readily when records and monetary transfers are automated. ICT will remain an important factor for the large-scale roll-out of new diagnostics and novel medicines; two examples of these applications in the last few years include the software successfully implemented for the transmission of result data from Xpert MTB/RIF and for active drug-safety monitoring for bedaquiline-implementing programmes. However, if not appropriately planned or implemented, digital health interventions could lead to failures, waste and disenchantment. Negative experiences may have long-standing repercussions and prejudice against broader efforts to automate work processes, depriving programmes of potential efficiencies and other benefits.

The application of digital health for TB presents the dual challenges of having to deal with rapidly evolving technologies that can offer new opportunities at every turn, and the need for the decision-makers and implementers to maintain a creative outlook when implementing a new strategy that demands a fundamental departure from previous approaches to TB control. However, in addition to following the rapidly advancing technology closely, the implementer is also in a position to evaluate the technology, and to help inform about when and how it is best applied. Increasing this body of evidence and the documented best practices on digital health will be an important resource for decision-makers, and needs to be enriched by more experience gathered systematically from the field of TB.

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

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Abstract

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

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

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

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

Background

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

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

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

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

Methods

Ethical considerations

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

Study setting

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

Sample processing

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

Culture and drug susceptibility testing

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

DNA extraction

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

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

RD analyses and spoligotyping

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

Data analysis

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

Results

Study population

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

Species identification

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

Spoligotypes

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

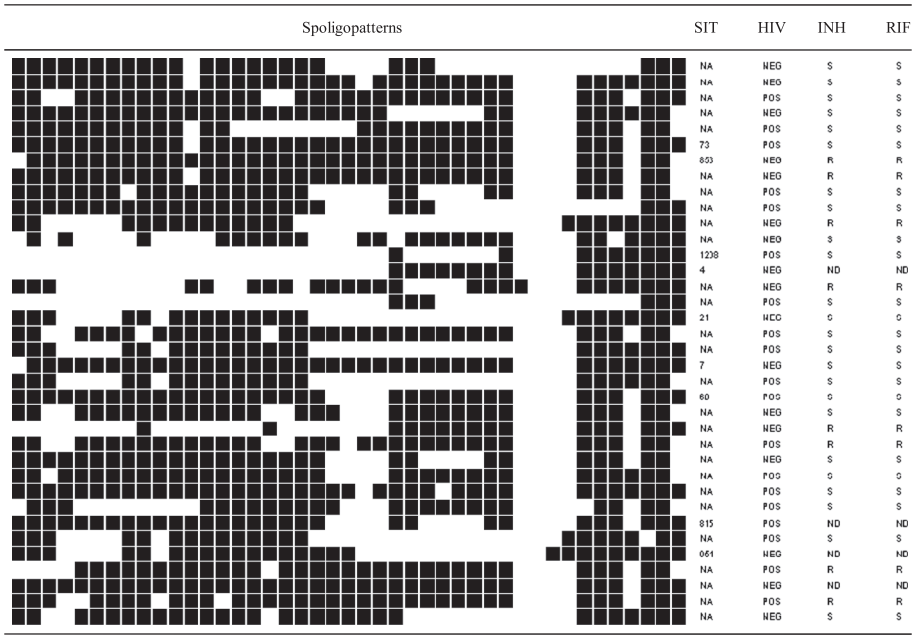

Figure 1 Spoligotype patterns of non-clustered *M. tuberculosis* strains in the study (N=36). SIT, spoligotype international type; filled boxes represent positive hybridization while empty boxes represent absence of spacers; label defines the lineage/sub lineage; NA, not available in SpolDB4.0; HIV,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

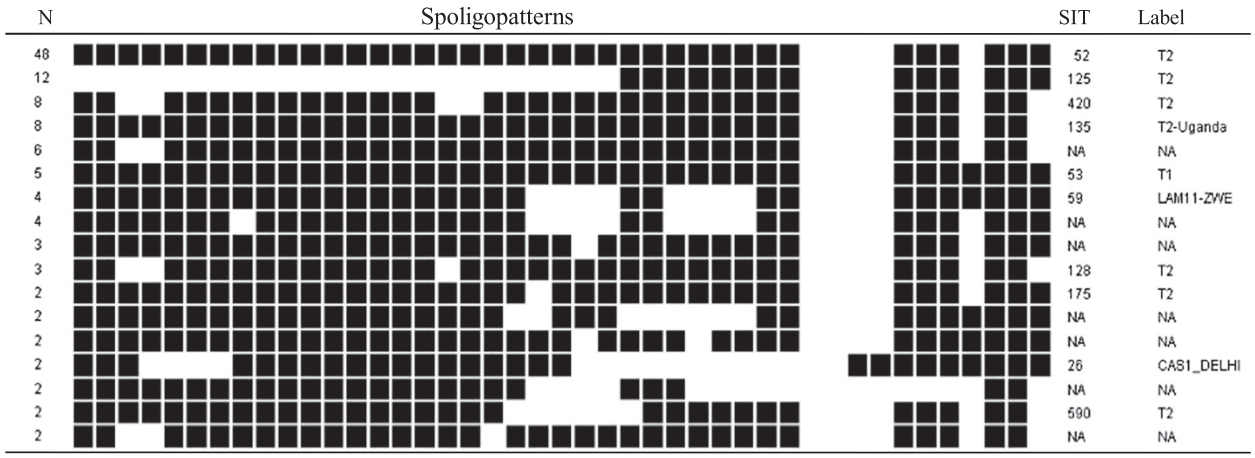

Figure 2 Spoligotype patterns of 115 clustered *M. tuberculosis* strains in the study. N, number of isolates per cluster; SIT, spoligotype international type; filled boxes represent positive hybridization while empty boxes represent absence of spacers; label defines the lineage/sub lineage; NA, not available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

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

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

Drug susceptibility patterns

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

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

Table 1 Patient demographic characteristics and associated drug susceptibility pattern

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

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

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

HIV sero-status and associated spoligotypes

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

Discussion

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

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

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

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

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

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

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

Conclusion

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

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

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

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RESEARCH ARTICLE

The Yield of Community-Based "Retrospective" Tuberculosis Contact Investigation in a High Burden Setting in Ethiopia

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Abstract

Objective

To determine the yield and determinants of retrospective TB contact investigation in selected zones in Ethiopia.

Materials and Methods

This was a community-based cross-sectional study conducted during June-October 2014. Trained lay providers performed symptom screening for close contacts of index cases with all types of TB registered for anti-TB treatment within the last three years. We used logistic regression to determine factors associated with TB diagnosis among the contacts.

Results

Of 272,441 close contacts of 47, 021 index cases screened, 13,886 and 2, 091 had presumptive and active TB respectively. The yield of active TB was thus 768/100, 000, contributing 25.4% of the 7,954 TB cases reported from the study zones over the study period. The yield was highest among workplace contacts (12,650/100, 000). Active TB was twice more likely among contacts whose index cases had been registered for TB treatment within the last 12 months compared with those who had been registered 24 or more months earlier (adjusted odds ratio, AOR: 1.77 95% CI 1.42–2.21). Sex or clinical type of TB in index cases was not associated with the yield. Smear negative (SS-) index cases (AOR: 1.74 955 CI 1.13–2.68), having index cases who registered for treatment within <12 months (AOR:

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Contributions:

Conceptualization: DJ BG MM ME.
Data curation: ZG ES NH DH.
Formal analysis: ZG DH NH.
Funding acquisition: MM YK YH PS.
Investigation: DJ ME BG ZG MM SH GN.
Methodology: ME DJ BG MM ZG.
Project administration: MM DJ ME YH YK PS ZG.
Resources: MM DJ ME.
Software: ES ZG BG NH DH.
Supervision: ME SH GN DJ MM.
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-variates, the rate of active TB was 1.77 times higher among contacts whose index cases registered for treatment within the last 12 months than contacts that had been exposed 24 or more months earlier (AOR: 1.77 95% CI 1.42–2.21). The rate of active TB was higher in the age group of 25–34 years (AOR: 1.80 95% CI 1.2–2.62) and 35–44 years (AOR: 2.14 95% CI 1.42–3.22) as compared to under-five children. The odds of active TB cases from neighbor (AOR: 1.35, 95% CI 1.02–1.78) and workplace (AOR: 3.95: 95% CI 2.21–7.03) were significantly higher than active TB cases detected from household contacts. However, the yield from contacts of "other" category was less than the yield from household contacts (AOR: 0.13, 95% CI 0.08–0.20).There was no significant difference in yield between close contacts of SS+ index cases and those of EPTB (AOR: 0.88: 95% CI 0.69–1.13) and SS- index cases (AOR: 1.19: 95% CI 0.95–1.49) (Table 2).

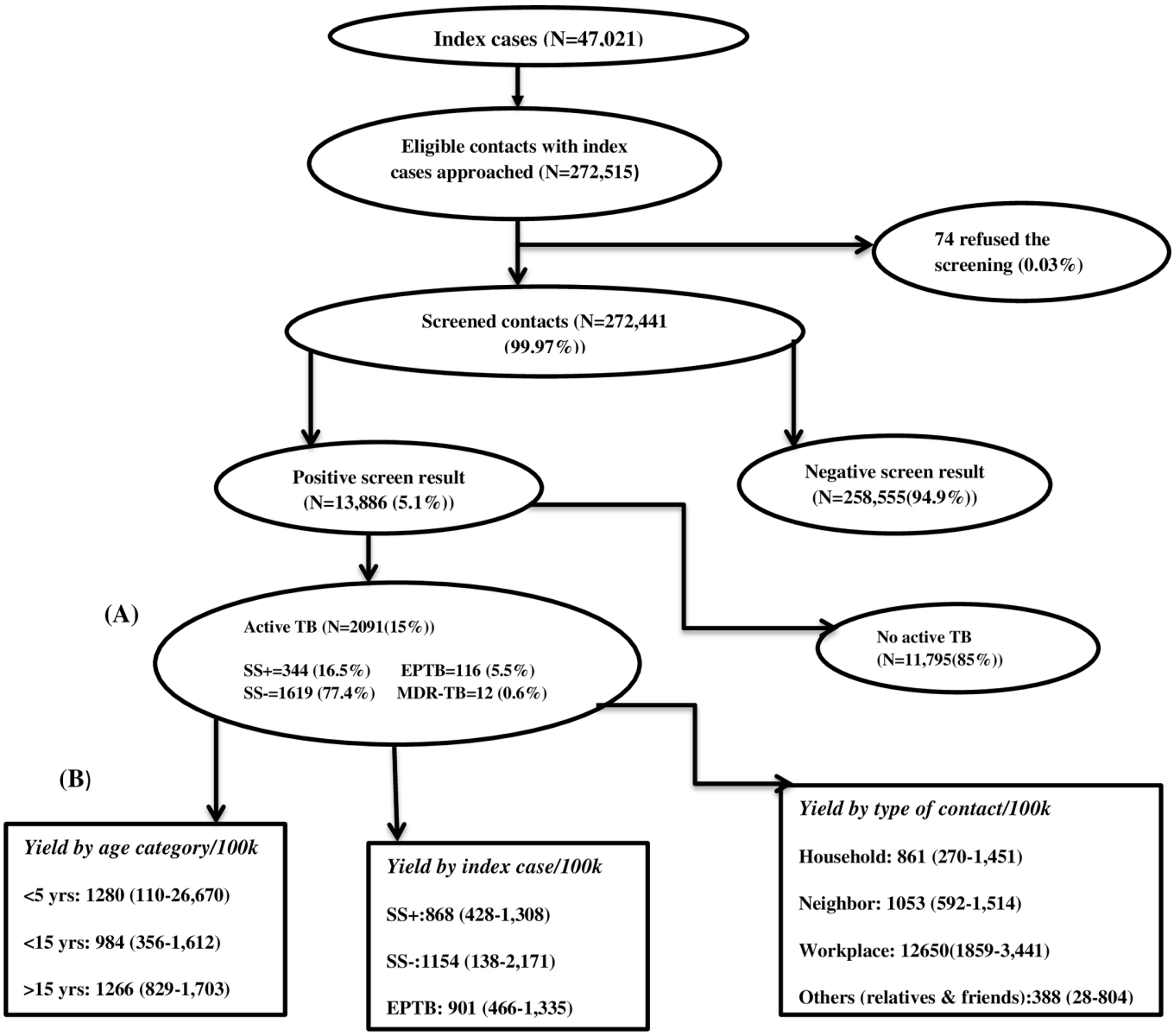
Being contact of SS- index cases (AOR: 1.74 95% CI 1.13–2.68), having index cases who registered for treatment within <12 months (AOR: 2.41 95% CI 1.51–3.84), and being household contact (AOR: 0.072 95% CI 0.01–0.52) were factors that were significantly associated with the occurrence of active TB in children (Table 3).

Discussion

To our knowledge, this is the first report of the yield of retrospective TB contact screening in a community setting in Ethiopia through which we were able to detect over two thousand TB cases. The yield was about six times the case notification rate in the study zones and contributed about a quarter of all notified cases over the same period. Our findings suggest that retrospective contact screening can be considered a useful strategy for identifying additional TB cases not addressed through the routinely implemented case finding strategies.

Earlier studies reported the yield of contact screening among household contacts of SS + index cases using prospective screening approach [11, 14, 25–29]. The yield of 0.96% among household contacts in the current study is comparable with what was reported by Salinas et al [30]. On the contrary, it is lower than the yield by the prospective approaches; 2.5% in similar setting in Ethiopia [11], 6.07% in South Africa [28] and the global average of 3.1% [31]. However, the overall yield in our study is about six times the case notification rate in the study zones during the same time period. The yield among contacts whose index cases registered for TB treatment within 12 months was eight times the TB case notification in the study zones. Thus, our finding clearly highlights the need to include retrospective contact screening, at least for contacts whose index cases registered for treatment within the past one year, as one of the strategies for case detection.

The 2.5% SS+ cases among the presumptive TB cases in this study might be underestimate but still relatively higher than the corresponding rate of 1.2% in the Ethiopian National TB prevalence survey [32]. However, the 106/100,000 prevalence of SS+ among the adult contacts is much higher than the result from the TB prevalence survey in Eritrea [33] and equivalent to the prevalence of 108/100,000 in the national TB prevalence survey in Ethiopia [32].



Ethiopia. (A) Contacts that fulfilled the criteria for presumptive TB were documented as screen result positive. Proportion of TB categories (SS+(smear positive TB), SS-(smear negative TB), EPTB (extra-pulmonary TB) & MDR-TB (multi-drug resistance TB)) was from all TB cases identified (2,091). **(B)** Yield of TB for age categories, type of index cases and contacts was computed per 100k (100,000) of their respective contacts. Ranges in parentheses are 95% Confidence Intervals.

Fig 1. Flow diagram of screening and yield of retrospective contact investigation, June-October 2014, Ethiopia.

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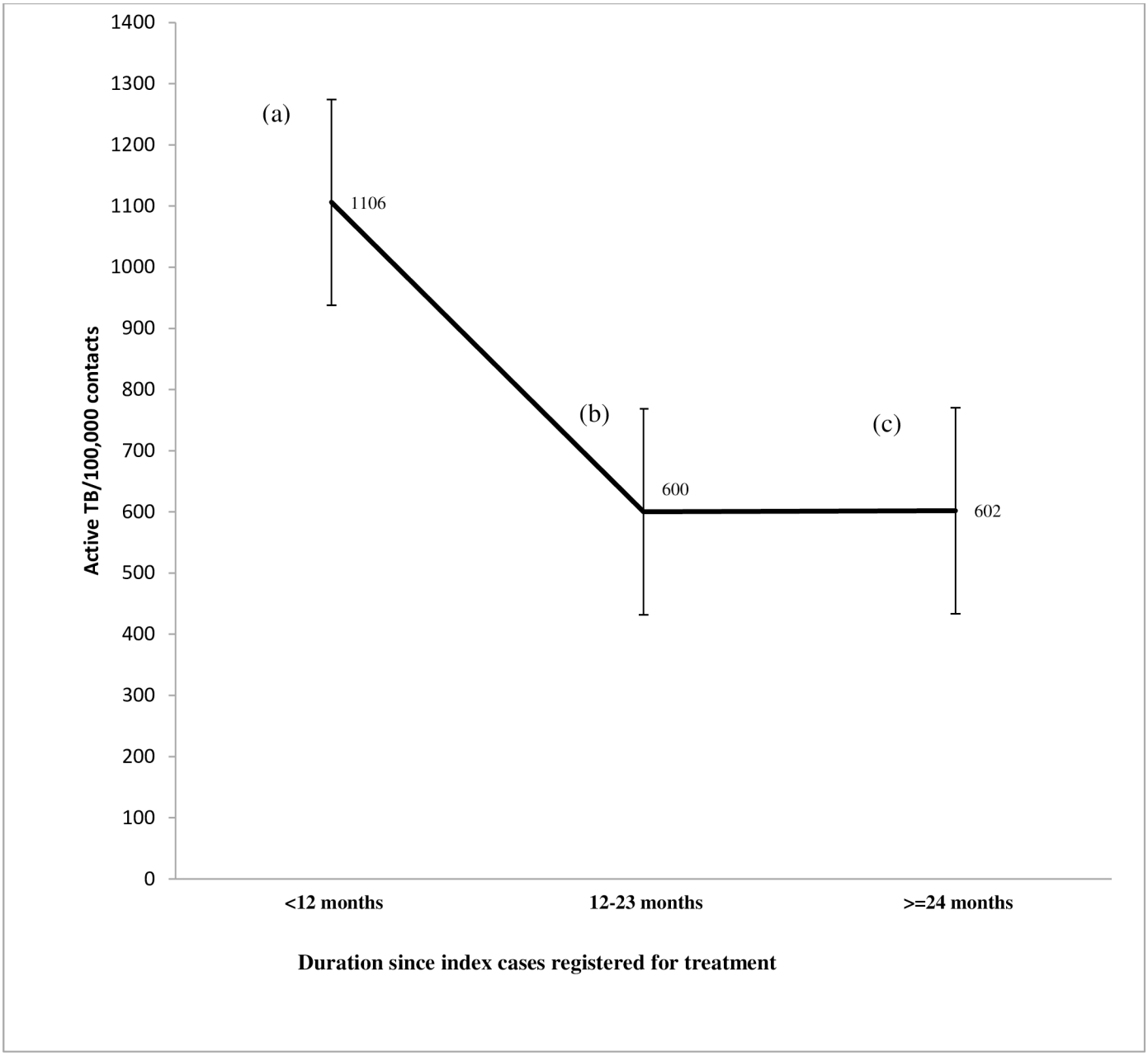

Line bars; (a) (923-1288), (b) (418-754) and (c) (423-749) indicate 95% Confidence Intervals (CIs) for the yield of TB per 100,000 of contacts of index cases registered for TB treatment during <12 moths, 12-23 months & >= 24 moths, respectively. The CI of the yield from contacts whose index case registered within one year during the study period is not overlapping and higher than the CI of the yields from contacts whose index cases registered for treatment during 12-23 months or more.

Fig 2. Yield per 100,000 contacts based on the time since index cases registered for TB treatment.

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Table 2. Factors associated with active TB in retrospective contact investigation, June–October 2014 Ethiopia.

Variables	Active TB case (%)		Active TB [1] versus non-TB[0] cases		
		COR	95% CI	AOR	95% CI
Year index cases registered for TB treatment					
<12 months	993 (1.4)	2.04	1.64–2.54	1.77	1.42–2.21
12-23months	400 (0.7)	0.98	0.74–1.30	0.93	0.7–1.24
> = 24 months	698 (0.7)	1			
Type of Index cases registered					
SS+	854 (0.9)	1			
EPTB	507 (0.7)	0.8	0.63–1.03	0.88	0.69–1.13
SS-	730 (1.1)	1.23	0.98–1.53	1.19	0.95–1.49
Age C**ategory of contacts**					
Children (<15 years)	581 (0.7)	0.68	0.54–0.84	0.55	0.44–0.69
Adult (>15 years)	1510 (1.0)	1			
Sex of Contacts					
Female	951 (0.74)	1			
Male	1140`(0.80)	1.15	0.95–1.40	1.12	0.92–1.37
Type of contacts					
House hold	1627(1.1)	1			
Neighbor	352(1.4)	1.23	0.94–1.62	1.35	1.02–1.78
Workplace	78(4.8)	4.5	2.55–7.94	3.95	2.21–7.03
Other	34(0.2)	0.14	0.09–0.22	0.13	0.08–0.20

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Our study revealed a significantly higher yield of active TB among workplace contacts as compared to other types of contacts. This might be due to the fact that the index cases share the same enclosed space for longer hour and the spaces might be overcrowded and poorly ventilated coupled with the little awareness on TB prevention [34]. A study on contact screening at workplace from Portugal revealed that the yield was 8.4 TB cases per index case [19]. This

Table 3. Determinants of active TB in children <15 years through retrospective contact screening, June-October 2014, Ethiopia.

Variables	Number (%) of active TB	Active TB [1] and no TB [0] in children <15 years of age			
		COR	95% CI	AOR	95% CI
Type of Index cases					
SS+	223 (0.6)	1			
SS-	242 (1.0)	1.85	1.20–2.84	1.78	1.16–2.75
EPTB	116 (0.5)	0.88	0.51–1.50	1.004	0.59–1.72
Time index cases completed treatment					
<12 months	313 (1.1)	2.69	1.69–4.27	2.4	1.50–3.82
12 months—23months	131 (0.6)	1.4	0.78–2.51	1.31	0.73–2.36
> = 24 months	137 (0.4)	1			
Type of Contacts					
Household	542 (0.8)	1			
Neighbor	32 (0.4)	0.47	0.21–1.08	0.51	0.22–1.17
Workplace and Others	7 (2.3)	0.12	0.03–0.51	0.14	0.035–0.58
Sex of contacts					
Female	312 (0.70)	1			
Male	269 (0.73)	0.95	0.64–1.39	Not applicable	Not applicable

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suggests that there is a need to consider contact tracing beyond households especially in congregated workplaces such as schools, mining areas and prisons. Further studies should include detailed work place related variables such as employment status, hours and working conditions so as to generate more evidence on factors associated with increased risk of TB in work place contacts.

We also involved neighbor visitors of the sick index cases for contact investigation. This is because most neighbors in rural Ethiopia are relatives and genetically related to the sick. It is also part of the tradition of Ethiopian society to visit and stay with the sick while they are possibly exposed. The yield was higher at 1.4% among the neighbor contacts. Cheng et al (2015) from Uganda showed that first degree relatives' contacts were more likely to be symptomatic for TB [18]. It was also shown by Lienherdt et al (2003) in Gambia that development of TB cases increased with first degree relatives compared with more distant and non-genetically related households [13]. In fact, it is possible that genetic factors contributed to the susceptibility to TB infection [15]. Also, Classen et al (1999) indicated the need to target contacts outside of households in high incidence TB areas to reduce TB transmission [35]. These studies from elsewhere suggest the need to consider close relatives for contact screening, and the higher yield among the neighbors in the current study suggests that retrospective contact is also a feasible strategy for contacts of neighbor and relatives.

The yield of TB among adult contacts was higher than that of child contacts, which is likely to be related with underdiagnoses among children due to diagnostic difficulties [36]. Most of the TB cases were also identified from close contacts of TB patients with SS+ which is in line with most studies [11, 15, 26, 27, 29, 30, and 37].The greater proportion of childhood TB was detected from the contacts of SS-. It could be due to the selective nature of the prospective contact screening through which contacts of SS+ cases might have already been identified and taken care of. However, it needs further clarification in future studies. The fact that SS- can contribute to TB transmission has been shown in other studies [15–17]. The strategy of screening only those in contact with SS+ cases is likely to miss about one third of infected individuals [38].

Through the retrospective contact screening approach, we also detected TB cases from close contacts of EPTB index cases. Likewise, there are studies which included EPTB as an index case during active case findings [12, 39]. Contacts of patients with EPTB were evaluated because there are possibilities of associated pulmonary TB (PTB) cases [15]. Laryngeal TB and pleural TB are EPTB but can transmit TB as well [15–22]. There is also the opportunity to identify the real index cases of the identified EPTB that failed to be detected through the routine case detection strategy. Thus, in settings where TB is highly prevalent and there is a challenge of delay in the diagnosis there are possibilities of missed TB cases in the community [40]. Seeking for contacts of EPTB could detect the undiagnosed and missed TB cases which could be the real index cases of the EPTB. These could be cases that shared other common index cases but failed to seek health service. Therefore, comprehensive contact tracing should be considered in high burden settings.

The findings in this study should be interpreted cautiously as there were some limitations. We used symptom screening and light microscopy to diagnose SS+. Hence, a chance of missing the SS+ cases cannot be ruled out [41] though our study was done at health facilities that participated in a regular AFB microscopy external quality assessment (EQA) with concordance of 95% on random blinded rechecking [42]. In other studies, using digital X-rays in addition to symptom screening and fluorescent microscopy for diagnosis could not also detect all SS + cases individuals [32, 33]. Also, we included limited number of variables which did not allow thorough evaluation of all the potential determinants of TB among contacts. In addition, only few of the neighbor close contacts were accessed and screened as most of them did not fulfill

the criteria of close contacts. However, this is the first study reporting the yield of retrospective contact screening from Ethiopia and perhaps one of a few globally [43]. The other strength of this study is the large number of contacts screened compared with earlier reports.

Conclusions

The yield of retrospective contact screening through community-based approach was about six times the case notification in the study zones and contributed a significant proportion of all cases notified in the study districts. The risk of TB was high among contacts irrespective of the type of TB in the index case. This highlights that retrospective contact screening can be of high yield strategy among all types of index TB cases especially within one year of the registration of the index case. The yield was highest among work place contacts, suggesting the need to prioritize work place interventions for TB prevention and control. Further implementation and evaluation of retrospective contact screening should be done in similar settings to validate these findings. Such evaluations should include cost and cost-effectiveness studies.

Supporting Information

S1 Dataset. Data set for the retrospective contact investigation study.
(DTA)

S1 Table. The contact investigation register.
(DOCX)

S1 Text. Information sheet and oral informed consent form.
(DOCX)

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

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

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Setting: In 2011, Ethiopia introduced a strategy of symptomatic tuberculosis (TB) screening for patients attending out-patient services to increase identification of presumptive TB.

Objective: To assess implementation and factors affecting symptomatic TB screening at out-patient departments in health centres in the Amhara Region, Ethiopia.

Design: Using a cross-sectional study design, 86 randomly selected public health centres providing DOTS were included in the study. Data were captured by reviewing TB registers and interviewing key informants at out-patient services.

Results: Of 86 health centres, 24 (28%) had poor symptomatic TB screening practices, defined as screening <80% of attending out-patients. Having an actively functioning multidisciplinary health centre team to assess TB services (aOR 2.29, 95%CI 2.23–30.80) and partner support for TB activities (aOR 4.84, 95%CI 1.05–22.40) were associated with higher TB screening rates, whereas availability of antiretroviral therapy was negatively associated. In all health centres combined, 1.6% of out-patient department attendees were identified as having presumptive TB.

Conclusion: A quarter of health centres had poor symptomatic TB screening practices in the out-patient services in this study. Strengthening multidisciplinary teams and expanding partner support are recommended to improve TB screening practices at out-patient services in Ethiopia.

In 2012, Ethiopia ranked eighth among the world's 22 high TB burden countries.[1] The Ethiopian TB case finding strategy for TB control consists of the detection of TB among all persons presenting to health services with symptoms indicative of TB.[2] By implementing the DOTS strategy, the country achieved a case detection rate of 64%.[1] The Amhara Region reports a case detection rate of 56%,[3] which is below both the international target of 70% and the national average.

In 2011, Ethiopia introduced a strategy to implement symptomatic TB screening for all persons attending out-patient services. This coincided with the introduction of the reformed Health Management Information System out-patient department (OPD) register to capture data on the screening and identification of patients with presumed TB. This strategy was supplemented by the updated national comprehensive training manual for clinical and programmatic management of TB, leprosy and TB-HIV (human immunodeficiency virus), which also highlights the need to screen every person visiting a health facility for TB.[4] There is no published information on the implementation of the strategy in the region or the country at large.

The objective of the present study was to assess the level of implementation and factors affecting symptomatic TB screening among out-patients attending public health centres in the Amhara Region.

STUDY POPULATION, DESIGN AND METHODS

An institution-based cross-sectional study was conducted from 30 September to 18 October 2013 in selected health centres in the Amhara Region, which has an estimated population of 18.9 million, of whom 87% live in rural areas.[3] There are 801 health centres in the region; each health centre provides services for on average 25 000 people within a 10 km radius. TB diagnostic and treatment services are provided free of charge at all government facilities. Public health centres providing DOTS services in OPDs were included.

A sample size of 86 health centres was obtained using the single-population proportion formula for finite populations in Open-Epi software (Emory University, Atlanta, GA, USA). We assumed 50% of the health centres to have good TB screening practices on review, with a 10% margin of error and 95% confidence levels.

Of the 10 administrative zones (defined as a group of adjacent districts) in Amhara, five (North Gondar, South Wollo, West Gojam, Awi and Oromia) were purposively selected based on their geographical distribution in the region, population size and accessibility. The 86 health centres were allocated to the selected zones proportionate to the number of health centres. The number of health centres in each zone was then selected using simple random sampling.

Data were collected using interviews with OPD case managers, record reviews (OPD and laboratory registration books) and observation (availability of TB screening job aids). A pre-tested structured questionnaire was used to assess the profile of the health centres, health professionals and TB screening-related variables for the period from 1 April to 30 June 2013. Data collectors were experienced health professionals trained and supervised by the study team during data collection.

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TABLE 1 Operational definitions

The following definitions were used:

- Functioning multidisciplinary team: clinic team composed of ART pharmacist, ART officer, ART nurse, TB focal person, laboratory personnel, OPD case team leader, counsellors, prevention of mother-to-child HIV transmission focal person, infection prevention officer, ART adherence case manager and head of health centre who meet every 2 weeks to discuss TB and HIV issues; minutes of meetings are kept
- Infection prevention committee: team consisting of representatives from each service delivery unit that meets every 2 weeks to discuss overall infection prevention and control, including TB infection control, and keeps minutes of meetings
- Patient overload: average number of patients per OPD room exceeds 24/day
- Presumptive TB case: any person who presents with symptoms and/or signs suggestive of TB, in particular, cough of ⩾2 weeks and/or constitutional symptoms (loss of appetite, weight loss, fever, night sweats and fatigue)
- Regular supervision by *woreda* health office: at least monthly supervision visits to health centres by *woreda* health officers
- Review meeting: a quarterly meeting conducted to evaluate performance against quarterly plan and recommendations made by health centres, *woreda* health office, the zonal health department and the regional health bureau, partners and other stakeholders
- Symptomatic TB screening practice: considered good if a health centre screened ⩾80% of all OPD attendants for TB during the study period
- TB training: training of OPD staff in the previous year on TB, TB-HIV, TB/leprosy or infection prevention
- *Woreda* officers: health professionals assigned at *woreda* (district) level and responsible for planning, supervising and evaluating health centres in their territory
- Written feedback from supervisors: reports outlining strengths and weaknesses of OPD services observed during supervision visits

ART = antiretroviral therapy; TB = tuberculosis; OPD = out-patient department; HIV = human immunodeficiency virus.

Each questionnaire was reviewed and checked for accuracy and completeness by the study team. Epi-Info™ version 3.5.1 (Centers for Disease Control and Prevention, Atlanta, GA, USA) was used for double data entry. STATA version 11.0 (Stata Corp, College Station, TX, USA) and SPSS version 16 (Statistical Package for the Social Sciences, Chicago, IL, USA) statistical packages were used for data analysis. The health centre was used as the unit of analysis, and descriptive statistics were used to determine the proportion of health centres with good screening practice (Table 1) and the yield of the screening. The mean was calculated for normally distributed data, while for skewed data the median was calculated. The association between response and explanatory variables was measured using odds ratios (OR) with 95% confidence intervals (CI) obtained from multivariate logistic regression analysis.

Ethics clearance was obtained from the Regional Ethical Review Committee of the Amhara Regional Health Bureau (Bahir Dar, Ethiopia). A letter of permission was obtained from each Zonal Health Department and the heads of health centres. Verbal consent was provided by study participants.

RESULTS

Characteristics of health centres

All 86 selected health centres were included in the study. The median number of out-patients seen per day and room was 15.8 (interquartile range 8.2). The median number of OPD rooms per health centre was 2.0, ranging from 1 (33.7% of the health centres) to 5 (2.3% of the health centres). Of the 83 health centres with sputum microscopy services, 13 (15.7%) experienced service interruptions of an average duration of 20 days during the study period.

Fifty-two (60.5%) health centres had an actively functioning multidisciplinary team (MDT) or infection prevention (IP) team, with existing documentation of meetings held. The mean number of meetings in a quarter was 2.7 (standard deviation ± 1.3). *Woreda* officers carried out supervisory visits to 79 (91.9%) of the health centres, and the number of visits ranged from 1 to 8 (median = 1). Supervision was monthly for a quarter of the health centres, while two thirds were irregularly supervised and nearly 10% were not supervised at all in 2012–2013 (Table 2). Seventy-four (86%) health centres had a partner organisation supporting TB activities in terms of supervision (94.6%), training (83.8%), provision of microscope (83.4%) and job aids (33.8%), furniture (28.4%) and other items, such as computers (14.9%). In the study facilities, 24.2% (89/368) of the health professionals had received training in TB or TB-HIV on at least one occasion during the previous year.

Proportion of health centres implementing symptomatic TB screening

Of the 86 health centres, three (3.5%) did not screen OPD patients for TB at all and two (2.3%) documented only bacteriologically confirmed TB patients and not presumptive TB cases; 24 (28%) screened <80% of OPD patients. The overall yield of the symptomatic TB screening was 1.6%, i.e., 16 presumptive TB patients/1000 screened OPD patients. The yield differed in centres with good (⩾80% screened) and poor (<80% screened) screening rates (1.8% and 0.8%, respectively). This difference was significant ($P = 0.002$). Variations in screening practice across the zones were observed. All health centres in the North Gondar Zone screened at least 80% of OPD patients, while health centres in the Awi and West Gojjam Zones screened only about one third of patients (Figure).

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TABLE 2 Frequency distribution of health centre characteristics, Amhara Region, Ethiopia, 2013

Variable	*n* (%)
Availability of job aids for symptomatic TB screening	
Yes	81 (94.2)
No	5 (5.8)
Sputum microscopy available	
Yes	83 (96.5)
No	3 (3.5)
Availability of ART service	
Yes	52 (60.5)
No	34 (39.5)
Functional MDT/IP team	
Yes	52 (60.5)
No	34 (39.5)
Supervision by *woreda* health officers	
Yes	79 (91.9)
No	7 (8.1)
Provision of supervision feedback	
Yes	69 (80.2)
No	17 (19.8)
Partner support for TB activities	
Yes	74 (86.0)
No	12 (14.0)
Conduct review meeting	
Yes	74 (86.0)
No	12 (14.0)

TB = tuberculosis; ART = antiretroviral therapy; MDT = multidisciplinary team; IP = infection prevention; *woreda* = district.

Factors associated with the implementation of symptomatic TB screening

TB training, availability of antiretroviral therapy (ART), partner support for TB activities, feedback from supervision, supervision, MDT/IP meetings, patient overload and conducting review meetings were investigated for association with good screening practice. In the bivariate logistic regression analysis, screening practice was only significantly associated with MDT/IP meetings. In multivariate logistic analysis, three independent variables (MDT/IP, $P = 0.002$; ART service, $P = 0.028$; and availability of partners, $P = 0.044$) were significantly associated with screening practice.

Health centres with an actively functioning MDT/IP team were 8.3 times more likely to screen ⩾80% of OPD patients than health centres without a team (Table 3). Health centres with partner support for TB activities were 4.8 times more likely to screen ⩾80% of OPD patients than health centres without partner support. Screening practice was significantly lower among health centres with ART services: centres without ART service were five times more likely to screen OPD patients for TB.

DISCUSSION

This study showed that 72.1% of the health centres screened ⩾80% of OPD patients for TB. This supports the finding of a study from Ghana that concluded that systematic active screening of OPD attendees is feasible under programme conditions.[5] One of the factors significantly associated with good screening practice was holding regular MDT/IP meetings to monitor TB activities. In addition, availability of partners to support TB activities and not having an ART service were also significantly associated with good screening practice at the OPD.

Twenty-four (27.9%) of the health centres had unsatisfactory symptomatic TB screening of OPD patients. This is higher than the proportion (10.9%) reported earlier by Heal TB among the Management Sciences for Health supported health centres in four zones.[6] This difference could be attributed to the continuous clinical mentorship, regular programme monitoring and other capacity building activities provided by the partner. In our study, in addition to Heal TB, other partners, such as the International Training and Education Centre for Health (I-TECH) and the Ethiopia Network for HIV/AIDS Treatment, Care & Support (ENHAT-CS), were active in the study zones. Although partner support differs in scope and content, all were providing support for TB activities. Health centres supported by partners focusing on TB were 4.8 times more likely to have good screening practice.

Having a functioning MDT/IP team was significantly associated with good TB screening practice, as health centres with teams were eight times more likely to screen ⩾80% of OPD patients. In these TB programme-specific facility level meetings, health professionals discuss case-finding efforts, such as symptomatic TB screening, community suspect referrals, contact screening, intensified case finding activities and the quality of DOTS provided. Health care workers (HCWs) working at different

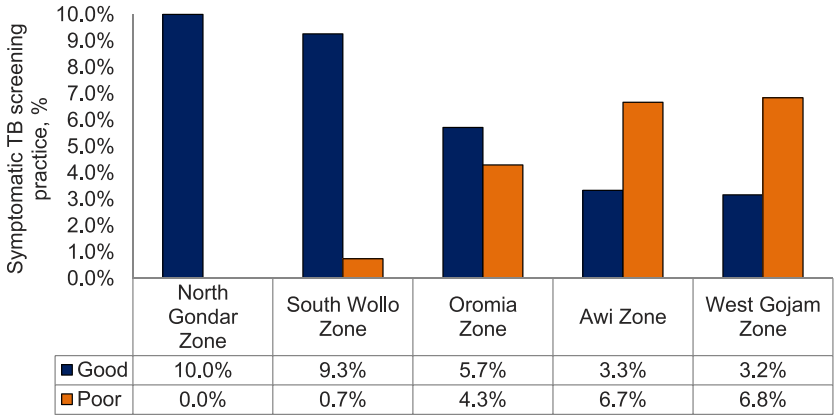

FIGURE Symptomatic TB screening practice at health centre out-patient departments by zone in the Amhara Region, Ethiopia, 2013. TB = tuberculosis.

TABLE 3 Bivariate and multivariate analysis of factors affecting screening practice, Amhara Region, Ethiopia, 2013

Variables	Screening practice		OR (95%CI)	aOR (95%CI)
	Good (⩾80%)	Poor (<80%)		
TB training				
Yes	36	15	0.83 (0.32–2.19)	0.49 (0.14–1.69)
No	26	9	1	1
Availability of ART service				
Yes	35	17	0.53 (0.19–1.47)	0.22 (0.06–0.85)*
No	27	7	1	1
Partner support for TB activities				
Yes	56	18	3.11 (0.89–10.86)	4.84 (1.05–22.4)*
No	6	6	1	1
Supervision by *woreda* health officers				
Yes	58	21	2.07 (0.43–10.04)	4.08 (0.69–24.12)
No	4	3	1	1
Functional MDT/IP team				
Yes	43	9	3.77 (1.41–10.12)*	8.29 (2.23–30.80)*
No	19	15	1	1
Patient overload				
Yes	10	3	0.74 (0.19–2.97)	0.53 (0.10–2.78)
No	52	21	1	1
Conduct review meeting				
Yes	52	22	0.47 (0.10–2.34)	0.18 (0.02–1.56)
No	10	2	1	1

*Statistically significant.
OR = odds ratio; CI = confidence interval; aOR = adjusted OR; TB = tuberculosis; ART = antiretroviral therapy; MDT = multidisciplinary team; IP = infection prevention; *woreda* = district.

entry points participate in these meetings.[7] MDT/IP team meetings help HCWs to evaluate their performance every 2 weeks and identify local solutions to strengthen services.

In this study, screening practices were significantly poorer among health centres with ART services. This could be a result of a shift in focus among health care providers to screen patients for TB in the HIV clinic rather than in the OPD. As ART clinics were not included in this study, this assumption needs further investigation. However, if confirmed this would be disturbing, as screening would then only focus on people living with HIV (PLHIV) and not all health centre attendees. Although PLHIV are at higher risk of TB, only 40% of TB cases in the region were co-infected with HIV.[3]

Reported OPD patient load was not associated with screening practice in the current study. However, a study in South Africa showed that clinics with a high patient load were less likely to screen than clinics with fewer attendees.[8] A study in Pakistan reported that both excessive workload and extremely low workload were associated with poor performance.[9] In our study, recent TB training of HCWs was not associated with TB screening practice. The study from South Africa indicated that follow-up training of HCWs increased the effectiveness of integrated TB-HIV screening.[8] This could be due to fact that some HCWs who attended training in our setting may not have been working in OPDs due to work rotation. HCWs with TB training should be assigned to TB clinics to strengthen anti-tuberculosis treatment.

The observed yield of presumptive TB at OPDs was 1.6%. This is lower than the World Health Organization estimate (5–10%) and reports from South India that 6.7% of out-patients in health centres were symptomatic for TB.[10,11] The possible reasons for the lower yield include lower magnitude of TB symptoms, poor screening quality and poor documentation. This should be investigated further.

Our study was limited by the small sample size, leading to wide CIs. Data were collected from existing records that may have been inaccurate. We were unable to link the health centre's OPD activity with TB-related laboratory activities, as both have different log books.

In conclusion, although the TB screening policy has been implemented widely in the Amhara Region, a quarter of the health centres still had poor symptomatic TB screening practices in the OPD services. To enhance TB detection, strengthening health centre TB meetings and expanding partner support for TB control are proposed. The negative association between the presence of ART services and OPD performance in TB screening needs to be further investigated.

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Contexte : En 2011, l'Ethiopie a introduit une stratégie de dépistage de la tuberculose (TB) basé sur les symptômes parmi les patients venant en consultation externe afin d'augmenter l'identification de patients suspects de TB.
Objectif : Evaluer la mise en œuvre et les facteurs affectant le dépistage symptomatique de la TB en consultation externe dans des centres de santé de la région d'Amhara, Ethiopie.
Schéma : Grâce à une étude transversale, 86 centres de santé publics, choisis au hasard et offrant des services DOTS, ont été inclus dans cette étude. Les données ont été recueillies grâce à une revue des registres et à des entretiens avec les personnes clé des services de consultations externes.
Résultats : Vingt-huit pour cent des centres de santé (24/86) avaient une pratique médiocre du dépistage symptomatique de la TB, définie comme un dépistage de <80% des consultants externes. Les facteurs associés à un dépistage plus exhaustif comprenaient le fait d'avoir un centre de santé actif et bien fonctionnel, une équipe multidisciplinaire discutant des services liés à la TB (aOR 2,29, IC95% 2,23–30,80) et un soutien d'un partenaire pour les activités liées à la TB (aOR 4,84, IC95% 1,05–22,40) ; par contre, la disponibilité du traitement antirétroviral y était négativement associée. Dans tous les centres de santé combinés, 1,6% des consultants externes ont été identifiés comme suspects de TB.
Conclusion : Dans cette étude, un quart des centres de santé avait une pratique de dépistage de la TB médiocre dans ses services de consultation. Il est recommandé de renforcer les équipes multidisciplinaires et d'étendre le soutien par un partenaire afin d'améliorer la pratique du dépistage de la TB dans les services de consultation externe en Ethiopie.

Marco de referencia: En el 2011 se introdujo en Etiopía una estrategia de detección sistemática de la tuberculosis (TB) sintomática en los pacientes que acuden a los servicios ambulatorios, con el objeto de mejorar el reconocimiento de los casos con presunción clínica de TB.
Objetivo: Evaluar la aplicación de la estrategia de detección sistemática y los factores que influyen sobre sus resultados en los servicios ambulatorios de los establecimientos de salud en la región de Amhara en Etiopía.
Método: En un examen transversal se seleccionaron de manera aleatoria, con el fin de participar en el estudio, 86 centros de atención sanitaria que prestan servicios de DOTS. Los datos se obtuvieron a partir del examen de los registros clínicos y mediante entrevistas a los informantes clave en los servicios ambulatorios.
Resultados: Se observó que en 28% (24 de 86) de los centros sanitarios las prácticas de detección sistemática de la TB sintomática eran deficientes, pues alcanzaban <80% de los pacientes ambulatorios. Los siguientes factores se asociaron con una tasa más alta de detección: un equipo multidisciplinario operativo que examine los servicios relacionados con la TB en el centro (ORa 2,29; IC95% 2,23–30,80) y el respaldo de los organismos asociados a las actividades relacionadas con la TB (ORa 4,84; IC95% 1,05–22,40); la oferta de tratamiento antirretrovírico ofreció una relación inversa con la detección de la TB. En general, se estableció el diagnostico presuntivo de TB en 1,6% de los pacientes ambulatorios que acudieron a todos los centros.
Conclusión: En un cuarto de los establecimientos sanitarios examinados en el presente estudio las prácticas de detección sistemática de la TB en los servicios ambulatorios eran deficientes. Se recomienda fortalecer los equipos multidisciplinarios y ampliar el respaldo de los asociados con el propósito de mejorar la detección de la TB en Etiopía.

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

Andre Gemal[1], Joel Keravec[2], Alexandre Menezes[3] 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 antiretroviral production [13,17]. First-line TB drugs, including fixed dose combination formulations, and some second-line TB drugs are currently manufactured by these PPML. [17] Farmanguinhos, one of the most innovative manufacturers of this network, developed the Rifampicin/Isoniazid (RH) 2:1 FDC tablet (currently undergoing registration process) and is working on the pharmacotechnical development of the Rifampicin/Isoniazid/Pyrazinamide/Ethambutol (RHZE) 4:1 FDC, through a public-private partnership (PPP) agreement with a WHO-pre-qualified Indian manufacturer [18].

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

Bottlenecks for TB drug manufacturing in Brazil

Economic incentives for production

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

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

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

Active pharmaceutical ingredients (API)

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

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

The manufacturing process

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

Internal technological development

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

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

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

Recommendations for addressing the identified bottlenecks

Economic incentives for production

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

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

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

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

API

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

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

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

The manufacturing process

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

Internal technological development

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

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

Summary

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

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

Abbreviations

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

Competing interests

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

Authors' contributions

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

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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.

1. Background

Globally, there were an estimated 9.6 million incident cases of TB in 2014. The best estimate of the case detection rate for all forms of TB globally in 2014 was 63%, whereas 3.6 million cases remained undetected[1]. The cases that remained undetected continue to suffer from TB disease and also transmit the disease to their contacts[2]. The regions that contributed for most of the undetected all-forms incident TB cases are south-east Asia and Africa[3]. The passive TB case finding has contributed significantly in the identification and management of TB cases presenting to health facilities[3,4]. There is still the need to exert further efforts geared toward improving TB case findings and possibly identify the undetected TB cases that would have been missed while using the conventional passive TB case finding approaches[5–7].

The World Health Organization (WHO) recommends systematic screening for active TB with the aim of early detection of TB cases and prompt treatment that ensures better treatment outcome and reduced TB transmission to contacts[8]. There is a strong recommendation that household contacts and other close contacts should be systematically screened for active TB[8,9]. The globally recommended initial diagnostic tests for presumptive TB cases identified among contacts were either sputum smear microscopy to identify acid fast bacilli (AFB) or a rapid molecular test like GeneXpert MTB/RIF[8,9].

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A total of 137,081 incident TB cases were diagnosed in Ethiopia in the 2014/15 fiscal year with a case detection rate of 67%[10]. In Ethiopia, TB case finding was mainly focused on passive case finding at health facilities and referrals by community health workers which were able to detect up to two-third of the annually estimated TB cases[11]. To improve the TB case finding, one of the new approaches recommended by the national TB program is TB screening among close and household contacts of infectious TB cases. The first line laboratory test for presumptive TB cases identified in the contact screening is sputum smear microscopy while GeneXpert MTB/RIF test is also recommended if the index TB case is a drug resistant TB patient or is at risk of harboring drug resistant TB[11].

The national GeneXpert MTB/RIF implementation guideline recommends its use among presumptive MDR TB cases that include symptomatic contacts of MDR-TB cases, and presumptive TB cases among HIV positive individuals and children below 14 years of age[12]. Studies have been confirming that GeneXpert MTB/RIF test had significantly higher yield than sputum smear microscopy in different settings including Ethiopia[13–15]. However, the wider decentralization and use of GeneXpert MTB/RIF in low income countries needs to be evaluated in terms of its cost, ongoing supplies, maintenance issues and the need for uninterrupted electric supplies. There is also a need to demonstrate the added advantage of GeneXpert MTB/RIF over conventional sputum smear microscopy in different settings including contacts[16,17]. Studies that compared the yield of GeneXpert MTB/RIF with smear microscopy among contacts of index TB cases are scarce.

In this study, the diagnostic yield of GeneXpert MTB/RIF was compared with that of Ziehl-Neelson (ZN) sputum smear microscopy among index TB cases and their household contacts.

2. Methods

2.1. Study design and setting

A cross sectional study was conducted among sputum smear positive index TB cases and their household contacts. The study was done at eleven TB diagnostic and treatment health centers in North Gondar zone of Amhara region, Ethiopia between May 2013 and April 2015. North Gondar Zone has a total population of 3.6 million with TB case notification rate of 119 per 100,000 population (Unpublished data, Management Sciences for Health, 2015). There are three hospitals and 133 public health centers providing TB prevention and control services in the zone. Health centers are operated by Nurses, Health Officers, Laboratory Technicians, Pharmacy Technicians and administrative staff. The eleven health centers included in the study were selected as they are closer to Gondar University Hospital so that sputum specimens for GeneXpert test could be transported easily. These health centers have been participating in the external quality assurance (EQA) program of the country for ZN microscopy. The false positivity and false negativity rate of AFB slide readings at health facilities against the EQA center readings in the study area were found to be 0.19% and 0.17% respectively (Unpublished data, Management Sciences for Health, 2015).

2.2. Identification of index TB cases and their household contacts

We trained TB focal persons in the eleven health centers on the data collection, symptomatic screening, sputum sample collection and referral. New AFB sputum smear positive patients diagnosed in the 11 health centers during the study period who had at least one household family member were included in the study. Once the patient was diagnosed, the address of the patient was recorded. The contact details of 119 consecutive smear positive index TB cases were noted. All index cases were either asked to bring their household contacts to the health center or visited at home by the study team composed of supervisors and community health workers called health extension workers (HEW) within 2 weeks of diagnosis. Household contact was defined as a person who shared the same enclosed living space for one or more nights or for frequent or extended periods during the day with the index case during the 3 months before commencement of the current treatment episode[9]. TB focal persons and both urban and rural HEWs were involved in registering the household contacts and screening of contacts for symptoms suggestive of TB.

2.3. Data collection and TB symptom screening

A baseline data was filled in a standardized questionnaire for each index smear positive TB case by the TB focal person in the health centers. The major information collected was socio-demographic data, signs and symptoms, duration of illness, contact history and the laboratory results. A family matrix form was used to register all household contacts. A standard questionnaire was administered by the TB focal person or HEWs to each household contact independently that included socio-demographic characteristics and relationship status to the index case. The TB focal person or HEWs registered the household contacts and screened them for the major signs and symptoms of TB. Household contacts with history of cough for two or more weeks or with two or more symptoms suggestive of TB were considered to have presumptive TB[8]. Presumptive TB cases were referred to the health center for further evaluation and laboratory investigation (ZN microscopy and GeneXpert).

2.4. TB diagnosis

Three sputum samples (Spot-Morning-Spot) were collected at the health centers from each household contact with presumptive TB. Morning sputum specimens were also collected from the 119 index TB cases for GeneXpert test. All the 119 index TB cases were already put on first line anti-TB drug treatment based on the ZN microscopy result and continued the treatment even if the GeneXpert test result turned out negative. The TB focal persons in the respective health centers transported the sputum samples to Gondar University hospital following the standard infection control and specimen transportation procedures (using cold box) for GeneXpert test. Trained senior laboratory personnel in the health centers and Gondar University hospital were engaged in conducting the ZN microscopy and GeneXpert tests, respectively. The laboratory personnel doing ZN microscopy and GeneXpert MTB/RIF test were blinded. The three samples from contacts were tested for AFB by ZN sputum smear microscopy and GeneXpert test was also done on the morning sputum sample. In addition, GeneXpert test was done on the morning sputum specimens collected from the index TB cases.

2.5. Data analysis

Data entry and analysis was performed using SPSS, Version 13 (SPSS Inc., Chicago, Illinois). Data was entered by an experienced data clerk under the supervision of the principal investigator. Frequency, percentage and 95% confidence interval of proportions were computed. The number needed to screen (NNS) and number needed to test (NNT) was also computed. NNS is the number of contacts required to be screened to detect a single case of active TB; NNT is the number of contacts with presumptive TB required to be investigated in the laboratory to detect a single case of active TB. The 95% confidence intervals of proportion among different

categories were compared: absence of overlap in 95% confidence intervals is considered as a statistically significant difference.

2.6. Ethical considerations

Ethical approval was obtained from the University of Gondar ethical review board [reference number RCS/P/05/485/2013 dated June 4th 2013]. Each study participant provided a written informed consent and permission was obtained from all health facilities. Written parental consent was also obtained for participants below the age of 18 years. Household contacts with positive TB result were treated in accordance with the national tuberculosis program recommendations[11]. Rifampicin resistant results by GeneXpert test were immediately communicated to each health centers for proper management of patients as per the national tuberculosis program recommendations[11].

3. Result

3.1. Characteristics of index cases

A total of 119 newly diagnosed index TB cases were registered during the study period. They were sputum smear positive by the ZN staining done in the laboratory of the respective health center. The index cases lived in 119 different households. Two-thirds of the index cases were urban residents and the male to female ratio was 1.38. Four-fifths of the index cases were in the age range 15 to 44 years with mean (SD) age of 31.2 (14.1) years (Table 1). Only 6 (5%) had past history of TB. GeneXpert MTB/RIF test was done for all index TB cases. The GeneXpert test among index TB cases revealed that 8/119 (6.7%) were negative for TB while 106/119 (89.1%) and 5/119 (4.2%) were rifampicin sensitive and rifampicin resistant TB, respectively.

3.2. The yield of active TB case finding among household contacts

A total of 393 contacts were identified in 119 households with contact to index TB cases ratio of 3.3. The contacts were between 1 and 94 years of age with Mean (SD) age of 24.6 (18.2). Out of 393 contacts, 353 (89.8%) were screened for symptoms suggestive of tuberculosis. A total of 41 (11%) of the screened contacts were found to have presumptive TB of which all with the exception of two under-five children were checked with ZN microscopy (spot-morning-spot) and GeneXpert MTB/RIF test. Of 39 presumptive TB cases with sputum samples, GeneXpert test diagnosed 14 (35.9%) cases of TB whereas the number of TB cases diagnosed by ZN microscopy was 5 (12.8%): a 64.3% increased positivity rate by GeneXpert versus ZN microscopy. The entire five cases positive by ZN microscopy were also positive for TB in the GeneXpert test. Two under-five children were diagnosed clinically and using X-ray as smear negative pulmonary TB cases (Figure 1). Of the 14 bacteriologically confirmed TB cases, one was found to be rifampicin resistant TB. A total of 108 (90.8%) households did not have any active TB case among the contacts, 8 households (6.7%) had one TB case each, 2 (1.7%) households had 2 TB cases each and 1 (0.8%) household had four TB cases diagnosed among the contacts.

Table 1
Socio-demographic characteristics of smear positive index tuberculosis cases

Characteristics	Frequency (%)
Residence	
Rural	44 (37.0)
Urban	75 (63.0)
Gender	
Male	69 (58.0)
Female	50 (42.0)
Age in years	
12-14	5 (4.2)
15-24	39 (32.8)
25-34	35 (29.4)
35-44	22 (18.5)
45+	18 (15.1)
Educational background	
No formal education	48 (40.3)
Primary education	24 (20.2)
Secondary education	40 (33.6)
Diploma and above	7 (5.9)
Occupation	
Farmer	25 (21.2)
Government employee	7 (5.9)
Domestic work	9 (7.6)
Petty trade	3 (2.5)
Daily laborer	32 (27.1)
Driver	5 (4.2)
Student	29 (24.6)
Other	9 (7.6)

3.3. The prevalence of TB among household contacts

Sixteen cases of tuberculosis were identified (two clinical and X-ray diagnosis; and one rifampicin resistant) through the household TB contact screening with overall prevalence of 4,532.6 per 100,000 contacts: bacteriologically confirmed TB was 3,966 per 100,000, rifampicin sensitive TB was 3,682.7 per 100,000 and rifampicin resistant TB was 283.3 per 100,000. The prevalence of TB in rural and urban residence was 4,458.6 and 4,591.8 per 100,000, respectively ($p>0.05$). The prevalence of TB among male and female contacts was 4,545.5 and 4,522.6 per 100,000, respectively ($p>0.05$). TB prevalence per 100,000 ranged from 2343.8 in the age group 15 to 34 years to 11,111.1 in the age group 60 years and above ($p>0.05$). With regard to relationship status with the index case, the prevalence of TB per 100,000 ranged from 2702.7 among sibling contacts to 6666.7 among other relatives ($p>0.05$) (Table 2).

3.4. Comparison of the performance of GeneXpert MTB/RIF versus ZN microscopy in TB household contact investigation

The prevalence of TB by using the GeneXpert diagnostic test was 3966.0 per 100,000 contacts while it was 1416.4 per 100,000 contacts by ZN microscopy. The number of contacts needed to screen (NNS) to find a single case of TB while using GeneXpert as a diagnostic test was 25 as compared to the 70 while using ZN microscopy. The number of presumptive TB cases needed to test (NNT) to diagnose a single case of TB while using GeneXpert was three and the corresponding number in using ZN microscopy was eight.

4. Discussion

The performance of GeneXpert MTB/RIF in identifying TB among household contacts of index cases was significantly higher as compared with ZN microscopy. Out of 14 bacteriologically confirmed TB cases among household contacts, nine cases (64.3%) would have been missed if we had relied on ZN microscopy alone. The number needed to screen and number needed to test to diagnose a single case of TB was significantly lower with the use of GeneXpert than ZN microscopy indicating the better efficiency of the former laboratory test. ZN microscopy needed three consecutive sputum samples while GeneXpert test was done using a single, morning sputum sample but with additional diagnostic yield.

Studies have shown that smear microscopy is able to detect TB in patients with advanced disease who discharge sufficient number of bacilli[18,19]. In our study, two-thirds of the TB cases among household contacts would have remained undiagnosed if

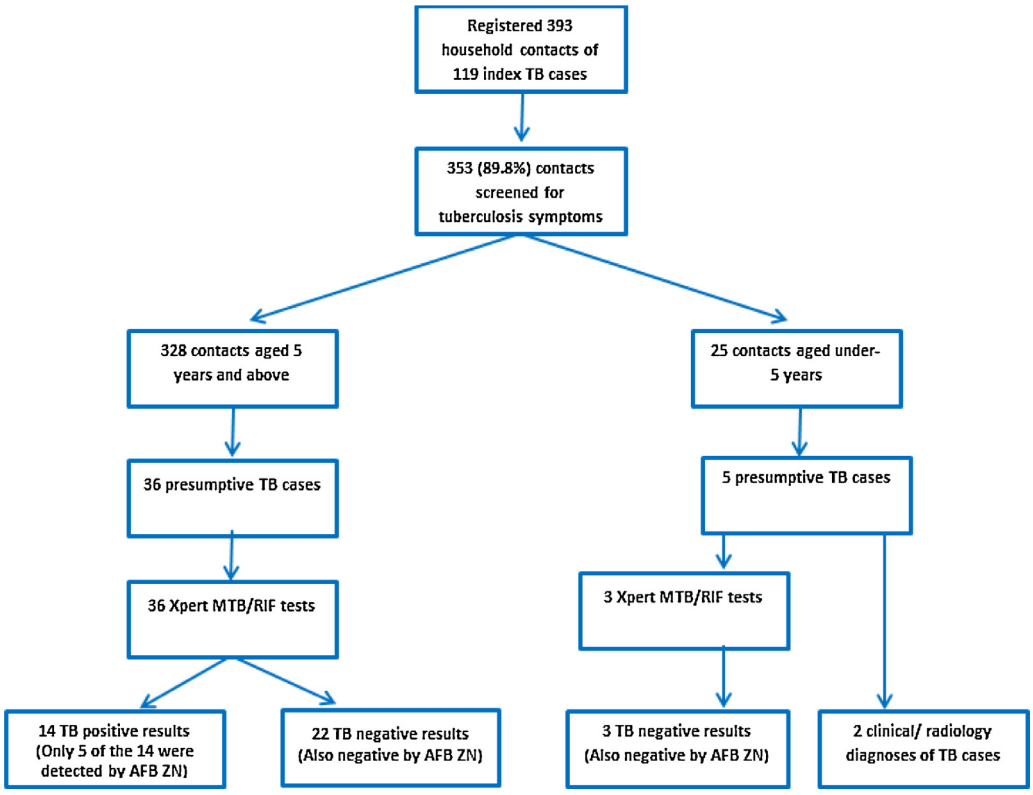

Fig. 1. Active case finding among household contacts of smear positive index TB cases.

GeneXpert test was not done. Hence, the contacts who harbor and discharge TB bacilli but couldn't be detected by the conventional smear microscopy would continue suffering with the disease and transmit the disease to their contacts unless we use a more sensitive test like GeneXpert to enable early identification of cases. Although the use of GeneXpert enabled better case detection among contacts, the wider use of GeneXpert in low income settings needs to be evaluated in terms of its cost-effectiveness, feasibility and the priority group to be targeted by the service[16,17]. Further clinical characterization of subsets of presumptive TB cases among TB contacts who would benefit most from GeneXpert MTB/ RIF testing could help to optimize its use in settings with limited resources.

Significant proportions of smear positive index TB cases by ZN microscopy were also confirmed positive by GeneXpert which signifies the quality of ZN microscopy service in the health centers. Eight (6.7%) of the already smear positive index TB cases (ZN microscopy) were negative for TB in the GeneXpert test. The incongruity can be attributed to either a false positive result by the ZN microscopy even though the EQA false positivity rate in the study area was 0.19% or the bacilli might have been mycobacteria other than tuberculosis as the GeneXpert only detects *Mycobacterium tuberculosis* complex strains. Rifampicin resistant TB, a surrogate marker for MDR-TB, was also diagnosed among 5 (4.2%) index cases who were put on first line anti-TB drugs based on ZN microscopy result alone at the health centers. It would have taken time for the health centers to suspect drug resistance TB in the course of first line treatment and consider drug susceptibility testing (DST). The rifampicin resistant TB burden among index cases in our study is greater than the 2.3% rate of MDR-TB (resistant to at least rifampicin and isoniazid) among new cases of TB and less than the 17.8% rate reported in previously treated TB cases in the national TB drug resistance survey[20]. One of the components of the End TB strategy emphasized on early diagnosis of tuberculosis including universal drug-susceptibility testing which is also supported by the findings of this study[21].

Although GeneXpert test has a cost implication, a single sputum test using GeneXpert would have improved the diagnostic capacity, reduced the number of sputum samples to be collected and enabled the immediate identification of drug resistant TB. A survey done in 24 countries in 2015 revealed that 8 countries, including Swaziland and South Africa from Africa, adopted GeneXpert test as a first line diagnostic test in the diagnosis of TB replacing smear microscopy[22]. It is advisable that countries like Ethiopia learn from the experience of countries that are using GeneXpert as a first line test for possible scale up of the GeneXpert test. There is a critical need for operational research to understand the pros and cons of decentralizing GeneXpert MTB/RIF test at the district level[16].

There were two households with four and two TB cases diagnosed among the contacts. It appears that there were households who had higher risk of transmission with resultant clustering of TB cases in the households. The clustering of TB cases in a household is more likely to be due to shared risk factor rather than individual level risk factor such as nutritional status, ventilation, air pollution or any other factor shared by household members[23–26]. Further analysis on the factors that fueled the TB transmission in those households was not done. There is a need to strengthen community TB care to ensure early diagnosis and treatment of index TB cases and reduce the risk of transmission to household and close contacts. TB infection control at household level is also an area that can be improved by educating community members regarding TB transmission, prevention and earlier health care seeking.

The overall prevalence of tuberculosis among household contacts using GeneXpert was 3,966 per 100,000 which is 20 fold of the estimated national prevalence of TB[1]. There was no significant difference in the diagnosis of TB among household

Table 2
Prevalence of TB among contacts by socio-demographic characteristics

Characteristics	Number of contacts	Number of presumptive TB (Row %)	Prevalence of TB diagnosis per 100,000; N (prevalence: 95% CI)[a]
Overall	353	41 (11.6%)	16 (4.5:2.8, 7.2)[b,c]
Residence			
Rural	157	13 (8.3%)	7 (4.4: 2.2, 8.9)
Urban	196	28 (14.3%)	9 (4.6: 2.4, 8.5)
Gender			
Male	154	15 (9.7%)	7 (4.5: 2.2, 9.1)
Female	199	26 (13.1%)	9 (4.5: 2.4, 8.4)
Age in years			
0-4	25	5 (20.0%)	2 (8.0: 2.2, 2.5)
5-14	106	10 (9.4%)	6 (5.7: 2.6, 1.2)
15-34	128	17 (13.3%)	3 (2.3: 0.8, 6.7)
35-59	67	6 (9.0%)	2 (2.9: 0.8, 10.2)
60 & above	27	3 (11.1%)	3 (11.1: 3.9, 28.1)
Educational background			
No formal education	147	18 (12.2)	12 (8.2: 4.7,13.7)
Primary education	97	13 (13.4)	4 (4.1: 1.6, 10.1)
Secondary education	56	9 (16.1)	-
Diploma and above	11	1 (9.1)	-
Marital status			
Single	217	26 (12.0)	9 (4.1: 2.2, 7.7)
Married	112	11 (9.8)	4 (3.6: 1.4, 8.8)
Divorced	10	1 (10.0)	1 (10.0: 1.8, 40.4)
Separated	2	0	-
Widowed	12	3 (25.0)	2 (16.7: 4.7,44.8)
Relation to index			
Head/ Spouse	93	8 (8.6%)	4 (4.3: 1.7, 10.5)
Son/Daughter	117	14 (12.0%)	7 (5.9: 2.9, 11.8)
Parent	33	4 (12.1%)	1 (3.0: 0.5, 15.3)
Sibling	74	8 (10.8%)	2 (2.7: 0.7, 9.3)
Other relative	30	5 (16.7%)	2 (6.7: 1.8, 21.3)
Non-relative	6	2 (33.3%)	-

[a] prevalence & 95% CI in thousands
[b] One case is RR TB
[c] Two cases are clinical diagnosis of TB

contacts by residence type, age, gender and type of relationship to the index case. However it is worth noting that the diagnosis of TB in the contacts was made largely based on laboratory confirmation except the two Pediatric cases diagnosed clinically and using X-ray. It is likely that more cases of clinical and extra-pulmonary TB might have been diagnosed subsequently from the presumptive TB cases which were not captured here due to the cross sectional nature of this study. It could have led to possible underestimation of the prevalence of all forms of TB among the household contacts.

The study needs to be interpreted with the following limitations in mind. The study did not consider some risk factors like HIV status of study participants and the condition of households, and the associated risk in the development of TB. The study also did not include the gold standard culture test to evaluate the sensitivity and specificity of ZN and GeneXpert test results. The use of standard operating procedures, availability of quality assurance mechanisms in the laboratories and involvement of highly qualified laboratory personnel are amongst the strengths of this study.

Our findings suggest that GeneXpert MTB/RIF test could lead to increased TB case detection among household contacts in addition to its advantage in the diagnosis of rifampicin resistant TB among contacts. The use of GeneXpert also helped in the identification of rifampicin resistant TB among newly diagnosed index TB cases in the health centers. There should be a consideration in using GeneXpert MTB/RIF as a point of care TB testing tool among high risk groups such as contacts especially in settings like Ethiopia where the burden of TB is high. Further study is recommended to analyze the cost-effectiveness and feasibility of scaling up GeneXpert as a first line test.

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Act local, think global: how the Malawi experience of scaling up antiretroviral treatment has informed global policy

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Abstract

The scale-up of antiretroviral therapy (ART) in Malawi was based on a public health approach adapted to its resource-poor setting, with principles and practices borrowed from the successful tuberculosis control framework. From 2004 to 2015, the number of new patients started on ART increased from about 3000 to over 820,000. Despite being a small country, Malawi has made a significant contribution to the 15 million people globally on ART and has also contributed policy and service delivery innovations that have supported international guidelines and scale up in other countries. The first set of global guidelines for scaling up ART released by the World Health Organization (WHO) in 2002 focused on providing clinical guidance. In Malawi, the ART guidelines adopted from the outset a more operational and programmatic approach with recommendations on health systems and services that were needed to deliver HIV treatment to affected populations. Seven years after the start of national scale-up, Malawi launched a new strategy offering all HIV-infected pregnant women lifelong ART regardless of the CD4-cell count, named Option B+. This strategy was subsequently incorporated into a WHO programmatic guide in 2012 and WHO ART guidelines in 2013, and has since then been adopted by the majority of countries worldwide. In conclusion, the Malawi experience of ART scale-up has become a blueprint for a public health response to HIV and has informed international efforts to end the AIDS epidemic by 2030.

Keywords: HIV/AIDS, Antiretroviral therapy, Malawi, Policy, World Health Organization

Abbreviations: 3TC, Lamivudine; AIDS, Acquired immune deficiency syndrome; ART, Antiretroviral treatment; AZT, Zidovudine; D4T, Stavudine; EFV, Efavirenz; GFATM, Global Fund to Fight AIDS, Tuberculosis and Malaria; HIV, Human immunodeficiency virus; NVP, Nevirapine; PEPFAR, President's Emergency Fund for AIDS Relief; PMTCT, Prevention-of-mother-to-child-transmission of HIV; TB, Tuberculosis; TB-DOTS, Tuberculosis directly observed treatment, short course; TDF, Tenofovir; UNAIDS, Joint United Nations Program on HIV/ AIDS; UNICEF, United Nations Children's Emergency Fund; WHO, World Health Organization

Main text

Background

In 2004, Malawi, which is one of the poorest countries in the world [1], started scaling up antiretroviral therapy (ART) on a national scale. Since 1985, the country had been struggling to cope with a massive HIV/AIDS epidemic, and when ART scale-up began in 2004, approximately 930,000 people (approximately 10 % of the population) were thought to be HIV-infected, there were an estimated 100,000 new HIV infections occurring annually and 170,000 people were thought to be in immediate need of ART without which they were likely to be dead within 2 years [2].

In January 2004, before the national scale-up of ART started, there were just nine facilities in the public sector delivering ART to about 3000 patients. Treatment was unstructured, few health care workers had received formal training in ART, patients in general had to pay for medication, and there were no national systems of monitoring and evaluation. Patients had restricted access to

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ART largely due to the requirement for CD4-cell count testing for which patients had to pay out of their own pocket. National ART guidelines, which were developed by a working technical committee formed by the National AIDS Commission and which were published in late 2003, laid out for the first time a simplified and standardised approach taking into account the severe health system constraints and the huge epidemic burden of disease [3]. These guidelines informed the national scale up plan that was launched in February 2004. Within 4 months, ART was being delivered at health facilities within the public sector, with treatment rapidly brought to scale in both public and private sectors in the subsequent years. By 30th June 2015, (11 years after the start of national scale-up) there were 711 ART clinics in the public and private sector that had newly registered 820,367 patients on ART [4]. Both the public and private health sectors implement the same standardised systems of delivering and monitoring treatment, and by the end of June 2015 a total of 565,105 patients were recorded as alive and on ART (see Table 1). Despite the large number of patients who died soon after accessing ART or who were lost to follow-up (which included unreported deaths), ART was estimated to have averted 275,000 deaths in Malawi [5].

Of the 15 million people globally living with HIV/AIDS and accessing ART as of mid-2015, over two thirds are in Africa [6]. Despite being a small country, Malawi has made a significant contribution to achieving this total both in terms of contributing substantial numbers of people on treatment and, importantly, contributing policy and service delivery innovations that have supported scale up in other countries. The aim of this paper is to discuss Malawi's preparations and implementation of ART scale up at the national level over the last 15 years and to assess how these have influenced the thinking and development of international guidelines.

Table 1 Characteristics and outcomes of patients ever started on antiretroviral treatment (ART) in Malawi up to June 30th, 2015

	Number	(%)
Total ART clinic registrations (these include first-time ART initiations, re-initiations after treatment interruption and patients transferring from one site to another)	1,025,754	(100)
Registration type:		
First time ART initiations	820,367	(80)
ART re-initiations after treatment interruption	11,520	(1)
ART transfers from one clinic to another	193,867	(19)
Gender at ART initiation:		
Male	369,284	(36)
Female	656,470	(64)
Non-pregnant	536,145	(82)
Pregnant	120,325	(18)
Age at ART initiation:		
Adults aged 15 years and above	936,603	(91)
Children 0–14 years	89,151	(9)
Reason for starting ART:		
Presumed severe HIV disease	3520	(<1)
Confirmed HIV infection—WHO Stage 1 or 2	447,066	(43)
Confirmed HIV infection—WHO Stage 3	467,590	(47)
Confirmed HIV infection—WHO Stage 4	100,379	(10)
Unknown	7199	(<1)
Primary outcomes by 30 June 2015:[a]		
Alive on ART	565,105	(69)
Lost to follow up	174,554	(21)
Stopped ART	3366	(<1)
Died	77,342	(10)
Total died:		
Died month 1	19,087	(25)
Died month 2	11,998	(16)
Died month 3	7075	(9)
Died month 4 and later	39,182	(50)

ART antiretroviral therapy, *WHO* World Health Organization, *HIV* human immunodeficiency virus

[a]these are primary outcomes for those who were first-time ART initiations ($N = 820367$

The data are taken and modified from reference 4

The thinking behind Malawi's First ART Guidelines

The Durban World AIDS Conference in 2000 was a turning point for sub-Saharan Africa in the fight against HIV/AIDS, and within the next 2–3 years a number of key events took place. The UN Secretary General Kofi Annan conceived the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM). President GW Bush of the United States launched the President's Emergency Fund for AIDS Relief (PEPFAR) with ambitious targets for HIV prevention, care and treatment. JW Lee, director general of the World Health Organization (WHO), along with the joint United Nations Program on HIV/ AIDS (UNAIDS), launched the "3 by 5" initiative—with the aim of getting 3 million people in developing countries on ART by 2005 [7]. The funds and international support to deliver and scale up ART to HIV-infected eligible persons in sub-Saharan Africa were now at hand.

The will to confront the HIV/AIDS epidemic in Malawi also found new energy and direction. In 2001, the directors and staff from the National TB Control Programme and the National AIDS Control Programme in Malawi published a viewpoint paper in the Lancet outlining their thoughts on an ART Framework for the resource-constrained arena of sub-Saharan Africa [8]. The authors proposed and discussed the goal, strategy, policy package and key operations that would be needed to deliver and monitor services and which were based on those that had been successfully used for implementing the global TB strategy. This paper was used by the leadership of the National AIDS Commission and the Ministry of Health, Malawi, as the blueprint and the core of the country's submission to the GFATM in 2002.

The country was successful about 1 year later in obtaining a large grant from the GFATM for ART scale up. The HIV Department of the Ministry of Health, working with various other country-based stakeholders, also used this Lancet paper to develop the nation's first ART Guidelines in 2003 [3], and the first national scale up plan in 2004.

The key was simplicity and standardisation, which took into account the weaknesses of the health sector, the serious shortfall in trained health care workers, especially doctors, throughout the country and the principle of equity of access—namely that the same standards of care would apply from north to south and from central hospital to peripheral health centre. Details of how the national scale up was to be done, and particularly how the response to ART was to be monitored and evaluated, were refined in subsequent publications from Malawi in 2004 [9, 10].

At the time of national scale up, WHO had already published two guidelines, one in 2002 and a revised version in 2003, emphasising a public health approach [11, 12]. The 2003 guidelines were those mainly used by sub-Saharan African countries to guide their initial ART scale up plans. These were valuable for clinical guidance about i) when to start ART, ii) what antiretroviral regimens to start with, iii) when and what drugs to change to if toxicity or failure occurred, iv) how to do clinical and laboratory monitoring and v) what to do for specific categories of patients such as pregnant women, children and patients with HIV-associated tuberculosis. However, there was no specific guidance at that time from the WHO on operational or programmatic issues such as the process by which patients should be enrolled and started on ART, how to monitor medication adherence, the registration of patients, recording or reporting systems to keep track of enrolled patients and their outcomes and drug procurement and distribution. A HIV/AIDS technical working group in Malawi developed the country's first standardised guidelines using the clinical guidance articulated in the WHO 2003 document, and complemented this with operational and programmatic guidance based on contextual principles of a public health approach, borrowing heavily from the experience with tuberculosis (Table 2) [3, 13].

Scaling up ART in Malawi

Factors important for success

A number of factors were important to the success of national ART scale up [14]. Malawi was not a U.S. President's Emergency Plan for AIDS Relief (PEPFAR) focus country, and financial support for ART scale-up was from one source only—the GFATM. This allowed the country to build and sustain a cohesive national programme with a uniform direction for scale-up and no competing interests.

The Malawi Ministry of Health, through the director and staff officers of the HIV Department, took clear leadership and assumed responsibility for national scale up. As a consequence all implementing partners and stakeholders agreed to work together with the Ministry to develop and use one national standardised system to deliver and monitor ART. Standardised systems were instituted in line with the national ART Guidelines, so that at whatever type of health facility ART was being delivered (tertiary care hospital, district or mission hospital or health centre), the same methods of assessing patients for eligibility for treatment, initiating first line treatment, and registering and reporting cases and outcomes were followed. The Ministry worked fast with stakeholders, implementers and donors to develop and then implement a 2-year (2004–2005) followed by a 5-year (2006–2010) scale up plan based on the national guidelines with clear objectives, activities and time-lines as well as specific details about where ART delivery sites should be situated.

An ART site accreditation process was established. This began with an intensive training schedule with novel training and assessment methods that took place in early 2004 and focused particularly on paramedical officers and nurses learning the ART guidelines and passing a formal examination based on these guidelines. Following classroom training, the paramedical officers and nurses had to undertake practical attachments at experienced ART sites in order to be certified as ART providers. Trained staff returned to their health facilities to brief the officers in charge, the district assembly, the neighbouring health centres and the community about ART. The HIV Department of the Ministry of Health then carried out a formal accreditation of the ART facility. Once accredited, the public was informed through announcements in the media that antiretroviral drugs (ordered some months before in good faith that the site would pass its assessment) were available and ART delivery could commence.

Every quarter, the HIV Department and its partners conducted supportive supervisory and monitoring visits to all ART sites in the country. During these visits, they ensured that health care workers were adhering to guidelines, checked and collected data for national reporting, provided encouragement and support to staff and recorded drug stock levels for drug forecasting and procurement planning [15]. Each quarter, facilities were awarded a certificate of excellence if the register and treatment cards were completed according to national guidelines and the cohort analyses had been accurately performed. Underperforming facilities were given warnings.

In the first few years of ART scale up, the HIV Department developed a centrally coordinated "push system"

Table 2 Main similarities and differences between the WHO 2003 ART Guidelines and the Malawi 2003 ART Guidelines

	WHO 2003 ART Guidelines	Malawi 2003 ART Guidelines
When to start ART	Stage 4, Stage 3, Stage 2 with CD4 count or Total Lymphocyte count below threshold, Stage 1 with CD4 count below threshold	Followed WHO Guidance
What to start	Choice of 4 first-line ART regimens based on d4T/AZT, 3TC or EFV/NVP	One first-line ART regimen only (d4T + 3TC + NVP) with alternatives if toxicity occurred
How to start ART	No specific advice	Advice about staging patients, group counselling and individual counselling and how to manage the first 2 weeks on half-dose nevirapine
Clinical and laboratory monitoring	Recommended tiered laboratory capabilities based on level of health care facility	Emphasised clinical monitoring only due to poor country-wide laboratory infrastructure
Adherence to medication	General advice about adherence and monitoring	Specific advice around pill counting
Children	Advice about dosing—recommendations for not splitting fixed-dose tablets	Advice about splitting first-line fixed-dose ART according to weight
HIV-Tuberculosis	Advice based on CD4 count or consideration of ART based on clinical judgement	Advice about starting all HIV-infected TB patients on ART in continuation phase with isoniazid and ethambutol
Standardised treatment outcomes on life-long ART	No advice given	Standardised treatment outcomes defined
Programmatic monitoring, recording and reporting	No advice given	Advice about patient identity cards, patient treatment master cards, patient ART registers and patient cohort analysis
Supervision	No advice given	Advice about quarterly supervision of all ART clinics including drug security checks
ARV drug procurement and distribution	No advice given	Advice about "start packs" and "continuation packs" and how to forecast drug needs

ART antiretroviral therapy, *WHO* World Health Organization, *HIV* human immunodeficiency virus, *TB* tuberculosis, *d4T* stavudine, *AZT* zidovudine, *NVP* nevirapine, *EFV* efavirenz

for ARV supply management. Six-monthly rounds of procurement and distribution (through UNICEF) were based on categorizing facilities according to their estimated burden of disease and by the number of new and retained patients on ART at the end of each quarter. Pre-packed kits with starter packs (for the first 2 weeks of treatment) and continuation packs were allocated and distributed based on this site-level quantification. Between 2004 and 2006, no stock-outs were encountered nationally or at individual sites [16].

Within 6 months of establishing ART in the public sector, the private sector was brought on board with their agreement to follow national systems, undertake a modified weekend ART training course with an examination of competence, and be accredited in the same way as the public sector. Private facilities received antiretroviral drugs free of charge, but charged patients for the drugs at approximately USD$3.5 per course of treatment per month. These monies were partly used to cover dispensing costs and partly to cover other costs of the programme, such as training and supervision.

Challenges

Challenges in the early years of ART scale up abounded. On the technical side, few children were accessing ART due to the absence of paediatric drug formulations and a dearth of paediatric specialists in the country who felt confident enough to provide care and treatment for this sub-group of patients. There were difficulties in managing patients with HIV-associated tuberculosis due to the well- known interactions between rifampicin and nevirapine. High early death rates after starting ART were a concern for health care workers, patients and the wider community-at large.

On the logistic side, huge efforts were required to keep up with the demands for stationary (patient registers and treatment cards), to undertake quarterly and countrywide supervision especially during the rainy season and to ensure a high quality delivery of services. In more recent times, the huge expansion of ART clinics, substantial annual increases in people initiating ART and a diversification of antiretroviral therapy regimens has put a strain on the procurement and distribution system for antiretroviral therapy drugs. Nevertheless, maintaining uninterrupted drugs supplies is a top priority for the ART programme. The April to June 2015 HIV report indicated that less than 2 % of ART sites experienced stock-outs for that quarter, with these stock-out events typically affecting small peripheral sites and usually being of short duration as a result of the bi-monthly scheduled distribution cycle and the ad-hoc stock relocation facility coordinated through a toll-free supply hotline [4].

During those early years, all countries in sub-Saharan Africa were tasked with the challenge to rapidly scale up ART in a context of limited resources. In order to share experiences with its neighbours, the HIV Department and its implementing partners presented on progress with national scale-up along with successes and challenges at international conferences, at meetings and committees convened by the WHO and in peer-reviewed publications [17, 18]. Data collected from the routine monitoring systems were used to show how ART scale up was benefiting the health sector in terms of reducing morbidity and mortality in health care workers and to support the quarterly supervision to all ART sites to ensure good quality data [19, 20]. A demographic surveillance survey in northern Malawi showed a significant reduction in mortality amongst adults within a year of offering ART services [21], and similar findings were observed through a more operational research study in the southern part of the country [22].

Using operational research to learn while doing

As there was no programmatic guidance from the WHO during these first few years of ART scale-up, Malawi undertook a number of operational research studies to generate local evidence to support activities and interventions around some key areas [23].

Cotrimoxazole preventive therapy

The high early mortality being documented for patients starting ART was of national and international concern [24]. While the efficacy of cotrimoxazole preventive therapy in reducing early mortality had been demonstrated in randomized trials [25], the routine use of this adjunctive treatment in the field was limited. An operational study implemented at ART clinics around the country showed that cotrimoxazole preventive therapy, given before or with ART, significantly reduced this early mortality [26]. The presentation of these data, along with additional evidence from other studies in Africa, led to a national policy decision that cotrimoxazole preventive therapy should always be given and continued indefinitely in any person starting ART: this policy was included in the second edition of the Malawi ART Guidelines [27], and formed part of the evidence base for the WHO 2006 guidelines on cotrimoxazole prophylaxis [28].

Task shifting and decentralisation

As ART scale up progressed, the need for increased expansion of services to rural areas became a priority among stakeholders. After much discussion, the medical and nursing councils of Malawi (who have regulatory responsibility and lay down the terms of reference for what doctors, paramedical officers and nurses can and cannot do) authorized nurses to initiate ART and the decision was made to extend HIV treatment services to peripheral health centres. This policy of task shifting and decentralisation was reflected in the third edition of the Malawi ART Guidelines in 2008 [29]. Subsequent operational research at health centres where nurses initiated ART showed that this policy was feasible and effective with treatment outcomes as good as those achieved from district hospitals [30, 31]. This evidence, which came several years ahead of formal evidence from randomized trials [32], helped to inform early WHO guidance on task shifting [33]. Subsequent experience in Malawi piloting less frequent clinic visits for stable patients on ART to reduce the clinic workload also informed the 2016 revision of the WHO ART guidelines [34].

Electronic medical record systems

While the national monitoring and reporting system initially performed well at facility and national level, it was essentially paper-based, and in busy clinics the rapidly growing cumulative burden of patients registered for ART threatened to overwhelm the capacity to collect, collate and analyse data on a quarterly basis. For busy sites with over several thousand patients cumulatively registered for ART, the tasks to manually count characteristics and outcomes for each individual patient took several days to perform each quarter and began to detract from patient care. The need for an electronic medical record system for use in busy clinics became an urgent imperative.

In 2005 a task force created by the HIV Department investigated the feasibility of introducing computers to capture patient data and produce cohort reports at ART clinics. Two electronic medical record system models were considered. The first model employed a dedicated clerk to enter patient information retrospectively from patient treatment cards to a single desktop computer. The second comprised computers in every clinic room, connected to a central server that stored the data. With the second model, designed by a local non-governmental organization called Baobab Health Trust, healthcare workers used simple, robust, touchscreen computers to enter patient information during clinical encounters at the point of care. Based on experiences of using these touchscreen systems in various domains in healthcare in Malawi since 2001, the task force chose the second model and established core functionality requirements for the touchscreen point of care system [35].

The system was first piloted at a busy ART clinic in a central hospital in 2005 and then rolled out to further hospital ART clinics in 2006 and 2007. Key challenges that needed to be overcome included: i) low computer literacy among target users, ii) the need for unique patient identifiers, iii) maintaining clean and reliable electrical power and iv) managing the transition from

paper to electronic-based records and accurately back-entering large numbers of paper-based treatment cards and registers. Baobab Health Trust approached and solved each of these challenges using hardware and software innovations [35].

On-going challenges include validating the accuracy of data in the electronic medical record system, the quarterly production of complete and accurate cohort reports, the logistics of nationwide supervision and the immediate attention needed when the computer-based systems become dysfunctional at a clinic. Despite these challenges, the system has been gradually scaled up and by 30th June 2015, a total of 495,974 patients had ever been registered for ART through electronic medical records at 60 government clinics throughout the country.

Malawi and Option B+

In 2010, guidance was issued from the WHO on prevention-of-mother-to-child-transmission of HIV (PMTCT) [36]. It was recommended that HIV-infected pregnant women have their CD4 cell count assessed. Women with a CD4 cell count < 350 cells/mm^3 or who were clinically immune suppressed based on WHO clinical staging were to start life-long ART for their own health while asymptomatic women with a CD4 count ≥350 cells/mm^3 were to be offered Option A (maternal zidovudine + infant antiretroviral therapy prophylaxis) or Option B (maternal triple antiretroviral therapy prophylaxis). This PMTCT strategy depended on countries having capacity to carry out CD4 testing for all HIV-infected pregnant women.

Malawi was requested to conduct a feasibility appraisal of this new guidance. The weak laboratory infrastructure in the country meant that CD4 count capacity was severely limited: for example, in quarter 4, 2010, only 60 out of 417 ART clinics in the country had a CD4 machine of which only 53 produced any results in that 3-month period [37]. Furthermore, antenatal care as the main point of diagnosis and management for HIV-infected pregnant women was highly decentralized and over 50 % of women needing PMTCT were seen at peripheral health centres. Option B (with triple ART taken from 14 weeks gestation to 1 week after all exposure to breast milk had ended) was the logical choice to keep procurement and distribution streamlined and drug administration manageable for peripheral health care staff. However, total fertility rate in Malawi was high at 5.6 births per women with a median duration of breastfeeding for each woman of 23 months [38]. Soon after the breastfeeding period had finished ART would be stopped, but many women would soon become pregnant again needing to restart ART. This stop-start approach to ART did not make sense programmatically. Nor did it make sense clinically as there was also evidence that CD4+ count guided interruption of ART was associated with increased morbidity and an increased risk of death [39].

The country therefore proposed a new strategy to offer all HIV-infected pregnant women lifelong ART regardless of WHO clinical stage or CD4 cell count, named Option B+ [38]. The rationale, the implementation and benefits of such a strategy have been evaluated in several studies and are shown in Table 3 [40–42]. This proposal was translated to national policy and implemented in Malawi in July 2011 [43]. The optimal delivery models for Option B+ in different settings are the subject of ongoing operational research to ensure high uptake and retention in care [44, 45].

Despite limited evidence of efficacy, the WHO incorporated Option B+ into its 2012 programmatic update on treating pregnant women and preventing HIV infection in infants [46], and then into its 2013 consolidated ART guidelines [47]. For programmatic and operational reasons, especially in generalized epidemics, a conditional recommendation with low quality evidence was made that all pregnant and breastfeeding women with

Table 3 Advantages of Option B+ in Malawi

Advantage	Explanation
Simple to implement	One tablet a day of TDF + 3TC + EFV for the woman with NVP infant prophylaxis for 6 weeks. Reinforces the nationwide message that ART is taken for life; procurement and distribution needs for the country made easier compared with having Option A or Option B.
Reduced vertical transmission from mother to child	For current pregnancy ART offers protection from time of administration and is continued in breast feeding period. For future pregnancies, ART offers protection from time of conception.
Avoids stop-start ART	Interrupted ART has risks for increased morbidity and mortality.
Improved maternal health and survival	Post-partum women in Zimbabwe with CD4 count > 350 cells/mm^3 have an elevated risk of death six times higher than non-infected women [40].
Reduced sexual transmission of HIV to discordant couples	HIV-infected persons on ART have significantly reduced risk of HIV transmission through sexual intercourse to non-infected partners even at high CD4 cell counts [41].
Reduced risk of tuberculosis	ART reduces the risk of tuberculosis in people living with HIV, even at high CD4 cell counts [42].
Treats hepatitis B infection	Tenofovir and lamivudine are active against hepatitis B virus, and about 15 % of people living with HIV in Malawi are also infected with hepatitis B.

ART antiretroviral therapy, *HIV* human immunodeficiency virus, *TB* tuberculosis, *TDF* tenofovir, *3TC* lamivudine, *EFV* efavirenz, *NVP* nevirapine

Table 4 Evolution of national and international guidance, and supporting evidence

Policy	Year of implementation in Malawi	Year recommended by WHO	Supporting evidence from randomized trials or systematic reviews
Lifelong cotrimoxazole preventive therapy	2006	2006 WHO Cotrimoxazole Guidelines [28]	Reference [51]
Task shifting for the delivery of ART	2003	2008 WHO Guidelines for task shifting [33]	References [32, 52]
Decentralization of ART delivery	2003	2013 WHO Consolidated Guidelines [47]	References [53, 54]
PMTCT Option B+	2011	2012 WHO Programmatic Update [46]	None
		2013 WHO Consolidated Guidelines [47]	

ART antiretroviral therapy, *PMTCT* prevention of mother to child transmission of HIV

HIV should initiate ART as lifelong treatment. The policy, probably because of its simplicity and potential for rapid scale up, was taken up quickly by countries, with the majority of countries adopting PMTCT Option B+ within 2 years [48]. Subsequent WHO guidelines released in late 2015 [49] and the new guidance in 2016 [34] recommend Option B+ as the preferred way to prevent mother-to-child transmission, to supersede all previous options. A recent evaluation of the first 3 years of Option B+ in Malawi has found that the risk of loss to follow-up during the third year is low and similar for patients retained for 2 years, with retention remaining stable as the Option B+ programme has matured [50].

Conclusion

The role of national policy initiatives as the driver for international policy development can rarely be established with certainty. Malawi's practical and pragmatic approach to developing national ART guidelines that acknowledged health system weaknesses and services needed to deliver and monitor treatment was well received by the international community. The national quarterly reports on all patients in the country being registered for ART along with censured standardised quarterly outcomes were unique in the early phases of scale up [18]. Malawi's public health stance to ART scale-up was adapted to its resource-poor setting, and despite pressure from both within and outside Malawi to use advanced laboratory technology to support the initiation and continuation of ART, this was resisted in favour of a more clinical and programmatic outcome orientated approach. This allowed a rapid and successful countrywide scale up, opened up the possibilities of decentralization and task shifting and paved the way for Option B+ 7 years after the first steps in ART delivery were taken.

Table 4 illustrates this evolution of national and international guidance along with the supporting evidence, further demonstrating that Malawi implemented interventions based on local evidence and context often long before there was supporting data from randomized trials and before WHO had released its international guidance [28, 32, 33, 46, 47, 51–54].

The launch of the new WHO Guidelines in 2015 recommending that ART be initiated in everyone living with HIV at any CD4 count and that daily oral pre-exposure prophylaxis be offered to anyone at substantial risk of HIV infection as part of combination prevention approaches will significantly impact global public health [49]. These recommendations form part of the revised consolidated guidelines on the use of ARV drugs to treat and prevent HIV infection published by WHO in 2016 [34], and these will facilitate the achievement of UNAIDS Fast-Track targets for 2020 [55].

Malawi had already formulated a "test and treat" approach in its' new national strategic plan, with implementation planned for 2016. It will be a major undertaking and one for which core principles such as uninterrupted drug supplies, patient adherence to therapy and compliance with follow-up will be needed for success, not only in Malawi but globally as well.

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Authors' contributions

ADH wrote the first draft of the manuscript to which all other authors (NF, AJ, EJS, EL, FC and DM) contributed. All authors (ADH, NF, AJ, EJS, EL, FC and DM) contributed to subsequent drafts and revisions of the paper in response to editorial and reviewer comment. All authors read and approved the final paper for submission. All authors are responsible for the views expressed in this paper and they do not necessarily represent the decisions or policies of their institutions.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

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Ethics approval and consent to participate

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Viewpoint

Keeping health facilities safe: one way of strengthening the interaction between disease-specific programmes and health systems

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Summary The debate on the interaction between disease-specific programmes and health system strengthening in the last few years has intensified as experts seek to tease out common ground and find solutions and synergies to bridge the divide. Unfortunately, the debate continues to be largely academic and devoid of specificity, resulting in the issues being irrelevant to health care workers on the ground. Taking the theme 'What would entice HIV- and tuberculosis (TB)-programme managers to sit around the table on a Monday morning with health system experts', this viewpoint focuses on infection control and health facility safety as an important and highly relevant practical topic for both disease-specific programmes and health system strengthening. Our attentions, and the examples and lessons we draw on, are largely aimed at sub-Saharan Africa where the great burden of TB and HIV/AIDS resides, although the principles we outline would apply to other parts of the world as well. Health care infections, caused for example by poor hand hygiene, inadequate testing of donated blood, unsafe disposal of needles and syringes, poorly sterilized medical and surgical equipment and lack of adequate airborne infection control procedures, are responsible for a considerable burden of illness amongst patients and health care personnel, especially in resource-poor countries. Effective infection control in a district hospital requires that all the components of a health system function well: governance and stewardship, financing, infrastructure, procurement and supply chain management, human resources, health information systems, service delivery and finally supervision. We argue in this article that proper attention to infection control and an emphasis on safe health facilities is a concrete first step towards strengthening the interaction between disease-specific programmes and health systems where it really matters – for patients who are sick and for the health care workforce who provide the care and treatment.

keywords health systems, disease-specific programmes, HIV/AIDS, tuberculosis, infection control

Introduction

At the recent XVIII International AIDS Conference in Vienna in July 2010, there was a well-attended 2-day pre-conference symposium entitled 'Bridging the Divide: Inter-disciplinary partnerships for HIV and Health Systems'. There were excellent presentations and much debate on global policy and the importance of strengthening health systems. Amongst some of us, however, there was a growing, unspoken concern regarding the need for concrete action to move this agenda forward, and we began to think about how we might translate the rhetoric into reality in the context of a district hospital or a health centre in a low-income country. Pertinent questions arose from attendees, two of which struck a cord with our concerns: '*Based on all the discussions, what would we do differently tomorrow?*'

and '*What on a Monday morning would entice HIV- and tuberculosis (TB)-programme managers to sit around the table with health system experts?*'

Long before this symposium was held, there had been much talk and writing on the interaction between health systems and disease-specific programmes, and the synergies and antagonisms of the effects of one in relation to the other (WHO Maximizing Positive Synergies Collaborative Group 2009). There are claims that disease-specific programmes overburden health systems that are already fragile in countries with few resources, and that they do not contribute to the strengthening of these systems. Others counter that weak health systems prevent progress in meeting disease-specific targets, and that disease-specific programs can contribute to strengthening health systems through their focus on specific outcomes (Ooms *et al.* 2008). The areas of mutual interest, the challenges and the solutions in this whole debate focus around the intersection between specific programmes and key components of the health system including governance and stewardship, financing, infrastructure development, procurement and supply chain management, human resources, health information systems, service delivery and supervision (Harries *et al.* 2009; Atun *et al.* 2010). The debate tends to be academic, largely focusing on international and national policy issues.

However, at the service delivery end of the spectrum in the context of HIV and TB programmes, one subject that epitomizes the intersection between disease-specific programs and the health system is infection control, an issue of critical importance for the safety of patients and health care workers. The issue of infection control is not new. In 1847, Ignaz Semmelweis, a Hungarian physician, showed that puerperal fever, a common cause of maternal mortality in the 19th century, could be drastically reduced by the simple means of hand washing with chlorinated lime solution in obstetric clinics (Semmelweis 1861). With the acceptance of Semmelweis's practice years after his death, puerperal fever is now an uncommon disease, even in resource-poor countries. However, the subject of infection control remains a crucial area of health care provision, especially in resource-poor countries in sub-Saharan Africa, and one which we think can help to strengthen the interaction between communicable disease programmes and health systems at the health facility level. In this paper, we enlarge on this theme. We highlight the risk of infections for patients and health workers attending health facilities, then outline the essential components for making infection control work in health facilities and finally conclude that infection control collaboration between HIV and TB programmes and health systems is the first step towards a broader framework that aims to strengthen health systems across general medicine, paediatrics, surgery and maternal health.

Risks of infection for patients and health care workers

At any one time, health care associated infections affect about 1.5 million people worldwide (Morris 2008). Around 5–10% of patients in hospitals in developed countries acquire health-care associated infections, the risks being considerably higher in poorer countries (Morris 2008). Examples of health care infections include the spread of methicillin-resistant *Staphylococcus aureus* and *Clostridium difficile*-related diarrhoea (most commonly as a result of poor hand hygiene practices), infection with HIV and hepatitis (as a result of low rates of testing donated blood, the re-use of syringes and needles or occupational needle-stick injuries), and nosocomial spread of *Mycobacterium tuberculosis* (as a result of poor airborne infection control).

In 2007, an estimated 85 million blood donations were given globally, yet 41 of 162 countries reported being unable to screen donated blood for one or more of the following infections: HIV, hepatitis B, hepatitis C and syphilis. Moreover, only 40% of blood donations in low-income countries were screened after basic quality assurance procedures (WHO, UNAIDS, UNICEF 2009). In Kenya, erroneous laboratory practices were cited as one of the most important causes of blood transfusion-related HIV transmission (Moore *et al.* 2001). Occupational needle stick injuries in nurses and surgeons are common throughout Africa, as a result of lack of safety devices or poor disposal mechanisms, and furthermore, there is a paucity or poor uptake of programmes offering post-exposure prophylaxis for those exposed to HIV or hepatitis B in this way (Newsom & Kiwanuka 2002; Van Oosterhout *et al.* 2009).

Health facility-based TB transmission is an important public health problem, exacerbated by the HIV/AIDS epidemic and the emergence of multidrug- and extensively drug-resistant TB. In areas of high HIV prevalence, HIV-related TB accounts for a large proportion of all admissions and outpatient consultations, resulting in intense risk for TB transmission within congested, poorly ventilated facilities (Corbett *et al.* 2007; Shenoi *et al.* 2010). Patients, especially those with HIV, who attend for long-term care almost certainly become exposed to appreciable, but generally unrecognized, levels of *Mycobacterium tuberculosis* in health facilities (Bock *et al.* 2007). This exposure in turn leads to infection and progression to TB disease. Health care workers are particularly at high risk of *Mycobacterium tuberculosis* and TB disease (Menzies *et al.* 2007). This can result in considerable morbidity and mortality (Harries *et al.* 2002), deepening the already

severe human resource crisis in low- and middle-income countries as well as creating fear and reluctance by health care workers to be assigned to HIV programs. Box 1 highlights some examples of infection risk at the health facility, the collaborative interventions and the mutual benefits that can be gained by both specific disease-control programs and health systems.

Making infection control work in health facilities

For infection control to work effectively in a district hospital or health centre and for the facility to become as safe as possible for patients and health-care workers, all the accepted building block components of a health system have to function well.

Box 1 Infection risk at health facility, collaborative interventions and mutual benefits for both disease control programs and health systems

Type of infection risk at health facility	Collaborative interventions	Mutual benefits
Spread of methicillin resistant *Staphylococcus aureus* and *Clostridium difficile* related diarrhoea	Provision of water sinks, soap and towels in out-patient and inpatient facilities	Encouragement of basic practice of hand-washing by health workers Reduced nosocomial transmission of infection to patients and health workers Reduction in hospital burden in terms of prolonged bed occupation and costs related to isolation and management of infected cases
Unscreened blood transfusions – risk of HIV, hepatitis B and C and syphilis	Procurement and uninterrupted supplies of rapid tests for screening	Improvement in quality standards of laboratory services Reduced transmission of infection to patients, health workers and their families Reduction in long term case load of HIV and chronic liver disease on health systems Improved trust and credibility of health services
Unsterile syringes, needles and medical or surgical equipment – risk of HIV and hepatitis B and C	Procurement and provision of adequate quantities of single use syringes and needles Provision and maintenance of sterilization equipment	Improvement in general standards of health facility hygiene Reduced morbidity associated with improved prevention Improved trust and credibility of services in key areas like vaccination and surgery
Health facility acquired tuberculosis (TB)	Improve cough etiquette and respiratory hygiene Improve patient-flow organization to reduce patient congestion Improve natural ventilation in hospital waiting rooms, consultation rooms and wards Systematic screening of health workers for TB on a scheduled basis Isoniazid preventive treatment for HIV positive health workers to prevent TB Antiretroviral treatment for eligible HIV-positive health workers	Improved patient and health worker friendly services Reduced health worker morbidity, mortality and attrition related to TB Reduced health worker absence from services because of TB and HIV Reduced risk of developing TB by both health workers and patients
Unsafe disposal of hospital generated waste – risk of sharp injury, secondary bacterial infections, HIV and hepatitis B and C	Set up a hospital waste management committee Set up a system for collection and disposal of waste Build incinerators and waste and needle disposal pits Make post exposure prophylaxis for HIV available	Cleaner and more pleasant hospital premises and facilities for both patients and health workers Reduce risk of injury and infections linked to sharps

Governance and stewardship: A multidisciplinary, infection control committee should be set up to provide the necessary guidance and accountability for local policy, plans, staff training, resource mobilization and reporting. Representation on the committee should be decided by the health facility, with guidance from the Ministry of Health, and could include clinical staff, nurses, laboratory and radiographic staff, administrative personnel as well as the community and people living with HIV.

Budgets from disease-specific programmes and district health allocations should be used in a coordinated manner to ensure sufficient financial support for specific activities. These could include (i) uninterrupted supplies of HIV, hepatitis and syphilis test kits for blood donations, (ii) installation of working sinks and purchase of soap and towels for hand hygiene, (iii) provision of fans and masks for appropriate airborne protection, and (iv) safety devices, proper waste disposal boxes for needles and syringes and functioning autoclaves for sterilizing surgical and medical equipment. Renovations or alterations to existing infrastructure might be necessary to improve control of airborne infection, and new infrastructure might be needed, for example to build guardian shelters so that relatives can cook and prepare food for their sick relatives allowing the wards to be kept free of smoke and cooking utensils.

In many low-income settings, a priority must be to prevent airborne TB transmission. Natural ventilation offers the most attractive and cost-effective tool for this (Escombe *et al.* 2007). More than 12 air changes per hour (the standard of care for preventing respiratory transmission of TB) can be achieved by open windows and doors, enlarged or additional windows (with attention to cross-ventilation), open sky-lights and the rebuilding of waiting rooms to make them open air, if appropriate. These renovations need not be costly and indeed provide much higher airflows than costly mechanical ventilation systems, which often function sub-optimally because of poor maintenance.

In many resource-poor countries, laboratory conditions and safety procedures are poor, particularly in relation to the diagnosis of TB, and there is therefore a need for more emphasis on standard operating procedures, education, training and supervision of staff to ensure that any policy guidelines that are produced are indeed acted upon (Nyirenda *et al.* 1998).

Attention must also be paid to other infections. For example, in malaria endemic areas, adult and children's beds in hospital wards should be fitted with insecticide-treated bed nets to avoid transmission in the health care setting. Safe waste disposal is a cross-cutting issue needing infrastructure, procurement and finances, and involves strategies for collection, transport and disposal at all levels of the health facility. Waste includes consumable materials such as syringes, needles and sputum containers as well as degradables such as food, laboratory specimens and placental tissue.

Procurement and supply chain management: An irregular supply of HIV and hepatitis test kits is an important barrier that prevents many low- and middle-income countries from screening blood collected for donations. Procurement of antiretroviral treatment (ART) for post-exposure prophylaxis is critical for protecting health care workers from HIV in the event of needle-stick injuries, although considerable advocacy and education are also needed to ensure that post-exposure prophylaxis is well utilized by the health workforce (Van Oosterhout *et al.* 2009). TB infection control practices depend on early case finding and timely treatment initiation in patients diagnosed with TB. Stock-outs of sputum containers, smear microscopy equipment (slides, reagents, functioning microscopes) and anti-tuberculosis drugs can severely hamper these efforts. Uninterrupted supplies are the key to sustaining important case finding and treatment activities.

Human resources: The world has a massive shortage of health workers, and no more so than in sub-Saharan Africa where an estimated 752 000 doctors and 670 000 nurses are needed to fill the gap between health care worker availability and health system needs (Hongoro & McPake 2004). There are various reasons for this workforce crisis, but low training capacity, poor working conditions, migration out of the health sector or out of the country and illness and death are the most important. Occupational health thus becomes a crucially important health system activity, demonstrating commitment to the well-being of the workers, both to ensure that health-care workers are given priority for health care protection and treatment and to further encourage their retention in the health system. Key interventions could include: offering HIV testing and the option for health workers who are HIV-infected to transfer to parts of the health facility that are at low risk of TB transmission; packages of care and treatment, including isoniazid preventive therapy for those heavily exposed to *Mycobacterium tuberculosis* and ART for health care workers who are HIV-infected (Makombe *et al.* 2007); and ART for occupational post-exposure prophylaxis.

Regular, reliable and timely collection and analysis of data is crucial for monitoring infection control. For the health care workforce, there are various indicators that could be measured. One of the agreed indicators for infection control measures in collaborative TB/HIV activities is the number of health care workers in a health facility who develop TB in the course of 1 year (WHO & UNAIDS 2009). This information requires an up-to-date inventory of health care workers in a given health facility

(as the denominator) and a registry to record data on occupational injuries such as needle sticks while on the ward or while performing surgery, the occurrence of serious diseases such as TB and HIV/AIDS and whether these have been treated with anti-tuberculosis drugs and ART, and finally deaths. Regular, timely data on the local health care workforce could help to empower a health facility with managing its human resource challenges. Measuring infection control in patients may be a more difficult task, but indicators could include measures of the number of surgical or obstetric infections occurring in the wards over time.

Service delivery: TB infection control depends on early identification, isolation and rapid initiation of effective treatment of tuberculosis suspects combined with good organization to avoid congestion and ensure appropriate patient-flow within facilities (WHO 2009). Nowhere is this more important than in HIV care clinics, where all patients either on ART or pre-ART should be screened for symptoms of TB whenever they come to the health facility. Health care staff need to focus on controlling the spread of airborne pathogens, by emphasising cough etiquette and respiratory hygiene, and ensuring that time spent admitted in healthcare facilities is minimized. Wherever possible, people living with HIV should be kept away from patients with suspected TB until TB treatment is initiated with evidence of response to such treatment. HIV infection control depends on use of universal precautions by health care workers, and appropriate safety procedures for handling of blood and body fluids.

None of the activities highlighted above, including the routine collection of data, will function unless there is regular supervision and review from within and without the health facility. Quarterly supervision, monitoring and evaluation of case finding and treatment outcomes in National TB Control Programmes has always been an essential component of the DOTS policy package, and this practice has been successfully extended to HIV care and treatment programmes as well (Libamba *et al.* 2006). Infection control committees would need to clearly dictate how these supervision activities are organized and implemented, with an important component being both positive and negative feedback to those responsible for infection control policy and practice within the health facility.

Conclusion

For health care workers in different disciplines in a busy district hospital or health centre to gather around the table on a Monday morning requires a topic of mutual interest, importance and relevance. Infection control and health facility safety fulfil these criteria, both for the health care worker fraternity and the constituency of patients who utilize the facility. Infection control fills the void, and provides relevant issues for discussion that require local leadership, a sound understanding of disease epidemiology, clarity of thought, community inputs and a pragmatic approach to finding solutions. Health systems cannot and should not be discussed in the abstract. They have to exist to optimally deliver services for real people, and they have to prevent and treat diseases that have names, such as TB and HIV/AIDS (El-Sadr & De Cock 2009). A focus on infection control provides the necessary specificity, the exemplary practice of which requires that all components of the health system function. This offers a first concrete start to bridging the current divide between disease-specific programs and health systems. It paves the way for a more comprehensive framework that embraces general medicine, paediatrics, surgery and maternal health and that takes into account other issues such as hospital antibiotic policy, hospital-acquired pneumonia, general hygiene, food hygiene and hospital laundry services. Without attention to infection control, hospitals risk again becoming regarded as places where you enter with one infection only to exit with another, and regressing backwards to those dark days in the 19th century when Ignaz Semmelweis dared to point the finger. In the 21st century we surely can do better.

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

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Abstract

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

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

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

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

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Background

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

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

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

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

In Adults:

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

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

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

In Children:

Cotrimoxazole should be offered to children in the following circumstances:

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

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

Reference [30]

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

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

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

Lessons learnt

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

Contextual placement of operational research within a programme setting

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

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

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

Disseminating and publishing results

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

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

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

MoH = Ministry of Health; ART = antiretroviral therapy

Translating research into policy and practice on the ground

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

Assessing the impact on programme performance

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

Summary

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

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

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

Ethics Statement

An ethics statement was not required for this work.

List of abbreviations used

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

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Authors' contributions

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

Competing interests

The authors declare that they have no competing interests.

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RESEARCH ARTICLE Open Access

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

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Abstract

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

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

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

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

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

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Background

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

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

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

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

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

Methods

Study area and study design

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

Study setting

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

Eligibility of study participants

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

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

Recruitment of study participants

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

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

Data collection

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

Data management and analysis

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

Ethical considerations

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

Results

Sociodemographic characteristics of study participants

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

TB-related conditions

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

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

Characteristics (variables)	Cases (n = 134)		Controls (n = 134)	
	Number	Percentage	Number	Percentage
Sex				
Male	81	60.5	64	47.5
Female	53	39.5	70	52.5
Age at the time of first anti-TB treatment (years)				
5–25	85	63.4	47	35.1
26–45	40	29.9	70	52.2
46–72	9	6.7	17	12.7
Marital status				
Single	85	63.4	60	44.8
Married	32	23.8	56	41.8
Divorced	16	11.9	9	6.7
Widow/widower	1	0.75	9	6.7
Educational status				
Up to fourth grade	15	11.2	25	18.6
Completed 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

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

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

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

Treatment-related conditions

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

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

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

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

Results from logistic regression analysis

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

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

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

Discussion

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

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

Characteristics	Case Number	Control Number	Crude OR (95% CI)	Adjusted OR (95% CI)
Individually adjusted for the remaining variables				
Number of pulmonary TB episodes				
One	29	119	1	1
Two or more	105	15	28.7 (14.6-56.5)	31.8 (8.7-115.5)
Ever interrupted anti-TB for at least a day				
No	41	124	1	1
Yes	93	10	28.1 (13.4-58.1)	13.1 (3.0-56.6)
Duration of first course of TB treatment (months)				
2–7	25	3	10.0 (2.9-34.1)	14.8 (2.3-96.4)
≥8	109	131	1	1
Adjusted for all variables				
Age when taking first-line anti-TB for the first time (years)				
46–72	9	17	1	1
26–45	40	70	1.1 (0.4-2.6)	1.4 (0.3-5.8)
5–25	85	47	3.4 (1.4-8.3)	4.6 (1.1-20.5)
Marital status				
Single	85	60	2.5 (1.4-4.3)	1.2 (0.5-3.3)
Married	32	56	1	1
Divorced/ separated	17	1	1.7 (0.75-3.7)	3.1 (0.7-13.2)
Educational status				
Up to fourth grade	15	24	1	1
Completed 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)
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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The yield of a tuberculosis household contact investigation in two regions of Ethiopia

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SUMMARY

SETTING: Amhara and Oromia regions, Ethiopia.

OBJECTIVE: To determine the yield of a household contact investigation for tuberculosis (TB) under routine programme conditions.

DESIGN: Between April 2013 and March 2014, TB clinic officers conducted symptom-based screening for household contacts (HHCs) of 6015 smear-positive TB (SS+ TB) index cases. Based on quarterly reported programme data, we calculated the yield in terms of number needed to screen (NNS) and number needed to test (NNT).

RESULTS: Of 15 527 HHCs screened, 6.1% had presumptive TB (8.5% in Oromia vs. 3.9% in Amhara). All forms of TB and SS+ TB were diagnosed in respectively 2.5% (Oromia 3.9% vs. Amhara 1.2%) and 0.76% (Oromia 0.98% vs. Amhara 0.55%) of contacts. The NNS to detect a TB case all forms and SS+ TB was respectively 40 and 132. The NNT to diagnose a TB case all forms and SS+ TB was respectively 2.4 and 8. Of 1687 eligible children aged <5 years, 323 were started on isoniazid preventive therapy.

CONCLUSIONS: The yield of the household contact investigation was over 10 times higher than the estimated prevalence in the general population; household contact investigations can serve as an entry point for childhood TB care.

KEY WORDS: index case; systematic screening; active case finding

PROGRESS HAS BEEN MADE WORLDWIDE in reducing the incidence of tuberculosis (TB) and associated deaths, mainly through passive case finding.[1] Active case finding is needed as an additional strategy to identify and treat the many missed cases of TB, which accounted for an estimated one third of all TB cases reported in 2012.[2] About 75% of these are concentrated in 12 countries, including Ethiopia.[2] Systematic screening for TB among close contacts of index cases is one of the strategies recommended to identify these cases.[3,4] Experience with household contact investigation is limited, but screening other high-risk groups contributed 1–9% of adult cases in five studies.[3–5]

Two systematic reviews of studies on household contact investigations in low- and middle-income settings showed that respectively about 4.5% and 3.1% of contacts were found to have active TB.[6,7] The median number of household contacts evaluated to find one case of active TB was 19 (range 14–300). The median proportion of contacts found to have latent tuberculous infection (LTBI) was just over 50% in both studies. The median number of contacts evaluated to find one person with LTBI was 2 (range 1–14). In the review by Fox et al., longer-term follow-up showed that TB incidence remained above the background rate for at least 5 years.[7] Evidence from these reviews and other studies suggests that contact investigation in high-incidence settings is a high-yield strategy for case finding.[8–10] Based on the available evidence, the World Health Organization (WHO) has developed guidance on contact investigation which extends to high-risk groups other than children aged <5 years and people living with the human immunodeficiency virus (PLHIV).[11] Other key international guidelines also recommend contact investigations.[12,13]

Operationalising this guidance requires experience in low-income, high TB burden settings. A few studies from sub-Saharan African countries have looked at the yield of contact investigation, and experience of nationwide implementation was reported from Morocco.[14,15]

Ethiopia's national TB guidelines provide a policy framework for contact investigation; however, these have not been adequately implemented.[16] Earlier reports from Ethiopia were limited to specific population groups and some geographic areas.[17,18]

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In the present paper, we present data on the yield of contact investigation in a large TB project in two regions of Ethiopia. Our objective was to report on the yield of contact investigation under routine programme conditions in a low-income, high TB burden setting.

METHODS

Study setting

With a population of almost 88 million, Ethiopia is the second most populous country in Africa; more than half of the Ethiopian population lives in the two regions of Amhara and Oromia, where this study was carried out.[19] As one of the 22 high TB burden countries, Ethiopia has an estimated TB prevalence rate of 247 per 100 000 population. The proportion of multidrug-resistant TB (MDR-TB) among new and previously treated cases was respectively 2.7% and 17.8% (unpublished data, Ministry of Health, 2014). Table 1 summarises key health and TB data for Ethiopia.

Donor-funded projects contribute a significant share of Ethiopia's health care financing.[25] The Federal Ministry of Health and the Regional Health Bureaux of Amhara and Oromia regions, in partnership with the Help Ethiopia Address the Low TB Performance (HEAL TB) Project, have been implementing a comprehensive TB prevention and control programme that includes contact investigation in the two regions since July 2011. All services were free and available in 2186 health centres and 64 hospitals in HEAL TB-supported regions.

Contact investigation procedure

In each zone of the two regions, HEAL TB assigned a clinical officer and laboratory expert who provided technical guidance and support to zonal and *woreda* (equivalent to district) TB officers on all aspects of TB care, including contact investigation. The team developed and disseminated standard operating procedures for contact investigation to participating health facilities; oriented zonal, woreda and health facility TB focal persons on contact investigation; and supplied the health facilities with registers and job aids. Woreda TB focal persons then conducted supportive supervision and monitored progress by instituting a quarterly reporting mechanism for contact investigation. Participating facilities attended quarterly and semi-annual review meetings at the zonal and subnational levels to review programme performance, identify gaps and develop corresponding action plans.

After obtaining informed verbal consent, TB clinic officers asked each newly diagnosed smear-positive TB (SS+ TB) patient to provide the names and contact details of each household member and recorded the information in the health facility contact register. On registration with the TB clinic, each index case was counselled to bring family members to the health facility for screening. At the clinic, the TB clinic officer screened family members for symptoms using the following criteria for presumptive TB: any household contact with a history of cough for $\geqslant 2$ weeks or with two or more constitutional symptoms suggestive of TB was considered to have presumptive TB. Presumptive TB cases with productive cough were referred for sputum examination by laboratory technicians using Ziehl-Neelsen or fluorescent light-emitting diode microscopy. Patients presumed to have smear-negative (SS–) TB, with persistent respiratory symptoms or extra-pulmonary TB, underwent additional investigations, including chest radiography and pathology, mainly in a hospital setting.

We defined an index case as the initially identified case of new or recurrent SS+ TB around whom a contact investigation was carried out. A household contact was a person who shared the same enclosed living space for $\geqslant 1$ nights or for frequent or extended periods during the day with the index case during the 3 months before the current treatment episode began.[11,26]

Data collection and analysis

Data were collected through the routine programme monitoring system using the contact register. The following variables were recorded: health facility and index cases, type of TB and treatment initiation date, age, household contacts, diagnostic results of close contacts, and treatment and prophylaxis status of contacts. The woreda TB focal person compiled all contact investigation data quarterly and submitted them to the zonal TB focal person. We aggregated the data at the regional and project levels using Excel (MicroSoft, Redmond, WA, USA). We calculated the yield of contact investigation in terms of number needed to screen (NNS) and number needed to test (NNT). NNS is the number of contacts required to be screened to detect a single case of active TB; NNT is the number of persons with presumptive TB required to be evaluated to detect a single case of active TB. We calculated the values with a 95% confidence interval (CI) using OpenEpi software (www.OpenEpi.com). $P < 0.05$ was considered statistically significant.

Ethical considerations

As routine programme data were used for this analysis, no ethics approval was sought. Contact screening was performed with full verbal consent of the patients, and information was handled confidentially. All contacts with confirmed TB received the standard anti-tuberculosis treatment regimen at health facilities. Contacts who failed to visit health facilities were encouraged to visit the nearby health facility or see a community health worker.

Table 1 Sociodemographic, health and TB data, Ethiopia, 2013–2014

Characteristic	Ethiopia	Amhara	Oromia
Estimated population, millions[19]	87 952 991	20 018 988	32 815 995
Estimated annual per capita income, $US[20]	470	—	—
Number of TB cases notified[21]	131 677	29 003	49 886
CNR for all forms of TB/100 000 population[21]	171	172	159
TB prevalence/100 000 population[22]	211		
Estimated HIV prevalence in adults[23]	1.3	1.3	0.8
MDR-TB among new cases, % (95%CI)[24]	2.3 (1.5–3.1)	—	—
MDR-TB among retreatment cases, % (95%CI)[24]	17.8 (13.3–22.4)	—	—

TB = tuberculosis; CNR = case notification rate; HIV = human immunodeficiency virus; MDR-TB = multidrug-resistant TB; CI = confidence interval.

RESULTS

Basic characteristics of study participants

Between 1 April 2013 and 30 March 2014, health facilities screened the household contacts of 6015 SS+ index cases in 627 health facilities across 21 zones in the Amhara and Oromia regions of Ethiopia. Of the 16 512 registered household contacts, 15 527 were screened (Figure). The ratio of household contacts screened to index cases was 2.5. Children aged <5 years constituted 11.2% of all screened household contacts. Only 19.2% of eligible children received isoniazid preventive therapy (IPT) (Table 2).

The yield of household contact investigation

We identified 949 presumptive TB cases, of whom respectively 389 and 118 were confirmed to have all forms TB and SS+ TB. The prevalence of presumptive TB was 6.1% (95%CI 5.7–6.5), with a higher rate in Oromia than in Amhara (8.5%, 95%CI 7.9–9.1 vs. 3.9%, 95%CI 3.5–4.4, χ^2 145, $P < 0.0001$). TB (all forms) was detected in 2.5% (95%CI 2.3–2.8) of all contacts screened; the yield was higher in Oromia (3.9%, 95%CI 3.5–4.4 vs. 1.2%, 95%CI 1.0–1.5, $P < 0.0001$). SS+ TB prevalence was 0.76% (95%CI 0.63–0.91); the rate was higher in Oromia (0.98%, 95%CI 0.8–1.2 vs. 0.55%, 95%CI 0.41–0.74; $P < 0.01$). SS+ TB constituted 30.3% of all forms of TB diagnosed; the rate was higher in Amhara than in Oromia (45.5%, 95%CI 36–55.2 vs. 25.2%, 95%CI 20.51–30.48, $P < 0.001$). However, the proportion of SS+ TB among those with presumptive TB did not differ significantly between the two regions: 14.1%, 95%CI 10.7–18.4 in Amhara vs. 11.6%, 95%CI 9.31–14.33 in Oromia (12.4% overall, $P > 0.1$).

The NNS values for presumptive TB, all forms of TB and SS+ TB were respectively 16 (95%CI 16–17), 40 (95%CI 39–41) and 132 (95%CI 131–134). The corresponding NNT values for all forms and SS+ TB were respectively 2.4 (95%CI 2.3–2.6) and 8 (95%CI 7–9) (Table 2). The yield of presumptive and all forms of TB was higher in children aged <5 years (14.1% vs. 5.1% and 3.5% vs. 2.4%, respectively); however, those aged ⩾5 years had a higher prevalence of SS+ TB (Table 3).

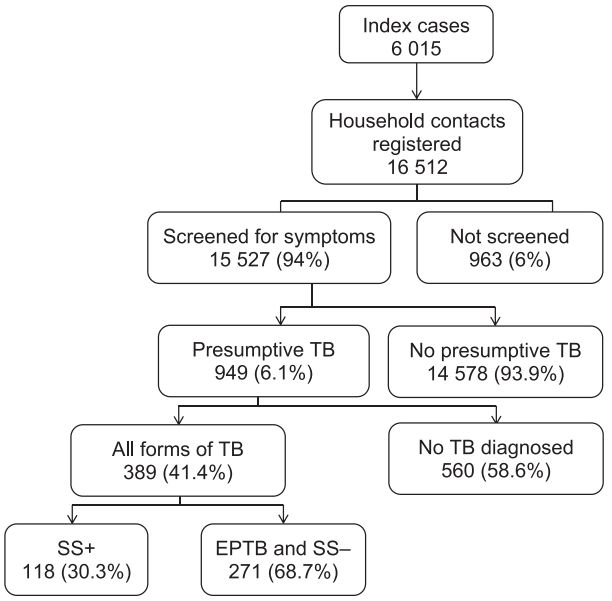

Figure Profile of contacts registered, screened and evaluated, Ethiopia, September 2014. TB = tuberculosis; SS = sputum smear; + = positive; EPTB = extra-pulmonary TB; – = negative.

DISCUSSION

In this study, we found a prevalence rate of all forms of TB among household contacts of SS+ TB index cases to be over 10 times higher than the prevalence estimate of 211/100 000 in the general population. The prevalence rate was about 18 times higher in the Oromia Region and 6 times higher in Amhara Region. The prevalence of SS+ TB, 0.76%, was about seven times higher than the prevalence estimate for SS+ TB of 0.108% in the national TB prevalence survey.[27] About six persons in every 100 household contacts had presumptive TB, with over one third of these eventually confirmed to have TB. The NNS to find a TB case was 40 and the NNT to diagnose a single case of TB was less than 3. Household contact investigations should therefore be prioritised as a high-yield strategy to improve TB case finding. Household contact investigation can also serve as an entry point for achieving high case-finding levels in children aged <15 years and high IPT coverage for children aged <5 years.

The TB prevalence of 2.5% among household

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

Characteristic	Amhara *n* (%)	Oromia *n* (%)	Total *n* (%)	*P* value
SS+ TB index cases	2 956	3 059	6 015	
Contacts screened	8 141	7 415	15 527	
Age <5 years	604 (7.4)	1 144 (15.4)	1 748 (11.2)	
Eligible for IPT	592 (98.0)	1 092 (95.5)	1 684 (96.3)	
Receiving IPT (95%CI)	133 (22.4) (19.3–26)	190 (17.4) (15.3–19.8)	323 (19.2) (17.4–21.1)	<0.01
Presumptive TB cases				
Total	319	630	949	
Contacts, % (95%CI)	3.9 (3.5–4.4)	8.5 (7.9–9.1)	6.1 (5.7–6.5)	<0.0001
NNS, *n* (95%CI)	26 (25–26)	12 (11–12)	16 (16–17)	<0.0001
All forms of TB cases diagnosed, *n* (95%CI)				
Total	99	290	389	
Contacts, % (95%CI)	1.2 (1.0–1.5)	3.9 (3.5–4.4)	2.5 (2.3–2.8)	<0.0001
Presumptive cases	31 (26–36)	46 (42–50)	41 (38–44)	<0.0001
NNS	82 (80–84)	26 (25–26)	40 (39–41)	<0.0001
NNT	3.2 (2.9–3.6)	2.2 (2–2.4)	2.4 (2.3–2.6)	<0.0001
SS+ TB cases diagnosed				
Total	45	73	118	
Contacts, % (95%CI)	0.55 (0.41–0.74)	0.98 (.8–1.2)	0.76 (0.63–0.91)	<0.01
Presumptive TB, % (95%CI)	14.1 (10.7–18.4)	11.59 (9.31–14.33)	12.4 (10.5–14.7)	>0.1
All forms, % (95%CI)	45.5 (36–55.2)	25.17 (20.51–30.48)	30.3 (26–35.1)	<0.0001
NNS, *n* (95%CI)	181 (177–185)	102 (99–104)	132 (130–134)	<0.01
NNT, *n* (95%CI)	7.08 (6.33–7.91)	8.63 (7.96–9.33)	8.04 (7.54–8.57)	<0.01

CI = confidence interval, SS+ = sputum smear-positive; TB = tuberculosis; IPT = isoniazid preventive therapy; NNS = number needed to screen; NNT = number needed to test.

contacts in our study is slightly lower than that reported (3.1%) in a recent systematic review.[7] The overall lower prevalence in our study could be attributed to the way in which the screening was organised. We did not perform house-to-house visits to identify TB among household contacts. In a high TB-HIV burden district in South Africa, for example, community-based targeted screening resulted in a TB prevalence of 6%, and most of the culture-confirmed TB cases were found among asymptomatic household contacts.[28] Moreover, as we used less sensitive diagnostic tools in our programme, the lower TB prevalence among household contacts in our study could be an underestimate, highlighting the need for more aggressive screening strategies using improved diagnostic tools. We screened 69% of the expected 3.6 family members (index cases excluded), assuming an average family size of 4.6. As the remaining family members are likely to be asymptomatic, there was a possibility of overestimating the TB yield. This might have led to some balancing effect on the above-mentioned underestimation.

Table 3 The yield of TB household contact investigation by age category, Ethiopia, April 2013–March 14

Characteristics	Age category			*P* value
	⩾5 years % (95%CI)	<5 years % (95%CI)	Total % (95%CI)	
Contacts screened, *n*				
Total	13 779	1 748	15 527	
Presumptive TB cases				
Total, *n*	702	247	949	
All screened	5.1 (4.7–5.5)	14.1 (12.6–15.8)	6.1 (5.7–6.5)	<0.0001
NNS, *n* (95%CI)	19.6 (19.3–19.9)	7.1 (6.7–7.4)	16.4 (16.1–16.6)	<0.0001
All forms of TB				
Total, *n*	325	64	389	
All screened	2.4 (2.2–2.6)	3.7 (2.9–4.6)	2.5 (2.3–2.8)	<0.001
Presumptive cases	46.3 (42.6–50.0)	25.9 (20.8–31.7)	41.0 (37.9–44.1)	<0.0001
NNS, *n* (95%CI)	42.4 (41.7–43.1)	27.3 (26.1–28.6)	39.9 (39.3–40.5)	<0.0001
NNT, *n* (95%CI)	2.2 (2–2.3)	3.9 (3.4–4.4)	2.4 (2.3–2.6)	<0.0001
SS+ TB				
Total, *n*	113	5	118	
All screened	0.82 (0.68–0.98)	0.29 (0.10–0.69)	0.76 (0.63–0.91)	<0.01
Presumptive cases	16.1 (13.6–19)	2.0 (0.73–4.8)	12.4 (10.5–14.7)	<0.0001
All forms	34.8 (29.8–40.1)	7.8 (3–17.4)	30.3 (26–35.1)	<0.0001
NNS, *n* (95%CI)	121.9 (119.9–124)	349.6 (333.4–366.4)	131.6 (129.5–133.7)	<0.0001
NNT, *n* (95%CI)	6.2 (5.8–6.7)	49.4 (43.4–55.9)	8 (7.5–8.6)	<0.0001

CI = confidence interval, TB = tuberculosis; NNS = number needed to screen; NNT = number needed to test; SS+ = sputum smear-positive.

NNS and NNT have been suggested as useful metrics for measuring the efficiency of TB screening programmes.[29] Some researchers have suggested measuring the efficiency of TB screening approaches in terms of resource allocation.[30] We used the NNS and NNT, as we did not capture the parameters suggested in the latter approach. In an active community-based screening study in an urban setting in Uganda, the NNS was 131.[29] Although the NNS in contact-screening studies can vary widely, the median is 45,[31] comparable to the NNS of 40 in our study. Similarly, the NNT of 2.4 in our study is better than the recommended value of 7.[32] However, both the NNS and the NNT varied significantly between the two regions, with Oromia having a smaller NNS and NNT than Amhara.

The reasons for the regional variations in the yield of contact investigation are not clear. In studies with populations with mixed or unknown HIV status, the population-level prevalence of TB and HIV, the screening strategy and the availability of culture services were not associated with yield of active TB case finding.[31] Our data were not disaggregated by HIV status; however, the HIV prevalence rate in Amhara Region is higher in both the general population and among TB patients.[23,33] On the other hand, as antiretroviral treatment (ART) coverage is higher in Amhara than in Oromia,[34] some population-level protective effect might have been conferred by ART, which is known to reduce TB incidence in PLHIV.[35] A more in-depth review of factors contributing to regional variations using data from different sources is needed.

The low IPT coverage in under-5 children is another area that needs to be addressed; however, published data on this population are limited. Among PLHIV, the IPT coverage rate was 18% in 2012.[21] Frequent stockouts of isoniazid and provider-related factors, such as fear of drug resistance, are cited as factors contributing to low IPT coverage rates among PLHIV in Ethiopia.[36] Lack of standardised monitoring tools and low level of awareness among health care providers appear to be the main challenges in our project zones.

The study has certain limitations: the data are not disaggregated by HIV status, sex or MDR-TB status; as sputum microscopy was the main diagnostic tool used in the study, generalising the results to settings that use culture or Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) is difficult; and lack of credible local evidence made comparisons with other studies difficult, necessitating comparisons with population-based surveys and WHO estimates. The study also has a number of strengths: this is the first large-scale experience of implementation of household contact investigation in Ethiopia, and one of few in low-income settings; the experience of IPT among children aged <5 years is also one of few in this setting.

CONCLUSIONS

The yield of household contact investigation was more than 10 times higher than the prevalence estimate in the general population, and served as an entry point for childhood TB care in two large regions of Ethiopia. It should therefore be scaled up to similar settings. However, more effort is needed to optimise its yield by using more sensitive diagnostic techniques, and to improve IPT coverage among under-5 children. Future studies should look into factors contributing to regional variations in the yield of contact investigation, underlying reasons for the low IPT coverage among children, cost and cost-effectiveness of various contact investigation approaches, and the performance of the Xpert assay for TB diagnosis in contacts.

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RESUME

CONTEXTE : Régions d'Amhara et d'Oromia, Ethiopie.
OBJECTIF : Déterminer le rendement de l'investigation des contacts domestiques pour la tuberculose (TB) dans des conditions de routine de programme en Ethiopie.
SCHÉMA : Entre avril 2013 et mars 2014, le personnel des dispensaires antituberculeux a réalisé un dépistage basé sur les symptômes auprès des contacts domestiques de 6015 cas index de TB à frottis positif (SS+ TB). En nous basant sur les données des rapports trimestriels du programme, nous avons calculé le rendement en termes de nombre de personnes à dépister (NNS) et de nombre de personnes à tester (NNT).
RÉSULTATS : Sur 15 527 contacts domestiques dépistés, 6,1% ont été présumés d'avoir la TB (8,5% à Oromia contre 3,9% à Amhara). Toutes les formes de TB et de SS+ TB ont été diagnostiquées chez 2,5% des contacts (Oromia 3,9% contre Amhara 1,2%) et 0,76% des contacts (Oromia 0,98% contre Amhara 0,55%), respectivement. Le NNS requis pour détecter un cas d'une forme quelconque de TB et de SS+ TB a été de 40 et 132, respectivement. Le NNT requis pour diagnostiquer un cas d'une forme quelconque de TB et de SS+ TB a été de 2,4 et 8, respectivement. Sur 1687 enfants éligibles âgés de moins de 5 ans, 323 ont débuté un traitement préventif par isoniazide.
CONCLUSIONS : Le rendement de l'investigation des contacts domestiques a été plus de 10 fois la prévalence estimée dans la population générale. Cette recherche peut constituer un point d'entrée pour la prise en charge de la TB de l'enfant.

RESUMEN

MARCO DE REFERENCIA: Las regiones de Amhara y Oromia en Etiopía.
OBJETIVO: Determinar el rendimiento diagnóstico de la investigación de los contactos domiciliarios de los casos de tuberculosis (TB) en el marco de las condiciones de un programa ordinario en Etiopía.
MÉTODO: Entre abril del 2013 y marzo del 2014, los funcionarios de los consultorios de TB llevaron a cabo un cribado sistemático basado en los síntomas de los contactos domiciliarios de 6015 casos iniciales de TB con baciloscopia positiva (SS+ TB). A partir de los datos programáticos trimestrales, se calculó el rendimiento según el número de personas cribadas (NNS) y el número de personas examinadas (NNT) que fueron necesarios con el fin de detectar un caso de TB activa.
RESULTADOS: En el 6,1% de los 15 527 contactos domiciliarios que participaron en el cribado se estableció una presunción diagnóstica de TB (8,5% en Oromia contra 3,9% en Amhara). Se estableció el diagnóstico de cualquier forma de TB en 2,5% de los contactos (el 3,9% en Oromia contra el 1,2% en Amhara) y de SS+ TB en el 0,76% (0,98% en Oromia contra 0,55% en Amhara). El NNS con el fin de detectar un caso de cualquier forma de TB fue 40 y la detección de un caso de SS+ TB necesitó el cribado de 132 personas. El NNT con el fin de detectar un caso de cualquier forma de TB fue 2,4 y un caso de SS+ TB necesitó el examen de ocho personas. De los 1687 niños menos de 5 años de edad que cumplían con los requisitos, 323 iniciaron el tratamiento preventivo con isoniazida.
CONCLUSIÓN: El rendimiento diagnóstico de la investigación de contactos domiciliarios de los casos de TB fue más de 10 veces superior a la prevalencia estimada en la población general. Esta medida ofreció una puerta de entrada a la atención de la TB de los niños.

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PLOS ONE

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

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Abstract

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

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

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

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Introduction

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

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

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

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

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

Methods

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

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

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

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

Sample size determination

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

Sampling Technique/Procedure

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

Data Collection and analysis

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

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

Ethical issues

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

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

Results

Socio-demographic, clinical and immunological characteristics of study participants

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

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

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

Clinical presentation of Tuberculosis in HIV positive persons after ART initiation

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

Bivariate analysis of factors associated with TB

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

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

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

Multivariate analysis: Factors independently associated with active TB

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

***significant at α = 0.05**.

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

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

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

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

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

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

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

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

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

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

Conclusion

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

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Author Contributions

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

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Variation and risk factors of drug resistant tuberculosis in sub-Saharan Africa: a systematic review and meta-analysis

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Abstract

Background: Prevalence of multidrug resistant tuberculosis (MDR-TB), defined as in vitro resistance to both rifampicin and isoniazid with or without resistance to other TB drugs, in sub-Saharan Africa (SSA) is reportedly low compared to other regions. These estimates are based on data reported to the World Health Organization (WHO) on drug resistance surveys, which may suffer from a reporting bias. We set out to evaluate the variation in prevalence of drug resistant tuberculosis (DR-TB) and its determinants across SSA countries among new and previously treated TB patients.

Methods: The aim was to perform a systematic review and meta-analysis of DR-TB prevalence and associated risk factors in SSA. PubMed, EMBASE, Cochrane and bibliographies of DR-TB studies were searched. Surveys at national or sub-national level, with reported DR-TB prevalence (or sufficient data to calculate a prevalence) to isoniazid (INH), rifampicin (RMP), ethambutol (EMB), and streptomycin (SM) conducted in SSA excluding the Republic of South Africa, published between 2003 and 2013 with no language restriction were considered. Two authors searched and reviewed the studies for eligibility and extracted the data in pre-defined forms. Forest plots of all prevalence estimates by resistance outcome were performed. Summary estimates were calculated using random effects models, when appropriate. Associations between any DR-TB and MDR-TB with potential risk factors were examined through subgroup analyses stratified by new and previously treated patients.

Results: A total of 726 studies were identified, of which 27 articles fulfilled the inclusion criteria. Studies reported drug susceptibility testing (DST) results for a total of 13,465 new and 1,776 previously treated TB patients. Pooled estimate of any DR-TB prevalence among the new cases was 12.6% (95% CI 10.6-15.0) while for MDR-TB this was 1.5% (95% CI 1.0-2.3). Among previously treated patients, these were 27.2% (95% CI 21.4-33.8) and 10.3% (95% CI 5.8-17.4%), respectively. DR-TB (any and MDR-TB) did not vary significantly with respect to study characteristics.

Conclusions: The reported prevalence of DR-TB in SSA is low compared to WHO estimates. MDR-TB in this region does not seem to be driven by the high HIV prevalence rates.

Keywords: Sub-Saharan Africa, Drug resistant tuberculosis, Risk factors, HIV, Survey

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Background

Globally, the World Health Organization (WHO) reports an estimated prevalence of 3.6% and 20.2% among notified TB cases for primary and acquired multidrug resistant tuberculosis (MDR-TB), respectively, with significant country and regional variations [1]. Despite the high burden of TB in sub-Saharan Africa (SSA) fuelled by HIV [1], drug resistance surveillance has not been widely done, with only 22 of the 46 countries reporting drug resistance data by 2005. These studies have been designed to establish a nationwide MDR-TB prevalence only, and most of them had small sample sizes to assess variations between subpopulations or identify potential risk factors of the prevalence of drug resistance [2]. Yet, the use of inferior TB drug regimens, high HIV infection rates, and a wide roll-out of ART may predispose countries in this region to high levels of drug resistant tuberculosis (DR-TB) [3]. In particular, previous exposure to anti-TB treatment is a well-established risk factor for DR-TB [4]. By 2010, a number of TB programs in SSA were still using the eight-months regimen of two months of ethambutol (EMB), isoniazid (INH), rifampicin (RMP), and pyrazinamide (PZA), followed by six months of EMB and INH. This regimen has been associated with lower cure rates and higher rates of relapse than the currently recommended six-months regimen in which rifampicin is given throughout treatment (two months of EMB,INH,RMP,PZA followed by four months of RMP and INH) [4]. Conversely, duration of RMP treatment beyond four months has been associated with increased risk of acquiring drug resistance in initially drug sensitive strains [5]. Additionally, there have been concerns that, in SSA, six months of directly observed therapy are often unfeasible, and RMP throughout would increase the incidence of MDR-TB, in particular in the context of high HIV prevalence and pre-existing INH resistance [6]. While some drug resistance studies have shown an association between HIV and DR-TB/MDR, data showing HIV as an independent risk factor for MDR-TB in individuals have been limited to particular settings [7]. Nevertheless, high mortality among HIV patients suffering from MDR or extensively drug-resistant tuberculosis (XDR: defined as resistance to any of the fluoroquinolones (such as ofloxacin or moxifloxacin) and to any of the three injectable second-line anti-TB drugs (amikacin, capreomycin, or kanamycin) in addition to MDR) [8] are major concerns to TB control programs in SSA. Finally, the association between RMP mono-resistance and HIV infection has also been documented [9]. Therefore, understanding the role of potential 'drivers' of DR-TB in SSA is important to guide intervention policies and future drug resistance monitoring in the region. We did a systematic review and meta-analysis of published and unpublished studies to establish the variation of DR-TB across SSA countries and its determinants.

Methods

Data sources

We searched PubMed, EMBASE, and Cochrane for original publications from 2003 to 2013 without language limitations. Search terms used included *anti-TB drug resistance, drug resistant tuberculosis, M/DR/XDR-TB, and (isoniazid or rifampicin or ethambutol or streptomycin or ofloxacin or fluoroquinolone or kanamycin or amikacin) resistance* for each country in SAA, excluding the Republic of South Africa (RSA). Each term was searched separately with a text string ending with the specific name of the country. We excluded RSA because drivers of DR-TB in this country are likely to be different and prevalence has been reported to be substantially higher than the rest of SSA countries [10]. We also searched bibliographies of other reviews and citations of the original articles identified. Reviewers obtained unpublished DR-TB studies through personal communication with experts and authors of papers identified.

Study selection

We included surveys carried out both at national or sub-national level reporting M/DR-TB prevalence or sufficient data to calculate a prevalence of resistance to isoniazid (INH), rifampicin (RMP), ethambutol (EMB), streptomycin (SM), and/or MDR (INH and RMP). Conference proceedings, chapters of books, and correspondences were excluded. Studies were considered of sufficient quality for inclusion if participants were classified as new or previously treated based on the WHO definition [11], the study covered a large geographical area (district, region, or entire country), and recommended laboratory procedures for culture and drug susceptibility testing (DST) were followed [12]. Studies conducted in a single health unit e.g. a referral hospital or a TB center, or those where fewer than 50 participants had DST were excluded to minimize bias of including non-representative samples of the population. Where cluster sampling was used, adjustment for the cluster design was a requirement for inclusion in this review.

Two authors conducted the electronic searches independently; the last search was conducted in June 2014. Selection of articles was done by both reviewers independently. Disagreements on articles to be included were resolved by consensus among the two authors.

Data extraction

We extracted data using pre-defined forms on: country of the study; sampling method; description of the facilities where the study was done; total number of patients enrolled in the study as per treatment category; number of patients with DST results; number of patients with a positive result for resistance to INH, RMP, EMB, SM, or

MDR-TB; and HIV prevalence among the participants (if available). HIV prevalence at national level for each country of interest was collected from the UNAIDS report 2013 [13]. Two authors extracted data independently and any discrepancies in the data extracted were resolved through discussions.

Data synthesis and analysis

According to WHO, resistance among new cases is defined as resistance to one or more anti-tuberculosis drugs in patients that have never been treated for TB. Resistance among previously treated TB patients, on the other hand, is defined as resistance to one or more anti-tuberculosis drugs in patients that have been treated for TB. It can be transmitted from another patient with DR-TB or acquired in patients diagnosed with pan-sensitive TB who have started TB treatment and subsequently develop resistance to one or more of the drugs used during the treatment. To generate data stratified for the resistance among the new and previously treated TB patients, we calculated pooled resistance prevalence along with the 95% confidence interval through meta-analysis using random effects models for MDR-TB and any DR-TB to the first line drugs (INH, RMP, EMB, and SM). We assessed the heterogeneity among reported prevalence using the I^2 statistic.

To explore the variation observed in the prevalence estimates, we did a subgroup analysis by stratifying studies by predefined variables. In particular, we categorized variables as follows: 1) by sub-region (Eastern sub-region included Burundi, Ethiopia, Kenya, Rwanda, Somalia, Uganda, and Tanzania; West Africa sub-region included Benin, Burkina Faso, Cameroon, Equatorial Guinea, Gambia, Ghana, Ivory Coast, and Nigeria; Southern sub-region: Botswana, Zambia, Mozambique, Madagascar, Swaziland, and Zambia; and Central Africa sub-region: Central African Republic and Chad); 2) HIV prevalence at a national level (countries with a prevalence of less than 5% compared to those with a prevalence of more than 5% in the general population); 3) type of survey (national or sub-national); 4) sampling method (random sampling or cluster sampling); 5) sample size (studies of less than 100 patients or more than 100 patients); and HIV prevalence among study participants (less than 40% compared to, equal to or more than 40%).

We avoided use of acquired resistance for these categories of patients due to limitations of this definition for acquired resistance as it does not put into consideration possibilities of re-infection with resistant forms and initial infection with resistant strains contributing to treatment failure, since capacity to ascertain resistance patterns prior to treatment initiation is rarely available under routine settings.

Results

We identified 725 citations through electronic data searches and one completed study with unpublished data. Out of these, 47 articles were selected for full text review, of which 20 articles were excluded for various reasons (Figure 1). Characteristics of the 27 articles included are summarized in Table 1. Of these 27 studies, 19 (70%) reported DR-TB data on both new and previously treated patients. Seven studies reported resistance among new cases only, while one study assessed DR-TB among the previously treated. Sixteen (59%) studies reported HIV testing, and HIV prevalence estimates at country level were available for more than 90% of the studies. Thirteen (48.1%) studies in total reported data at national level. Compared to other regions, the eastern region contributed the highest number of articles, five of which were from national surveys.

DR-TB data was reported for a total of 15,462 sputum smear-positive TB patients in the 27 articles included from 2003 to 2013. Of these, 13,645 (88.4%) and 1,776 (11.6%) were new and previously treated patients, respectively. All reported estimates for any resistance and MDR-TB among new and previously treated patients are presented separately by study in Figure 2. In Figure 3, we then present pooled estimates for all resistance patterns, including MDR-TB among new and previously treated patients. Prevalence of any DR-TB and of MDR-TB were higher among patients who had been previously treated for TB (Figures 2 and 3). Overall, the pooled prevalence of any DR-TB among new and previously treated patients was 12.6% (95% CI 10.6-15.0%) and 27.2% (95% CI 21.4-33.8), respectively; while MDR-TB among the new and previously treated patients was 1.5% (95% CI 1.0-2.3) and 10.3% (95% CI 5.8-17.4), respectively. Summary estimates for any DR-TB among new and previously treated TB cases were highest for INH [7.8% (95% CI 6.5-9.4) and 23.1% (95% CI 15.9-32.2)] and lowest for EMB [1.9% (95% CI 1.3-2.8) and 8.7% (95% CI 4.7-15.3)] (Figure 3). Resistance to RMP in new cases, 2.0% (1.5-2.8) was also very low (Figure 3).

Variation of DR-TB with key study characteristics

In Figures 4 and 5, we present the subgroup analyses for the prevalence of any DR-TB and MDR-TB by study characteristics. Overall, we observed larger variations in the pooled estimates by subgroup with respect to any DR-TB, compared to MDR estimates.

Regional variations

Prevalence of any DR-TB among new cases varied from 10.4% (95% CI 8.2- 13.1, n = 6) in the Southern region to 17.0% (12.4-23.0, n = 2) in the Central region. Any DR-TB among previously treated TB patients was highest in East Africa with levels of 29.2% (95% CI 21.4-38.6,

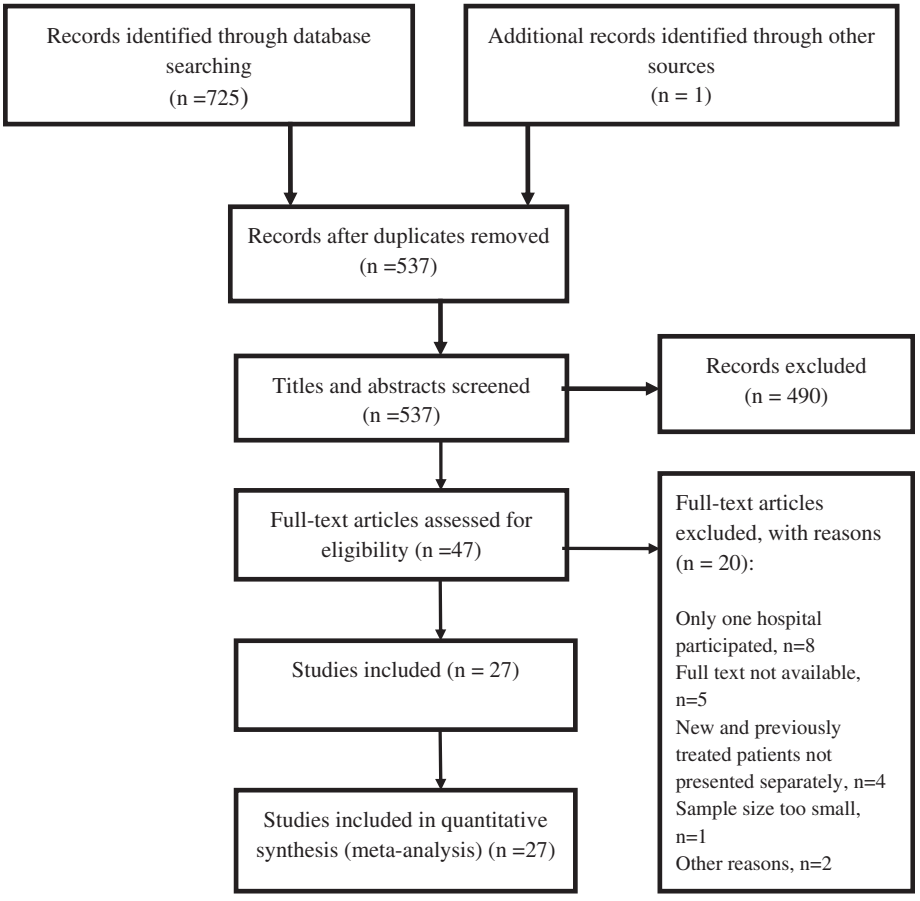

Figure 1 PRISMA flow chart.

n = 8) and lowest in the Southern African countries, 24.0% (95% CI 13.0-40.0, n = 6). MDR TB among new patients was lowest in Central Africa at 1.2% (95% CI 0.3-5.5, n = 2) and highest in Western Africa, 2.3% (95% CI 1.0-4.8, n = 3), while MDR-TB among previously treated was highest in Southern region, 11.7% (95% CI 5.0-25.0, n = 6) and lowest in Eastern region, 9.6% (95% CI 4.7-18.4, n = 9). We did not observe significant variations in pooled estimates of any DR-TB or MDR-TB in the sub-regions as shown by the overlap in the 95% CIs of our estimates (Figures 4 and 5).

Country-level HIV prevalence

Analysis of any DR-TB among new cases in relation to HIV infection rates (Figure 4) showed somewhat higher resistance rates of 13.9% (95% CI 10.5-18.2, n = 12) in countries where HIV prevalence was lower than 5%, compared to countries where the prevalence was equal to or higher than 5%, [11.2% (95% CI 8.7-14.2, n = 12)], while DR-TB among the previously treated was almost the same among settings with these different HIV prevalence rates (26.1%, n = 8 vs 25.4%, n = 9). Primary MDR-TB in settings with less than 5% HIV prevalence was 1.9% (95% CI 1.1-3.2 n = 9) as compared to 1.5% (95% CI 0.8-2.8 n = 12) in settings where the HIV prevalence equal to or higher than 5%. MDR-TB among previously treated patients in countries with lower than 5% HIV prevalence was 8.3% (95% CI 3.4-18.8, n = 11) compared to 11.0 (95% CI 5.8-19.9, n = 9) in countries with HIV prevalence of equal to or higher than 5%. However, differences were small with largely overlapping 95% confidence intervals.

TB/HIV co-infection

Where HIV testing was done as part of the survey (Figure 4), we observe a higher prevalence of DR-TB among new cases in studies where HIV was lower than 40% among the study participants [16.1% (95% CI 12.5-20.6, n = 11)] as compared to 9.6% (95% CI 6.8-13.6, n = 4) in studies where HIV prevalence among participants was equal to or higher than 40%. Analysis of DR-TB among previously treated cases in relation to these HIV co-infection rates shows the same rates in these two settings, those studies with lower than 40% HIV co-infection and

Table 1 Characteristics of studies included in the review of variation of M/DR-TB in SSA; 2003–2013

Author	Study year	Country	Study description	Patient category	Sample size (included in DST)	HIV prevalence in the study (%)	Country HIV prevalence (%)	DST method	Type of resistance tested
Minime-Lingoupou F *et al.* [21]	2009	Central African Republic	Sub-national survey. TB health facilities in Bangui and Bimbo.	New patients	233	26	N/A	LJ	INH, RMP, SM, EMB
Asmamaw D. *et al.* [22]	2004	Ethiopia	Sub-national survey. Twenty-four TB health facilities in Addis Ababa.	New patients	231	29.6	2.9	LJ	INH, RMP, SM, EMB
Abdelhadi O. *et al.* [23]	2009-2010	Chad	Sub-national survey. Number of TB facilities not provided.	New patients	135	25	3	LJ	INH, RMP, SM, EMB
Yimer S.A. *et al.* [24]	2008	Ethiopia	Sub-national survey. Number of TB facilities in Amhara not provided.	New patients	112	26.9	1.9	MGIT	INH, RMP, SM, EMB
Urassa W. *et al.* [25]	2001-2004	Tanzania	Sub-national survey. Five TB health facilities in Dar es Salaam.	New patients	887	53	5.7	LJ	INH, RMP, SM, EMB
Ndungu PW. *et al.* [26]	2010	Kenya	Sub-national survey. Five TB health facilities in and around Nairobi.	New patients	356	26.3	6.6	MGIT/LJ	INH, RMP, SM, EMB
Matee M. *et al.* [27]	2005-2006	Tanzania	Sub-national survey: Thirty-seven TB facilities of Temeke district.	New patients	226	N/A	5.8	LJ	INH, RMP, SM, EMB
Lukoye D. *et al.* (a) [28]	2008	Uganda	Sub-national survey. Twenty-two TB health facilities in Kampala.	New and PT patients	557	30.9	6.7	LJ	INH, RMP, SM, EMB. Km and O
Sanders M. *et al.* [29]	2008	Burundi	Sub-national survey. Seven TB health facilities in Bujumbura.	New and PT patients	859	N/A	2.2	LJ	INH, RMP, SM, EMB, PABA
Lukoye D. *et al.* (b) [30]	2009-2011	Uganda	National survey.	New and PT patients	1537	30.7	7.3	LJ	INH, RMP, SM, EMB, KM and OFX
Umubyeyi A. N. *et al.* [31]	2004-2005	Rwanda	National survey.	New and PT patients	701	N/A	3.3	LJ	INH, RMP, SM, EMB
Irenious S. *et al.* [15]	2011	Somalia	National survey.	New and PT patients	946	N/A	N/A	Hain	INH, RMP only
Chonde TM *et al.* [32]	2006-2007	Tanzania	National survey.	New and PT patients	1,167	N/A	5.8	LJ	INH, RMP, SM, EMB
Tessema B. *et al.* [33]	2009	Ethiopia	Sub-national survey. Five TB health facilities in north west Ethiopia.	New and PT patients	260	25.4	1.7	LJ	INH, RMP, SM, EMB, CPM, OFX, AM, MFX, Amino Salicylic Acid
Chanda M. *et al.* [34]	2006	Zambia	Sub-national survey. Six TB health facilities in Ndola district.	New and PT patients	361	N/A	13.2	LJ	INH, RMP, SM, EMB

Table 1 Characteristics of studies included in the review of variation of M/DR-TB in SSA; 2003–2013 *(Continued)*

Nunes E.A. *et al.* [35]	2002-2003	Mozambique	Sub-national survey. Number of TB health facilities not provided.	New and PT patients	111	N/A	9.8	LJ	INH, RMP, SM, EMB
Nelson L.J. *et al.* [36]	2002	Botswana	National survey.	New and PT patients	2,425	60	25.7	LJ	INH, RMP, SM, EMB
Ramarokoto H. *et al.* [37]	2005-2007	Madagascar	National survey.	New and PT patients	1,275	N/A	0.6	LJ	INH, RMP, SM, EMB
Samo Gudo P. *et al.* [38]	2007-2008	Mozambique	National survey.	New and PT patients	1,200	N/A	11.5	LJ	INH, RMP, SM, EMB
Sanchez-Padilla E. *et al.*	2009	Swaziland	National survey	New and PT patients	633	79.9	25.8	MGIT or LJ	INH, RMP, SM, EMB
Edgbola R.A. *et al.* [39]	1999	Gambia	National survey.	New and PT patients	225	N/A	2.1	LJ	INH, RMP, SM, EMB
Affolabi D. *et al.* [40]	2002-2004	Benin	Sub-national survey. National Pneumo-Phthisiology hospita receiving patients from Benin and surrounding countries	New and PT patients	470	10.2	2.3	LJ	INH, RMP, SM, EMB
Tudo G. *et al.* [41]	2004	Equatorial Guinea	Sub-national survey. Number of TB health facilities not provided.	New and PT patients	236	13.5	3.6	LJ	INH, RMP, SM, EMB
N'guesesan K. *et al.* [42]	2005	Ivory Coast	National survey.	New patients	320	N/A	4.9	LJ	INH, RMP, SM, EMB
Sangare L. *et al.* [43]	2010	Bukina Furso	National survey.	New and PT patients	416	28.7	1.3	LJ	INH, RMP, SM, EMB
Ellis Awusu-Dabo *et al.* [44]	2001-2004	Ghana	National survey.	New and PT patients	216	25.9	4.7		INH, RMP, SM, EMB, Thiacetazone
Jurgen Noesk *et al.* [45]	2012	Cameroon	Sub-national. Twenty-nine TB health facilities in Litoral region.	PT patients	233	26	N/A	LJ	INH, RMP, SM, EMB, Km and GFX
Mbulo G.M.K. *et al.* Results of the national drug resistance survey in Zambia. (in preparation)	2008	Zambia	National survey.	New and PT patients	883	47.6	13.3	LJ	INH, RMP, SM, EMB

Abbreviations: *DST* drug susceptibility testing, *INH* isoniazid, *RMP* rifampicin, *EMB* ethambutol, *SM* streptomycin, *Km* kanamycin, *GFX* gatifloxacin, *CPM* capreomycin, *OFX* ofloxacin, *AM* amikacin, N/A, not available, *LJ* Löwenstein Jensen, *MGIT* mycobacteria growth indicator tube, *PT* previously treated patient.

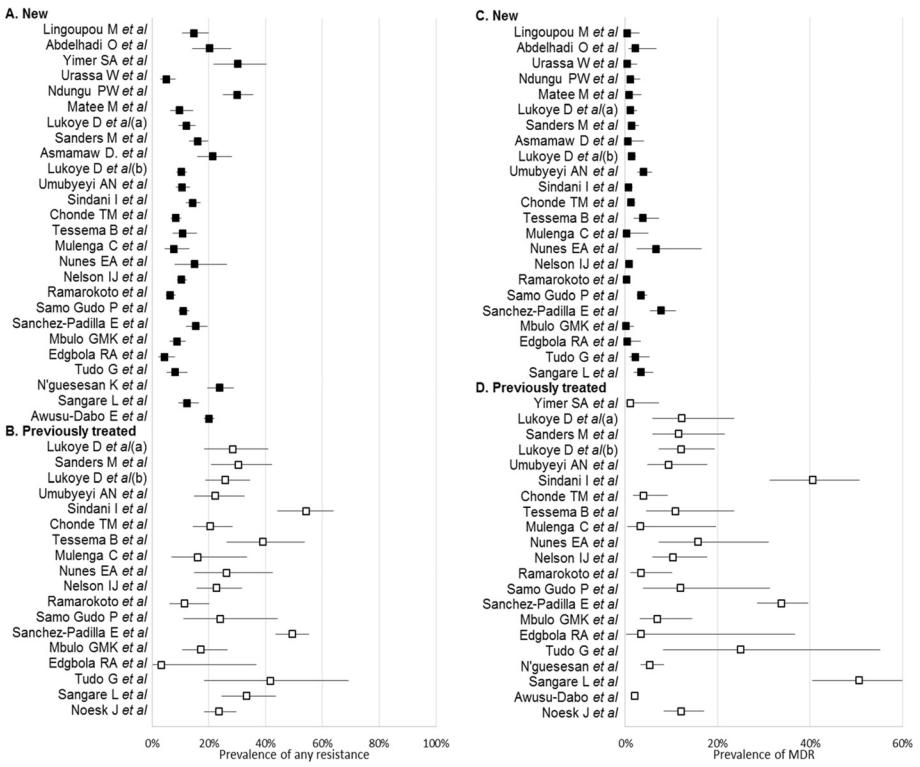

Figure 2 Forest plot of prevalence of any resistance and MDR among new and previously treated patients.

equal to or more than 40% of HIV co-infection, [29.1%, 95% CI = 24.3-34.4 n = 6 and 28.5% 95% CI 12.4-53.0 n = 3]. MDR among new cases in studies where TB/HIV co-infection rates were lower than <40% was 1.8% (1.2-2.7, n = 9); and 1.0% (0.2-5.7; n = 4); in studies with equal to or higher than 40% TB/HIV co-infection. MDR-TB among previously treated patients where TB/HIV co-infection was lower than 40% among the participants was 10.6% (95% CI = 3.6-27.8, n = 8) and 14.6% (95% CI 4.4-38.6, n = 3) where equal to or higher than 40% of the

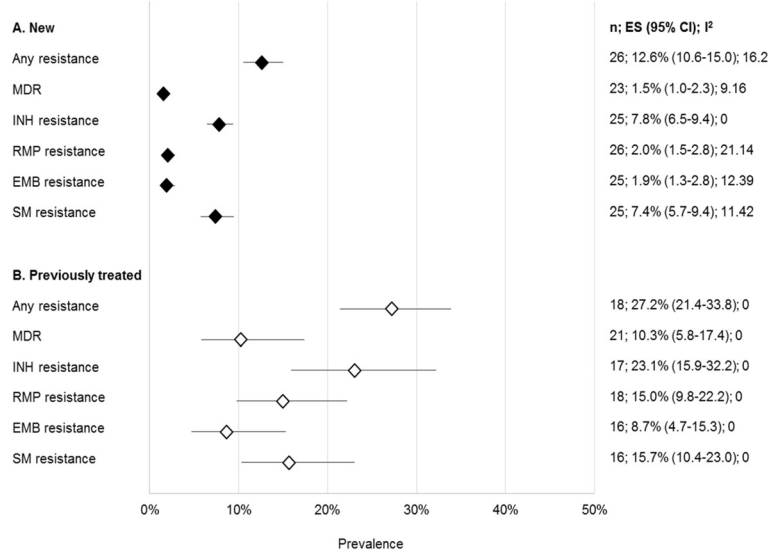

Figure 3 Pooled estimates for all resistance patterns among new and previously treated patients. Abbreviations: n, number of studies; ES, estimate; INH, isoniazid; RMP, rifampicin; EMB, ethambutol; SM, streptomycin.

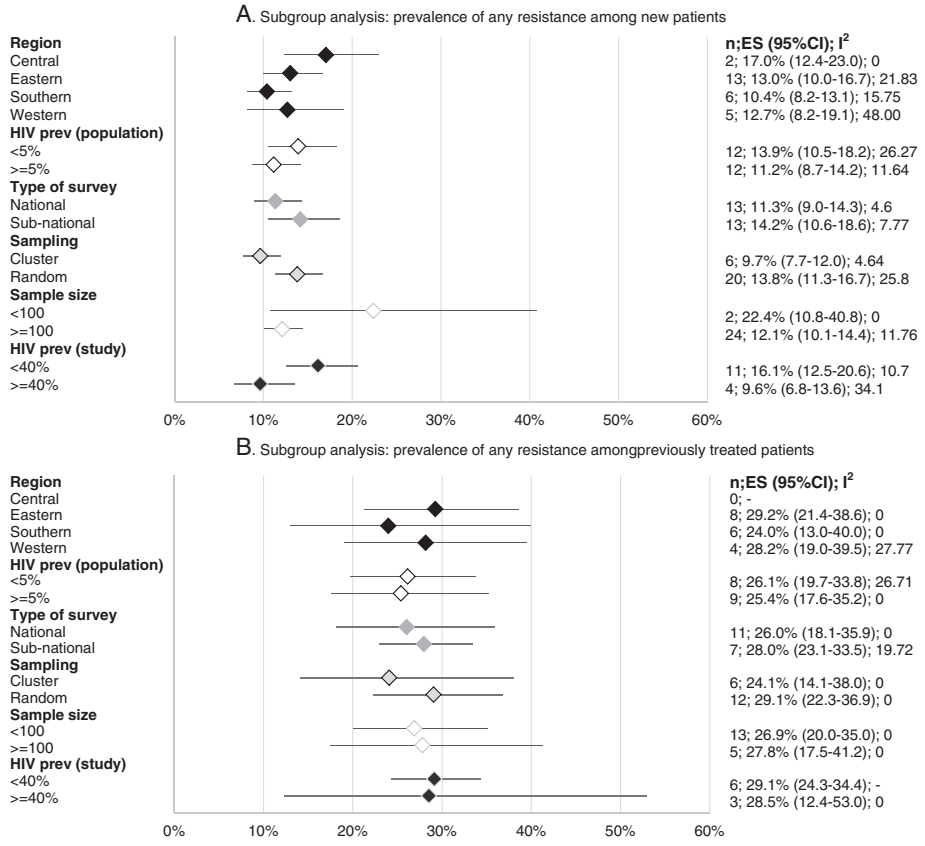

Figure 4 Subgroup analysis: prevalence of any drug resistance. Abbreviations: n, number of studies; ES, estimate. Where data is missing, it means that such a region did not have any study fitting that classification for inclusion in the analysis.

participants were HIV co-infected, although this difference was also not significant (Figure 5).

Study geographical coverage

Generally, articles reporting national surveys estimated lower rates of any DR-TB among new cases 11.3% (95% CI = 9.0-14.3, n = 13) as compared to sub-national reports 14.2% (95% CI 10.6-18.6, n = 13). Any acquired DR-TB was similar in the national (26.0%; 95% CI 18.1-35.9, n = 11) and sub-national surveys (28%; 95% CI-23.1-33.5, n = 7) (Figure 4). MDR estimates among new cases were the same in both national and sub-national studies at 1.6% (95% CI 0.9- 2.8, n = 11) and 1.6% (95% CI 1.0-2.5, n = 12) respectively, as were MDR rates among the previously treated: 10.5% (95% CI 4.7-21.7, n = 13) versus 11.0% (95% CI 5.8-19.9, n = 8), respectively (Figure 5).

Sampling design

Studies that applied a cluster sampling design reported lower rates of any DR-TB 9.7% (7.7-12.0; n = 6) in new cases than studies where random sampling was used 13.8% (11.3-16.7; n = 20); DR-TB rates among previously treated patients in these two study designs were 24.1% (14.1-38.0; n = 6) and 29.1% (22.3-36.9 n = 12) respectively. Rates of MDR-TB followed a similar trend with MDR-TB among the new patients in studies that used cluster and random sampling designs reporting MDR-TB rates of 1.0% (0.5-2.1; n = 6) and 1.8% (1.1-2.9; n = 17), respectively. MDR-TB among the previously treated category in studies that used cluster design was 9.9% (3.7-24.3; n = 6), similar to that in studies where random sampling was used [10.3% (5.1-19.9; n = 15)]. All the differences in these measurements did not show statistical significance (Figures 4 and 5).

Sample size

Studies with sample sizes of less than 100 participants reported significantly higher rates of any DR-TB among new cases, 22.4% (95% CI 10.8-40.0, n = 2) compared to studies where 100 or more participants were recruited, 12.1% (95% CI 10.1-14.4, n = 24). Levels of DR-TB among the previously treated were almost the same in both categories of sample size, 26.9% (95% CI 20.0-35.0, n = 13) and 27.8% (95% CI 17.5-42.1, n = 5). For either category of study size, MDR levels amongst new cases followed similar trends, significantly higher 6.7% (95% CI 2.5-16, n = 1)

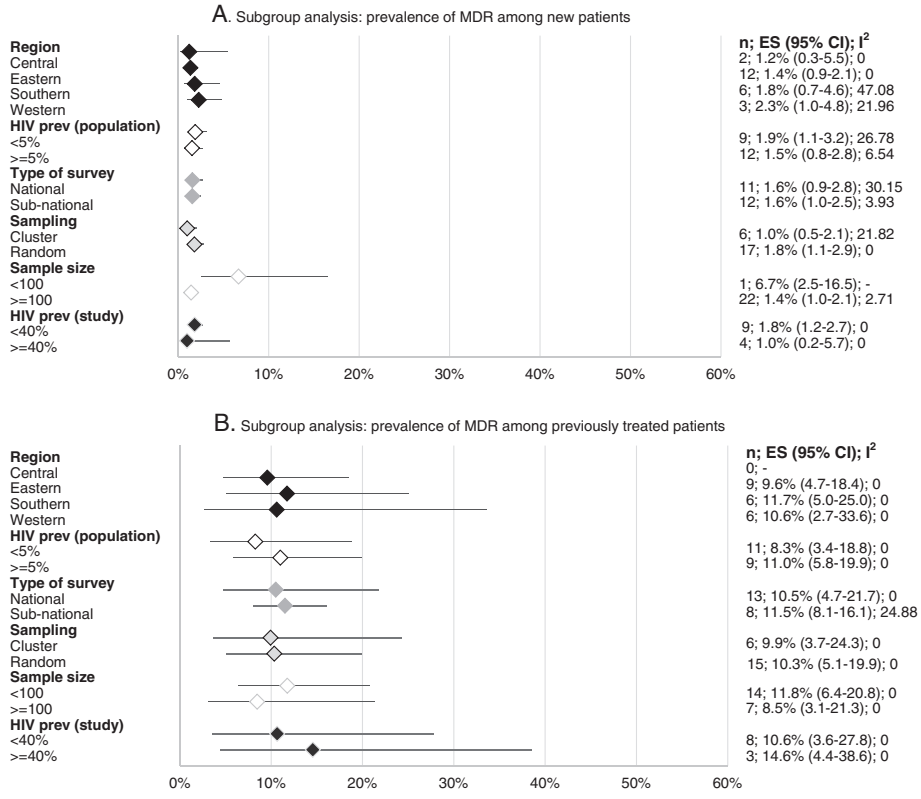

Figure 5 Subgroup analysis: prevalence of MDR-TB. Abbreviations: n, number of studies; ES, estimate, MDR- TB, Multi-drug resistant tuberculosis. Where data is missing, it means that such a region did not have any study fitting that classification for inclusion in the analysis.

in studies with less than 100 participants as compared to 1.4% (95% CI 1.0-2.1, n = 22) in studies with larger sample sizes. Although slightly higher, levels of MDR-TB among previously treated patients in studies with less than 100 participants, 11.8% (6.4%-20.8%, n = 14), this difference was not statistically significant as compared to studies with 100 participants or more, 8.5% (95% CI 3.1%-21.3%, n = 7).

Publication bias

Finally, in Figure 6, we explored graphically the possibility of a publication bias. We did not observe an indication of such a bias in the studies included.

Discussion

In our study, we reviewed variations and risk factors of DR-TB in SSA. We found that levels of any DR-TB and MDR-TB are lower in SSA than reported globally [1]. In particular, our results show MDR-TB prevalence estimates as almost half as compared to the global average reported by WHO for both new (1.5% vs 3.6%) and previously treated TB patients (10.3% vs 20.2%) [2]. These consistent low levels occur in settings with high rates of HIV, largely attributed, among other factors, to the late introduction of RMP and limited availability of TB drugs on the open market outside national TB programs [14] in this region. According to the subgroup analyses, rates of (M)DR-TB remain generally low regardless of the study geographical coverage, sample size, HIV co-infection rates, and sub-region where the study was conducted. This finding happens at a time when more information on rates and factors associated with of DR-TB in this region is emerging, as more countries conduct surveys at national and sub-national level [14], although data on DR-TB from SSA is still limited [10]. The observed low levels of (M)DR-TB may also reflect the functionality of TB control programs in this region. Previous studies have shown that countries where standardized regimens are available and properly implemented, where quality drugs are regularly supplied, and where systems are in place to ensure patients' adherence are less likely to report high rates of (M)DR-TB. From our findings, such explanation can be supported by the high rates of MDR-TB from the Horn of Africa included in our review, which could have resulted from a break down in the public health system and therefore in the functionality of the TB program due to civil strife also observed elsewhere in the world [16,17]. Therefore, regional variations in MDR-TB rates might be considered a proxy measure for functionality of national TB programs which should alert national governments

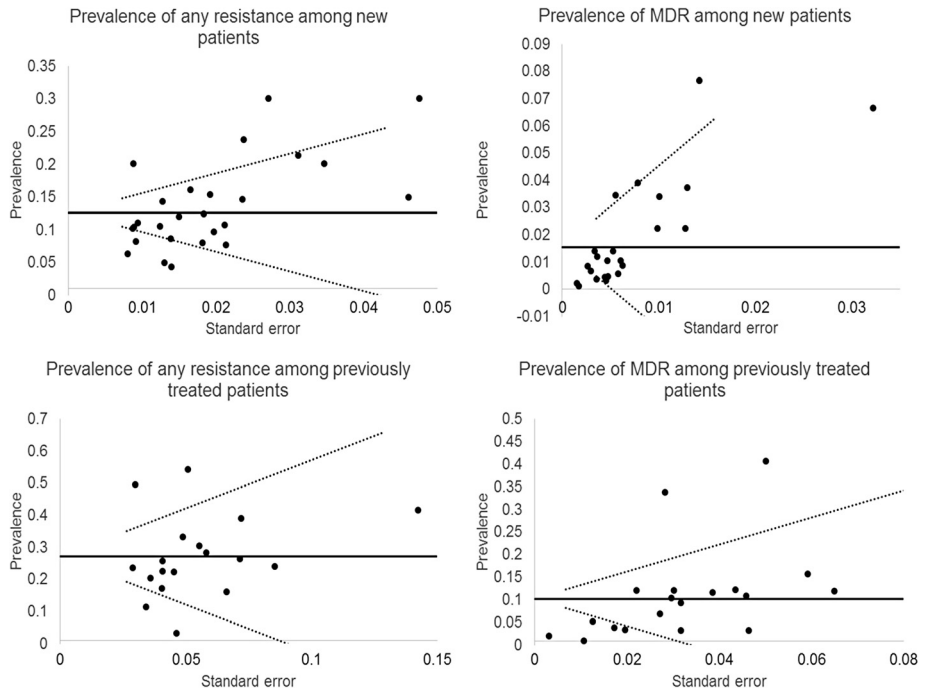

Figure 6 Funnel plot exploring publication bias. The horizontal line represents the summary prevalence and guidelines are given to indicate the 95% confidence interval for this estimate.

and donor communities for timely interventions. The role of *Mycobacterium tuberculosis* (MTB) strains in transmissibility and its potential to develop DR in this region should not be ignored. As observed in some settings, particular MTB strains predominant in specific localities have been associated with varying rates of MDR-TB [18]. Hence, more molecular studies are required to examine and explain possible associations of the predominant MTB strains with the observed prevalence of DR-TB in SSA. Our findings seem to imply that transmission-related factors such as late diagnosis, nosocomial spread, and delay in initiation of second-line treatment as observed in most settings of this region have not led to increase in (M)DR-TB above the minimum WHO estimates. However we observe higher rates of resistance to INH and SM than other drugs in our analysis, also documented earlier, attributed to the long history of INH and SM use in management of TB and to the stepwise acquisition of DR by MTB to these two drugs [19].

Lower levels of MDR-TB (1.5%) in settings with higher HIV prevalence at population level, also observed where HIV testing was included in the study design, could result from less participation rates of (M)DR-TB/HIV co-infected patients in surveys due to either severe illness or higher risk of death [8]. Where collection of individual HIV data was included in the study design, we found higher rates of MDR-TB (25%) among previously treated patients in studies where HIV prevalence was lower, possibly due to the same explanation and the possibility of suspected high MDR-TB rates in such populations.

We observed levels of any RMP resistance among new cases (1.5%) in the analysis close to the reported prevalence of MDR-TB (2.0%). This finding is of significant relevance in the current global and regional efforts to accurately and timely diagnose MDR-TB with the scale-up of molecular technology like GeneXpert MTB/RIF, providing quick results of RMP resistance as a proxy to MDR-TB. In fact, in many SSA countries, access to culture and DST facilities is limited and molecular technologies might ease access to MDR-TB diagnosis and reduce the time spent between diagnosis and initiation of the patient on treatment. High levels of INH and SM resistance found in our review, also documented elsewhere, need to be monitored closely in relation to the potential increase in treatment failure and relapse rates with the current first-line drugs [20]. In light of the recommended roll-out of the RMP-through regimen by WHO, especially in high HIV burden settings such as SSA, TB programs need to ensure correct use of RMP in drug -susceptible cases to avoid adding RMP resistance to the already high levels of INH resistance, likely to lead to high MDR-TB rates.

Finally, we observe higher rates of MDR-TB in smaller studies as compared to larger ones possibly arising from the difference in the core objectives of the studies. Studies with small sample sizes are usually done to explore

possibilities of high MDR-TB rates in specific populations. Similarly, DR-TB rates in sub-national studies are higher than in the national surveys since, in most cases, sample sizes in such studies tend to be smaller, non-representative of the population, and sometimes do not apply standardized methodologies, although we aimed to exclude such studies from our analysis. The lower (M)DR levels observed in cluster surveys as compared to surveys where random sampling was applied may have a similar explanation. Cluster sampling designs are usually applied where the study population is large and covering a wider geographical area for optimal use of resources without compromising the quality of the data. Consequently, lower (M)DR rates in cluster surveys could have been a proxy to the large sample sizes involved.

As demonstrated by the publication bias sub-analysis, we observed no tendency from authors to publish papers showing more or less resistance more frequently that could distort our findings.

Limitations

Our review had some limitations. Of 44 countries in SSA (excluding the Republic of South Africa), only 20 countries had done studies that fulfilled our inclusion criteria, of which studies from five countries were not on a national scale. Many of the DR-TB surveys identified during our searches were excluded because they took place at a single health facility or had not stratified patients according to their treatment history.

Although the association between HIV infection and DR-TB is still controversial and deserves further exploration, ten of the 27 studies analyzed did not include HIV testing. It was, therefore, difficult to draw meaningful conclusions. Similarly, we did not review data on national ART coverage due to challenges associated with accessing accurate data to examine a possible relationship between ART roll-out and levels of MDR-TB. Finally, results on second-line DST were not reported for the majority of studies. This could be a reflection that most countries in SSA had not initiated MDR-TB treatment at the time of the study and the possibilities of finding XDR-TB were limited, although this analysis would be important especially in settings where some fluoroquinolones (a cornerstone of second-line drug regimens) are widely used for treatment of other bacterial infections.

We excluded the republic of South Africa on the basis of high levels of MDR-TB and XDR-TB rates in comparison to other countries of SSA [1,8], possibly fuelled by high nosocomial transmission rates in the context of very high rates of TB/HIV co-infection reported in this country. We assumed that including such studies could potentially skew our results towards higher DR-TB or MDR-TB estimates.

Conclusions

Our analysis showed low levels of MDR-TB in sub-Saharan Africa compared to WHO estimates, with higher resistance to INH and SM as reported elsewhere in the world. There are no major variations in MDR-TB burden by sub-region and evidence of association between MDR-TB and HIV infection rates did not show statistical significance. We attribute these low levels to the limited existence of anti-TB drugs outside the national programs, late introduction of RMP in SSA, and wide use of fixed drug combinations. Since these factors may apply to other settings where rates of MDR-TB are higher, more studies are required to explore other possible explanations for the low levels of MDR-TB in SSA, such as the role of predominant MTB strains in generation and transmission of DR-TB in this region

Abbreviations

ART: Anti-retroviral therapy; DR-TB: Drug resistant tuberculosis; DST: Drug susceptibility testing; EMB: Ethambutol; INH: Isoniazid; MDR-TB: Multi Drug Resistant Tuberculosis; RMP: Rifampicin; RSA: Republic of South Africa; SM: Streptomycin; SSA: Sub-Saharan Africa; TB: Tuberculosis; WHO: World Health Organization; XDR- TB: Extensively drug resistant tuberculosis; PZA: Pyrazinamide.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

DL, FGJC, WS, GBG ad MLJ conceived the idea. DL and WS did literature search, identified and agreed on studies for inclusion and, extracted the data. GBG, DL, FGJ did data synthesis and analysis, DL and GBG wrote the initial draft. All co-authors reviewed the final draft before submission. All authors read and approved the final manuscript.

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Reducing the price of treatment for multidrug-resistant tuberculosis through the Global Drug Facility

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Problem Many countries have limited experience of securing the best prices for drugs and have little negotiating power. This is particularly true for the complex, lengthy and expensive regimens used to treat multidrug-resistant tuberculosis.
Approach The Stop TB Partnership's Global Drug Facility is dedicated to improving worldwide access to antituberculosis medicines and diagnostic techniques that meet international quality standards.
Local setting The Global Drug Facility is able to secure price reductions through competitive tendering among prequalified drug manufacturers and by consolidating orders to achieve large purchase volumes. Consolidating the market in this way increases the incentives for suppliers of quality-assured medicines.
Relevant changes In 2013 the Global Drug Facility reduced the price of the second-line drugs it supplies for multidrug-resistant tuberculosis: the overall cost of the longest and most expensive treatment regimen for a patient decreased by 26% – from 7890 United States dollars (US$) in 2011 to US$ 5822 in 2013.
Lessons learnt The price of treatment for multidrug-resistant tuberculosis supplied by the Global Drug Facility was reduced by consolidating orders to achieve large purchase volumes, by international, competitive bidding and by the existence of donor-funded medicine stockpiles. The rise in the number of suppliers of internationally quality-assured drugs was also important. The savings achieved from lower drug costs could be used to increase the number of patients on high-quality treatment.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

Tuberculosis remains a major global public health problem. According to a 2014 report from the World Health Organization (WHO), only 97 000 patients of the estimated 300 000 patients with multidrug-resistant tuberculosis worldwide were receiving treatment.[1] Access to quality medicines for patients in need is restricted by the limited availability of funding, which is often compounded by poor knowledge of drug management (e.g. storage and distribution) and a lack of staff and facilities. To increase cure rates, it is important that antituberculosis medicines are affordable and that systems are in place for providing proper care at all levels.

Many countries have limited experience in securing the best possible prices for drugs and have little negotiating power since they are not able to consolidate purchases into large volumes. This is especially true of the medicines needed for multidrug-resistant tuberculosis, where treatment is complex and can last two years or more. Moreover, these medicines are much more expensive than those for drug-sensitive tuberculosis.[2,3]

The Global Plan to Stop Tuberculosis, which was launched by the Stop TB Partnership, identified universal access to high-quality care for all people with the disease as one of its central objectives.[4] Today, access to quality-assured drugs is promoted by key stakeholders such as the WHO Prequalification Programme,[5] the Global Fund to Fight AIDS, Tuberculosis and Malaria, UNITAID and the Global Drug Facility, which was established by the Stop TB Partnership.

Global Drug Facility

The Global Drug Facility is dedicated to improving access worldwide to tuberculosis medicines and diagnostic techniques that meet international quality standards. In practice, the facility provides only internationally quality-assured medicines that are manufactured under stringent conditions so that countries and their governments can be confident they will always receive high-quality medicines. This stringency ensures that risk of developing drug-resistance is minimized. Recent studies show that the substandard and falsified drugs readily available on the private market have probably contributed to the development of antituberculosis drug-resistance in low- and middle-income countries.[6,7]

Today a growing number of antituberculosis medicines are able to meet international quality standards, as verified by the WHO Prequalification Programme or other stringent drug regulatory authorities. In this context, the Global Drug Facility has contributed significantly to drug volume consolidation and has, over the years, consistently secured lower prices for quality-assured antituberculosis medicines.[8]

Price reductions

In 2013, as in previous years, the Global Drug Facility reduced the price of the second-line drugs it supplies for the treatment of multidrug-resistant tuberculosis. This has resulted in a significant decrease in the overall cost of treatment. Fig. 1 illustrates the change between 2011 and 2013 in the cost of the longest and most expensive regimen for treating multidrug-resistant tuberculosis, one of many regimens available worldwide. For a 24-month treatment course, the cost of

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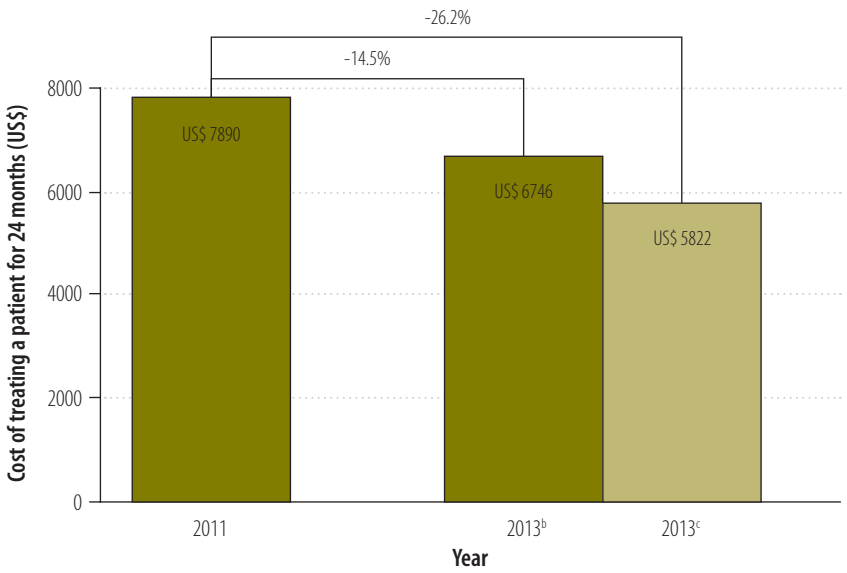
Fig. 1. **Cost of selected treatment[a] for multidrug-resistant tuberculosis from the Global Drug Facility, 2011–2013**



US$; United States dollars.

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

[b] Cost of treatment from the same suppliers as in 2011.

[c] The lowest-cost treatment in 2013.

Box 1. **Summary of main lessons learnt**

- The increase in the number of suppliers of internationally quality-assured, second-line drugs for multidrug-resistant tuberculosis provided the competition needed for the Global Drug Facility to secure consistently low prices.
- The price of drugs supplied by the Global Drug Facility was reduced by: (i) consolidating orders to achieve large purchase volumes; (ii) transparent, international, competitive bidding; and (iii) medicine stockpiles funded by donors.
- The savings achieved from the lower cost of high-quality medicines can be used to increase the number of patients treated.

treating one patient decreased by up to 26% – from 7890 United States dollars (US$) to US$ 5822 – over this period. In calculating costs, we used nominal prices obtained from the Global Drug Facility and did not adjust for either inflation or exchange rates.

The price reductions obtained by the Global Drug Facility were secured through a competitive and transparent tendering process among the manufacturers of prequalified, antituberculosis drugs and by the facility's continuing efforts to consolidate orders. During this time, the number of suppliers of quality-assured drugs for multidrug-resistant tuberculosis has increased. In 2012, a capacity assessment carried out by the Global Drug Facility found that a greater number of manufacturers were now able to supply internationally quality-assured, second-line drugs for multidrug-resistant tuberculosis and that, as a result, production capacity could, if required, be rapidly expanded to satisfy twice the current demand.

The actions of the Global Drug Facility have also led to an increase in the number of courses of treatment for multidrug-resistant tuberculosis delivered. In 2013, the facility delivered a sufficient quantity of various drug combinations to provide 32 000 courses of treatment, compared with 19 600 courses in 2011.

Discussion

A summary of the main lessons learnt from the operation of the Global Drug Facility is given in Box 1. First, the expansion of the supplier base for internationally quality-assured, second-line drugs for multidrug-resistant tuberculosis ensures competition in the drug market that enabled the Global Drug Facility to consistently secure low prices. Second, the ability of the Global Drug Facility to increase the volume of drug purchases by consolidating orders from different purchasers also contributed to lower costs, as did the system of competitive bidding involving long-term agreements and the existence of the donor-funded rotating stockpile. The stockpile also helped decrease delivery times. Third, the resulting drug cost savings led to an increase in the number of courses of treatment delivered. In the future, these savings could be used by governments and donors to further increase the number of patients treated, which could, in turn, contribute to even greater consolidation of orders and, hence, to additional reductions in the cost of quality-assured drugs. ■

Competing interests: None declared.

ملخص

خفض أسعار علاج السل المقاوم للأدوية المتعددة من خلال مرفق الأدوية العالمي

المشكلة تعاني بلدان عديدة من محدودية خبرات تأمين أفضل الأسعار للأدوية وليس لديها سوى صلاحيات تفاوض قليلة. وينطبق هذا بوجه خاص على نظم العلاج المعقدة والطويلة وباهظة الثمن التي تستخدم لعلاج السل المقاوم للأدوية المتعددة.

الأسلوب يتخصص مرفق الأدوية العالمي التابع لشراكة دحر السل في تحسين الوصول على الصعيد العالمي إلى الأدوية المضادة للسل وتقنيات التشخيص التي تلبي معايير الجودة الدولية.

المواقع المحلية يستطيع مرفق الأدوية العالمي تأمين انخفاضات في الأسعار من خلال إجراء مناقصات تنافسية بين صانعي الأدوية المؤهلين مسبقاً وعن طريق تعزيز الطلبات لتحقيق أحجام شراء

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

التغيّرات ذات الصلة في عام 2013، قام مرفق الأدوية العالمي بخفض أسعار أدوية الخط الثاني التي يقوم بتوريدها لمكافحة السل المقاوم للأدوية المتعددة: وانخفضت التكلفة الإجمالية لأطول نظم العلاج وأبهظها ثمناً للمريض بمقدار 26 ٪ – أي من 7890 دولاراً أمريكياً في عام 2011 إلى 5822 دولاراً أمريكياً في عام 2013.

الدروس المستفادة تم خفض أسعار علاج السل المقاوم للأدوية المتعددة الذي يقوم بتوريده مرفق الأدوية العالمي عن طريق دمج الطلبات لتحقيق أحجام شراء ضخمة، عن طريق إجراء مناقصات دولية تنافسية وعن طريق إنشاء مخزونات احتياطية من الأدوية الممولة من المانحين. وكان الارتفاع في عدد موردي الأدوية مضمونة الجودة على الصعيد الدولي مهماً كذلك. ويمكن استخدام الوفورات الناتجة عن خفض تكاليف الأدوية لزيادة عدد المرضى الذين يتلقون العلاج عالي الجودة.

摘要

通过全球药物机构降低多耐药性肺结核的治疗费

问题 许多国家在制定最佳药物价格上经验有限，几乎没有谈判权。对于复杂、漫长且昂贵的多耐药性肺结核疗程来说尤其如此。

方法 遏制结核病合作关系全球药物机构（The Stop TB Partnership’s Global Drug Facility）致力于改善全球对符合国际质量标准的抗痨药物和诊断技术的使用。

当地状况 全球药物机构能够通过在具有资格的药物制造商间竞标并借助合并订单实现大量购买来确保药物降价。以这种方法整合市场提高了优质药物供应商们的积极性。

相关变化 2013 年，全球药物机构降低了供应给多耐药性肺结核病的二线药物价格。肺结核病人耗时最长、最昂贵的治疗总费用降低了 26%，从 2011 年的 7890 美元降至 2013 年的 5822 美元。

经验教训 通过合并订单实现的大量购买、国际竞标以及捐助者资助的药物库存，全球药物机构降低了其供应的多耐药性肺结核药物的价格。国际优质药物供应商数量的增加也起了重要作用。药物成本降低节省下来的资金有助于让更多病人获得高质量的治疗。

Résumé

Réduction du prix du traitement pour soigner la tuberculose multirésistante aux médicaments par le biais du Dispositif mondial d’approvisionnement en médicaments

Problème De nombreux pays ont peu d’expérience dans l’obtention des meilleurs prix pour les médicaments et sont en position de faiblesse pour négocier. Cela est particulièrement vrai pour les traitements complexes, longs et coûteux qui sont utilisés pour traiter la tuberculose multirésistante aux médicaments.

Approche Le Dispositif mondial d’approvisionnement en médicaments du partenariat Stop TB est dédié à l’amélioration dans le monde de l’accès aux médicaments antituberculeux et aux techniques de diagnostic qui répondent aux normes de qualité internationales.

Environnement local Le Dispositif mondial d’approvisionnement en médicaments est capable de garantir des réductions de prix via des appels d’offre compétitifs lancés auprès des fabricants de médicaments pré-qualifiés et via le regroupement des commandes pour arriver à de grands volumes d’achat. Cette manière de procéder à des achats groupés augmente les incitations aux fournisseurs pour qu’ils produisent des médicaments de qualité garantie.

Changements significatifs En 2013, le Dispositif mondial d’approvisionnement en médicaments a réduit le prix des médicaments de deuxième intention qu’il fournit pour la tuberculose multirésistante aux médicaments: le coût global du protocole thérapeutique le plus long et le plus coûteux a diminué de 26% – de 7890 dollars des États-Unis d’Amérique (US$) en 2011 à 5822 US$ en 2013.

Leçons tirées Le prix du traitement pour la tuberculose multirésistante aux médicaments fourni par le Dispositif mondial d’approvisionnement en médicaments a été réduit par les achats groupés pour parvenir à de grand volumes d’achats, par les appels d’offre internationaux et compétitifs, et par l’existence de réserves de médicaments financés par les donateurs. La hausse du nombre de fournisseurs de médicaments de qualité garantie dans le monde a également été importante. Les économies réalisées grâce à la baisse des coûts des médicaments pourraient être utilisées pour augmenter le nombre de patients bénéficiant de traitement de qualité élevée.

Резюме

Снижение стоимости лечения туберкулеза с множественной лекарственной устойчивостью при помощи Глобального механизма по обеспечению лекарственными средствами

Проблема Многие страны имеют небольшой опыт обеспечения минимальных цен на лекарственные препараты и ограниченные возможности ведения переговоров. Это особенно верно, когда речь идет о сложных, продолжительных и дорогостоящих схемах приема лекарств, применяющихся при туберкулезе с множественной лекарственной устойчивостью.

Подход Глобальный механизм по обеспечению лекарственными средствами Партнерства «Остановить туберкулез» предназначается для расширения доступа к противотуберкулезным лекарственным препаратам и соответствующим международным стандартам качества методам диагностики во всем мире.

Местные условия Глобальный механизм по обеспечению лекарственными средствами позволяет обеспечить снижение цен за счет конкурсных закупок у прошедших предварительную проверку производителей лекарственных препаратов и объединенных заказов, увеличивающих объемы закупок. Такое консолидирование рынка более эффективно стимулирует

поставщиков лекарственных средств гарантированного качества.
Осуществленные перемены В 2013 г. Глобальный механизм по обеспечению лекарственными средствами позволил снизить стоимость лекарственных препаратов второй линии, поставляемых для лечения туберкулеза с множественной лекарственной устойчивостью: общая стоимость наиболее продолжительной и дорогостоящей схемы приема лекарств для одного пациента снизилась на 26% — с 7 890 долларов США в 2011 г. до 5 822 долларов США в 2013 г.
Выводы Стоимость препаратов для лечения туберкулеза с множественной лекарственной устойчивостью, поставляемых при помощи Глобального механизма по обеспечению лекарственными средствами, снизилась за счет составления объединенных заказов, увеличивающих объемы закупок, проведения международных конкурсных торгов и наличия запасов лекарственных препаратов, приобретенных благодаря спонсорскому финансированию. Кроме того, важную роль сыграл рост количества проверенных поставщиков лекарственных препаратов, соответствующих международным стандартам качества. Средства, сэкономленные благодаря снижению стоимости лекарственных препаратов, могут быть использованы для увеличения количества пациентов, получающих высококачественное лечение.

Resumen

Reducir el precio del tratamiento para la tuberculosis multirresistente mediante el Servicio Farmacéutico Mundial

Situación Muchos países tienen una experiencia limitada en garantizar los mejores precios de medicamentos y poco poder de negociación, lo cual es particularmente cierto en el caso de los regímenes complejos, largos y costosos utilizados para tratar la tuberculosis multirresistente.
Enfoque La asociación Stop TB del Servicio Farmacéutico Mundial se dedica a mejorar el acceso a nivel mundial a los medicamentos antituberculosos y las técnicas de diagnóstico que cumplen con los estándares internacionales de calidad.
Marco regional El Servicio Farmacéutico Mundial es capaz de lograr reducciones de precios mediante la licitación competitiva entre fabricantes de medicamentos precalificados y la consolidación de pedidos para lograr grandes volúmenes de compra. Consolidar el mercado de esta manera aumenta los incentivos para los proveedores de medicamentos con garantía de calidad.
Cambios importantes En 2013, el Servicio Farmacéutico Mundial redujo el precio de los medicamentos de segunda línea que suministra para la tuberculosis multirresistente: el coste total del régimen de tratamiento más largo y más caro para un paciente disminuyó un 26 % – de 7890 dólares de Estados Unidos (US$) en el 2011 a US$ 5822 en 2013.
Lecciones aprendidas El precio del tratamiento para la tuberculosis multirresistente suministrado por el Servicio Farmacéutico Mundial se redujo mediante la consolidación de pedidos a fin de comprar grandes volúmenes, la licitación internacional competitiva y la existencia de arsenales de medicina financiados por donantes. También fue importante el aumento del número de proveedores de medicamentos con garantía de calidad internacional. Los ahorros obtenidos al disminuir los costes de medicamentos podrían aprovecharse para aumentar el número de pacientes que reciben un tratamiento de alta calidad.

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From availability to uptake: planning for the introduction of new, child-friendly anti-tuberculosis formulations

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SUMMARY

BACKGROUND: Assessing the state of country readiness for the introduction of new, child-friendly anti-tuberculosis formulations can highlight potential bottlenecks, facilitate early planning, and accelerate access to appropriate treatment for children with tuberculosis (TB).

METHODS: To understand pathways and potential obstacles to the introduction of new pediatric formulations, we performed a desk review of key policy documents and conducted 146 stakeholder interviews in 19 high-burden countries.

RESULTS: Issuance of World Health Organization (WHO) guidance serves as the trigger for considering adoption in most countries; however, the degree of alignment with WHO recommendations and duration of introduction processes vary. Endorsement by experts and availability of local evidence are leading criteria for adoption in upper-middle- and high-income countries. Ease of administration, decreased pill burden, and reduced treatment costs are prioritized in low- and lower-middle-income settings. Countries report an average of 10 steps on the path to new treatment introduction, with core steps taking between 18 and 71 months.

CONCLUSIONS: The process of new treatment introduction is complicated by diverse country processes, adoption criteria, and evidence requirements. Challenges differ between low- and middle-to-high-income countries. Responsiveness to the unique hurdles faced across settings is important in ensuring a sustainable market for improved pediatric anti-tuberculosis treatment.

KEY WORDS: introduction; adoption; timelines; access; pathways

IN RECENT YEARS, there has been a call to action to mobilize political will and resources for the neglected epidemic of childhood tuberculosis (TB). The need for improved, child-friendly treatment for both drug-susceptible and drug-resistant TB has been identified as a cornerstone of this agenda.[1] Real and perceived concerns about the size of, and fragmentation in, the pediatric TB market, however, have engendered commercial inertia. These factors have contributed to the current access crisis, whereby even 5 years after World Health Organization (WHO) issuance of guidance on optimal dosing for the treatment of TB in children, there are no quality-assured, correctly dosed, child-friendly TB formulations on the global market.[2,3]

In the absence of child-friendly treatment options, providers and parents have been forced to crush adult pills or use existing, inappropriately dosed pediatric formulations to treat children with TB, options that have been shown to increase the risk of poor treatment outcomes, non-adherence, and loss to follow-up among children.[4–6]

Since 2013, a new initiative spearheaded by the Global Alliance for TB Drug Development and the WHO has brought together commercial partners, policy makers, donors, national TB programs (NTPs), and child health stakeholders to catalyze the market for child-friendly anti-tuberculosis treatment. Through this effort, it is expected that appropriately dosed, dispersible, fixed-dose combinations (FDCs) for the treatment of drug-susceptible TB will be available through the Global Drug Facility (GDF) by late 2015.

Before improved treatments can translate into better outcomes in children with TB, they must be made available to pediatric patients in high-burden countries (HBCs) throughout the world.[7] Lessons learned from previous treatment introductions suggest that the process of country introduction and scale-up is often poorly defined, and associated timelines are protracted.[6] Suppliers report that slow country uptake, erratic procurement, and fragmented demand for pediatric TB products contribute to manufacturing inefficiencies and wastage, deterring

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Table 1 Interview affiliations

	Organization							
Country	NTP	Health Ministry	Procurement	Regulatory	WHO	Expert	NGO	Total
Afghanistan	1	1		1		1	1	5
Bangladesh	1		1	2	1			5
Brazil	2	1	1	1	1	1		7
Cambodia	5			4	1		2	12
China	1		1	1	1	5		9
Democratic Republic of Congo	1			1	1	1	2	6
Ethiopia	1	3	1	2	1			8
India	2				1	3		6
Kenya	2	1	1	1	1	2		8
Myanmar	1	2	1		1			5
Nigeria	2	1	2		1	1	1	8
Pakistan	1		1	1	1	1		5
Philippines	5	1	2	1	1	1		11
Russia	2		2	1	1	1		7
South Africa		1	1			5	1	8
Tanzania	4	1	1	1	1			8
Thailand	4		3	1	1	3		12
Uganda	1	1	1	1		1		5
Viet Nam	6	1			2	1	1	11
Total	42	14	19	19	17	27	8	146

NTP = National Tuberculosis Program; WHO = World Health Organization; NGO = non-governmental organization.

further investment in the childhood TB treatment market.

This article assesses the state of country readiness for the introduction of new pediatric TB formulations and identifies potential bottlenecks on the road to introduction, implementation, and scale-up of new anti-tuberculosis formulations. Clarifying adoption and introduction pathways can facilitate efforts to navigate hurdles, supporting a healthy market for life-saving therapies for children with TB.

METHODS

To understand pathways and potential obstacles to the introduction of new treatments for childhood TB, we conducted qualitative research in 19 of 22 HBCs (Table 1). Three HBCs—Indonesia, Mozambique, and Zimbabwe—were excluded from the study due to time and capacity constraints.

An initial literature review of key policy documents, including national TB strategic plans, TB treatment guidelines, essential medicines lists (EMLs), procurement manuals, regulatory guidelines, budgets, grant plans, and program reviews, was performed. Findings were entered into a standardized data form. Informant interviews were then conducted to validate and expand upon findings from the desktop review. Interviewees were identified through a combination of purposive and snowball sampling. Predetermined criteria included selection of representatives from the NTP, WHO country office, national regulatory authority, procurement office, and the essential medicines committee of each country. Representatives were then asked to identify additional individuals and organizations involved in TB program decision making, such as TB technical working group members, professional societies, development partners, non-governmental organizations, civil society, and 'experts'.

Interview tools were developed and refined by the research team. Interviewers were then trained in the administration of the study tool, a structured questionnaire covering topics such as policy change processes, evidence requirements, decision-making criteria and influencers, procurement and regulatory requirements, and planning sequences and timelines.

In all, 146 interviews were conducted between December 2014 and April 2015 (see Table 1 for affiliations). Interviews were conducted in person in all countries, with the exception of China, Russia, and a subset of interviews in Myanmar. Informed consent was obtained verbally using a standard script. Ethics committee involvement was not required, as the scope of inquiry was institutional processes rather than individuals. Data from interviews were entered directly into an Excel template (MicroSoft, Redmond, WA, USA), cleaned, and validated. Data were then aggregated, coded, and analyzed by the core study team. Results were compared and discrepancies were discussed and resolved by the team.

Study limitations include the potential for recall error or personal bias in the data, given the relatively small sample size per country. These risks were mitigated through triangulation of findings with data from the published literature, and by purposively sampling diverse institutional representatives to

enable multiple perspectives. Limitations also include the study's almost exclusive focus on the public sector TB market, given its disproportionate relevance for TB control efforts (Table 1).

RESULTS

Treatment introduction processes

Stakeholders were asked to describe the steps involved in introducing new TB treatments in their respective countries. The average number of procedural steps reported by participants was 10 (range 7–13), with introduction processes in most countries commencing upon issuance of WHO guidance on new treatments (Table 2). Updates to national treatment guidelines, guideline dissemination, forecasting, procurement transition, and training are core elements of the introduction process across all HBCs; WHO EML inclusion and GDF product availability are less central to the introduction processes in most countries (Table 2).[8]

Timelines associated with introduction vary significantly across HBCs. Reported transition times for a few key steps—including registration, national guideline change, forecasting, and procurement—range from <2 years in countries such as Afghanistan, Bangladesh, and the Democratic Republic of Congo (DRC) to >5 years in countries such as China and South Africa, with a median time across HBCs of 24 months (2 years) (Figure 1).

Of 19 countries participating in the study, 18 reported provisions in place that potentially shorten regulatory timelines. This included 8 countries with fast track registration procedures, 3 that allow regulatory exemptions, and 7 with both fast track and waiver provisions. On the other hand, additional procedural and planning processes across all countries, and requirements for local clinical, cost-benefit, or pilot studies in a subset of countries—including Russia, India, China, South Africa, Uganda, and Viet Nam—serve to further prolong introduction timelines.

Policy adoption criteria

The WHO consistently serves as a catalyst for considering treatment adoption across HBCs. While WHO guidance serves as a trigger for consideration of new treatments in 15 of the 19 countries surveyed, the degree to which countries accept WHO endorsement as a proxy for local review processes differs between low- and middle-to-high-income countries (Figure 2). Although important, WHO recommendation alone is insufficient to trigger guideline change among upper-middle-income and high-income countries (UMICs and HICs), such as South Africa, Thailand, Russia, and China and in India, where endorsement by experts and availability of local evidence on new treatments are seen as priority criteria for adoption (see Appendix for a full listing of countries by World Bank income classification).

Among most low- and lower-middle-income countries (LIC/LMIC), limited capacity to independently execute additional studies and the cascade of influence through funding agencies, such as the Global Fund to Fight AIDS, TB, and Malaria (The Global Fund), drive close alignment with WHO guidelines. Practical considerations, such as decreased pill burden, ease of administration, and reduced costs of treatment, are reported to be leading influencers of treatment adoption in these settings (Figure 2).

Of 19 HBCs participating in the study, 15 (79%) have adopted into national treatment guidelines either the WHO's 2010 'Rapid Advice' or its 2014 dosing recommendations for treatment of drug-susceptible TB in children;[3,9] however, the four countries that have not as yet officially adopted WHO dosing recommendations—Brazil, China, DRC, and India—represent 47% of the estimated burden of pediatric TB across the HBCs and 49% of the burden among countries participating in the study (Figure 3).[10]

Market readiness for new pediatric TB formulations

Existing preferences for treatment of drug-susceptible TB in children may have a bearing on country receptiveness to new pediatric TB formulations. Country practices are currently divided between those that use pediatric FDCs (63%), those that use loose pediatric drug formulations (16%), those that split or crush adult tablets (11%), and those that use a mixture of product types (11%) to treat childhood TB (Figure 4). While there are signs that attitudes may be shifting, experts in countries such as Russia, China, and India have historically been reluctant to implement FDC formats, given either providers' preferences for individually tailored dosing approaches or the lack of locally generated evidence on FDC effectiveness. The majority of countries (84%), however, report an eagerness to switch to pediatric FDCs, once appropriately dosed treatments are available (Figure 4).

Procurement channels for first-line drugs (FLDs) for children and adults are currently divided between quality-assured and non-quality-assured, locally and globally supplied networks. Of the 19 countries surveyed, seven (37%) report exclusively securing quality-assured FLDs through the GDF. A recent study suggests that procurement volumes of FLDs for children through the GDF platform reflect approximately 12% of notified pediatric TB cases in the HBCs.[11] The remaining countries report procuring FLDs through national or international competitive bidding, or a mixture of approaches (Figure 5). Among nine countries procuring some or all FLDs locally, seven report regulatory or procedural provisions prioritizing locally sourced drugs (Figure 5).

Table 2 Reported steps from new treatment availability to introduction

Countries	Steps*												
	WHO recommends	WHO adds to EML	National treatment guidelines updated	Dissemination of new guidelines	Addition to national EML	Product registration	Training	Product quality surveillance	Pharmacovigilance	Product available through GDF	Forecasting/ procurement	Other steps†	Total number of steps
Afghanistan	√	√	√	√	√	√	√			√	√		9
Bangladesh	√	√	√	√	√	√	√	√	√	√	√	√ √	13
Brazil	√		√	√	√	√	√	√	√		√	√	10
Cambodia	√		√	√	√		√	√	√	√	√		9
China			√	√	√	√	√				√	√	7
Democratic Republic of Congo	√	√	√	√	√	√	√	√	√	√	√		11
Ethiopia	√	√	√	√	√	√	√	√	√	√	√		11
India			√	√		√	√	√	√		√	√	8
Kenya	√	√	√	√	√	√	√	√	√		√	√ √	12
Myanmar	√		√	√			√				√	√ √ √	8
Nigeria	√	√	√	√	√	√	√	√	√	√	√		11
Pakistan	√	√	√	√	√	√	√	√	√	√	√		11
Philippines	√		√	√	√	√	√	√	√		√	√	10
Russia			√	√	√	√	√				√	√ √	8
S Africa	√	√	√	√	√	√	√	√	√		√	√	11
Tanzania	√	√	√	√	√	√	√	√	√	√	√	√	12
Thailand	√		√	√	√	√	√	√	√		√	√	10
Uganda	√	√	√	√	√	√	√	√	√	√	√		11
Viet Nam	√	√	√	√	√	√	√	√	√	√	√	√ √	13
Total countries	16	11	19	19	17	17	19	15	15	10	19	18	

* The sequence of 'steps' represented in the table is not indicative of the order of processes in specific countries.
† Each √ represents one step. Potential steps mentioned include technical committee review, import license, local clinical trial, budget approval, approval by the Global Fund to Fight AIDS, Tuberculosis and Malaria, among others.
WHO = World Health Organization; EML = Essential Medicines List; GDF = Global Drug Facility.

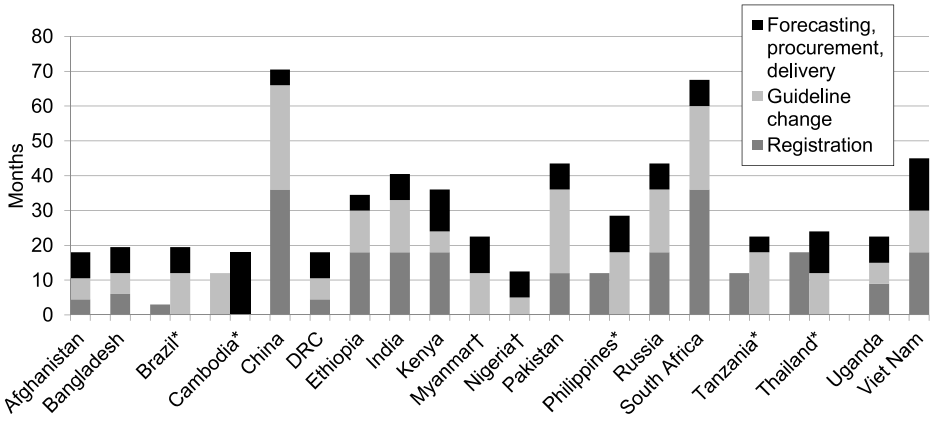

Figure 1 Estimated median time for key steps toward product availability. *Indicates that more than one of these processes may occur in parallel. †Stakeholders report that registration is not required as a condition for introduction of new anti-tuberculosis drugs. DRC = Democratic Republic of Congo.

DISCUSSION

Readiness for the introduction of new pediatric TB formulations is marked by country-level demand, the presence of a receptive policy environment, and the existence of a pathway for the rapid introduction of new treatment formulations. The criteria for the adoption of new treatments differ across low- and middle-to-high-income countries. While WHO guidance serves as the primary trigger for considering the adoption of new anti-tuberculosis treatment formulations across settings, the degree of alignment around WHO recommendations and the duration of national policy adoption processes vary significantly. Among UMICs and HICs, such as South Africa, Thailand, Russia, and China, and in India, both treatment endorsement by experts and the availability of local evidence on new treatments are seen as critically influencing adoption. Donor requirements in most LIC and LMIC settings, on the other hand, drive convergence around WHO-recommended treatments.

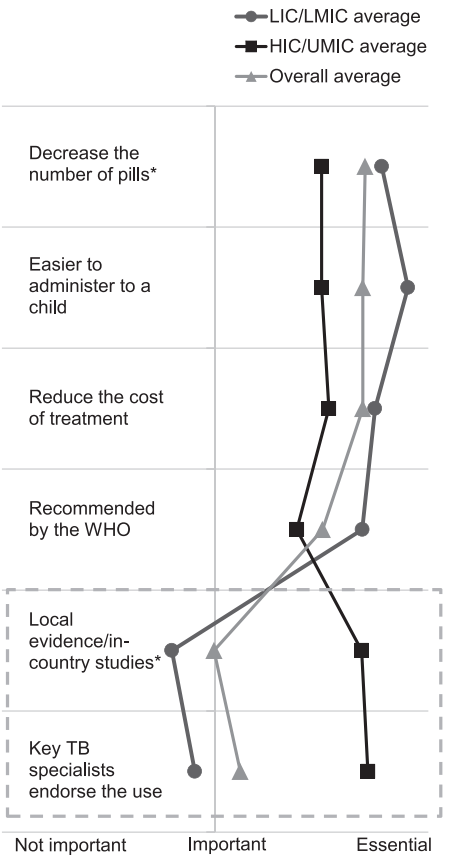

Figure 2 Key criteria for treatment adoption. *Myanmar data on the number of pills and Brazil data on local evidence not available. WHO = World Health Organization; LIC = low-income country; LMIC = low-middle-income country; HIC = high-income country; UMIC = upper-middle-income country.

Interview participants reported standard timelines for drug registration, guideline change, forecasting, procurement, and delivery of new treatments as ranging from 18 to 71 months across the HBCs. Strong expressions of interest in the new FDCs (84% of countries) and expedited regulatory provisions for treatments of public health priority (95% of countries) highlight the potential to accelerate time-to-market for forthcoming child-friendly anti-tuberculosis formulations in some settings; however, additional country-specific procedures in other settings — such as requirements for EML inclusion, product quality testing, pharmacovigilance, and generation of local clinical and non-clinical evidence—further prolong introduction timelines.

Procurement practices for pediatric TB treatments currently remain fragmented across formulation types and procurement channels, and while most countries have adopted WHO dosing guidance, those countries that have not represent approximately half of pediatric TB cases. For small treatment markets, such as the market for first-line pediatric TB formulations, convergence of procurement practice around WHO-recommended treatments and quality-

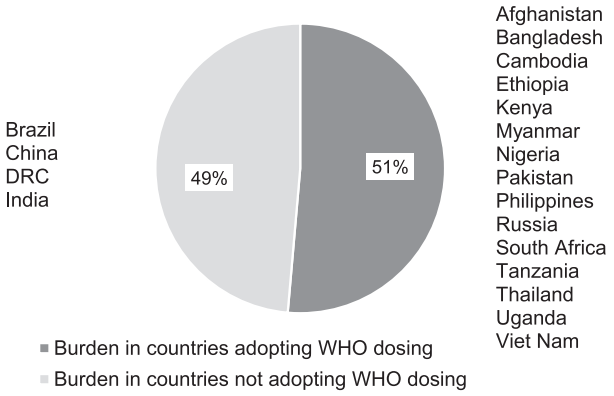

Figure 3 Burden in countries per WHO guideline adoption status. WHO = World Health Organization; DRC = Democratic Republic of Congo.

assured supply through platforms such as the GDF can drive affordability by facilitating demand consolidation to foster manufacturing economies of scale. As home to almost half of all new adult and pediatric TB cases in the 22 HBCs, middle-to-high-income HBCs, such as the BRICS countries (Brazil, Russia, India, China, and South Africa), are also critical in driving solutions to the childhood TB problem.[10] The current non-alignment of some middle- and high-income countries with WHO treatment recommendations and hurdles to introduction—related to slow policy change processes, localized evidence requirements, trade protections, and arduous regulatory provisions—hinder the rapid integration of new treatments in these settings. Failure to capture such a significant portion of the treatment population poses a fundamental threat to both affordability and market sustainability, and can deter further commercial investment in this and other small but essential public health markets.

Identifying opportunities to promote harmonization of treatment practices and requirements across high-, middle-, and low-income TB-endemic settings—including greater mutual recognition of strin-

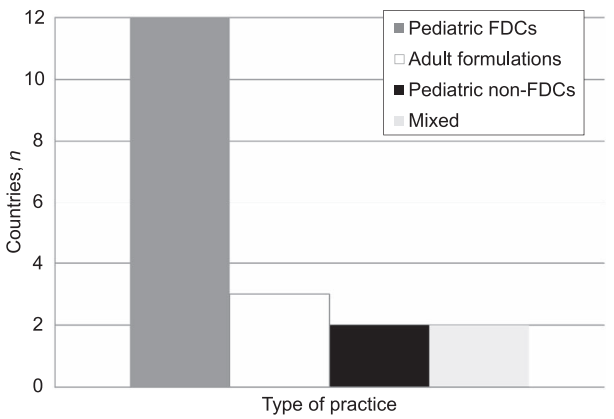

Figure 4 Formulation practices. FDC = fixed-dose combination.

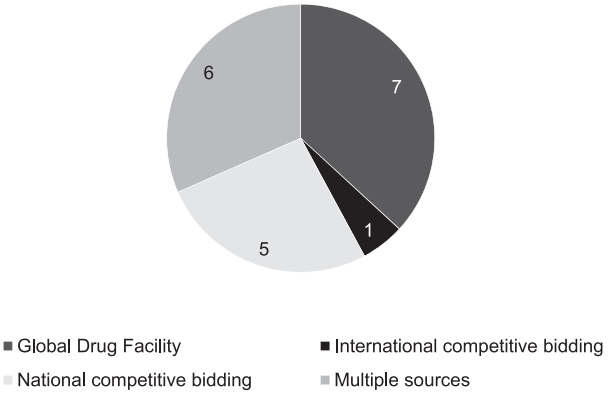

Figure 5 Source of country first line drug supply.

gent regulatory authority or WHO prequalification standards and alignment around normative treatment recommendations—could help accelerate access to life-saving treatments for childhood TB. The recent agreement of BRICS Health Ministers to collaborate in scaling up research on, and access to, new TB treatments represents an important step in the right direction; however, continued political will and resources will be needed.[12]

CONCLUSIONS

Before improved treatments can translate into better outcomes for children with TB, they must be made available to pediatric patients across the TB-endemic world. The process of treatment introduction and scale-up is complicated by a variety of country-specific introduction processes, adoption criteria, and administrative and evidence requirements. The challenges faced differ significantly between low- and middle-to-high-income countries. Clarifying adoption and introduction pathways can facilitate efforts to navigate hurdles and support a healthy market for life-saving therapies for children with TB. In addition, the development of strategies that are responsive to the unique hurdles faced across settings is important in accelerating access to, and ensuring a sustainable market for, new pediatric TB treatments.

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Conflicts of interest: SM is employed by the Global Alliance for TB Drug Development, whose activities are aimed at developing and making available improved therapies for TB. RG, PP, and MS are employed by Management Sciences for Health (Arlington, VA, USA), which provides technical assistance with drug management

in many of the high-burden countries. Other authors declare no conflicts of interest.

The financial sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of this report.

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APPENDIX

World Bank Country and Lending Group Classifications, 2015[1]

Low-income economies	Afghanistan, Bangladesh, Cambodia, Democratic Republic of Congo, Ethiopia, Kenya, Myanmar, Tanzania, Uganda, Zimbabwe
Lower-middle-income economies	India, Nigeria, Pakistan, Philippines, Vietnam
Upper-middle-income economies	South Africa, Brazil, Thailand, China
High-income economies	Russian Federation

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RESUME

CONTEXTE : Evaluer le niveau de préparation du pays à l'introduction de nouvelles formulations pour la tuberculose (TB) acceptables par les enfants peut mettre en lumière des goulots d'étranglement potentiels, faciliter une planification précoce et accélérer l'accès à des traitements appropriés pour les enfants atteints de TB.

MÉTHODE : Pour comprendre le cheminement et les obstacles potentiels à l'introduction de formulations TB pédiatriques correctement dosées, nous avons réalisé une revue approfondie des principaux documents de politique et conduit 146 entretiens avec des parties prenantes dans 19 des 22 pays les plus touchés (HBC).

RÉSULTATS : La publication de la guidance de l'Organisation Mondiale de la Santé (OMS) sert de premier déclencheur pour envisager l'adoption dans la majorité des HBC ; cependant, le degré d'alignement avec les recommandations de l'OMS et la durée des procédures d'introduction dans le pays varient. L'approbation par des experts et la disponibilité de preuves locales relatives aux nouveaux traitements sont les critères principaux d'adoption dans les HBC à revenu moyen supérieur et élevé. La facilité d'administration, la réduction du nombre de comprimés et la réduction du coût du traitement sont les priorités des pays à revenu faible ou intermédiaire. Les pays font état d'une moyenne de 10 étapes dans la procédure d'introduction de nouveaux traitements, les étapes principales prenant entre 18 et 71 mois.

CONCLUSION : Le processus d'introduction de nouveaux traitements et leur expansion sont compliqués par un ensemble de procédures d'introduction spécifiques à chaque pays, par les critères d'adoption, et les besoins de preuves. Les défis diffèrent entre les pays à revenu faible et moyen et ceux à revenu élevé. Les stratégies qui répondent aux obstacles particuliers affrontés dans différents contextes sont importantes pour assurer un marché durable afin d'améliorer le traitement anti-tuberculeux de l'enfant.

RESUMEN

MARCO DE REFERENCIA: La evaluación del grado de preparación de un país para la introducción de nuevas formulaciones de medicamentos antituberculosos adaptados a los niños pone de manifiesto los eventuales cuellos de botella del procedimiento, facilita una planificación temprana y acelera el acceso a los tratamientos apropiados para los niños con diagnóstico de tuberculosis (TB).

MÉTODOS: Con el propósito de comprender los mecanismos de introducción de las formulaciones pediátricas con dosis apropiadas y los posibles obstáculos que pueden surgir, se llevó a cabo una revisión exhaustiva de los principales documentos normativos y se realizaron entrevistas a 146 interesados directos en 19 países con alta carga de morbilidad (HBC) por TB.

RESULTADOS: La publicación de las directrices de la Organización Mundial de la Salud (OMS) constituye el principal incentivo de la adopción de nuevos tratamientos en la mayoría de los HBC; sin embargo, el grado de cumplimiento de estas recomendaciones y la duración de los mecanismos de introducción en los países varía en los diferentes entornos. La aprobación por los expertos y la existencia de datos fidedignos locales sobre los nuevos tratamientos son los criterios fundamentales de la adopción en los países con alta morbilidad e ingresos medios altos y altos. En los países con ingresos medios bajos y bajos se da prioridad a las consideraciones prácticas como la facilidad de administración, una baja cantidad de comprimidos y el bajo costo del tratamiento. Los países notifican un promedio de 10 etapas en el procedimiento de introducción de los nuevos tratamientos y las etapas básicas duran 18–71 meses.

CONCLUSIÓN: La introducción y la ampliación de escala de los nuevos tratamientos se dificultan por la diversidad de mecanismos, criterios de adopción y la exigencia de datos fidedignos en cada país. Los obstáculos difieren de manera significativa en los países de ingresos bajos e ingresos medios a altos. Las estrategias sensibles a las dificultades específicas encontradas en los diferentes entornos son importantes para garantizar un mercado sostenible para mejorar el tratamiento contra la TB pediátrica.

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

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SUMMARY

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

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

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

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

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

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

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

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

STUDY POPULATION AND METHODS

Setting

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

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

Methods

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

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

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

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

RESULTS

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

Table 1 Overview of study methodology

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

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

Table 2 Characteristics of study population

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

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

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

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

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

Table 3 Health care seeking behaviour

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

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

Health care seeking behaviour

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

Comorbidities

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

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

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

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

Table 5 Financial impact of TB on patients

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

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

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

Impact of TB

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

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

DISCUSSION

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

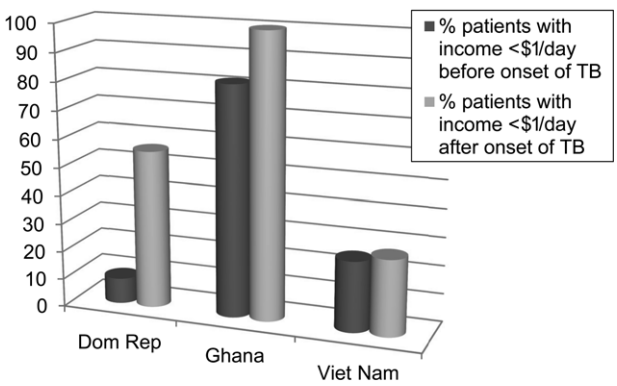

Figure Patients below US$1/day poverty line before and after onset of TB. TB = tuberculosis.

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

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

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

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

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

Limitations

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

CONCLUSIONS

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

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RÉSUMÉ

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

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

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

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

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

RESUMEN

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

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

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

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

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

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RESEARCH ARTICLE Open Access

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

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Abstract

Background: Multi drug resistant tuberculosis (MDR-TB) is an emerging challenge for TB control programs globally. According to World health organization, 2012 report Ethiopia stands 15th out of the 27 high priority countries in the world and 3rd in Africa. Updated knowledge of the magnitude of MDR-TB is so substantial to allocate resources, and to address prevention and control measures. Therefore, the aim of this study was to assess the prevalence of MDR-TB and associated risk factors in West Armachiho and Metema districts of North Gondar.

Methods: A cross-sectional study was conducted in West Armachiho and Metema districts between February 01 and June 25, 2014. A total of 124 consecutive smear positive pulmonary tuberculosis patients were included in the study. Socio-demographic and possible risk factor data were collected using a semi-structured questionnaire. Drug susceptibility testing was first performed for rifampicin using GeneXpert MTB/RIF. For those rifampicin resistant strains, drug susceptibility testing was performed for both isoniazid and rifampicin to identify MDR-TB using the proportional method on LJ media. Data were analyzed using statistical Package SPSS version 20; binary logistic regression was used to assess the association. *P*-values < 0.05 were considered as statistically significant.

Results: Of 124 smear-positive pulmonary TB patients, 117 (94.4 %) were susceptible to Rifampicin, while 7 (5.7 %) were confirmed to be resistant to Rifampicin and Isoniazid. The overall prevalence of MDR-TB was 5.7 % (2.3 % among new cases and 13.9 % among previously treated cases). History of previous treatment (OR = 7, *P* = 0.025) was significantly associated risk factor for MDR-TB.

Conclusion: The overall prevalence of MDR-TB was 5.7 % among cases at five health centers and a history of previous treatment was found to be a risk factor for being infected by an MDR-TB strain. Therefore, maximizing early case detection and treatment, strengthening TB infection control activities and proper implementation of DOTS are recommended to reduce the burden of MDR-TB.

Keywords: Tuberculosis, MDR-TB, Risk factors

Background

Tuberculosis (TB) remains a major global health problem. In 2012, World health organization (WHO) estimated 8.6 million people developed TB and 1.3 million died from the disease [1]. Even more, according WHO 2014 report, the morbidity and mortality rate were increased by 400,000 and 200,000 cases, respectively, with reference to the previous WHO report [2]. Besides both reports presented that the mortality of the disease was predominantly observed in human immunodeficiency virus (HIV) co-infection, thus 320,000 (2012) and 360,000 (2013) patients were died due to HIV co-infection. Tuberculosis compound by the spread of multidrug resistant (MDR) strains becomes a prime global concern, 450,000 and 480,000 multidrug resistant tuberculosis (MDR-TB) cases were reported in 2012 and 2013 respectively. Based on WHO 2014 report, the prevalence of MDR-TB among new and previously treated cases was 3.5 % and 20.5 % respectively. These estimates are essentially unchanged from 2012 [1, 2].

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Emerging and spread of drug resistance TB has encountered as a great challenge in Africa region, Sub-Saharan Africa in particular. Information on the extent of MDR-TB from Africa region is very limited, probably due to poor laboratory facilities, poor surveillance mechanisms and reporting procedures, outdated databases and sub-optimal coverage of the infrequent surveys. Sub-Saharan Africa stands the burden of both very high TB incidence and the highest HIV prevalence rates in the world, and represents 14 % of the global burden of new MDR-TB cases [3].

Moreover, on the basis of WHO 2012 report, Ethiopia stands 15th out of the 27 high priority countries in the world and 3rd in Africa following South Africa and Nigeria with (1600 and 480) among new and retreatment cases respectively were MDR-TB cases [4]. According to the drug resistance survey conducted nationwide, the prevalence of MDR-TB was; 1.6 % in newly diagnosed TB and 11.8 % among previously treated TB cases. The country's burden of MDR-TB in 2009 was estimated to be 1500 (870–2600) and 420 (230–740) among new and re-treatment cases respectively. Despite being a huge global threat, access to treatment is very limited with only 10 % of the estimated MDR-TB cases among notified TB cases in 2009 in the high MDR-TB countries and 11 % globally were enrolled in treatment [5, 6].

In West Armachiho and Metema districts, information regarding TB treatment interrupters, relapses, and failure cases were not well documented. According to the national comprehensive TB/HIV and Tuberculosis & Leprosy guideline these are criteria for suspicion of MDR-TB. Moreover, as to our knowledge, there are only limited data regarding MDR-TB in this particular study area. Therefore, current knowledge on the prevalence of MDR is so substantial to provide useful information on the implementation of standard chemotherapy regimens designed and recommended by WHO for tuberculosis patients who have or have not been treated previously.

Moreover, drug resistance rate can also serve as a useful parameter in the evaluation of the quality of current and past chemotherapy program i.e. direct observed treatment, short course (DOTS). Therefore, understanding the drug susceptibility patterns of *M. tuberculosis* (MTB) is very crucial to treat patients, to decide health priorities, to allocate resources, to monitor the emergency of resistance for planning effective use of anti-TB drugs, to generate knowledge for health workers working in the study area as well as will serve as a preliminary information for health programmers to give special attention and design a package in the national TB control program that addresses such areas where hundred to two hundred thousands of people are employed in huge farms for the production of crops.

Methods

Study area, study design, participants and data collection

A cross-sectional study was conducted in West Armachiho and Metema districts from Feburary 01 to June 25, 2014. A total of 124 smear positive patients were consecutively enrolled through convenient sampling technique. From those patients we gathered; socio-demographic characteristics (gender, age, residence, religion, occupation, marital status, income, ethnicity and education status) and possible risk factors (HIV, smoking, TB contact history, diabetes, fasting, history of prison, BCG vaccination status). Besides from each patient, standard volumes of sputum sample were collected after patients had given instructions accordingly.

Sputum decontamination, isolation, identification & drug susceptibility testing

Smear positive sputum samples were re-confirmed using Gene X-pert and decontamination and further homogenization were done according to Petroff's method. Isolates were identified by using typical colony characteristics on Lowenstein-Jensen (LJ) media and standard biochemical tests. Gene x-pert machine was used to assess rifampicin (RIF) resistant strains, after a while RIF resistant MTB isolates were tested for isoniazid (INH) and RIF using the indirect proportional method on LJ medium. The proportion method calculates the proportion of resistant bacilli present in a strain. Two appropriate dilution of the bacilli, 10^{-2} and 10^{-4}dilutions (undiluted = 10^{6} to 10^{8} CFU/ml), were inoculated on drug-containing and drug-free media. Below a proportion (critical proportion = 1 %), the strain was classified as sensitive; otherwise classified as resistant. Patient's HIV status was collected from the TB unit register at TB clinic of respective health facilities. Quality control was done for gene x-pert (sample processing and probe check) and LJ medium (standard strains of MTB H37Rv-ATCC27294).

Data analysis

Data were entered and analyzed using SPSS version 20.0. Bivariate logistic regression analysis was used to assess the association. *P*-values < 0.05 were considered as statistically significant.

Ethical consideration

Ethical clearance was obtained from the School of Biomedical and Laboratory sciences, University of Gondar. Written permission was obtained from North Gondar Zone Health Department to West Armachiho and Metema Woreda Health Offices and respective health centers. Study participants were recruited after getting written consent.

Results

A total of 124 smear positive tuberculosis patients were included from five different heath centers in West Armachiho and Metema districts. The health centers were Abderafi, Abirihajira, Metema Yohannes, Gendewuha and Metema Hospital.

A majority, 80 (64.5 %) of the study participants were males, the mean and median age of the study subjects were 32 and 29 years respectively. Their age ranges from16–75 years. Nearly half, 46 (48.1 %) were in the age range of 26–35 year, while 37 (29.8 %) were below 25 years old. Of the 124 study subjects, 66 (53.2 %) were urban inhabitants and 59 (47.6 %) were farmers/day laborers. The majority, 116 (93.5 %) of the study subjects were Christians by religion while the rest 8 (6.5 %) were Muslims. More than half, 64 (51.6 %) were illiterate. More than half of new and previously treated cases were males (Table 1).

The proportion of smear positive tuberculosis cases in each health facilities were as follows: Abderafi 49 (39.5 %), Metema Hospital, 34 (29.8 %), Abirihajira 21 (12.9 %), Metema Yohannes 16 (12.9 %) and Gendewuha 4 (3.2 %).

Prevalence of Multi- drug resistant tuberculosis (MDR-TB)

Sputum samples of the 124 smear positive tuberculosis patients were tested for MDR-TB by using Gene-Xpert MTB/RIF technique and conventional solid culture, The overall prevalence of MDR-TB was 7 (5.6 %, 95 % CI; 2.4–10.5 %) and prevalence of MDR-TB among new smear positive TB cases was 2 (2.3 %, 95 % CI; 0–5.9 %) and among previously treated smear positive TB cases 5 (13.9 %, 95 % CI; 2.9–25.7 %). Of the 26 who were reported to have been cured with prior treatment, 1 (3.8 %) and from10 who were reported to have failed or defaulted from prior treatment, 4 (40 %) were relapsed MDR-TB cases. Among 41 patients whose occupation was farmer/daily laborer, 2 (4.9 %) had primary MDR-TB; of 47 whose occupation was other than farmer/day laborer none (0.0 %) had primary MDR-TB. The majority of confirmed MDR-TB subjects were males 6 (85.7 %) and two of the confirmed MDR cases were co-infected with HIV (28.6 %) while, the other five were sero-negative.

Among the five health facilities, MDR-TB cases were obtained from Abderafi health center and Metema District Hospital. Three MDR-TB cases (one from new smear positive study subjects and two from retreatment cases) were identified from Abderafi health center. The other four MDR-TB cases (one from new smear positive study subjects and three from retreatment cases) were identified from Metema hospital.

Table 1 Socio-demographic characteristics of TB patients West Armachiho and Metema districts, Northwest Ethiopia February 01 to June 25, 2014

Variable	Total TB cases (*N* = 124)	New active TB cases (*N* = 88)	Retreatment TB cases (*N* = 36)
Age group in years			
≤25	37 (29.8 %)	31 (35.2)	6 (16.7)
26–35	57 (46 %)	38 (43.2)	19 (52.8)
36–45	16 (12.9)	11 (12.5)	5 (13.9)
≥46	14 (11.3)	8 (9.1)	6 (16.7)
Gender			
Male	80 (64.5)	53 (60.2)	27 (75)
Female	44 (35.5)	35 (39.8)	9 (25)
Resident			
Urban	66 (53.2)	47 (53.4)	19 (52.8)
Rural	58 (46.2)	41 (46.6)	17 (47.2)
Occupation:			
Farmers and day laborers	59 (47.6)	41 (46.6)	18 (50)
House wife	28 (22.6)	21 (23.9)	7 (19.4)
Government employee	8 (6.5)	8 (9.1)	0
Merchant	16 (12.9)	13 (14.8)	3 (8.3)
Driver	5 (4)	1 (1.1)	4 (11.1)
Student	8 (6.5)	4 (4.5)	4 (11.1)
Income/month:			
<500 birr	39 (31.5)	29 (33)	10 (27.8)
500 birr - 999 birr	55 (44.4)	39 (44.3)	16 (44.4)
≥1000 birr	25 (20.2)	16 (18.2)	9 (25)
No means of income	5 (4)	4 (4.5)	1 (2.8)
Religion:			
Christian	116 (93.5)	82 (93.2)	34 (94.4)
Muslim	8 (6.5)	6 (6.8)	2 (5.6)
Ethnicity:			
Amhara	102 (82.3)	77 (87.5)	25 (69.4)
Tigre	22 (17.7)	11 (12.5)	11 (30.6)
Educational status:			
Illiterate	64 (51.6)	42 (47.7)	22 (61.1)
Primary school	36 (29.0)	26 (29.5)	10 (27.8)
Secondary school	17 (13.7)	14 (15.9)	3 (8.3)
Diploma and above	7 (5.6)	6 (6.8)	1 (2.8)
Marital status:			
Married	62 (50)	44 (50)	18 (50)
Un married	45 (36.3)	35 (39.8)	10 (27.8)
Widowed	5 (4)	4 (4.5 %)	1 (2.8)
Divorced	12 (9.7)	5 (5.7)	7 (19.4)

Rifampicin resistant Non-MDR-TB

Sputum samples of 124 smear positive pulmonary TB cases were processed using Gene-X pert MTB/RIF for detection of MTB and identification of RIF resistant strain. Of these only seven smears positive cases were found to be RIF resistant. Sputum samples of RIF resistant cases were further diagnosed with LJ medium for growth of MTB and detection of INH resistance as well as confirmation of RIF resistant strain. The result showed RIF resistant non-MDR-TB isolates were not observed from all RIF resistant isolates that were detected by Gene-X pert MTB/RIF for drug susceptibility testing. All seven RIF resistant isolates were found to be MDR-TB cases.

Risk factors for MDR-TB

The relationship between individual exposure variables and MDR-TB status is shown in Table 2. Association between potential exposure variables and MDR-TB were analyzed. Socio-demographic determinants such as age, sex, residence, occupation, income, religion, fasting, ethnicity, educational status, marital status, and factors such as contact history, history of imprisonment, number of rooms in the house, family number in the household, rooms for sleeping, number of windows and use of substances like cigarette smoking and other clinical characteristics such as, diabetes, history of previous anti-TB treatment, outcome of previous treatment, BCG vaccination, HIV status, history of taking illegal anti-TB treatment were assessed.

All the variables that were considered important were entered into the binary logistic regression models and analysis showed there were significant association between MDR-TB and history of previous anti-TB treatment (OR: 7, 95 % CI = 1. 2–37.6, $P = 0.025$). However, there were no significant association between other variables and MDR-TB. After adjustment for interactions among the independent variables with the binary regression model; analysis also showed there were no significant association between independent variables and prevalence of MDR-TB ($P > 0.05$) with each factor other than previous treatment history.

Discussion

The burden of MDR-TB becomes increasing in alarming pace with function of time particularly in the poorest countries. Before 20 years ago, reports showed that the prevalence of MDR-TB was almost nil or 1 % in different parts of Ethiopia [7–9]. Though, nowadays high proportion of MDR-TB were notified within the country [10, 11]. It is well understood that bacterial and environmental factors play a great role in the spread of MDR-TB. Within the population MTB, spontaneous mutation in genes responsible for drug resistance for all first line and

Table 2 Factors associated with the MDR-TB status among Pulmonary TB cases, West Armachiho and Metema districts, Northwest Ethiopia, February 01 to June 25, 2014

Variable	MDR-TB		Crude OR	*P*-value
	Positive (*N* = 7)	Negative (*N* = 117)		
Age group				
≤25	1	36	2.77 (0.16, 47.56)	0.483
26–35	4	53	1.02 (0.11,9.90)	0.987
36–45	1	15	1.15 (0.07,20.34)	0.922
≥46	1	13	1	
Gender				
Male	6	79	3.49 (0.41, 29.9 4)	0.255
Female	1	43	1	
Resident				
Rural	4	54	1.56 (0.33, 7.26)	0.574
Urban	3	63	1	
Occupation:				
Farmer and day laborers	4	55	1.50 (0.32, 7.01)	0.604
Other	3	62	1	
Ethnicity:				
Tigre	3	19	3.87 (0.80,18.70)	0.092
Amhara	4	98	1	
Educational status:				
Illiterate	2	62	5.17 (0.41, 65.68)	0.206
Primary school	3	33	1.83 (0.16,20.71)	0.624
Secondary school	1	16	2.67 (0.14,49.76)	0.511
Diploma and above	1	6	1	
Fasting				
Yes	3	73	0.45 (0.10, 2.12)	0.313
No	4	44	1	
History of smoking				
Yes	2	33	1.02 (0.19, 5.51)	0.983
No	5	84	1	
BCG vaccination				
Yes	1	27	0.71 (0.13, 3.89)	0.698
No	6	90	1	
History of previous treatment				
Yes	5	31	6.94 (1.28, 37.60)	0.025
No	2	86	1	
HIV status				
Yes	2	26	1.40 (0.25, 7.64)	0.698
No	5	91	1	
History of prison				
Yes	1	17	0.98 (0.11, 8.66)	0.986
No	6	100	1	

Note that: *N* number of subjects, *OR* Odds Ratio

some second line drugs, thus scenarios are highly pronounced by misuse of drugs results in rapid selection of drug resistant mutants [12].

The present study demonstrated MDR-TB is a serious issue of concern in the study area; hence the overall prevalence of MDR-TB was 5.6 % (95 % CI, 2.4–10.5 %). Which is comparable with previous reports from 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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PLOS ONE

RESEARCH ARTICLE

Decentralization of Acid Fast Bacilli(AFB) External Quality Assurance Using Blind Rechecking for Sputum Smear Microscopy in Ethiopia

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Abstract

Introduction

Ethiopia achieved a rapid expansion of TB microscopic centers for acid fast bacilli (AFB). However, external quality assurance (EQA) services were, until recently, limited to few regional and sub-regional laboratories. In this paper, we describe the decentralization experience and the result of EQA using random blinded rechecking.

Materials and Methods

The routine EQA quarterly report was compiled and analyzed. A positive result by the microscopic center while the EQA center reported negative result is categorized as false positive (FP). A negative result by the microscopic center while the EQA center reported positive is considered false negative (FN). The reading of EQA centers was considered a gold standard to compute the sensitivity, specificity, positive predictive (PPV) and negative predictive values (NPV) of the readings of microscopic centers.

Results

We decentralized sputum smear AFB EQA from 4 Regional Laboratories (RRLs) to 82 EQA centers and enrolled 956 health facilities in EQA schemes. Enrollment of HFs in EQA was gradual because it required training and mentoring laboratory professionals, institutionalizing internal QA measures, equipping all HFs to perform diagnosis, and establishing more EQA centers. From 2012 to 2014 (Phase I), the FP rate declined from 0.6% to 0.2% and FN fell from as high as 7.6% to 1.6% in supported health facilities (HFs). In HFs that joined in Phase II, FN rates ranged from 5.6 to 7.3%. The proportion of HFs without errors has

increased from 77.9% to 90.5% in Phase I HFs and from 82.9% to 86.9% in Phase II HFs. Overall sensitivity and specificity were 95.0% and 99.7%, respectively. PPV and NPV were 93.3% and 99.7%, respectively.

Conclusion

Decentralizing blinded rechecking of sputum smear microscopy is feasible in low-income settings. While a comprehensive laboratory improvement strategy enhanced the quality of microscopy, laboratory professionals' capacity in slide reading and smear quality requires continued support.

Introduction

Direct sputum microscopy for acid-fast bacilli (AFB) using light microscopy is the most widely used tuberculosis (TB) diagnostic and monitoring tool worldwide [1–4]. Quality-assured TB microscopy is one of the key elements of DOTS in the STOP TB strategy of the World Health Organization (WHO) [4]. It is simple and cost effective and does not require sophisticated training or setup [4–6]. But it does require a very good system of quality assurance [6–7].

Quality assurance consists of quality control (QC), external quality assurance (EQA), and quality improvement (QI). To yield reliable, reproducible results, all three components should be implemented across the laboratory network [8]. Reliable AFB microscopic results such as smear positivity rates also help planners to understand the progress of TB control measures [9–11]. Implementation of EQA for microscopy helps to improve the quality of diagnosis of TB and measure the cure rates of TB patients on treatment. EQA is needed to ensure that smears are performed and interpreted correctly and that all microscopy centers perform at an acceptable level [5,11,12].

Despite rapid expansion of TB microscopic centers in Ethiopia for Ziehl-Neelsen (ZN), EQA services were, until recently, limited to a few regional and sub-regional laboratories. To fill this gap, the Ethiopian Public Health Institute (EPHI) introduced a decentralized EQA system using randomized blinded rechecking (RBRC) [7]. RBRC involves the collection of smears from the microscopy center laboratory for blinded re-reading at a regional reference laboratory (RRL) or other designated EQA center, with feedback to the microscopy center [7]. WHO has recommended this approach to evaluate the performance of AFB microscopy centers [13].

RBRC has been used successfully in many pilot and research projects [9,13–16]. In India, for example, RBRC has been used to measure the performance of laboratories and assess errors [13,16]. In other settings, it has been used for QI of diagnosis and monitoring of treatment response [17,18] and for QA where culture or fluorescent microscopies cannot be routinely used [19]. In Ethiopia, we supported the implementation of a decentralized EQA system for ZN microscopy over 1,600 health facilities (HFs) in two large regions. This paper presents the process of decentralization, its outcomes, and the factors that contributed to successful establishment of RBRC services.

Materials and Methods

Setting

In Ethiopia, which is one of the 22 high-TB-burden countries,[5] the Federal Ministry of Health (FMOH) provides guidance for implementation of the national TB program, while the EPHI is

responsible for all laboratory-related standardization and quality issues. In 2008, EPHI designed an EQA system for sputum smear Z-NAFB microscopy [7]. The system was organized so that EPHI conducts panel testing for RRLs and the RRLs conduct RBRC of sputum smear slides for hospitals. Selected hospitals with good EQA performance ($\geq$ 95% concordance for 2–3 quarters) conduct EQA for health centers in their catchment areas (Fig 1).

Operationalization of decentralized EQA

The Amhara and Oromia Regional Health Bureaus (RHBs) receive support from the US Agency for International Development (USAID) through the Help Ethiopia Address the Low Performance of TB (HEAL TB) project managed by Management Sciences for Health. The RHBs operationalized the decentralized EQA model through a process that involved several stakeholders.

When the project began in 2011, QA measures for AFB were weak and in most cases HFs had no QA mechanism. Following a baseline assessment, HEAL TB supported the RHBs to design a decentralized EQA system. The support included training laboratory personnel, providing standard registers, supplying microscopes and reagents, and providing quarterly supportive supervision and on-site technical support to every HF. During supervision visits, laboratory experts checked for complete registration and proper storage of the sputum smear slides and sequential labeling. The senior laboratory expert assisted in establishing internal QA measures during the site visits, including weekly checking of reagent quality with five known negative and positive slides. When errors were identified, the laboratory experts explored the cause of the error and took corrective measures with the HF laboratory personnel. After two or three quarters of follow-up and on-site support, the HFs were ready to join the country's RBRC scheme. To assure their quality, reagents were prepared at national or regional level and distributed to all health facilities.

Training of district TB focal persons as supervisors and slide randomization

Once the HFs were prepared for EQA participation, trained *woreda* (district) TB focal persons took the lead in supervising them. The woreda TB focal persons were trained in supervisory skills for laboratories, including checking for proper registration, labeling, and storage of slides. Every quarter the woreda TB focal persons supervised each HF in their catchment area and randomized slides for blinded rechecking following the Lot Quality Assurance Sampling guidelines for AFB slides. The nationally agreed-on sample size is based on 80% sensitivity, 100% specificity, and accepting number $d = 0$ (Table 1) [20]. The TB focal persons then delivered the collected slides to the RRLs or EQA hospitals to conduct the EQA. The EQA readers were laboratory experts from the RRLs or hospitals, who were different from those who randomized the slides.

Blind re-checking procedures

The experts involved in EQA reading have demonstrated a 95% concordance rate for at least two quarters. EPHI assesses the RRLs' EQA through panel testing, since EPHI does not routinely collect slides for patient care. RRLs check hospitals' EQA quarterly, and designated hospitals check the EQA of health centers (Fig 1). The quality officer of the EQA center assigns slides to a reader (controller). After the first reader completes the reading, the result is submitted to the quality officer to reconcile with the initial reading of the microscopic center. The quality officer assigns all discrepant slides from the first reader to a second reader (senior expert). If the result of the second reader agrees with that of the first, it becomes the final result.

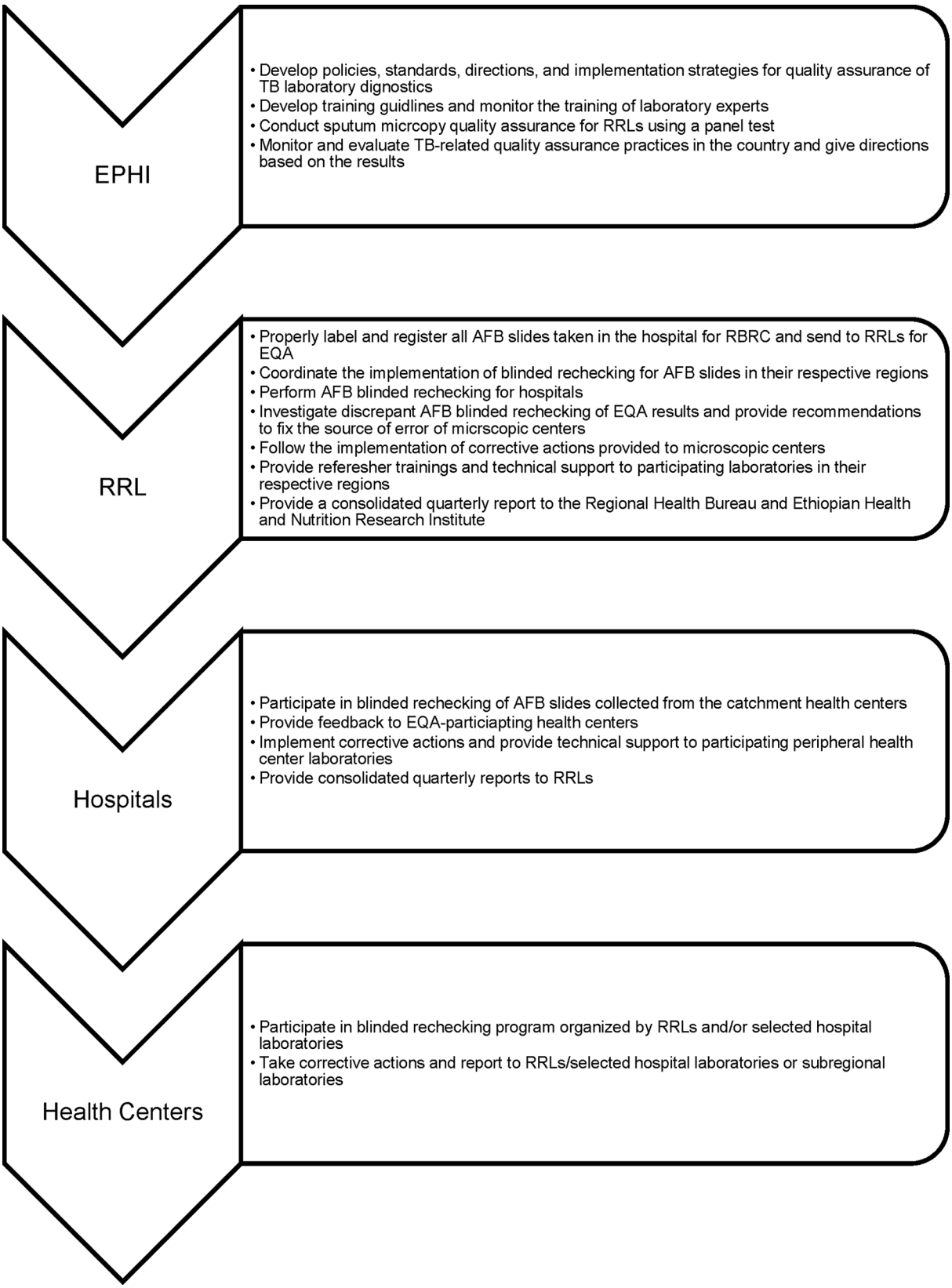

Fig 1. Model for decentalized AFB random blinded rechecking in Ethiopia.

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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)

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If the readings are still discordant, a third expert reads the slide, and any two concordant expert readings become the EQA result. The RRLs or hospital controllers travel to health facilities with discordant slides to identify the cause of the discordance (e.g., poorly functioning microscope, reader capacity, quality of reagent, or fading). The final result is recorded after agreement with the HF laboratory professionals is reached. (Fig 2). If the final result is different from the original report of the microscopic center, it is communicated to the treating clinicians for decision making Each EQA center covers 11–15 HFs (Table 2), and controllers conduct EQA mostly in their spare time and are paid overtime. EQA reading takes one month, and on-site evaluations of HFs with discordant slides, takes another two months.

Data management and analysis

The reading results of peripheral laboratories were entered in Excel, the EQA results tabulated, and the analysis done based on internationally accepted definitions. The false-positive and false-negative errors were calculated using standard definitions [21]. A positive result by the microscopic center while the EQA center reported negative result is categorized false positive (FP). Similarly, if the microscopic center indicates a negative result while the EQA center reported positive, it is considered false negative (FN). Sensitivity, specificity, and positive and negative predictive values of the readings were then calculated using the EQA center controller's final result as a gold standard, per the international guideline [20].

Ethical Considerations

The Ethiopian Public Health Institute (EPHI) has released an AFM microscopy EQA guideline to be implemented in all microscopy centers and using a Lots Quality Assurance, sputum smear slides collected through to the routine clinical practice are randomized for RBRC. The data for this paper is acquired through this routine lab quality monitoring system, but not collected from patients directly for research purpose. As per the guiding, the sputum smear slides randomized have no patient identification information and the result is reported to evaluate the lab performance, but not directly related to patient management. EPHI has given the permission to publish the experience from the nationally reported data as the practice of decentralized EQA system has much application for low-income countries.

Results

Baseline data

During the first phase of project implementation (July 2011-June 2013), 691 DOTS-providing HFs were supported through HEAL TB in Amhara and Oromia regions. At baseline in October 2011, 465 HFs were providing TB diagnostic services, and 104 were participating in sporadic AFB on-site quality checks but not RBRC using proper sampling. By the end of 2013, the remaining 226 non-diagnostic HFs were equipped to become diagnostic and all 629 were

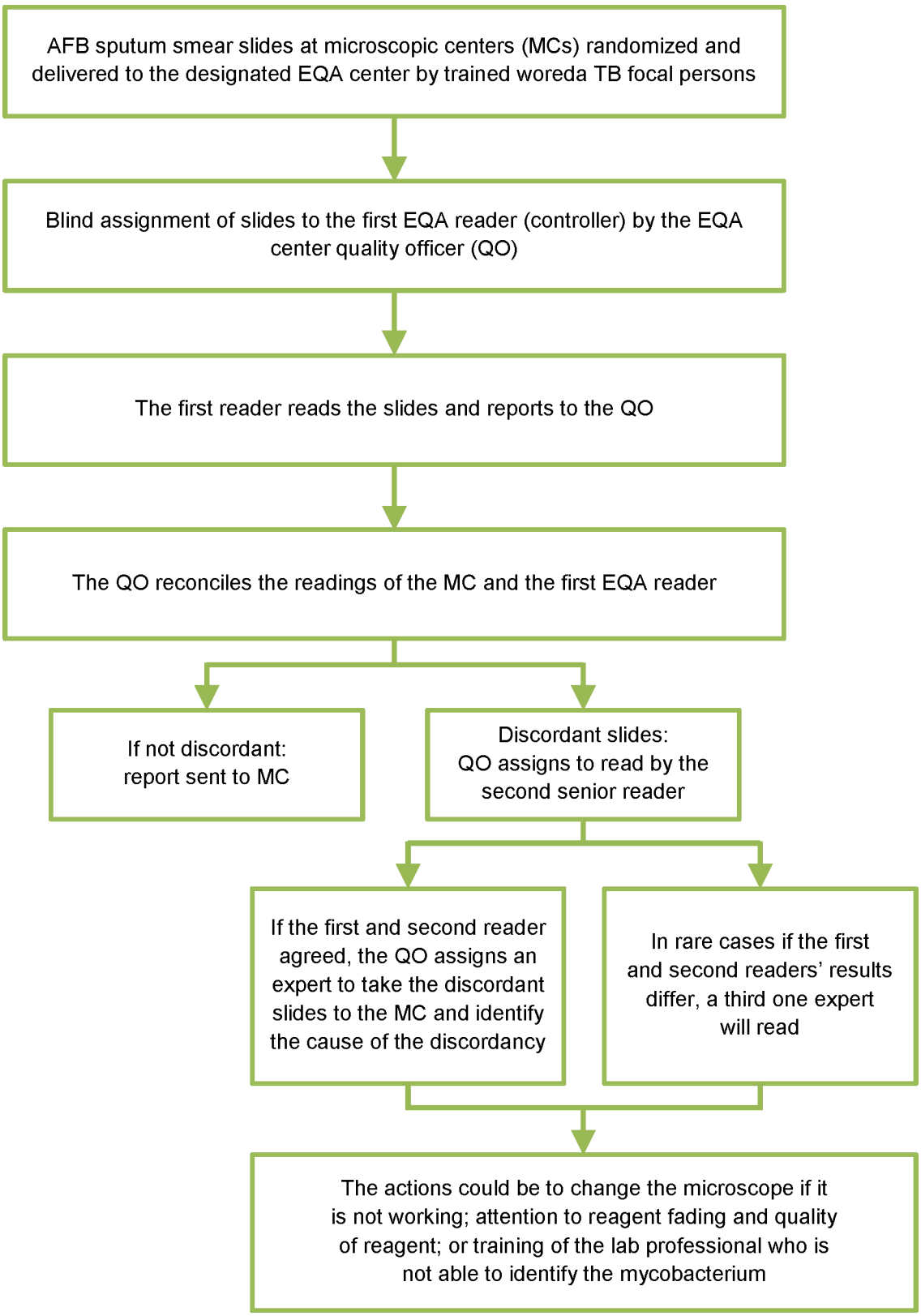

Fig 2. Flow chart of procedures for blinded random rechecking.

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Table 2. AFB microscopy EQA coverage for all HEAL TB-supported zones, April 2012-June 2014.

Indicator	April-June 2012	July-Sept 2012	Oct-Dec 2012	Jan-Mar 2013	April-June 2013	July-Sept 2013	Oct-Dec 2013	Jan-Mar 2014	April-June 2014
Total number of HFs participating in EQA RBRC	353	413	533	607	583	773	872	956	895
Total number of slides collected for EQA	13,809	16,275	22,421	27,477	22,805	30,681	37,086	41,323	36,955
Total number of EQA centers	22	38	39	40	40	56	74	80	82
Ratio HF to EQA center	16	11	14	15	15	14	12	12	11

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enrolled in RBRC. During the second phase of the project (July 2013-present), 909 more HFs were included and at the time of this analyses 335 of them were enrolled in RBRC. The rest were under mentorship to be part of the RBRC scheme.

Trends in EQA participation

The number of diagnostic HFs participating in RBRC increased from none at baseline to 956 by the end of March 2014. Ninety-one percent of the 691 DOTS centers in Phase I HFs were able to participate in the quarterly RBRC scheme, while the remaining 9% were checked on site because of low slide volume. Of the Phase II HFs, 37% have started to participate in EQA. In June 2014, the number of EQA-participating facilities decreased because the HFs with heavy patient loads shifted from Ziehl-Neelsen microscopy to iLED (light-emitting diode) fluorescence microscopy. Enrollment of HFs in EQA was gradual because it required training and mentoring laboratory professionals, institutionalizing internal QA measures, equipping all HFs to perform diagnosis, and establishing more EQA centers (Table 2).

The EQA centers grew from 4 at baseline to 82 by the end of June 2014 (Table 2). Between April 2012 and June 2014, the EQA centers had read 248,832 slides. In Phase I HFs the false-positive rate declined from 0.6% (95% CI, 0.4–0.7) to 0.2% (95% CI, 0.2–0.3) and false negatives had a steady decline from 7.6% (95% CI, 6.1–9.6) to 1.6% (95% CI, 1.0–2.6) over two years, with a slight increase in the last quarter in Phase I HFs (Table 3, Fig 3). The denominator used to calculate the false negative is positive readings and for that false positives is negative readings. The proportion of HFs with no errors at this increase in Phase I reached 90.5% as opposed to 77.9% at the beginning of the project (Fig 4). In Phase II HFs the false-negative rate ranged from 5.6% to 7.3% while false positives ranged from 0.5% to 0.3% (Table 3, Fig 3).

By the end of the study, overall sensitivity and specificity for the Phase I HFs were 95% and 99.7%, respectively, and the positive predictive value (PPV) and negative predictive value (NPV) were 93.7% and 99.7% respectively. In Phase II HFs, sensitivity and specificity were 94.1% and 99.6% respectively. The PPV and NPV were 93.3% and 99.7% respectively.

In Phase I HFs, the average quality of staining at baseline was 71.1% and by June 30, 2014, it reached 81.4%. In Phase II HFs, it increased from 61.7% at baseline to 72.7% by June 2014. Smear thickness also improved, from 62.1% to 69.8% in Phase I HFs, but in Phase II HFs it improved from 59.3% to 71% and then decreased to 57.0%. In Phase I HFs cleanliness of the slides improved from 72.6% to 86.3%, but in Phase II HFs cleanliness improved from 80.7% to 88.4% and then declined to 81.6% in June 2014 (Table 4).

Discussions

This study demonstrates that decentralizing AFB EQA services to hospitals is a feasible, low-cost approach for countries like Ethiopia that have few higher-level laboratories [8,13,22,23]. With

Table 3. False-negative and false-positive rates per quarter, April 2012-June 2014.

Quarter-Year	Phase I: Implementation Zones			
	Number of slides collected from microscopic centers		Error rates reported by the EQA centers	
	Negative results by the laboratory	Positive rate by the laboratory	%[95%CI] false-negative slides	%[95%CI] false-positive slides
II- 2012	12,894	915	7.6 [6.09, 9.56]	0.6 [0.44, 0.70]
III- 2012	15,373	902	7.5 [5.78, 9.21]	0.6 [0.51, 0.76]
IV- 2012	21,248	1,173	6.0 [4.74, 7.48]	0.4 [0.33, 0.51]
I- 2013	26,171	1,306	4.8 [(3.71, 6.05]	0.3 [0.26, 0.40]
II- 2013	21,563	1,242	3.1 [2.29, 4.27]	0.3 [0.22, 0.36]
III- 2013	23,444	1,268	4.0 [3.06, 5.26]	0.4 [0.30, 0.46]
IV- 2013	24,420	1,203	2.2 [1.53, 3.26]	0.1 [0.09, 0.19]
I- 2014	25,158	1,114	1.6 [(1.01, 2.56]	0.2 [0.14, 0.24]
II- 2014	21,046	894	5.2 [4.16, 7.18]	0.2 [0.18, 0.31]
Phase II: Implementation Zones				
Quarter-Year	Negative results by the laboratory	Positive rate by the laboratory	%[95%CI] false-negative slides	%[95%CI] false-positive slides
III- 2013	5,636	333	5.6 [3.39, 8.43]	0.5 [0.37, 0.76]
IV- 2013	10,848	615	5.4 [3.82, 7.46]	0.4 [0.34, 0.59]
I- 2014	14,335	716	4.9 [3.52, 6.74]	0.3 [0.19, 0.36]
II- 2014	14,356	659	7.3 [5.65, 9.71]	0.3 [0.19, 0.36]

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the decentralized approach, nearly 1,000 HFs participated in RBRC. It takes approximately 6–9 months to prepare the HFs for RBRC, but in Phase II, 335 HFs enrolled in EQA, which was faster than expected because of the experience gained during Phase I implementation.

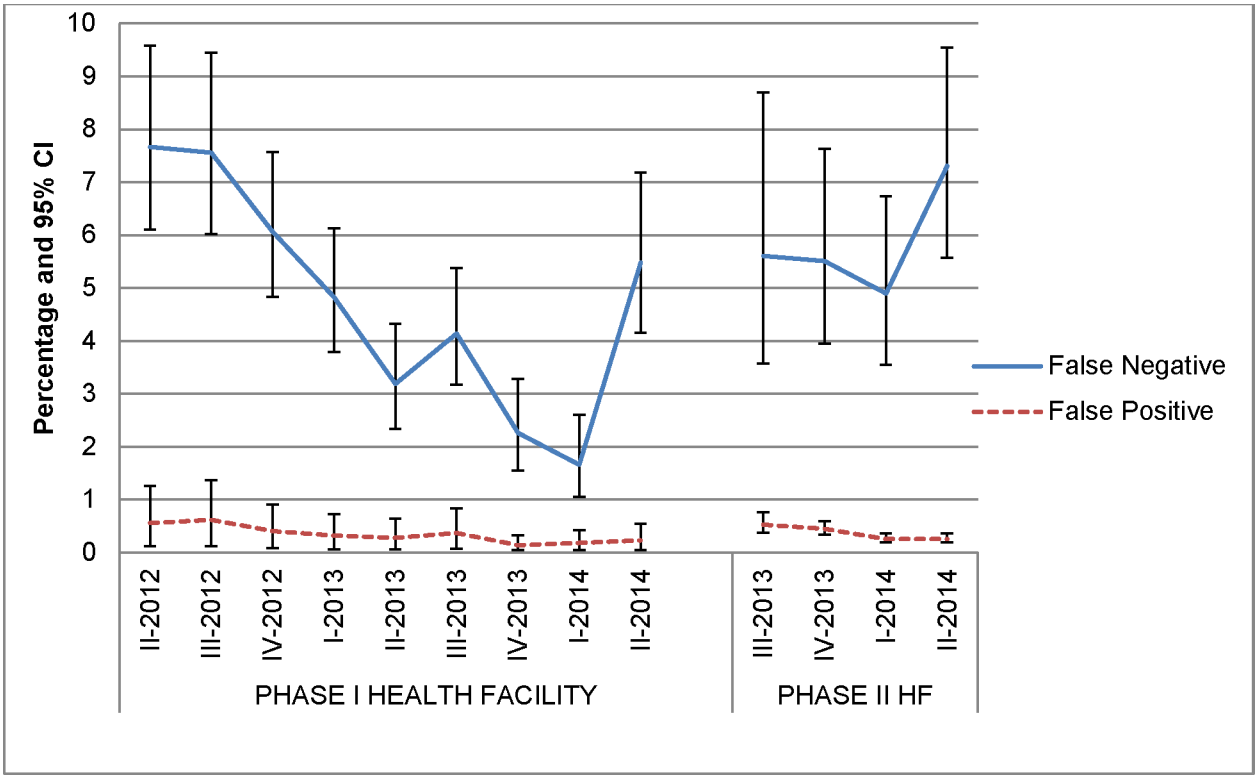

Fig 3. Health facilities' reported false-negative and false-positive error rates per quarter, April 2012-June 2014.

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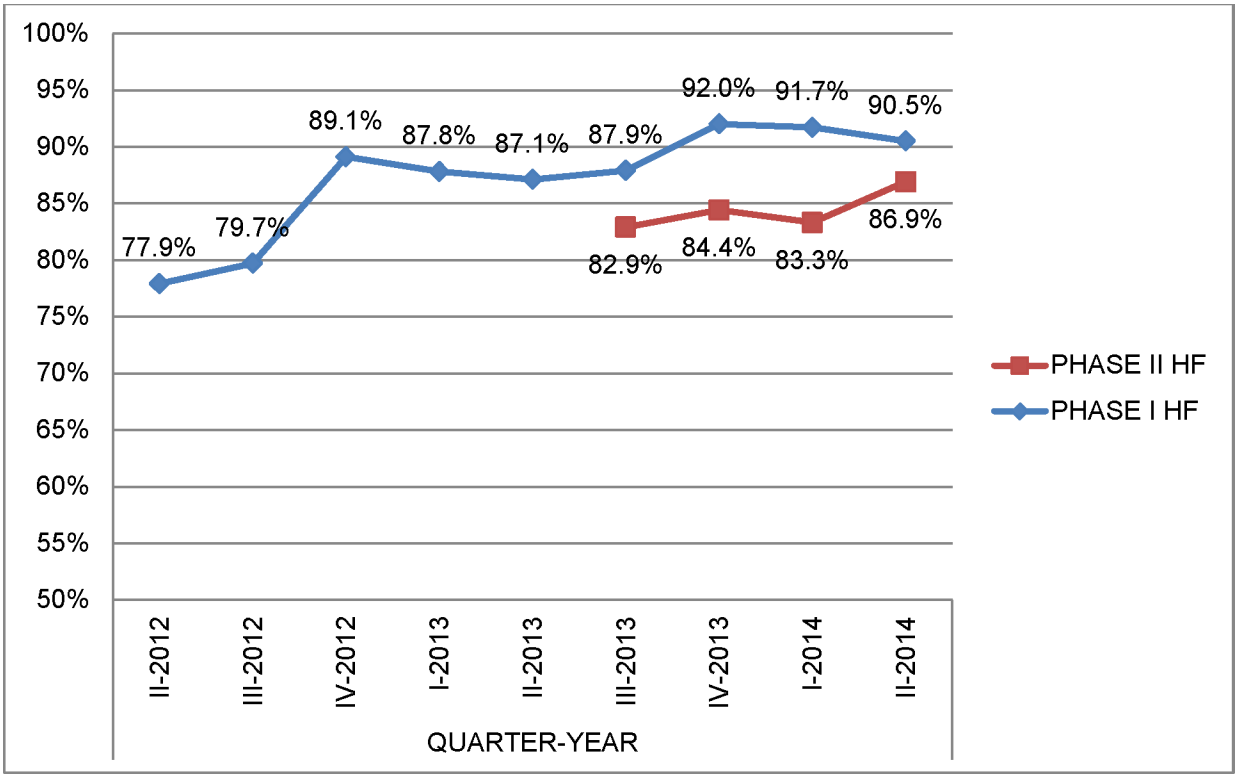

Fig 4. Percentage of health facilities without any error per quarter, April 2012-June 2014.

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The rapid capacity building of HFs in sputum smear microscopy, coupled with on-site supervision, helped decrease the numbers of false-positive and false-negative slides. Other countries have reported improvements using similar mechanisms [8,18] Our experience is that the proportion of HFs with no errors improved from quarter to quarter but the error rate fluctuated because of HFs enrolled in EQA for the first time or new, less-trained laboratory professionals assigned to the HFs. The HFs began EQA in different phases, but in three quarters the false-negative rate declined significantly (Table 3). In 507 Phase I HFs with EQA results, for example, in April-June 2014, only 48 contributed to the reported errors. False-positive errors were low from the beginning, and there was statistically significant improvement in both phases.

Another possible reason for errors was smear quality, although there were improvements from quarter to quarter because of comprehensive capacity building (Table 4). We addressed challenges by providing refresher training at sites with poor performance and at laboratories with new personnel. In addition, the EQA centers served as mentors and trainers for new laboratory professionals and underperforming laboratories. Every week the HF also checks reagent quality with known negative and positive slides. RRL staff also visit and identify the causes of errors with the HFs' laboratory experts. If fading is suspected, they re-stain the slides and read them on-site with the same microscope used for diagnosis by the HF.

The overall sensitivity of 95.0% and specificity of 99.7% in our health facilities are high, per international standards [20], and the national recommendation about the sample size for RBRC for Ethiopia might need revision. The revised international recommendation for EQA of AFB smear microscopy is to use a 75–80% sensitivity rate to calculate sample sizes for blinded rechecking [7,20]. Ethiopia has already adopted this recommendation, so the sample

Table 4. Sputum smear quality assessment by the EQA centers, April 2012-June 2014.

Phase I Implementation Zones						
Quarter	**Number of HFs enrolled in EQA**	**Total number of sampled slides**	**Good-quality staining (%)**	**Smear thickness (%)**	**Cleanliness of slides (%)**	**Evenness of smearing (%)**
II- 2012	353	13,809	71.1	62.1	72.6	53.0
III- 2012	413	16,275	69.8	62.5	82.4	59.1
IV- 2012	533	22,421	72.9	67.1	83.7	63.7
I- 2013	607	27,477	74.9	71.1	84.8	66.1
II- 2013	583	22,805	75.4	70.3	87.1	67.5
III- 2013	626	24,712	75.1	67.7	85.2	67.2
IV- 2013	603	25,623	77.2	71.8	88.3	69.7
I- 2014	614	26,272	78.2	70.9	85.4	68.8
II- 2014	560	21,940	81.4	69.8	86.3	66.6
Total		*201,334*				
Phase II Implementation Zones						
Quarter	**Number of HFs enrolled in EQA**	**Total number of sampled slides**	**Good-quality staining (%)**	**Smear thickness (%)**	**Cleanliness of slides (%)**	**Evenness of smearing (%)**
III- 2013	147	5,969	61.7	59.3	80.7	54.7
IV- 2013	269	11,463	63.9	59.7	79.7	51.7
I- 2014	342	15,151	77.0	71.0	88.4	65
II- 2014	335	15,015	72.7	57.0	81.6	55.0
Total		*47,498*				

doi:10.1371/journal.pone.0151366.t004

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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EDITORIAL

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

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

What is not reflected in these estimates is the substantial number of patients whose TB—and MDR-TB—goes undetected, for whom diagnostics and drugs are not purchased, budgeted, manufactured, or even projected. Although the number of invisible patients is uncertain, recent estimates are that up to a third of global TB cases are not notified[3] and therefore would lack access to appropriate diagnosis and care, even if universal DST for notified cases were implemented. These invisible patients will continue to transmit TB (and MDR-TB) to their families and communities until their disease resolves spontaneously or they die.

As the authors note, improved surveillance systems—in which the number of notified cases approximates the true number of incident cases—would permit the true burden of cases requiring second-line treatment to be known. This longer-term solution requires investment in public health infrastructure so that all TB cases can access the health system and all diagnostic centers have adequate capacity to diagnose and notify TB. The World Health Organization, and several of the authors cited in the article by Royce et al.,[1] are among those actively working to improve TB surveillance within countries.[4]

In parallel, solutions are urgently needed to bring appropriate care to the full half million—visible and invisible—patients newly suffering from MDR-TB each year. Unprecedented opportunities exist to improve the diagnosis and treatment of MDR-TB, with new interest in enhanced TB screening,[5] innovative efforts to diagnose TB cases that might previously have gone undiagnosed,[6,7] new technologies that allow for rapid detection of drug resistance in the periphery,[8] and promising new drugs on the horizon.[9] Use of the new technologies can also provide important updates to estimates of drug resistance prevalence. Twenty-one of the 29 country estimates used in the paper by Royce et al. rely on survey data from 2007 or earlier. In a number of these settings, planned or ongoing implementation of drug resistance surveillance systems—with rapid diagnostics—provides an opportunity to update these dynamic figures and inform planning for global drug supply and financial needs. We believe that projections of the resources required to confront this problem should be based on the best estimates of true numbers of patients suffering from MDR-TB, and not only those who are currently notified and visible to TB programs. Failure to secure resources that permit access to diagnosis and effective MDR-TB treatment for all patients, even if invisible, will result in continued transmission and needless deaths.

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RESEARCH ARTICLE Open Access

Tuberculosis retreatment 'others' in comparison with classical retreatment cases; a retrospective cohort review

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Abstract

Background: Many of the countries in sub-Saharan Africa are still largely dependent on microscopy as the mainstay for diagnosis of tuberculosis (TB) including patients with previous history of TB treatment. The available guidance in management of TB retreatment cases is focused on bacteriologically confirmed TB retreatment cases leaving out those classified as retreatment 'others'. Retreatment 'others' refer to all TB cases who were previously treated but with unknown outcome of that previous treatment or who have returned to treatment with bacteriologically negative pulmonary or extra-pulmonary TB. This study was conducted in 11 regional referral hospitals (RRHs) serving high burden TB districts in Uganda to determine the profile and treatment success of TB retreatment 'others' in comparison with the classical retreatment cases.

Methods: A retrospective cohort review of routinely collected National TB and Leprosy Program (NTLP) facility data from 1 January to 31 December 2010. This study uses the term classical retreatment cases to refer to a combined group of bacteriologically confirmed relapse, return after failure and return after loss to follow-up cases as a distinct group from retreatment 'others'. Distribution of categorical characteristics were compared using Chi-squared test for difference between proportions. The log likelihood ratio test was used to assess the independent contribution of type of retreatment, human immunodeficiency virus (HIV) status, age group and sex to the models.

Results: Of the 6244 TB cases registered at the study sites, 733 (11.7 %) were retreatment cases. Retreatment 'others' constituted 45.5 % of retreatment cases. Co-infection with HIV was higher among retreatment 'others' (70.9 %) than classical retreatment cases (53.5 %). Treatment was successful in 410 (56.2 %) retreatment cases. Retreatment 'others' were associated with reduced odds of success (AOR = 0.44, 95 % CI 0.22,0.88) compared to classical cases. Lost to follow up was the commonest adverse outcome (38 % of adverse outcomes) in all retreatment cases. Type of retreatment case, HIV status, and age were independently associated with treatment success.

Conclusion: TB retreatment 'others' constitute a significant proportion of retreatment cases, with higher HIV prevalence and worse treatment success. There is need to review the diagnosis and management of retreatment 'others'.

Background

The World Health Organization (WHO) treatment guidelines recommend that all previously-treated TB patients should be managed according the TB retreatment category, while their sputum is cultured and tested for drug susceptibility (DST) [1]. However, few countries have the required laboratory capacity to improve access to DST services to all TB retreatment patients. Therefore, many countries remain unclear on the best management of TB retreatment cases. Of particular concern is the category of TB patients classified as retreatment 'others'. These refer to all TB cases, previously treated but with unknown outcome of that previous treatment or who return for treatment with bacteriologically negative pulmonary or extra-pulmonary TB. This study uses the term classical retreatment cases to refer to all bacteriologically confirmed relapse, return after failure and return after lost to

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follow-up (LTFU) cases as a distinct group from retreatment 'others'.

Uganda has limited capacity to conduct culture and DST investigations in TB retreatment patients. A study conducted in three regional referral hospitals (RRHs) in Uganda showed that only 13 % of 114 registered relapse smear-positive or treatment after failure cases had their sputum samples sent to National TB Reference Laboratory for culture and DST [2]. Since 2002, Uganda has notified an increasing number of TB retreatment cases from 1500 to about 4000 cases per year [3]. Of the 47,650 total TB cases Uganda notified to the WHO in 2013, 4028 (8.5 %) were TB retreatment cases [4]. TB retreatment 'others' constituted a third of the total retreatment cases notified in 2012 [3].

An important step in understanding how to manage retreatment 'others' is to better understand their outcomes. Previous studies in other settings have observed different treatment outcomes, HIV status and management approaches between classical TB retreatment cases and retreatment 'others' [5–7]. A study in India found that retreatment 'others' significantly had better treatment outcomes than classical retreatment cases [7]. Another study in Zimbabwe found that retreatment 'others' constituted 40 % of recurrent TB with no difference in treatment outcomes by HIV status [6]. 65 % of retreatment cases in Malawi were retreatment 'others' with over half of them treated with standard TB regimen for new cases [5]. This study seeks to add this emerging evidence base on how this group of patients differs by setting, to answer the following research question: what is the profile and treatment success of TB retreatment 'others' compared to the classical retreatment cases in Uganda?

Methods

A retrospective hospital-based review of routinely collected TB data on TB retreatment patients started on TB treatment from 1st January to 31st December 2010. The data were extracted between May and June 2012.

Study setting

This study was conducted in 11 RRHs of Uganda serving mostly districts with high TB burden. In 2009, it was observed that districts with RRHs notified an average of 114 retreatment cases each compared to an average of 32 retreatment cases notified by districts without RRHs (unpublished NTLP reports). The study thus systematically selected 11 high burden RRHs based on the burden of TB. The study sites were: Arua, Fort-Portal, Gulu, Hoima, Jinja, Kabale, Lira, Masaka, Mbarara, Mbale and Soroti RRHs.

Case definitions and treatment of retreatment TB patients

In Uganda, a TB retreatment case is defined as a person previously treated with anti-TB drugs for a month or more and is being treated again, in line with WHO definitions [1, 8]. The retreatment category is further classified either as 'relapse', 'treatment after failure', 'return after LTFU' or 'others'. Relapses are patients who become bacteriologically positive after having been treated for TB and declared cured or treatment completed. Treatment after failure are patients who, while on first line anti-TB treatment are bacteriologically positive at 5 months or later during the course of treatment. Return after LTFU patients are those who return to treatment and are bacteriologically positive after having interrupted treatment for more than 2 months. Retreatment 'others' refer to all TB cases that do not fit the above definitions such as patients with history of TB treatment for a month or more but with no bacteriological confirmation of TB for the current episode.

In line with WHO definitions, Ugandan NTLP classifies treatment outcomes as; cured, treatment completed, treatment failure, died, LTFU and transferred-out. Treatment success refers to a combination of cured and treatment completed. In this study, adverse outcome refers to a combination of LTFU, died, treatment failure and transferred-out.

The retreatment regimen in Uganda consists of two (2) months streptomycin (S), rifampicin (R), isoniazid (H), pyrazinamide (Z), and ethambutol (E). This is followed by one (1) month RHZE and five (5) months RHE. The retreatment regimen(2SRHZE/1RHZE/5RHE) is recommended for all bacteriologically positive TB retreatment cases [1, 8]. Both NTLP and WHO guidelines are silent on the management of TB retreatment 'others' in settings with limited TB DST capacity. In Uganda, it is at the discretion of the clinician to decide the TB treatment regimen to use in the management of retreatment 'others'. At the time of the study, routine culture and DST for retreatment cases had been rolled out to the study sites with varying levels of implementation [2].

Study variables, source of information and data collection

Records of routinely collected variables within the hospitals' unit TB registers that were analyzed included: patient demographic (age and sex); clinical (disease classification, pre-treatment smear status and HIV status); treatment-related (type of retreatment and treatment regimen) characteristics and treatment outcomes. In Uganda, each TB patient is registered in the unit TB register by the health facility staff at the start of treatment and individual patient records updated at every visit during the course of treatment. The district TB and Leprosy supervisor (DTLS) enters TB patients registered on treatment from all TB diagnostic and treatment

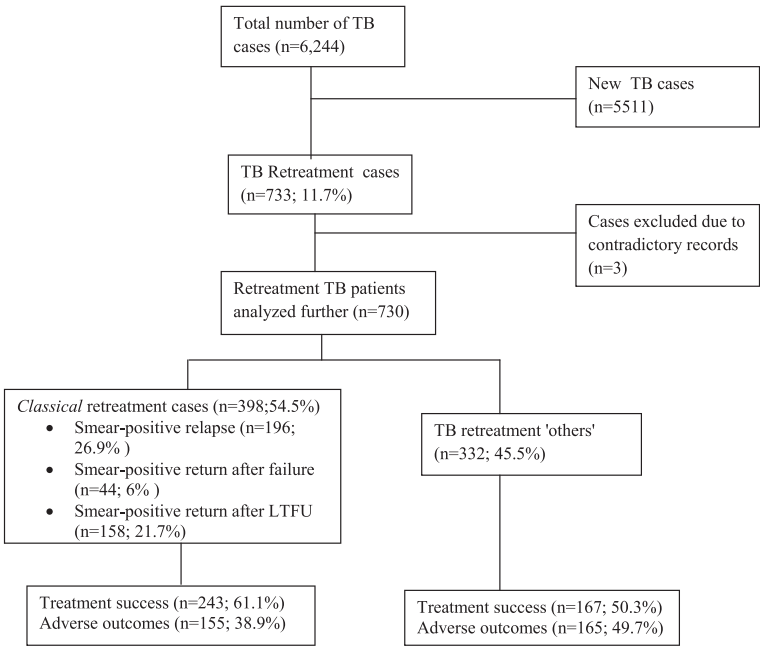

Fig. 1 Proportion of TB retreatment cases and outcomes at eleven regional referral hospitals, Uganda

health facilities within that particular district into the district TB register. Information on patients that transferred to other facilities within the same district is captured by the DTLS and conveyed back to the registering facility. More information on patients transfers between districts in the same zone is exchanged during quarterly zonal performance reviews attended by DTLSs before compiling quarterly district TB and Leprosy reports on notification and treatment outcomes. At the time of the study, the reporting unit at the NTLP central unit was the district. Using an anonymous standardized data collection tool, study variables were extracted from the hospital' TB unit registers by one trained research assistant and all entries were verified by the first author. The respective district TB registers were used to ascertain definitive patient treatment outcomes that were missing in the unit registers.

Data entry and analysis

Data was entered into EpiData version 3.1 (The EpiData Association, Odense, Denmark)and analyzed in STATA version 11.2 (Stata Corp, College Station, TX, USA).

HIV status was categorized into positive, negative and unknown. Age was categorized using cut offs that made meaningful differences between the categories. Descriptive analysis of patient characteristics was computed. Distribution of patient characteristics by type of retreatment cases (classical vs. retreatment 'others') was computed. The differences in distribution of categorical characteristics were compared using Chi-square test for difference between proportions at a significance level of *P*-value equal to 0.05.

Treatment outcome was analyzed as a binary variable of success versus all other outcomes. Odds ratio was the measure of association. Logistic regression was used to identify patient characteristics that were independently associated with treatment success. Characteristics that had *P*-value equal or less than 0.05 at bivariate level were assessed further in a multivariate model. In the multivariate analysis, characteristics that were not significant at *p*-value equal or less than 0.05 were dropped. The multivariable model was determined using forward regression with a two-sided *P*-value equal or less than 0.05. Sex was included as a priori in the final model. The log likelihood ratio test was used to assess the independent contribution of explanatory variables to the models.

Ethical approval

As this study was a review of routinely collected NTLP data at RRHs, approval was obtained from Ministry of Health and Joint Clinical Research Centre Institutional Review Board as the local ethical body. The protocol was also approved by London School of Hygiene Tropical Medicine ethics review committee.

Results

Of the 6244 TB cases registered at the 11 RRHs, 733 (11.7 %) were retreatment cases (Fig. 1). Three retreatment cases were excluded from subsequent analyzes due to contradictory records. Table 1 shows that majority of

Table 1 Frequency of retreatment TB patients' characteristics and their distribution by type of retreatment cases registered at the eleven RRHs, 2010 ($n = 730$ cases)

Characteristic	All retreatment cases	Type of retreatment cases		*P*-value*
		Classical TB retreatment cases;	TB retreatment 'others';	
	n (%)	$n = 398$ (%)	$n = 332$ (%)	
Sex				
Male	523 (71.6)	308 (77.4)	215 (64.8)	<0.001
Female	207 (28.4)	90 (22.6)	117 (35.2)	
Age (years)[a]				
<15	39 (5.4)	3 (0.8)	36 (10.8)	<0.001
15-44	509 (69.8)	293 (73.8)	216 (65.1)	
>44	181 (24.8)	101 (25.4)	80 (24.1)	
Anatomical site				
Pulmonary	689 (94.4)	398 (100.0)	291 (87.7)	<0.001
Extrapulmonary	41 (5.6)	0 (0.0)	41 (12.3)	
Disease classification				
Sputum smear-positive	400 (54.8)	398 (100.0)	2 (0.6)	<0.001
Sputum smear-negative	267 (36.6)	0 (0.0)	267 (80.4)	
No smear done	22 (3.0)	0 (0.0)	22 (6.6)	
Extrapulmonary	41 (5.6)	0 (0.0)	41 (12.4)	
HIV status				
Negative	266 (36.4)	174 (43.7)	92 (27.7)	<0.001
Positive	424 (58.1)	200 (50.3)	224 (67.5)	
Unknown	40 (5.5)	24 (6.0)	16 (4.8)	
Retreatment sub-category				
Sputum smear-positive relapse	196 (26.9)	196 (49.3)	0 (0.0)	<0.001
Sputum smear-positive failure	44 (6.0)	44 (11.1)	0 (0.0)	
Sputum smear-positive return after LTFU	158 (21.6)	158 (39.7)	0 (0.0)	
Retreatment 'others'	332 (45.5)	0 (0.0)	332 (100.0)	
Treatment regimen				
Retreatment: 2SRHZE/1RHZE/5RHE	582 (79.7)	378 (95.0)	204 (61.5)	<0.001
New: 2RHZE/6EH or 2RHZ/4RH	116 (15.9)	19 (4.8)	97 (29.2)	
Other regimen[b]	32 (4.4)	1 (0.2)	31 (9.3)	

**P*-values are from Pearson's chi-squared test or Fisher's exact test for the difference in the distribution of the categorical characteristics across the types of retreatment cases

[a]1 patient had missing data

[b]Other regimen included: 3RHZE/5RHE = 13; 2SRHZ/4-12RH = 14; 2SRHZE/6EH = 2; 3SRH/6RH = 1; unknown = 2

retreatment cases were males (71.6 %) and in age group 15–44 years (70 %). Overall, 690 (94.5 %) retreatment cases had a documented HIV test result.

Retreatment 'others' constituted 45.5 % of retreatment cases. Like the classical retreatment cases, retreatment 'others' were mostly males (65 %), and in the age group 15–44 years (65 %). Significantly, lesser (62 %) of retreatment 'others' were treated with the standard retreatment regimen (2SRHZE/1RHZE/5RHE) compared to 95 % of classical retreatment cases. About a third of the retreatment 'others' were treated with the standard regimen for new TB patients.

Table 2 shows that HIV prevalence was higher among retreatment 'others' (70.9 %) than classical retreatment cases (53.5 %). HIV co-infection was 61.5 % among 690 retreatment patients that had a documented HIV test result. Females had a higher HIV prevalence (70.7 %) than males (57.8 %). Of the 424 patients with an HIV-positive test result, 385 (91 %) and 221 (52 %) were provided with Cotrimoxazole preventive therapy (CPT) and antiretroviral therapy (ART) respectively.

Table 3 shows that treatment was successful in 410 (56.2 %) of the 730 retreatment cases. Adverse outcomes were; 16.4 % LTFU, 9.9 % died, 2.6 % failed on treatment

Table 2 Prevalence of HIV by patient characteristics, retreatment type among retreatment TB patients with known HIV test results at eleven RRHs, Uganda ($n = 690$)

Characteristic	Total		Classical retreatment cases		'Others' retreatment cases		*P*-value*
		HIV Positive		HIV Positive		HIV Positive	
		n (%)		*n* (%)		*n* (%)	
Overall	690	424[b] (61.4)	374	200 (53.5)	316	224 (70.9)	<0.001**
Sex							
Male	492	284 (57.8)	289	145 (50.2)	203	139 (68.5)	0.022
Female	198	140 (70.7)	85	55 (64.7)	113	85 (75.2)	
Age group, years[a]							
<15	35	24 (68.6)	3	2 (66.7)	32	22 (68.8)	<0.001
15-44	488	316 (64.8)	277	157 (56.7)	211	159 (75.4)	
>44	166	83 (50.0)	94	40 (42.6)	73	43 (58.9)	
Anatomical site							
Pulmonary	650	391 (60.2)	374	200 (53.5)	276	191 (69.2)	<0.001
Extrapulmonary	40	33 (82.5)	0	0 (0.0)	40	33 (82.5)	
Treatment regimen							
Retreatment: 2SRHZE/1RHZE/5RHE	553	329 (59.5)	357	192 (53.8)	196	137 (69.9)	<0.001
New:2RHZE/6EH or 2RHZ/4RH	106	73 (68.9)	16	8 (50.0)	90	65 (72.2)	
Other regimen	31	22 (71.0)	1	0 (0.0)	30	22 (73.3)	

**P*-values are from either Pearson's chi-squared test of Fischer's exact tests for the difference between given characteristics and the type of retreatment among only HIV positive patients
***P*-value from Z-test for two proportions
[a]1 patient had missing data on this variable
[b]Cotrimoxazole preventive therapy and antiretroviral treatment were documented among 385 (91 %) and 221 (52 %) of all HIV positive TB retreatment patients respectively

while 5.1 % transferred-out and 9.9 % were not-evaluated. Table 4 shows that retreatment 'others' were associated with reduced odds of treatment success [odds ratio (OR) =0.65, 95 % CI 0.48, 0.87] compared to the classical retreatment cases. Anatomical site and treatment regimen were not associated with treatment success. Using multivariable analysis, odds of treatment success remained lower among retreatment 'others' compared to the classical retreatment cases after adjusting for age group, HIV status and sex (Adjusted OR (AOR)) = 0.60, 95% CI 0.44, 0.82). Unknown HIV status was significantly associated with lower odds of treatment success compared to known HIV status (AOR = 0.44, 95% CI 0.22, 0.88). Together with type of retreatment case, age group (less than 15 years) became significantly associated with treatment success (AOR = 2.32, 95% CI 1.12, 4.81).

Discussion

Retreatment 'others' constitute almost half of the retreatment cases in the RRHs of Uganda. Compared to the classical retreatment cases, more cases of retreatment 'others' were HIV positive. And more than a third of retreatment 'others' were not managed with the standard retreatment regimen. Fewer (half) retreatment 'others' succeeded on treatment (50.3 %) compared to six in ten of the classical retreatment cases (61.1 %). Lost to follow

Table 3 Outcomes of retreatment cases by WHO retreatment category

Type of retreatment	Treatment outcome		Adverse outcomes				
	Successful	Adverse	Failure	Died	LTFU	Transfer-out	Not -evaluated
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Smear-positive relapse: $n = 196$	134 (68.4)	62 (31.6)	9 (4.6)	9 (4.6)	23 (11.7)	7 (3.6)	14 (7.0)
Smear-positive return after failure: $n = 44$	30 (68.2)	14 (31.8)	4 (9.1)	3 (6.9)	5 (11.4)	0 (0.0)	2 (4.5)
Smear-positive return after LTFU: $n = 158$	79 (50)	79 (50.0)	3 (1.9)	19 (12)	26 (16.4)	12 (7.6)	19 (12.0)
Retreatment 'others': $n = 332$	167 (50.3)	165 (49.7)	3 (0.9)	41 (12.3)	66 (19.9)	18 (5.4)	37 (11.0)
Total; $n = 730$	410 (56.2)	320 (43.8)	19 (2.6)	72 (9.9)	120 (16.4)	37 (5)	72 (9.9)

$P < 0.001$ for the difference between the type of retreatment and treatment outcome using Pearson's chi-squared test

Table 4 Patient characteristics associated with binary treatment success among TB retreatment cases registered in eleven RRHs of Uganda ($n = 730$)

Characteristics	Total	Treatment Success n (%)	Unadjusted OR (95 % CI)	*P*-value*	Adjusted[b] OR (95 % CI)	*P*-value*
Overall	730	410 (56.2)				
Type of retreatment case						
Classical retreatment cases	398	243 (61.1)	1.00		1.00	
Retreatment 'others'	332	167 (50.3)	0.65 (0.48, 0.87)	0.004**	0.60 (0.44, 0.82)	0.001**
HIV status						
Positive	424	236 (55.7)	1.00		1.00	
Negative	266	159 (59.8)	1.18 (0.87, 1.62)	0.288	1.13 (0.82, 1.56)	0.452
Unknown	40	15 (37.5)	0.48 (0.24, 0.93)	0.030**	0.44 (0.22, 0.88)	0.020**
Age group[a]						
15-44	509	292 (57.4)	1.00		1.00	
<15	39	27 (69.2)	1.67 (0.83, 3.37)	0.143	2.32 (1.12, 4.81)	0.024**
≥45	181	90 (49.7)	0.73 (0.52, 1.03)	0.073	0.75 (0.53, 1.06)	0.102
Sex						
Male	523	296 (56.6)	1.00		1.00	
Female	207	114 (55.1)	0.94 (0.68, 1.30)	0.708	0.97 (0.69, 1.35)	0.844
Anatomical site						
Pulmonary	689	388 (56.3)	1.00			
Extrapulmonary	41	22 (53.7)	0.90 (0.48, 1.69)	0.739		
Treatment regimen						
Retreatment: 2SRHZE/1RHZE/5RHE	582	322 (55.3)	1.00			
New: 2RHZE/6EH or 2RHZ/4RH	116	66 (56.9)	1.07 (0.71, 1.59)	0.756		
Other regimen	32	22 (68.8)	1.78 (0.83, 3.82)	0.137		

*Wald P-value
**Significant at $P = 0.05$
[a]1 patient had missing data
[b]Adjusted for HIV status, age, and sex

up was the commonest adverse outcome for both retreatment groups.

Nearly half of the retreatment cases in this study were retreatment 'others' compared to one in three cases notified nationally [3]. Probably, RRHs receive mostly very sick patients whose sputum is likely to test negative on Ziehl Neelsen (ZN) smear test due to their inability to mount an immune response and/ or produce sufficient sputum for microscopy. In addition, the TB diagnosis in RRHs is likely to be made by relatively highly qualified clinicians with capacity and/or bias to rely on their clinical acumen to diagnose TB even in the absence of a positive AFB sputum result. The presence of high TB-HIV co-infection rates in our study may account for the observed high proportion of retreatment 'others' [9]. The proportion of retreatment 'others' in this study is comparable to those from Zimbabwe and India [6, 7], but less than the proportion observed from a study conducted in a large registration centre of Malawi [5].

Overall, treatment success was low at 50 % in retreatment 'others' and 61 % in classical retreatment cases, compared to 71 % treatment success notified to WHO [3]. This study considered patients in referral hospitals who may be different from other TB patients from lower levels of care on a number of factors. Due to the referral cascade, patients with atypical forms of TB or drug-resistant TB are likely to be managed at RRHs and hence likely to exhibit poor treatment outcomes. However, the observed factors like the weakness in recording and reporting system, inability to track these patients (15 % of participants didn't have definitive outcomes) and the low uptake of ART (52 %) among HIV co-infected patients may also explain the low treatment success. The 52 % ART uptake observed in the study population was higher than the national average of 24 % [10]. The difference between treatment success in this study and that reported to WHO may be because we evaluated all retreatment cases registered and not only classical retreatment cases that are routinely evaluated. Nonetheless, the

results support previous findings from a smaller study conducted in three RRHs in Uganda [2].

The outcomes for retreatment 'others' in this study were worse than those of retreatment 'others' reported in India as compared to the classical retreatment cases [7]. This difference across settings may be influenced by factors such as difference in treatment regimens' [5], drug resistance [11], co-morbidity [12], delay in diagnosis or even misdiagnosis [5, 13], adherence levels or having another pulmonary or extra-pulmonary disease for which they are not adequately treated.

Similar to the results reported in previous studies [5, 6], this study found that a higher proportions of retreatment 'others' were co-infected with HIV compared to the classical retreatment cases. Just like in other studies, we found that patients' knowledge of their HIV status is beneficial [9, 14, 15]. 90 % of study participants that were found to be HIV-positive were started on CPT and half of them started on ART as well. The high uptake of HIV testing coupled with good initiation of CPT in this study could have resulted in observing no difference in treatment success between HIV-positive and negative patients. Age group and unknown HIV status were only significant independent predictors, but did not modify the effect of type of TB retreatment case on treatment outcome.

The findings of this study should be viewed with the following limitations. Firstly, this was a retrospective study utilizing hospital TB registers which could be prone to inaccuracies resulting from poor recording and completeness in the patient data and compromise the validity of the finding. However, this study found that 94.5 % of smear-positive retreatment cases had smear result correctly recorded. In addition, completeness of treatment outcomes was improved by use of the district TB registers whereby 28 % (176/621) of definitive outcomes among study participants were obtained.

We could not establish treatment outcomes in 15 % of the study participants even after reviewing district TB registers. There were no differences in patient characteristics between those who had complete information on the outcomes and those who had missing outcomes. However, the high proportion of missing treatment outcome could have introduced bias in determining treatment success or underreported deaths or LTFU among the study participants.

This study highlights the importance of ensuring appropriate management for retreatment 'others' given the relatively poor outcomes. A first key step is to ensure that this high number of retreatment 'others' is not a result of misdiagnosing drug-resistant TB or a false positive diagnosis of TB. More accurate TB diagnostic tools like the GeneXpert MTB/RIF that are currently available in all the study sites may have a role in providing access to a confirmation of TB in this special group.

Secondly, the continued notification of high proportions of retreatment 'others' to national authorities and Global TB Program calls for clear guidance on the management of retreatment 'others' including further definition of treatment regimen(s) in high HIV prevalence settings and limited TB diagnostic capacity. A future prospective study involving culture and drug-susceptibility testing could be conducted in programmatic settings to further understand the appropriate treatment regimens in such patients.

Thirdly, the observed high LTFU in the retreatment patients especially the retreatment 'others' calls for focused and innovative interventions to ensure treatment adherence in this group of patients. Social incentives and community outreach may have a role to play in reducing the loss to follow-up of these groups.

Fourthly, high HIV prevalence among retreatment cases especially the TB retreatment 'others' calls for better strategies of improving provision of the full range of TB/HIV collaborative services to reduce the burden of HIV in this group of patients.

Finally, further research is recommended at different levels of the TB treatment program to further clarify the importance of patient, health worker and system related factors on treatment success among retreatment cases to complement the findings of this study; and design the most appropriate response to ensure favorable outcomes from this underserved and evaluated group of TB patients.

Abbreviations

AFB: Acid fast bacilli; AOR: Adjusted odds ratio; ART: Antiretroviral therapy; CI: Confidence interval; CPT: Cotrimoxazole preventive therapy; DST: Drug susceptibility testing; DTLS: District TB and Leprosy supervisor; E: Ethambutol; H: Isoniazid; HIV: Human immunodeficiency virus; LFTU: Lost to follow up; LSHTM: London School Of Hygiene and Tropical Medicine; MTB/RIF: Mycobacterium tuberculosis and rifampicin-resistance mutations; NTLP: National Tuberculosis and Leprosy Programme; OR: Odds ratio; R: Rifampicin; RRHs: Regional referral hospitals; S: Streptomycin; TB: Tuberculosis; WHO: World Health Organization; Z: Pyrazinamide; ZN: Ziehl Neelsen.

Competing interests

The authors declare no conflict of interest.

Authors contributions

Substantial contributions to conception and design, acquisition of data or analysis and interpretation of data (MGN, HJK, PM, AV). Manuscript writing and revising for intellectual content and approval for journal submission (MGN, HJK, MB, PM, AV). All authors read and approved the final manuscript.

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Research article

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

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Abstract

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

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

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

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

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

Background

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

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

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

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

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

Methods

Setting

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

Study design and data collection

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

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

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

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

Analysis

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

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

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

Results

General patient's characteristics

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

Presenting symptoms

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

Patient's knowledge on TB

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

Risk factors for TB patients delay

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

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

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

Health facility delay

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

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

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

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

Total delay

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

Discussion

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

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

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

Table 2: Risk factors for patients delay.

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

*n = 26 were missing

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

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

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

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

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

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

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

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

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

Conclusion

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

Competing interests

The authors declare that they have no competing interests.

Table 4: Risk factors for health facility delay

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

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

Authors' contributions

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

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Research article

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

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Abstract

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

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

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

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

Background

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

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

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

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

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

Methods

Setting

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

Study design and data collection

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

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

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

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

Operational definitions

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

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

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

Ethical considerations

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

Analysis

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

Results

Baseline profile of the study participants

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

Comparison of smear positive PTB patients by cough duration

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

Comparison between smear positive TB patients and place of first consultation

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

Comparison of smear positive PTB patients by clinic

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

Risk factors associated with smear positive results

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

Discussion

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

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

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

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

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

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

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

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

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

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

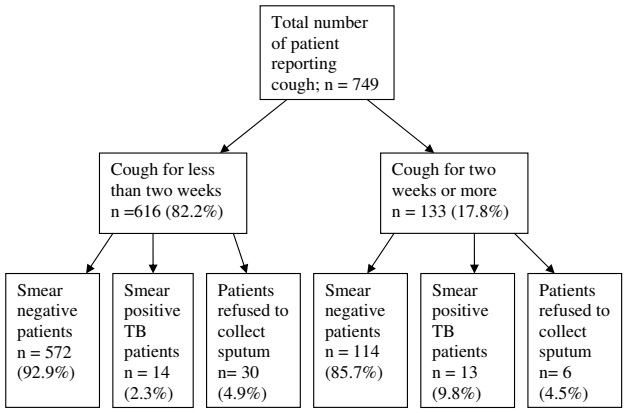

Figure 1
Comparison of smear results by cough duration.

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

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

Conclusion

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

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

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

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Research

Performance of LED fluorescence microscopy for the detection of tuberculosis in Rwanda using Zeiss Primo Star

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Abstract

Introduction: Ziehl-Neelsen (ZN) bright-field microscopy is time-consuming, with poor sensitivity, even under optimal conditions. Introduction of Primo Star iLED fluorescent microscopy (FM) may improve TB case finding at referral hospitals in Rwanda. The study aimed to determine the acceptability and effectiveness of iLED in a low resource setting. **Methods:** Between June 2009 and May 2010, the Rwandan TB Program and National Reference Laboratory carried out demonstration studies with iLED at a referral hospital in the capital, Kigali, and a rural district hospital in Nyamata, taking conventional FM as Gold Standard. **Results:** Agreement between the iLED and rechecking at the Reference Laboratory were deemed "almost perfect" (kappa = 0.81-1.00) across three of four site-phase combinations. The exception was Nyamata District Hospital during the validation phase, which was deemed "substantial" agreement (kappa = 0.61-0.80). However, the 100% concordance at both demonstration sites during the continuation phase shows technicians' rapid command of the new iLED microscope in a relatively short time. The lower overall positivity rate obtained in the rural clinic is not related to the performance of the microscope (or technicians), but is attributable to a significant increase in total number of patients and samples screened through active case finding. **Conclusion:** Laboratory technicians demonstrated high acceptance of iLED. Additionally, fluorescent microscopy reduces the time necessary for examination by more than half. The high level of agreement between iLED and FM during implementation in both sites provides initial evidence for iLED to replace current methods.

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Introduction

Sputum smear microscopy for acid-fast bacilli (AFB) using Ziehl-Neelsen (ZN) staining remains the most cost-efficient tool available to diagnose tuberculosis (TB) in low-resource countries. This method is rapid, inexpensive, and highly specific for detecting AFB in high-burden settings. However, the main limitation is its low and variable sensitivity, exacerbated in high HIV prevalence settings [1]. High TB-HIV co-infection rates and low TB case detection impede disease control in many TB endemic settings, notably sub-Saharan Africa [2]. Furthermore, where workloads are high, the amount of time spent examining smears compromises sensitivity [3]. A recent systematic review demonstrated that fluorescence microscopy (FM) is, on average, 10% more sensitive than conventional bright-field microscopy in detecting AFB in clinical specimens, with comparable specificity, and takes significantly less time [4]. However, widespread implementation of FM in disease-endemic settings remains limited due to several factors, including the short life and high cost of mercury vapor lamps; difficulty in maintaining machines; the need for a darkroom; and strict requirements for electrical power supply. Light-emitting diodes (LEDs) for FM have been identified as an alternative to conventional FM for screening of AFB [5, 6]. LED lamps do not have the disadvantages of mercury vapor lamps, with life expectancy averaging around 50,000-100,000 hours (10-20 years) of use [5]. They can also run on batteries [5, 7, 8]. Several commercial LED systems are now available, either as stand-alone microscopes or as add-on adapters to conventional microscopes [9]. Data published so far on LED microscopy for TB show that results in terms of sensitivity and specificity are comparable or better with LED than mercury vapor lamps [6, 7, 10-13]. **Study objectives**: This demonstration project evaluated the effectiveness of employing the Primo Star iLED fluorescence microscope (subsequently referred to as iLED) for case finding of TB under routine conditions in one referral and one rural setting in Rwanda. Microscopists without prior experience in FM were solicited in order to determine operational and clinical performance, as well as acceptability of the technology to laboratory staff. **Study design**: This project was conducted at two sites: Nyamata district hospital (DH) in Bugesera district and the Centre Hospitalier Universitaire de Kigali (CHUK) in Kigali. Nyamata DH is a 100-bed hospital with a catchment area of about 300,000 people. CHUK is a 509-bed national referral hospital (RH) serving the capital city, Kigali, with a catchment area of approximately 1 million people. The implementation of iLED was carried out in five phases: (1) ZN baseline; (2) iLED training and appraisal (five days); (3) validation (one month); (4) implementation (three months); and (5) continuation (six months).

Methods

Ethics statement: The evaluation was approved by the Ethical Review Committee of the Ministry of Health (Kigali, Rwanda) under Protocol Number 58/RNEC/2009 and by the Institutional Review Board of Columbia University IRB-AAAC6248 (New York, NY, USA). Written consent was not obtained because microscopy for AFB smears is the standard of care in Rwanda as part of regular clinic monitoring and evaluation of Tuberculosis. During validation, all sputum results obtained though iLED were rechecked systematically by the National Reference Laboratory before results were provided to patients for management. The implementation phase was only allowed once iLED was validated as a replacement for light microscopy with similar or better sensitivity, therefore not placing patients at risk of misdiagnosis. Written consent to participate in the study was not sought from the microscopists or their supervisors because the introduction of the iLED only minimally increased the workload and only for a short duration (1 month) during the whole study. Participants were informed about the purpose and impact of the study, and microscopists readily participated enthusiastically. The need for collecting documented informed consent was waived by the IRB. **Phase 1: ZN Baseline**: The aim of this one-month phase was to establish a baseline, under study conditions, of false positivity and negativity rates for ZN. TB treatment decisions were based on ZN results. All incoming sputum smears were stained for ZN examination under routine conditions. Slides were read using the available conventional bright-field microscope (1000x). After reading, all slides were kept in slide boxes, which were labeled to specify the study phase, study site, box number, and slide ID. Once every two weeks, the National Reference Laboratory (NRL) study supervisor collected all boxes. NRL study technicians rechecked all slides using conventional bright-field microscopes. Discrepant slides, if any, were sent to the Supra National Reference Laboratory (SNRL) in Germany for rereading. **Phase 2: Training and Appraisal**: A standardized five-day training course for microscopists and supervisors participating in the study was conducted. All eight participants had skills in ZN microscopy but not conventional FM. Participants after learning the purpose and impact of the study, participated readily. Following the training, all technicians involved

in the project filled out a questionnaire about several features of the iLED, including installation and first use, training, and optics and handling. **Phase 3: validation**: The validation phase lasted one month. Each sputum sample at the study sites was stained using Auramine O and examined by the iLED at 400x magnification. Patient management was based solely on the rechecking results carried out by the NRL. Staining solutions were prepared by NRL using Merck staining reagents (Catalogue 41000, Auramine O, item number 1013010050, lot number ZC 253201532) and provided to the study sites once per month, taking into consideration the limited shelf life of Auramine O. All readings (including rechecking) were done within 48 hours of staining. Results were quantified according to the scale presented in **Table 1**. NRL rechecked all slides using conventional FM. Rechecked results were provided to study sites the next day for timely patient management. The semi-quantitative scale for rechecking by NRL was different than the one used by study sites (**Table 2**). Discordant slides, if any, were sent to the SNRL for final discussion. The study sites were allowed to proceed to phase four only if the following performance targets were met: (1) 95% accordance between validation results of microscopy center and supervisory site; (2) quality of Auramine O stains acceptable in 100% of slides examined; and (3) fewer than two false results in a proficiency testing panel of 10 pre-defined slides.

Phase 4: implementation phase: The procedures were the same as during the validation phase. The duration of this phase was three months, and patient management was now based on iLED results. Supervision and rechecking by the NRL study supervisor were carried out using Lot Quality Assurance Sampling (LQAS). The sample size was calculated by NTP/NRL based on the positivity and number of negative smears, but the frequency of rechecking was decreased from daily to once every two weeks. Rereading by NRL was done using conventional FM at 400x magnification. Discordant slides, if any, were sent to the SNRL in Germany for umpire reading. Rechecked results were provided to study sites. **Phase 5: continuation and expansion**: The continuation phase lasted six months, and patient management was based on iLED results. Supervision and rechecking by NRL supervisors was carried out according to national Rwandan External Quality Assurance guidelines. Fifteen slides were collected quarterly and rechecked by NRL using conventional FM at 400 x magnification. Discordant slides, if any, were sent to the SNRL in Germany for umpire reading. Rechecked results were provided to study sites. After the six-month continuation phase, and following the availability of the compiled results of the previous phase, the demonstration project coordinator allowed all sites to use the iLED method routinely under program conditions. **Data entry and analysis**: All data and results were recorded in phase-specific forms and sent to NRL and NTP. An electronic database was completed on-site. Positivity agreement between methods at the study laboratories (DH or CHUK) and the National Reference Laboratory was assessed using Cohen's Kappa, which corrects for agreement by chance. Strength of agreement was evaluated using guidelines from Land is and Koch [14]: <0 = poor; 0-0.20 = slight; 0.21-0.40 = fair; 0.41-0.60 = moderate; 0.61-0.80 = substantial; 0.81-1.00 = almost perfect.

Results

Baseline: At the DH in Nyamata, all incoming sputum samples (100) from 37 patients, using the Spot-Morning-Spot criteria, were examined using ZN staining during the baseline phase. The positivity rate of the slides was 11% (11/100 -**Table 3**) with only one low false positive (LFP) as determined following rechecking. The LFP result had no negative public health consequence on the accurate diagnosis of the patient. There were no poorly stained slides reported by the NRL. At CHUK in Kigali, all incoming sputum samples (205) from 94 patients (Spot-Morning-Spot) were analyzed. The positivity rate for the samples was 7.3% (15/205 - **Table 4**) and two quantification errors (QEs) were reported following rechecking at NRL. The two QEs, corresponding to two samples from two different patients, had no negative public health consequence. There were no poorly stained slides reported by the NRL for CHUK during the rechecking of the baseline. For the comparison between results obtained by the DH in Nyamata and the NRL, Kappa was 0.947 [95% CI: 0.84, 1.00], which indicates an almost perfect agreement between the two laboratories (see results in **Table 5**). For the comparison between CHUK and NRL, Kappa was 1.000 due to full agreement (**Table 5**).

Validation phase: In Nyamata, all incoming samples (100) from 39 patients were screened. The positivity rate decreased to 4% (4/100 - see Table 3) and there were 1 low false positive and 1 low false negative (LFN) errors reported. Additionally, 15 samples were reported as having poor stains. The LFN and LFP errors, corresponding to two samples from the same patient, would not have a negative public health consequence and were probably due to administrative errors. However, as per protocol, diagnosis was made solely on the basis of the rechecking by the NRL. Kappa was

0.740 [95% CI: 0.38, 1.00], which indicates substantial agreement between the laboratories (**Table 5**). In CHUK, all incoming samples (202) from 87 patients were screened. The positivity rate significantly increased from baseline to 22.3% (45/202 - see Table 4) and there was one LFN reported. Since only one sample was collected for that particular patient, the LFN error would have had a negative public health consequence on the accurate diagnosis of the patient. The patient was adequately treated following rechecking by NRL. Nine samples were reported as having poor stains by the NRL. Kappa was 0.986 [95% CI: 0.96, 1.00'> 1.00], which indicates an almost perfect agreement between laboratories (**Table 5**). No errors were detected at the proficiency panel test. Both sites were allowed to proceed to the implementation phase.

Implementation phase: In Nyamata, following LQAS, 44 samples (corresponding to 44 patients) were rechecked by the NRL study supervisor. The positivity rate for samples increased from validation to 9.1% (4/44) but remained lower than in the baseline phase (**Table 3**). No reading/diagnosis errors were reported by the NRL. However, there were six poorly stained samples. Kappa was 1.000 due to full agreement (**Table 5**). In CHUK, following LQAS, 45 samples from 45 patients were rechecked. The positivity rate for samples increased further from baseline and validation to 31.1% (14/45), as shown in Table 4. Only one LFN and three poor stains were reported by the NRL. It is not possible to say whether the LFN error had a negative public health consequence, since the other two samples from this particular patient were not rechecked and could have been positive. Kappa was 0.949 [95% CI: 0.85; 1.00], which indicates an almost perfect agreement between laboratories (**Table 5**).

Continuation phase: In Nyamata, 16 samples were read from January through March by iLED at the site and conventional FM at NRL, and 100% concordance was observed. From April through June, an additional 11 samples were rechecked and all results concurred. At CHUK, there were 15 samples screened from January through March and 100% concordance was observed. Sixteen additional samples were screened from April through June and 100% concordance was also observed. **Technicians' appraisal**: the appraisal took place after training of the technicians. ***Installation and first use:*** All technicians felt that installation of the iLED was easy and that the manual was comprehensive and easy to read and understand. ***Training:*** The technicians participating in the iLED project felt that for technicians already trained in ZN microscopy (such as themselves), an iLED training of 1-5 days was suitable. However, for technicians not familiar with ZN microscopy, an iLED training of 3-20 days was suitable. Technicians also felt that NTPs can readily use the current manual developed by the manufacturer for implementation of LED microscopy without major changes.

Optics and handling: All technicians were satisfied with the contrast, color, intensity, and signal-to-noise ratio of the iLED. All technicians were very satisfied with the resolution and depth of focus of the iLED. All technicians also felt that the field of view of the iLED is more homogenously illuminated compared to the standard view. All of them were very satisfied with the overall handling features of the microscope. All technicians also felt that it was convenient or very convenient to switch between bright field and fluorescence. Only one technician surveyed felt that the toggle field was not robust. All technicians felt that no darkroom was needed when using iLED, a really convenient feature of iLED compared to regular FM. All technicians also agreed that the dazzling protection for the eyepieces was useful. None of the technicians surveyed reported any technical problems with the microscope overall.

Discussion

Compared to classical FM with mercury vapor lamp, LED FM is more user-friendly and benefits from a high acceptability by technicians. Microscopes do not require warm-up and cool-down time, a considerable advantage when power supply is erratic, and the LED light source is considered safer than the mercury vapor lamp. LED systems developed for AFB smears consist either of modules that can be fitted to a conventional microscope, or a complete microscope with built-in LED as the light source, such as the iLED. While Partech (Münster, Germany) and Cytoscience (Fontaines, Switzerland) have both developed complete LED FM microscopes, these microscopes are less appropriate for TB than iLED since they are monocular. Using a camera and monitor might be an appropriate solution, but not in less-developed countries. iLED, a binocular FM microscope with built-in LED lamp for epi-fluorescence has produced very good results in reference laboratories [13]. So far, very few reports on these systems exist. These rare reports, however, show excellent performance compared to ZN microscopy [15, 16]. Our study is the first direct evaluation of iLED in Rwanda. LED add-on kits have been designed for different common types of

bright field microscopes. The complete installation is not difficult, but it requires slightly more time and care, which could be a disadvantage from the end-user perspective. As difficulty in acceptance by inexperienced microscopists seems to be the main obstacle to the use of FM outside referral laboratories, this may prove to be a major advantage of transmitted LED light FM, as reported earlier from Tanzania [8]. It also remains to be seen whether complete binocular LED microscopes using epi-fluorescence, rather than transmitted light, will meet the same acceptance level with the progressive decentralization of FM to peripheral hospitals and health centers. Our study shows that the acceptability amongst the staff using iLED was extremely high and proficiency in adequate usage was rapid. Compared to traditional bright-field methods, LED fluorescence methods using Auramine O staining allows up to four times faster screening. The detection rate is also estimated to be at least 10% higher. While we did not directly compare the positivity rates between ZN and iLED, we monitored the positivity rate over time during our study.

In Nyamata, the positivity rate surprisingly decreased during the validation phase (Table 5). This result compares with previously established data from the National TB Programme, which has shown that in the last quarter of 2009 and first quarter of 2010, during which our study took place, there was an overall decrease in positivity rate that is not related to the performance of the microscope (or the technicians) but is rather attributable to a significant increase in total number of patients and samples screened. Indeed, the positivity rate dropped to 7.7% during our study, compared to 9.2% the year before. This increase in the total number of patients screened may be the result of the impact of Community Health Workers (CHWs) in Bugesera District (where Nyamata DH is located), who have been involved in active case finding, therefore casting a wider net for overall screening of TB suspects and decreasing the positivity rate at the Nyamata Center. One of the expected issues associated with the change from ZN to Auramine staining for the purpose of our study was a difficulty in preparing and then subsequently reading the slides adequately using the Auramine protocol. Indeed, a few of the smears in the various phases were reported as having poor stains. We believe these could be explained by the fact that some laboratory technicians were not completely proficient in staining the slides appropriately, as can also sometimes be the case for ZN. However, this was not an issue throughout the study as the number of slides poorly stained gradually decreased at both sites. Agreement between the iLED and rechecking at the Reference Laboratory were deemed "almost perfect" (kappa = 0.81-1.00) across three of four site-phase combinations. The exception was Nyamata District Hospital during the validation phase, which was deemed "substantial" agreement (kappa = 0.61-0.80). However, the 100% concordance at both demonstration sites during the continuation phase shows technicians' rapid command of the new iLED microscope in a relatively short time. Technicians can therefore be easily trained to switch from ZN microscopy to LED FM with a high success rate. This should be of interest to national TB control programs that are interested in improving their overall case detection rate but cannot yet invest in the newer, molecular-based technologies currently being rolled out.

Conclusion

In our study, the use of iLED FM module in both a referral hospital and rural clinic setting was associated with a high concordance rate as compared to a Reference Laboratory using conventional FM. The high level of agreement between iLED and FM during our study in multiple sites, combined to the fact that fluorescent microscopy reduces the time necessary for examination by more than half, provides initial evidence for the iLED to replace current standard methods. The iLED microscope also excelled in terms of user-friendliness and acceptance by users.

Competing interests

The authors declare no competing interests.

Authors' contributions

AUN, MG, and YBA conceived the study and participated in its design and coordination. MT and GV participated in the design and coordination of the study. BN performed all statistical analysis. All authors helped to draft the manuscript and read and approved the final manuscript.

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Tables

Table 1: Semi-quantitative scale used for reading with Iled

Table 2: Semi-quantitative scale for rechecking with conventional FM

Table 3: Distribution of slides by outcome at different phases of the study evaluation at Nyamata Hospital

Table 4: Distribution of slides by outcome at different phases of the study evaluation at CHUK

Table 5: Statistical analysis of diagnostic outcomes by site at Nyamata District Hospital (DH) and at the Centre Hospitalier Universitaire de Kigali (CHUK) by either LM or iLED

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Table 1: Semi-quantitative scale used for reading with iLED

IUATLD Scale (1000field =HPF) Result	**iLED** (400x magnification: 1 length =40 fields = 200HPF
Negative	Zero AFB /1 length
Scanty	1–19 AFB/1 length
1+	20–199 AFB/1 length
2+	5–50 AFB/1 field on average
3+	>50 AFB/1 field on average

Table 2: Semi-quantitative scale for rechecking with conventional FM

IUATLD Scale (1000field =HPF) Result	**Conventional FM** (200-250x magnification: 1 length =30 fields = 300HPF
Negative	Zero AFB /1 length
Scanty	1–9 AFB/1 length
1+	30–299 AFB/1 length
2+	10–100 AFB/1 field on average
3+	>100 AFB/1 field on average

Table 3: Distribution of slides by outcome at different phases of the study evaluation at Nyamata Hospital

Quantification	**Negative**	**Positive**	**Scanty**	**Total**	**%Positive**
Baseline	89	8	3	100	11.0%
Validation	96	1	3	100	4.0%
Implementation	40	3	1	44	9.1%
Continuation	0	23	4	27	100.0%

Table 4: Distribution of slides by outcome at different phases of the study evaluation at CHUK

Quantification	Negative	Positive	Scanty	Total	%Positive
Baseline	190	14	1	205	7.3%
Validation	157	25	20	202	22.3%
Implementation	31	12	2	45	31.1%
Continuation	2	22	7	31	93.5%

Table 5: Statistical analysis of diagnostic outcomes by site at Nyamata District Hospital (DH) and at the Centre Hospitalier Universitaire de Kigali (CHUK) by either LM or iLED

Site	Phase	Method	N	Sens.	Spec.	Cohen's Kappa	Kappa 95% CI
DH	Baseline	LM	100	1.000	0.989	0.947	[0.84, 1.00]
CHUK	Baseline	LM	205	1.000	1.000	1.000	[1.00, 1.00]
DH	Validation	iLED	100	0.750	0.990	0.740	[0.38, 1.00]
CHUK	Validation	iLED	202	0.978	1.000	0.986	[0.96, 1.00]
DH	Implementation	iLED	44	1.000	1.000	1.000	[1.00, 1.00]
CHUK	Implementation	iLED	45	0.933	1.000	0.949	[0.85, 1.00]

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Research

Knowledge of tuberculosis management using directly observed treatment short course therapy among final year medical students in South Western Nigeria

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Key words: Tuberculosis, Directly observed treatment short course therapy (DOTS).

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Abstract

Introduction: Equipping medical graduates with the competence to manage tuberculosis is not just imperative but also urgent as the diseases have been consistently listed as one of the major causes of morbidity and mortality in Nigeria. However, there were no baseline studies done on knowledge of final year medical students on various aspects of TB diagnosis and management under directly observed treatment short course therapy (DOTS) which forms the basis of this study. **Methods:** A total of 241 final year medical students from three medical colleges in Nigeria were interviewed. The questions assessed their knowledge about various modes of transmission, symptoms and management of tuberculosis under DOTS. **Results:** More than half of the respondents (i.e. 69%) had poor knowledge on TB disease. Only 33.6% mentioned sputum smear as the best tool of diagnosing TB according to guideline. Poor knowledge was also exhibited when asked of various categories under DOTS treatment regimen, as 46.1% correctly mentioned cat 1 and 2. Minority 18.7% and 6.7% had complete knowledge of 6 months duration for new TB cases and 8 months for re-treatment cases respectively. Less than one tenth, i.e. 4.6% and 2.9% could correctly defined what is called a new TB case and re-treatment cases according to standard guideline. **Conclusion:** The study reveals gross inadequacies in TB knowledge and management practices among Nigerian final year medical students. There is urgent need for incorporation of National TB guideline into existing undergraduate medical education curriculum as well as students rotation through activities in DOTS clinic.

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Introduction

Tuberculosis (TB) has re-emerged as a major global public health concern since the mid-1980s. Globally, Tuberculosis accounted for 1.2 - 1.5 million deaths (including mortality due to Tuberculosis as well as TB and HIV co-infection), 85% of this occurring in developing countries and 26% in Africa [1]. Thus, TB ranks as the second highest cause of adult mortality after HIV in the world. It also tends to affect men more than women, mostly among the economically productive age group. [1] Factors contributing to the re-emergence include pervasive poverty and lack of good governance, the HIV/AIDS epidemic poor public health services, rapid population growth and rapid urbanization [2].

TB is a highly contagious and fatal disease of public health concern particularly in low income countries. [3] It remains a major cause of high morbidity and mortality in these countries despite considerable decline in prevalence in the developed world [4]. Unfortunately, it affects mainly the economically productive age group despite the availability of cure [5]. The disease spreads through air by droplet nuclei and the micro-organisms enter the body through lung inhalation. So, only people with pulmonary TB are infectious. This form of disease is the most frequent, [3] occurring in more than 80% of cases. The extra-pulmonary TB are almost never infectious, unless with concomitant pulmonary TB [3]. However, TB could actually affect any part of the body. Most infected people (80-90%) will never become ill with TB unless with seriously compromised immunity. Nevertheless, each active TB case will infect on average between 10 and 15 people every year [1,5].

In Nigeria, there were 33,000 deaths resulting from TB disease in year 2009. [1] Despite the availability of proven interventions such as the use of anti-TB drugs reported to produce a cure rate of up to 87%, there are differing trends in the incidence of re-treatment and new MDR cases. Likewise, there is a strong political commitment to combat TB and this has led to the establishment of National Tuberculosis and Leprosy Control Programme (NTBLCP), an arm of the Federal Ministry of health given the mandate to control TB and leprosy in Nigeria. The vision of the Programme is "Nigeria free of TB" while its goal is to reduce TB to a level at which it is no longer a public health problem. In line with this vision, the NTBLCP adopted the WHO recommended DOTS strategy in 1993 and the Stop TB strategy 2006 and has since then scaled-up implementation to all the 36states and FCT with significant improvement in DOTS expansion from 40% in 2006 to 63% in 2010 (1 DOTS centre/25,000 population) to achieve 70% case detection and 85% cure rate. [6] There has been a steady increase in total number of all forms of TB cases notified from 90,311 in 2008; 90,447 in 2010 to 93,050 in 2011 (the latter representing a CNR of 58/100,000 pop for all forms of TB) still below the 70% case detection target [7].

Medical schools are one of the important portals for management of patients with TB. DOTS centers have also been established in these colleges to increase access to TB treatment. Medical schools play an important role not only in the building of medical expertise but also in the socialization of future physicians. Societies expect these institutions to train students to competently and holistically handle common health problems. To widen access and improving quality of TB services as well as for giving hands on training to students, involvement of medical colleges is paramount. Knowledge of tuberculosis is assimilated in parts over all the years in the medical college. A TB clinic posting exposes the medical student to the practical aspects of Tuberculosis treatment, giving them an insight in to the day to day working of a DOTS clinic. Medical colleges play a central role in training and shaping the attitudes of the future generations of medical practitioners.

However, there is a dearth of data regarding the level of knowledge about TB and DOTS among medical students who are the budding doctors and can make an impact on TB control. Previous studies conducted in Nigeria and other countries worldwide focuses on the knowledge of TB and its management among practicing doctors, both in private or public sector showing considerable variation in prevention, evaluation and treatment strategies, indicates less than optimal performance and highlight the need for further education and training in issues relating to tuberculosis among physicians [8-12].

Physicians in the future need to be aware of the epidemiology, determinants, screening, and management of re-emerging infections such as tuberculosis. Increased exposure and education in both academic and clinical settings is crucial if medical students are to become competent in this arena. In view of the above background, this study was conducted with objective of assessing knowledge of the final year medical students in three medical colleges in Nigeria, about various aspects of diagnosis and management of TB under Directly observed treatment short course therapy (DOTS).

Methods

This study was carried out in Southwestern Nigeria. Government of Nigeria adopted the WHO recommended DOTS strategy as the national modality for the treatment of Tuberculosis, and the strategy had been effective in Nigeria like in many other parts of the world. However, most TB programmes are donor driven, though the federal Government through the NTBLCP coordinates TB response efforts in the country. There are 8 medical schools in the Southwestern region, 4 owned by Federal and 4 owned by states governments. Lectures on DOTs and rotation through PHCs and DOTs centers are usually incorporated into the medical school curriculum which final year medical students would have passed through before certified as a medical doctor

This is a descriptive cross sectional study among medical students in Southwestern Nigeria. All medical students in their final year constitute the target population. Eligible participants were registered final year MBBS students in selected medical schools. Sample size was estimated using the Leslie's Fischer's formular for single proportion using a prevalence of 16%. The minimum calculated sample size of 206 was increased to 242 to take care of non response.

Sampling was done in the multistage fashion. Three out of 8 medical schools in Southwestern Nigeria were selected using simple random sampling employing simple balloting. In stage 2 and for a medical school, 2 out of 4 groups of final year medical students on clinical rotation were also randomly selected using simple balloting. Questionnaires were equally allocated in each sampling stage. In stage three, a list of medical students per rotation group was made, and a systematic sampling method of 1 in 3 names on the list was made to reach the respondents for this study.

Research instruments were semi structured self administered pre tested questionnaires administered by trained lecturer assistant from each of the selected medical schools. Study variables include their knowledge, perception and practice of DOTs regimen including diagnosis and management and treatment of tuberculosis.. The

questionnaires had multiple choice questions, and also single or multiple responses of possible options that were correct. The subjects had a choice of not answering any question they did not know. Data were collected over a period of 3 months after making a total of 6 visits to the medical schools.

Ethical approval to conduct the study was obtained from LTH ethical review committee while a written consent was obtained from each respondent. A total of 241 finalists were interviewed. Data collected was analyzed using SPSS statistical package after data cleaning, and ensuring data validity through random checks and double entry of data. Frequency data were generated. Both bi and multivariate logistic regression were done in addition to Chi squared testing to demonstrate association between variables of interest. P value was set at less than or equal to 0.05 for all inferential statistics having to do with significance tests.

Results

All two hundred and forty one respondents returned useful and completely filled questionnaires. The respondent's age ranged between 20 - 49 years with a mean age 26 + 3 years and a modal age group 25 - 29 years. There were more males 147 (60.7%) than female 95 (39.3%). Majority of the respondents were Christians 189 (78.1%) while the remaining 52 (21.9%) were Moslems (**Table 1**).

Likewise in terms of TB diagnosis according to National guideline, 87 (33.6%), 85 (35.3%) and 73 (30.3%) mentioned sputum smear, chest x-ray and sputum culture respectively. In addition, only 29 (11.9%) was able to mention three methods used for diagnosis tuberculosis i.e. chest x-ray, sputum smear and sputum culture (**Table 2**).

The correct classification of patients into Cat 1 and Cat 11 was done by 111 (46.1%) of respondents while only 83 (34.5%), 16 (6.7%), 9 (3.7%) were able to identify correctly regimen duration for new tb, re-treatment and tb treatment among children. However, only 4 (1.7%), 7 (2.9%) were able to define correctly new tb and re-treatment tb cases (**Table 3**).

Discussion

The study revealed gross inadequacies in the knowledge of tuberculosis management according to DOTS regimen among final year medical students in South Western, Nigeria. Less than half of the respondents mentioned sputum smear, chest X-ray and sputum culture as means of diagnosing tb according to National guideline. A very similar finding was observed among medical interns in Turkey with 28.8% but higher findings recorded among interns in ido-ekiti, South Western Nigeria and Belgore where ZN staining for AFB was identified as the best diagnostic procedure/technique for PTB by 74 (62.7%) and 71.1% respectively [13-15].

Likewise, it is worrisome to know that only 34.5% and 6.7% were able to identify correctly regimen duration for new and re-treatment tuberculosis cases according to standard guidelines. This low level could be the result of deficiency in TB education in most Nigerian medical schools and affiliated teaching hospitals. This is made much worst by absence of effective DOTS centers in many tertiary centers including the teaching hospitals. However, since National Tuberculosis and Leprosy Control Program (NTBLCP) is already in place, though yet to achieve its global targets of 70% case detection despite adoption of DOTS strategy in the early 90s, there is need for additional support by effective and well trained medical practitioners towards achieving the target. The onus lies on the medical colleges and the curriculum to produce well trained and skilled medical practitioners. The knowledge level of graduating doctors and their attitudes may influence national TB control programs.

As far as the rank of Nigeria among the 22 high burden countries for TB, only 1.7% and 2.9% were able to define correctly new tb and re-treatment tb cases. Such low level was observed among final year medical students in tertiary level health facility in India where 16% 5th year medical students were able to classify patients according to drug regimen and category [16]. Knowledge about the terms as cured was also not satisfactory as only 1.7% correctly defined cure. Our result was lower when compared to a similar study among medical finalist in India where 30% of students mentioned correct definitions [16].

There is an urgent need for massive increase in awareness of DOTS among medical students. First, federal government must enforce the establishment of strict and dedicated DOTS clinic in all tertiary hospitals. Second, medical students must rotate through DOTS clinic and practically participate in all its activities, including performance of ZN staining for sputum smear microscopy. The revision of existing medical education curriculum in Nigeria should focus on incorporation of national TB guidelines into TB teachings in schools. The appropriate authority should ensure the circulation and availability of TB guidelines to every practicing medical doctor in the country. This will encourage medical practitioners to inculcate diagnostic and prescription practices that are in accordance with the national TB guidelines [17].

Conclusion

Tuberculosis being the major public health problem in Nigeria, needs a higher priority in the medical curriculum. The knowledge level of final year medical students in the present study was found to be poor for the various aspects of tuberculosis management under DOTS programme. This study highlights the inadequate and incomplete knowledge of medical undergraduates regarding TB treatment using DOTS, and emphasizes the need for more regular training sessions along with strict supervision of trainees. This study thus concludes that TB/DOTS clinic posting and training should be made mandatory for all the medical students to increase their knowledge and skills for effective management of patients with tuberculosis and thereby in the long run preventing the further rise of MDR and XDR TB cases. As long as TB continues to plague the country, empowering future physicians with competent knowledge of TB and DOTS remains a most viable solution. Based on the experience, we suggest the following: full integration of the TB control-DOTS curriculum across all levels and medical schools in Nigeria; faculty orientation and training on implementing the curriculum in their classes; access to instructional materials on TB control and DOTS; administrative support for the full implementation of the curriculum.

Competing interests

The authors declare no competing interests.

Authors' contributions

Olarewaju Sunday conceived the idea for the study, interviewed selected individuals and provide the result. He also performed the literature search and drafted introduction, results, discussion and conclusion of the study. Adebimpe Wasiu revised and edited the manuscript particularly the methodology aspect. Adenike Olugbenga-Bello and Olarewaju Oladimeji revised and edit the manuscript. All authors read and approved the final version of the manuscript.

Tables

Table 1: Socio-demographic status of respondents
Table 2: Knowledge on TB diagnosis and follow up by National Guideline
Table 3: Knowledge of respondents on TB classification and treatment by National Guideline

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Table 1: Socio-demographic status of respondents		
Variable (N=241)	**Frequency**	**Percentage**
Sex		
Male	147	60.7
Female	95	39.3
Marital status		
Single	204	84.0
Married	36	14.9
Separated	2	0.8
Religion		
Christian	189	78.1
Moslem	52	21.9
Ethnicity		
Yoruba	179	74.0
Hausa	10	4.0
Ibo	53	22.0
Age group		
20 -24	70	28.9
25- 29	150	62.0
30-34	18	7.0
35-39	3	1.2
40 -44	1	0.4

Table 2: Knowledge on TB diagnosis and follow up by National Guideline		
Variable (Multiple responses allowed)	**Frequency**	**Percentage**
Sputum smear	87	33.6
Chest x-ray	85	35.2
Sputum culture	73	30.3
Using three methods (Sputum smear, chest x-ray and sputum culture)	29	11.9
Using two methods (Sputum smear and chest x-ray)	29	11.9
Using one method (Sputum smear only)	88	36.4

Table 3: Knowledge of respondents on TB classification and treatment by National Guideline		
Variable	**Frequency**	**Percentage**
Cat 1 and Cat 11	111	46.1
6 months regimen for new cases	45	18.7
8 months regimen for new cases	38	15.8
8 months regimen for re-treatment cases	16	6.7
6 months regimen for children	9	3.7
Cured definition	4	1.7
New TB case definition	11	4.6
Re-treatment case definition	7	2.9

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RESEARCH ARTICLE Open Access

The role of AFB microscopy training in improving the performance of laboratory professionals: analysis of pre and post training evaluation scores

Pawlos Reji[1], Getachew Aga[2] and Gemeda Abebe[3*]

Abstract

Background: Tuberculosis (TB) remains major cause of morbidity and mortality due to any one of infectious agent worldwide. In low income countries, Ziehl-Neelsen sputum smear microscopy is the only cost-effective tool for diagnosis and monitoring of patients on treatment. In order to have efficient AFB microscopy centers, it is imperative to have continuous refresher training for laboratory professionals and strong External Quality Assessment (EQA) system). However, very little data exists as to the effect of in-service training on performance of laboratory personnel in Ethiopia.
The objective of this study was to investigate the role of AFB microscopy refresher training on the performance of laboratory professionals.

Methods: A cross-sectional retrospective study was conducted to appraise theoretical and practical performance of laboratory professionals before and after AFB microscopy training. Theoretical assessment was based on standard questions while practical assessment was based on smear reading of 10 standard slides. Data on eight rounds of a five days training at Adama regional laboratory on AFB microscopy in 2009 was obtained and analyzed using SPSS 16.0 statistical software.

Result: The pre-training mean score of the theoretical knowledge and practical skills were 61.8% and 75.7%, respectively. The post training mean scores were 84.2% and 89.2% for theoretical knowledge and practical skills, respectively. The increase in mean score of both theoretical and practical assessment was statistically significant ($p < 0.0001$). Post training mean score of theoretical knowledge was higher among diploma holders trainees than the BSc degree counter parts ($p = 0.001$). The mean scores on practice before and after training was dependent on participation in previous AFB microscopy trainings ($p < 0.0001$). Proportions of trainees with both major and minor errors were found to decrease after they were trained. Trainees who have had previous training were found to commit less errors than those who were not participated in previous training ($p < 0.0001$).

Conclusion: Training has improved theoretical and practical performance of laboratory professionals. Pre-placement and continuous training irrespective of lab professionals qualification and service year and sustainable EQA are highly recommended to ensure quality of AFB microscopy service.

Keywords: Tuberculosis, AFB, Refresher training, Scores

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Background

Tuberculosis remains major cause of morbidity and mortality due to any one of infectious agent worldwide. It is estimated that one third of the worlds population is infected with *M. tuberculosis* and this result in an estimated eight million new cases annually [1]. Among these new cases 2 to 3 million deaths occur annually [2]. Most of the tuberculosis cases and deaths are reported in developing countries [1]. As per the World Health Organization (WHO) report of 2011, Ethiopia ranks seventh among the 22 tuberculosis high burden countries. According to the report, the estimated prevalence and incidence of all forms TB in Ethiopia was 394 and 261/100,000 population, respectively [3].

Case detection through quality assured bacteriology is an essential element of the WHO STOP TB Strategy [4]. In low income countries, Ziehl-Neelsen sputum smear microscopy is the only cost-effective tool for diagnosing patients with infectious tuberculosis and to monitor their progress in treatment [5]. It yields timely results but the sensitivity is low as compared fluorescent microscopy and culture [6,7].

In order to have an efficient TB microscopy centers, it is imperative to have strong External Quality Assessment (EQA) in which laboratory results are checked by an external agency. Moreover, refresher training for laboratory professionals involved in Acid Fast Bacilli (AFB) microscopy at peripheral health facilities is important [8-10]. EQA which consists of blind rechecking, panel/proficiency testing and onsite supervision is important to identify errors so that corrective actions can be taken to improve the overall performances of microscopy centers [11]. Training of professionals along with sustainable EQA is important to improve the technical competency of laboratory professionals in every aspects of AFB microscopy [12,13].

Studies in Africa and other different parts of the world have shown that effective and sustainable EQA and training programs are significant in improving the performance of AFB microscopy centers [10,14,15]. In Ethiopia multiple trainings have been conducted but most of the training data were not analyzed to see the overall effect of training on performance of the professionals that can be measured in terms of scores on theoretical and practical assessments. Therefore, the aim of present study was to appraise the performance of laboratory professionals before and after they were trained in AFB microscopy in Oromia region.

Significance of the study

Despite many AFB microscopy trainings, investigation on training data is not commonly practiced in Ethiopia and other countries. Investigation of training data is important as it can provide information on performance of trainees so that appropriate interventions can be planed. Therefore the finding of this study will alert trainers to plan for enhanced quality of AFB microscopy trainings and policy makers in tuberculosis control program to give attention to continuous on job AFB microscopy training towards enhanced case detection and better control of tuberculosis.

Ethical considerations

Before the commencement of the investigation, official approval was obtained from the ethical clearance committee of Oromia region health bureau (IRB number BEFO/BTFH/1-8/2066). Adama regional laboratory was also officially communicated and permission was obtained to get trainees' information from the training data base.

Methods

Retrospective investigation was conducted in December 2011 to assess effect of AFB microscopy training on performance of laboratory professionals. Data on eight rounds of a five days training for 316 trainees on AFB microscopy in 2009 was obtained and analyzed. All these trainees were enrolled at different times in the eight rounds of training and their evaluation was based on their score on pre and post training assessment on theory and practice. Both theoretical and practical assessments were corrected by the trainers who were senior medical laboratory professionals with at least Bachelors degree in medical laboratory technology and minimum of 5 years of service. All of them were certified with training of trainers (TOT) in AFB microscopy.

Theoretical evaluation was based on standard multiple choice questions corrected out of hundred. Practical assessment was based on smear reading on a set of 10 stained panel slides that were prepared and graded as per the standard procedure [11]. Each trainee was provided with 10 stained slides and the reading was corrected out of 100 in which 10 point was given for correct reading, 5 point for Quantification Error (QE) and 0 point for any type of false reading (Low False Positive, High False Positive, Low False Negative or High False Negative) as per the scoring system of proficiency in reading [16]. The overall evaluation system was based on the following table (Table 1).

Using data collection format, trainees' score on pre and post training theoretical and practical assessments as well as information on their characteristics including sex, qualification, service year, participation in previous training and their facility type was collected from the training data base of Adama regional laboratory. Data was entered and analyzed using SPSS statistical soft ware (version 16) at a statistical significance of $p < 0.05$. The mean theoretical and practical scores as well as error types with their rates on smear reading before and after

Table 1 Evaluation system for AFB microscopy errors

Result of trainees	True results of standard slides				
	Negative	1-9 AFB/100 field	1+	2+	3+
Negative	Correct	LFN	HFN	HFN	HFN
1–9 AFB/100 field	LFP	Correct	Correct	QE	QE
1+	HFP	Correct	Correct	Correct	QE
2+	HFP	QE	Correct	Correct	Correct
3+	HFP	QE	QE	Correct	Correct

LFP- low false positive, HFP- high false positive, LFN- low false negative, HFN- high false negative, QE- quantification error.

training were determined. Mean score before and after training was compared using paired T test. The effect of trainees' characteristics on their theoretical and practical scores as well as error rates before and after training was statistically tested using logistic regression analysis.

Results

Characteristics of trainees

Out of 316 trainees, 259 (82%) were males, 238 (75.3%) with qualification of diploma, 270 (65.5%) with service year ranging from 0 to 3 years, 169 (53.5%) did not participate in similar previous trainings and 236 (74.3%) were from government health institutions. No trainee with BSc degree had service year of eight or more. Analysis of training data has shown that more than half of the trainees enrolled in 2009 have not been participated in previous trainings (Table 2). Out of total trainees with qualification of BSc degree, 97.4% and 2.6% had service year of 0–3 and 4–7, respectively (Figure 1).

Theoretical and practical scores of trainees

Data on pre training evaluation have shown that the mean score of the trainees in the theoretical assessment was 61.8% with minimum score of 20%, maximum score of 100%. Pre training practical assessment has shown that the mean, minimum and maximum scores of trainees were 75.7%, 20%, 100%, respectively. Analysis of post training evaluation has shown that the mean, minimum and maximum scores of trainees in theory were 84.2%, 40%, and 100%, respectively. Data on post training evaluation revealed that the mean, minimum and the maximum, scores were 89.3%, 50% and 100%, respectively in practical performance. Post training mean score of trainees in theory and practice was significantly increased ($P < 0.0001$).

Table 2 Frequency distribution of characteristics of trainees, Adama regional laboratory, 2009

Characteristics		Frequency n (%)
Sex	Male	259(82.0)
	Female	57(18.0)
Qualification	Diploma	238(75.3)
	Degree	78(24.7)
Service year	0–3	207(65.5)
	4–7	63(19.9)
	8–11	37(11.7)
	12–15	4(1.3)
	> = 20	5(1.6)
Previous training	Yes	147(46.5)
	No	169(53.5)
Health institution	Government	236(74.3)
	Private	80(25.7)

Theoretical and practical scores by characteristics of trainees

Trainees' characteristics were investigated to identify their effect on mean score of theoretical knowledge before and after training. The pre training theoretical mean score was not affected by any of the investigated trainees' characteristics but post training assessment has shown that the mean score of theory was higher among diploma holder trainees than the degree counter parts ($p = 0.001$) (Table 3). Pre and post training mean score in practice was not dependent on trainee's sex, qualification and service year ($P > 0.05$). But it was observed that both pre and post training mean scores in practice was higher among trainees who have had previous training than those who have had no such training ($P < 0.0001$). It was also found that the mean score of practice after training was higher among participants from private health institutions than the government counterparts ($P < 0.011$) (Table 4).

Type of errors committed by trainees

Pre and post training score analysis on type and error rates has shown that majority of trainees committed quantification error but the percentage of trainees with this type of error substantially decrease after they were trained ($p = 0.02$). Before the training 12.4% of trainees were found to commit minor error of low false negative but after training, the percentage of trainees with this error were found to decrease ($p < 0.0001$) (Table 4). Similarly, the microscopic reading result of 5.5% of the trainees

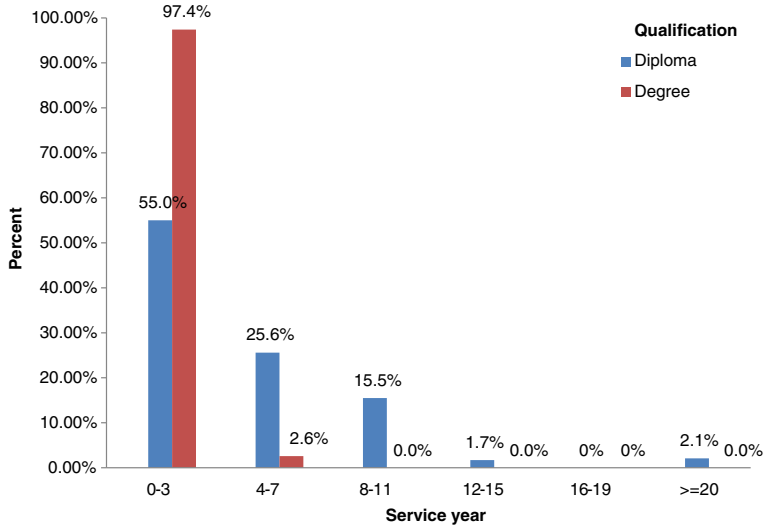

Figure 1 Distribution of trainees by service year and qualification, Adama regional laboratory, 2009.

was found to be high false positive before trainings however after the training only 1% of participants were found to commit high false positive result (p = 0.031). Before and after the whole rounds of trainings, it was also observed that 9% and 35% of trainees respectively, have correctly read all slides (P < 0.0001) (Table 5).

Error rates by trainee's characteristics

Analysis of effect of trainees' characteristics on error rates was carried out after categorizing all types of errors to one group (error), and correct reading in to no error. Accordingly, more males (95%) than females (92.1%) were found to commit at least one error in microscopic reading before training, but the difference was not statistically significant (p = 0.208). Except participation in previous training, other trainees' characteristics were also not associated with smear reading errors. Trainees who have participated in previous training than those who have not, were found to read all slides without error (p < 0.0001) (Table 6).

Discussion

In 2009, eight rounds of trainings were conducted for 316 laboratory professionals with objective to strengthen

Table 3 Pre and post training theoretical mean score on smear reading by different characteristics of trainees, Adama regional laboratory, 2009

Trainees' characteristics		Pre training theoretical mean score in %	SD	P-value	Post training theoretical mean score in %	SD	P-value
Sex	Male	61.8	15.3	0.857	83.9	11.6	0.578
	Female	62.2	16.2		85.5	11.9	
Qualification	Diploma	61.8	13.9	0.970	85.5	11.2	0.001*
	Degree	61.7	19.4		80.1	12.3	
Service year	0–3	62.5	16.0	0.987	83.4	11.8	0.904
	4–7	57.8	15.6		85.4	11.3	
	8–11	63.9	10.0		86.5	11.2	
	2–15	59.5	16.3		88.0	10.4	
	> = 20	67.6	18.9		81.4	14.7	
Previous training	Yes	62.5	16.6	0.461	85.2	12.1	0.129
	No	61.1	14.4		83.3	11.4	
Health institution	Government	62.4	16.4	0.126	83.8	12.1	0.354
	Private	59.8	12.0		85.2	10.2	

SD = standard deviation, * = statistically significant.

Table 4 Pre and post training practical mean score on smear reading by different characteristics of trainees, Adama regional laboratory, 2009

Trainees' characteristics		Practical pre-training			Practical post- training		
		Mean score in %	SD	P-vale	Mean score in %	SD	P-value
Sex	Male	75.2	13.9	0.386	89.1	10.8	0.986
	Female	78.3	15.6		89.9	11.3	
Qualification	Diploma	76.0	13.5	0.134	90.3	10.2	0.008*
	Degree	74.7	16.4		86.2	12.1	
Service year	0–3	75.8	15.0	0.396	88.7	11.3	0.737
	4–7	76.8	12.9		91.8	8.7	
	8–11	72.5	12.5		87.5	11.8	
	2–15	73.8	11.7		90.8	6.2	
	> = 20	83.2	11.7		93.8	8.5	
Previous training	Yes	84.7	10.0	<0.0001*	91.9	10.9	<0.0001*
	No	67.9	12.7		87.0	10.3	
Health institution	Government	75.9	15.3	0.660	88.5	11.3	0.011*
	Private	75.2	10.6		91.7	9.1	

SD = Standard deviation, * = statistically significant.

AFB microscopy service in Oromia region. Data on those trainings were retrospectively investigated to measure the effect of training on performance of trainees in the form of post test assessment. Most of the trainees were diploma graduates with maximum service year of 20 years. On the contrary, those participants with qualification of BSc degree have minimal service years and this may be due to the fact that the BSc degree program in Ethiopia has started recently. Nearly half of the trainees enrolled in the current investigation have also had similar training before.

Training along with other interventions is very important to strength AFB microscopy centers [13]. The purpose of training is to improve the performance of professionals and this requires analysis of training data as it is important for planning. Our investigation on training data has revealed that trainees have significantly improved their performance both in theoretical knowledge and practical skills. The average pre training proficiency of trainees on smear reading was found to be 75.6% but it was increased to 89% after the training. In routine panel testing, participants are expected to score a proficiency of 80% in smear reading [16]. Proficiency of the trainees was lower than the standard before they were trained but due to the effect of training they were able to attain the standard score. Studies in other countries have also reported similar findings [9,10,14]. Besides improving the proficiency, training can also motivate, update on new information and facilitate ways to share experience so that laboratory professionals can thrive for better services.

Table 5 Distribution of trainees by microscopic smear reading error type before and after training, Adama regional laboratory, 2009

Error type	Before training in %	After training in %	p-value
Quantification error	66.2	57.0	0.020*
Low false negative	12.4	1.4	<0.0001*
Low false positive	3.4	3.3	0.549
High false negative	3.5	2.3	0.062
High false positive	5.5	1.0	0.031*
No error	9.0	35.0	<0.0001*

* = statistically significant.

In routine AFB microscopy set ups, laboratory professionals have different back grounds in terms of qualification, training, experience and others. Therefore it is important to consider all these characteristics for possible interventions during training as well as analysis of training data. In the current investigation, post training theoretical performance of laboratory professionals with qualification of BSc degree was lower than the diploma graduates. In principle, the performance of BSc degree graduates is expected to be better than diploma graduates. The observed difference may be due to lack of attention resulting from over confidence by BSc degree graduates during trainings.

In pre and post practical assessment, trainees who have participated in previous similar training have shown better performance than those who have not been trained previously. This finding indicates that training and retraining is important to improve practical performance of laboratory professionals. Other studies have also reported

Table 6 Pre and post training error by characteristics of trainees, Adama regional laboratory, 2009

Trainees' characteristics		Pre training error (n = 316)			Post training error (n = 316)		
		Yes n(%) N (%)	No n(%) N (%)	P-value	Yes n(%) N (%)	No n(%) N (%)	P-value
Sex	Male	246(95)	13(5)	0.208	179(69.1)	80(30.9)	0.064
	Female	52(91.2)	5(8.8)		32(56.1)	25(43.9)	
Qualification	Diploma	227(95.4)	11(4.6)	0.125	152(69.9)	86(36.1)	0.071
	Degree	71(91.0)	7(9.0)		59(75.6)	19(24.4)	
Service year	0–3	196(94.7)	11(5.3)	0.492	143(69.1)	64(30.9)	0.280
	4–7	58(92.1)	5(7.9)		38(60.3)	25(37.7)	
	8–11	36(97.3)	1(2.7)		25(67.6)	12(32.4)	
	12–15	4(100)	0(0)		3(75.0)	1(25.0)	
	> = 20	4(80)	1(20)		2(40.0)	3(60.0)	
Previous training	Yes	130(88.4)	17(11.6)	<0.0001*	75(51.0)	72(49.0)	<0.0001*
	No	168(99.4)	1(0.6)		136(80.5)	33(19.5)	
Health institution	Government	219(92.8)	17(7.2)	0.051	164(77.7)	47(23.3)	0.099
	Private	79(98.8)	1(1.2)		72(68.6)	33(31.4)	

* = statistically significant.

the importance of on job training in improving performance of laboratory professionals involved in AFB microscopy [9,13,15]. In addition to training, it is also important to implement sustainable EQA program to have efficient AFB microscopy centers [13,17]. In the post training practical assessment, it was also observed that participants from private health facilities have performed better than those from government (p = 0.011). This could be due to the fact that trainees from private health facilities might have participated with more attention to achieve better to cope up with strict rules and regulations in private health facilities.

In routine AFB microscopy, both minor (QE, LFN, and LFP) and major (HFN, HFP) errors occur at a different rates as a result patient management as well as TB control program can be affected depending on the magnitude and type of error. Our investigation has identified higher rate of QE which is comparable with other study in Mexico [13] but study in India has reported higher rate of LFN than QE [15]. In our study, significant number of participants had previous similar training, but participants in the study of India were fresh graduates. This could be the possible reason for the observed variation.

Proportion of trainees who committed false positive (LFP and HFP) and negative (LFN and HFN) errors were significantly reduced after they were trained, but these errors are not totally avoided. Data from other studies [9,10,15] have also shown similar finding. This could be due to the inherent low sensitivity of Ziehl-Neelsen AFB microscopy, technical problems which can be tackled through continuous refresher training and other interventions. In routine EQA, any major error (HFP or HFN) or any HFP with more than three LFN is not acceptable performance, but lower rates of minor error can be acceptable if the numbers do not demonstrate trends. Unlike QE, false negative and false positive errors have significant impact on patient management as well as the TB control program [16]. Hence, improving the competency of professionals' thorough refresher training, implementation of EQA and other interventions are critically important to reduce or avoid these types of errors.

In our investigation, it was found that participants who have participated in previous similar trainings were found to commit fewer errors than those who had no previous training. This finding may indicate the actual performance in facilities. Ideally, it is important to evaluate the impact of training on performance of microscopy centers. A post training evaluation on impact of AFB microscopy training in Ghana has reported better performance of AFB microscopy centers [9]. The successive improvement of case detection in Oromia region from previous 32% to current 39% (unpublished report) indicates the improved performance of AFB microscopy centers and this could be due continuous refresher trainings and other interventions.

Our study was not without limitations. The main pitfall of our study was the fact that it failed to conduct impact assessment at each health facility where the trainees were based after the training on case detection due to financial constraints.

Conclusions

In conclusion, training has improved theoretical and practical performance of laboratory professionals. Training has reduced minor error (QE, LFN, and LFP) and major error (HFN and HFP) but it has not totally avoided these errors. Pre-placement and continuous training irrespective of laboratory professionals' qualification and service year, and sustainable EQA are highly recommended to ensure quality AFB microscopy service.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

PR was involved conception and design of the study, data analysis and write up; GA was involved in data collection and analysis; GAbebe was involved in data analysis and reviewed the paper critically. All the authors read the final paper and approved it.

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Understanding private retail drug outlet dispenser knowledge and practices in tuberculosis care in Tanzania

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SUMMARY

SETTING: Private sector accredited drug dispensing outlets in Morogoro and pharmacies in Dar es Salaam, Tanzania.

OBJECTIVE: To assess 1) the level of knowledge about tuberculosis (TB) among dispensers in Tanzania's retail pharmaceutical sector; 2) practices related to identification of patients with suspected TB; 3) the availability of educational materials and training; and 4) the availability of first- and second-line anti-tuberculosis treatment in retail drug outlets.

DESIGN: A cross-sectional descriptive study involving the administration of a structured questionnaire among drug dispensers in 122 pharmacies and 173 accredited drug dispensing outlets.

RESULTS: Private retail drug outlets are convenient; most are open at least 12 h per day, 7 days/week. Although 95% of dispensers identified persistent cough as a symptom of TB, only 1% had received TB-related training in the previous 3 years; 8% of outlets stocked first-line anti-tuberculosis medicines, which are legally prohibited from being sold at retail outlets. The majority of respondents reported seeing clients with TB-like symptoms, and of these 95% reported frequently referring clients to nearby health facilities.

CONCLUSION: Private retail pharmaceutical outlets can potentially contribute to TB case detection and treatment; however, a coordinated effort is needed to train dispensers and implement appropriate referral procedures.

KEY WORDS: pharmacy; public-private partnerships; referral and consultation; drug seller

IN THE MID-1980s, Tanzania was the first African country to introduce DOTS, the World Health Organization's (WHO) internationally recommended strategy for tuberculosis (TB) control. By 2010, Tanzania had surpassed the global treatment success (88%) and case detection (77%) targets, and had halved the 1990 TB mortality rate.[1] However, in the same year Tanzania had approximately 60 000 new TB case notifications;[1] today, it remains one of the world's 22 high TB burden countries. Continued efforts are needed to reduce the number of new TB cases in Tanzania and take it off the list of high-burden countries.

An assessment of the private health sector in Tanzania revealed that it provides a substantial contribution to health care services in the country. While the use of private health services never exceeds 34% of all services provided, patients tend to be more likely to access the private sector for problems that can be treated with medical commodities, such as fever or cough.[2] Furthermore, while patients of all wealth quintiles utilise private facilities, those from the bottom three quintiles comprise nearly 50% of all people seeking treatment for fever and/or cough.[2] Low-income households are more susceptible to TB, and for many, private retail pharmaceutical outlets are their first point of contact with the health system. If properly engaged, private pharmaceutical outlets can be involved in many aspects of TB control, including case detection, providing treatment support and limited dispensing of anti-tuberculosis drugs to those with a prescription.[3]

The contribution of public-private mix (PPM) to TB control has been well documented in the literature. A study in India demonstrated that large-scale implementation of PPM for TB care and control was not only cost-effective, it also significantly reduced patient financial burden as a result of fewer

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patients seeking care outside of the scope of the national TB control program and therefore paying a higher price for anti-tuberculosis medicines.[4] Another study in Indonesia found that collaboration between the public and private sector increased TB case detection.[5] The value of PPM has also been recognized in international guidelines, with PPM comprising one of the core components of the global Stop TB Strategy,[6] and the WHO and the International Pharmaceutical Federation (FIP; The Hague, The Netherlands) issuing a joint statement encouraging the collaboration of national TB programs and national pharmacy associations to improve TB control.[7]

The Tanzanian Ministry of Health and Social Welfare, through the National Tuberculosis and Leprosy Programme (NTLP), has committed to engaging the private sector and expanding TB and TB-HIV (human immunodeficiency virus) services in private health facilities.[8] The present study was conducted to assess TB knowledge among dispensers in the retail pharmaceutical sector, to determine practices related to the identification and management of patients with suspected TB, to assess the availability of educational materials and training, and to determine the availability of first- and second-line anti-tuberculosis treatment. We defined private retail pharmaceutical outlets as pharmacies, predominantly in urban areas, and accredited drug dispensing outlets (ADDOs), predominantly in rural and peri-urban areas. The findings from this study will help enable the NTLP and partners to develop strategic interventions for engaging the retail pharmaceutical sector in Tanzania in TB diagnosis and care in line with the WHO/FIP 2011 recommendations.[9]

STUDY POPULATION AND METHODS

This was a cross-sectional descriptive study design involving the administration of a structured questionnaire to dispensers in retail drug outlets. The questionnaire assessed TB knowledge and pharmacy practices, and inquired as to whether anti-tuberculosis drugs were stocked at the outlet. All questionnaire items were structured to categorize responses. Before full deployment, the questionnaire was pre-tested and all questions were validated through field testing in outlets in Dar es Salaam, Tanzania. Outlets included registered private retail pharmacies authorized by the Tanzania Food and Drugs Authority (TFDA) to sell and dispense all prescription medicines, and ADDOs, described elsewhere,[10,11] which are legally authorized by the TFDA to sell and dispense a limited list of essential prescription medicines.

The study locations were Dar es Salaam City and the Morogoro region. Dar es Salaam has nearly 60% of all registered retail pharmacies in the country,[12] contributes 22% of all notified TB cases nationwide, and represents an urban population. The Morogoro region ranks seventh in national TB case notifications, has had ADDOs operating for several years, and represents peri-urban and rural populations. We estimated the sample size to include approximately 30% of all eligible registered pharmacies and ADDOs. We determined the sampling interval based on the total number of outlets in each region and randomly selected pharmacies and ADDOs by selecting the first on the list, then counting every second outlet from the list until the final sample included respondents from 122 private pharmacies and 173 ADDOs.

Interviews were conducted in person with dispensers, and the data were analyzed using SPSS statistical software version 16 (Statistical Product and Service Solutions, Chicago, IL, USA). Data collectors included representatives from the NTLP, Pharmacy Council and TFDA, along with community pharmacists, district pharmacists and district NTLP coordinators. To assure data quality, all data collectors were trained before being assigned to one of four teams, with each team led by a supervisor who ensured the completeness and accuracy of data during interviews. Two data entry clerks double-checked each entry to ensure accuracy.

Before data collection, approval was sought from the TFDA, the Pharmacy Council, and the NTLP. After being briefed on the purpose of the study, pharmacy and ADDO dispensers were asked to participate and were interviewed after providing informed consent. Data collectors verbally assured participants of the confidentiality of the information collected, their anonymity and the freedom to withdraw consent at any time during the process. Meetings were also held with district officials where the study was proposed before data collection.

RESULTS

Characteristics of the study population

The vast majority (83%) of dispensers interviewed in this study were female; 61% dispensers in pharmacies had secondary education compared to only 41% of those working in ADDOs, and 39% of all dispensers had primary education. Dispensers working in pharmacies had a statistically significantly higher level of education than those working in ADDOs ($P = 0.000$). Of those interviewed at pharmacies, 10% identified themselves as pharmacists; however, there were no pharmacists identified at the ADDOs. Of all dispensers in the pharmacies and ADDOs, 15% did not have any health training background.

Accessibility and referral linkages

Service accessibility was measured by the number of days and hours outlets were open for operation. Most ADDOs and pharmacies were open for at least 12 h

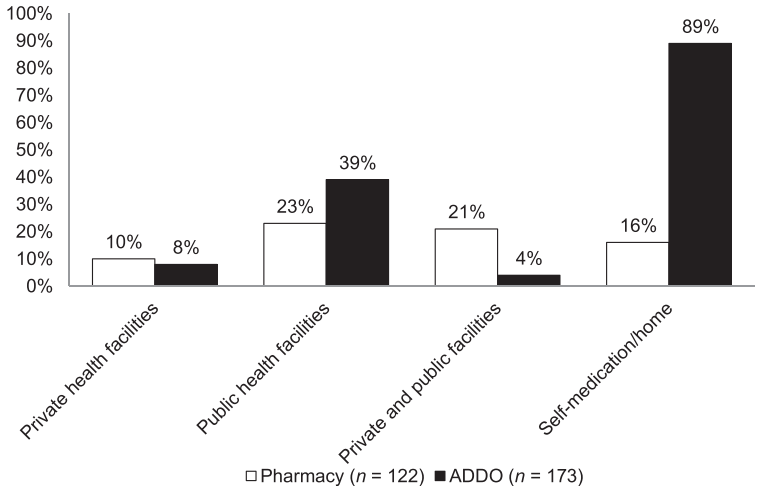

Figure Retail outlets' sources of clients (multiple responses allowed).

per day (85% and 67%, respectively), with approximately 70% of pharmacies and 60% of ADDOs operating 7 days per week. To assess referral linkages between ADDOs and pharmacies with other health services, we measured the walking time to the nearest public or private health facility and asked about the sources of clients at outlets. Approximately 88% of retail outlets were near a health facility, and dispensers reported that it took less than 30 min to walk to the closest facility. While most pharmacies reported that health facilities were their primary source of clients, the majority of ADDO clients came directly from home to seek care (Figure).

TB knowledge and practices among respondents

The vast majority of dispensers (91%) knew that TB is contracted by breathing air containing TB-causing micro-organisms. Many respondents, however, did not report knowing the factors that contribute to the spread of TB; 33% correctly identified poor ventilation in the house, approximately one half correctly noted overcrowding and one third correctly identified the presence of TB patients in the house or community. Dispensers working in retail pharmacies were significantly more likely to identify overcrowding ($P = 0.019$) or poverty ($P = 0.035$) as a factor contributing to TB transmission.

Patients with TB can present with a variety of symptoms, such as persistent cough lasting $\geqslant 2$ weeks, low grade fever, coughing blood and loss of weight. Among interviewed dispensers, 95% correctly identified persistent cough as a symptom, but the next most commonly recognized symptom—weight loss—was identified by only 49% of respondents (Table 1). ADDO dispensers were significantly more likely to name this symptom than those working in retail pharmacies (55% vs. 41%, respectively; $P = 0.018$).

While nearly all respondents recognized that there were negative consequences of not completing anti-tuberculosis treatment, including TB recurrence and death, only 30% were aware of the risk of developing drug-resistant TB (Table 1). ADDO dispensers were significantly more likely to recognize this risk, with 39% aware of resistance vs. 17% of pharmacy dispensers ($P = 0.000$). Two thirds of respondents had learned about TB symptoms during their formal education; the second most frequent source of knowledge cited was family members, relatives and friends. Other sources, such as community sensitization meetings, television, radio and billboards, contributed less than 5% each. Only 1% of respondents reported receiving any TB-related training in the previous 3 years.

Practice in TB case detection

Many respondents in both retail pharmacies and ADDOs (63% and 61%, respectively) reported seeing clients with TB-like symptoms in the 2 weeks before the interview. Of these, 95% reported referring the client to a nearby health facility, 8% dispensed broad-spectrum antibiotics and 14% dispensed cough syrup. Importantly, only 4% of both retail pharmacies and ADDOs referred patients with TB-like symptoms with a written note to a nearby health facility. Dispensers working in pharmacies were significantly more likely to report doing nothing when they saw clients come in with TB symptoms as compared to those working in ADDOs ($P = 0.025$).

Demand for and availability of anti-tuberculosis medicines

Despite the fact that first-line anti-tuberculosis medicines are prohibited from sale at retail outlets, 18% of surveyed pharmacies stocked at least one first-line anti-tuberculosis medicine, compared with 2% of ADDOs; however, none stocked fixed-dose combinations. For second-line anti-tuberculosis med-

Table 1 Knowledge about TB symptoms and the consequences of not completing anti-tuberculosis treatment among respondents

	Type of outlet		
	Pharmacy ($n = 122$) *n* (%)	ADDO ($n = 173$) *n* (%)	Total ($n = 295$) *n* (%)
TB symptoms*			
Persistent cough (⩾2 weeks)	115 (94)	166 (96)	281 (95)
Coughing blood	23 (19)	45 (26)	68 (23)
Fever for ⩾2 weeks	47 (39)	67 (39)	114 (39)
Loss of weight†	50 (41)	95 (55)	145 (49)
Excessive night sweats	47 (39)	48 (28)	95 (32)
Chest pains	25 (20)	30 (17)	55 (19)
Shortness of breath	12 (10)	18 (10)	30 (10)
Fatigue, malaise	32 (26)	48 (28)	80 (27)
Don't know	3 (2)	4 (2)	7 (2)
Consequences of not completing anti-tuberculosis treatment*			
Patient dies‡	63 (52)	118 (68)	181 (61)
Patient deteriorates	26 (21)	30 (17)	56 (19)
Recurrence of TB‡	67 (55)	120 (69)	187 (63)
Patient continues to infect others	15 (12)	27 (16)	42 (14)
Patient develops drug-resistant TB‡	21 (17)	67 (39)	88 (30)
Don't know	3 (2)	4 (2)	7 (2)

* Multiple responses allowed.
† ADDO dispensers were significantly more likely to name this symptom than those working in retail pharmacies (55% vs. 41%, respectively; $P = 0.018$).
‡ ADDO dispensers were significantly more likely to name patient death ($P = 0.009$), recurrence of TB ($P = 0.023$) and development of drug-resistant TB ($P = 0.000$) than pharmacy dispensers.
TB = tuberculosis; ADDO = accredited drug dispensing outlet.

icines, 68% of pharmacies and 50% of ADDOs stocked at least one second-line anti-tuberculosis medicine. In Tanzania, second-line regimens are authorized to be stocked at retail pharmacies because they are used for other diseases; however, ADDOs are not allowed to stock them (Table 2). A higher proportion of ADDO dispensers (43%) saw clients who specifically asked for anti-tuberculosis medicines as compared with pharmacy dispensers (35%).

Only half of the retail outlets (49%) surveyed reported keeping any kind of records for their clients, with ADDOs being significantly more likely to do so than pharmacies (39% and 10%, respectively, $P = 0.000$). Only 1% of all dispensers had any educational materials on TB available for their customers.

DISCUSSION

While similar studies have been conducted in Tanzania to assess knowledge and practices about malaria among drug sellers, and map care-seeking behavior for childhood illnesses and other health conditions,[13–15] this is the first study to assess TB awareness and practices among dispensers at Tanzania's private retail drug outlets. Our study found that many clients expect retail pharmaceutical outlets to supply and dispense anti-tuberculosis medicines, which is perhaps not surprising given that a previous study reported that 62% of retail pharmacy consultations were for cough.[16] While only 8% of dispensers in this study stocked first-line anti-tuberculosis medicines, approximately 4 in 10 saw clients who requested these medicines. Until the NTLP engages retail dispensers fully and ensures regulatory monitoring for anti-tuberculosis medicines, retail pharmaceutical outlets will continue to be under pressure to stock first-line medicines illegally and dispense them outside the DOTS strategy. These actions have the

Table 2 Availability of anti-tuberculosis medicines at retail outlets

	Type of outlet		
Anti-tuberculosis drugs stocked	Pharmacy ($n = 122$) *n* (%)	ADDO ($n = 173$) *n* (%)	Total ($n = 295$) *n* (%)
First-line drugs*	22 (18)	3 (2)	25 (8)
Second-line drugs†	83 (68)	86 (50)	169 (57)‡

* Sale prohibited by law at retail outlets.
† May be legally stocked in retail pharmacies because they are used to treat a variety of other conditions.
‡ Over 95% of pharmacies and ADDOs stocked fluoroquinolones (ciprofloxacin, levofloxacin and ofloxacin); the remaining pharmacies only stocked kanamycin and amikacin.
ADDO = accredited drug dispensing outlet.

potential to increase inappropriate use of anti-tuberculosis medicines and contribute to a rise in drug-resistant TB cases.

Studies carried out in other high TB burden countries have found similar misconceptions and knowledge gaps among retail pharmaceutical sellers regarding TB transmission, case detection and treatment; however, significantly higher rates of improper dispensing of TB medicines, mismanagement of TB cases, and development and spread of drug-resistant strains of TB were observed in countries that allow the sale of first-line anti-tuberculosis medicines in the private sector.[17–19] While Tanzania has largely managed to control the supply and sale of anti-tuberculosis medicines in its private retail pharmaceutical outlets (Sheikh K, Uplekar M. Regulating tuberculosis medicines: a policy analysis in six countries, unpublished), failure to involve the retail pharmaceutical sector in TB control efforts—including in the dispensing of anti-tuberculosis medicines—could lead to an increase in the unregulated distribution of these medicines as a result of client demand.

Although the dispensers' level of education was significantly lower in ADDO than pharmacies, their knowledge about TB was higher than in pharmacies. This is a result of years of investment to improve ADDO standards through training about all common illnesses including TB, regulatory monitoring, incentives and record keeping.[10,11,20] No similar efforts have been directed at retail pharmacies.

There are a variety of lessons to be learned from a similar effort to engage private pharmacists in Mumbai, India.[21] A total of 194 retail pharmacists were trained in case detection, a referral mechanism and DOTS protocols, and were provided with DOTS posters to display. In 2012, government TB clinic records showed a cumulative referral of 430 cases of persons suspected of having TB, of whom 17% had confirmed TB.[17] Training for pharmacists was scaled up and a significant number of pharmacists have since participated in the training and are administering DOTS. The system has proved beneficial for the pharmacists, who report that they enjoy offering a social service, as well as for the clients, who note that it is more convenient, more economical and less stigmatizing than receiving treatment at a TB clinic. A key component of the Indian effort to engage private pharmacists included listing those who completed the program in the DOTS directory of the local TB offices. The Indian Pharmaceutical Association then followed up with the pharmacists by telephone to inquire about their DOTS-related work.[21] This simple monitoring mechanism creates a sense of accountability and should be a part of any TB public-private intervention.

As retail pharmaceutical dispensers in this study rarely gave written referrals to health facilities for clients presenting with TB-like symptoms, any future dispenser training should include not only TB education, but also support for dispenser screening and referral. For example, a system could be established with a screening checklist for retail pharmacists and ADDO dispensers, standardized referral forms, a directory of facilities that provide NTLP TB diagnosis and treatment, and a register of pharmacy-referred TB patients. In addition, opportunities for health education could be enhanced by creating TB communication materials for pharmacies and ADDOs to display and distribute to clients.

CONCLUSION

The potential for retail pharmaceutical outlets to play a larger role in TB case detection is demonstrated by the fact that they are widely used, operate longer hours than health facilities, and most already see clients presenting with TB-like symptoms. However, the limited TB knowledge among staff, the lack of training and low rates of written referral indicate the need for a coordinated effort to engage this sector in TB case finding and to strengthen their linkage to TB diagnostic centers.

The NTLP, in collaboration with partners, used these study findings to develop an intervention to engage the retail pharmaceutical sector in TB control. The intervention includes a comprehensive training program covering proper identification and referral of TB patients, standard procedures for DOTS, and best practices for keeping client and drug registers. On completion of the training, private pharmacies and ADDOs will be certified by the NTLP to identify persons with TB symptoms and formally refer them to a nearby health facility (private or public) with diagnostic capacity. The outcomes of this intervention are currently being assessed and will be reported in a future publication.

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RESUME

CONTEXTE : Officines privées accréditées de délivrance de médicaments à Morogoro et pharmacies à Dar es Salaam, Tanzanie.

OBJECTIF : Evaluer 1) le niveau de connaissances en matière de tuberculose (TB) parmi les revendeurs dans le secteur de la pharmacie de détail en Tanzanie ; 2) les pratiques relatives à l'identification des patients suspects de TB ; 3) la disponibilité de matériel éducatif et de formation ; et 4) la disponibilité du traitement de première et de deuxième intention dans les officines de revente de médicaments.

SCHÉMA : Une étude descriptive transversale impliquant l'administration d'un questionnaire structuré à des vendeurs de médicaments dans 122 pharmacies et 173 officines de revente accréditées.

RÉSULTATS : Les officines privées de revente accréditées sont commodes car la majorité sont ouvertes au moins 12 h par jour, sept jours par semaine. Bien que 95% des revendeurs aient identifié une toux persistante comme un symptôme de TB, seulement 1% avaient bénéficié d'une formation relative à la TB pendant les 3 dernières années ; 8% des officines de revente disposaient d'un stock de médicaments anti-tuberculeux de première intention, dont la vente est interdite par la loi dans les officines. La majorité des répondants a affirmé avoir vu des clients présentant des symptômes évocateurs de TB et parmi eux, 95% ont déclaré référer fréquemment leurs clients à des centres de santé proches.

CONCLUSION : Les officines privées de revente pharmaceutiques peuvent contribuer à la détection des cas de TB et à leur traitement, cependant un effort coordonné est nécessaire pour former les revendeurs et mettre en place des procédures de référence appropriées.

RESUMEN

MARCO DE REFERENCIA: Los puntos autorizados de venta de medicamentos en el sector privado de Morogoro y las farmacias en Dar es Salaam, en Tanzania.

OBJETIVOS: Evaluar: 1) el grado de conocimientos sobre la tuberculosis (TB) de los proveedores del sistema de venta de medicamentos al público en Tanzania; 2) las prácticas en materia de detección de los pacientes con presunción de TB; 3) la existencia de materiales pedagógicos y de capacitación; y 4) la existencia de medicamentos antituberculosos de primera y segunda línea en los puntos de venta al público.

MÉTODO: Se llevó a cabo un estudio transversal descriptivo, mediante la administración de un cuestionario estructurado a los proveedores de medicamentos en 122 farmacias y 173 puntos autorizados de venta de medicamentos.

RESULTADOS: Los puntos de venta del sector privado son prácticos, pues en su mayoría atienden como mínimo 12 h al día y 7 días a la semana. Aunque el 95% de los proveedores reconoció la tos persistente como un síntoma indicativo de TB, solo 1% de ellos había recibido una capacitación en materia de TB en los últimos 3 años. El 8% de los puntos de distribución contaba con existencias de medicamentos antituberculosos de primera línea, cuyo comercio está prohibido en estos puntos de venta. La mayoría de los proveedores que respondieron al cuestionario manifestó haber atendido clientes con síntomas indicativos de TB y el 95% declaró que solía remitirlos a los establecimientos de salud cercanos.

CONCLUSIÓN: Los puntos de venta de medicamentos del sector privado podrían contribuir a la detección de casos de TB y a su tratamiento, siempre y cuando se emprenda un esfuerzo coordinado de capacitación de los proveedores y se pongan en práctica procedimientos de remisión apropiados.

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

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Abstract

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

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

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

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

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

Introduction

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

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

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

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

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

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

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

Methods

Settings

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

Study participants and data collection

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

Occurrence of adverse events and the analysis of data

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

Results

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

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

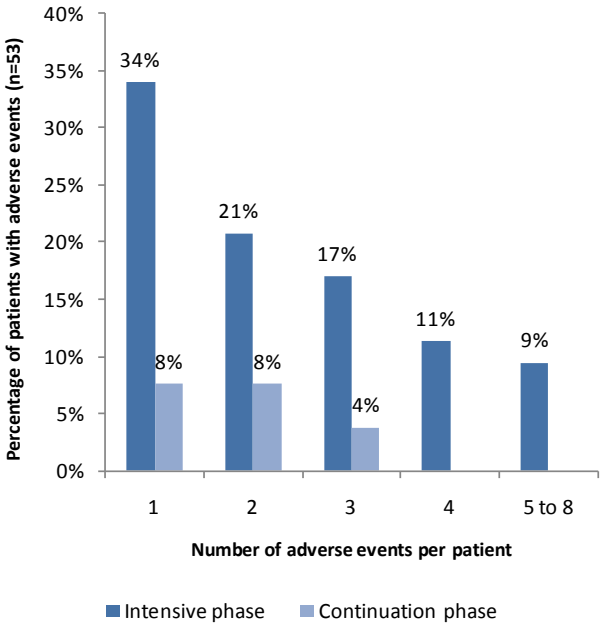
Characteristic	n (%)
Gender	
Male	38 (64%)
Female	20 (34%)
Missing	1 (2%)
Age (years), SD	**34.7 ± 9.4**
Male	36.9 ± 8.4
Female	31.0 ± 10.2
Weight (kg), SD	**52.5 ± 11.3**
Male	53.6 ± 7.8
Female	49.8 ± 16.4
Occupation	
Unemployed	18 (31%)
Employed	20 (34%)
Student	1 (2%)
Missing	20 (34%)
Type of TB	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

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

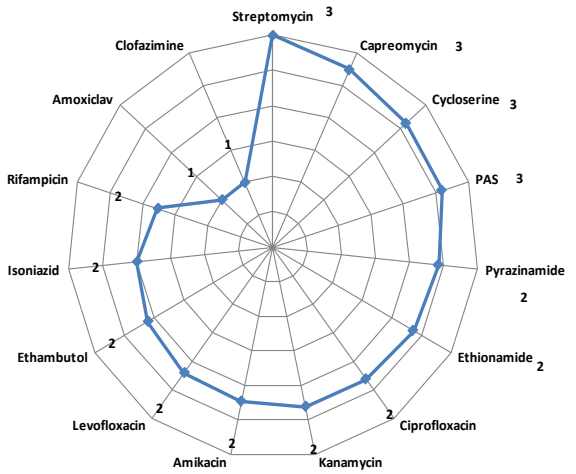


* As percentage of number of patients with HIV co-infection

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

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

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



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

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

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

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

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

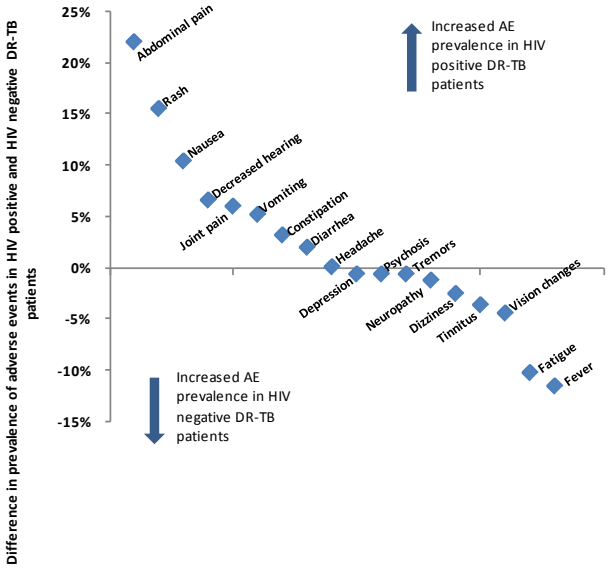
*53 of the 59 patients reported to have experienced at least one DR-TB treatment-related adverse event. All the 53 patients had either completed or were still in the intensive phase of treatment at the time of data collection. †49 of the patients had progressed into the continuation phase of treatment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

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

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

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

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



Discussion

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

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

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

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

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

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

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

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

Strength of the study

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

Limitation of the study

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

Conclusion

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

Authors' contributions

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

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Conflict of interest

None

Funding source

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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 disease[6] and the challenges inherent to diagnosing TB in such patients.[7] The lack of availability of TST capacity also demonstrates the difficulty in attempting to identify HIV-infected patients most likely to benefit from IPT, that is, those with positive TST.[8]

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

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

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

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

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 $P < 0.05$.

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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

Balewgizie Sileshi[1*], Negussie Deyessa[2], Belaineh Girma[3], Muluken Melese[3] and Pedro Suarez[4]

Abstract

Background: Tuberculosis (TB) is the leading cause of mortality in high HIV-prevalence populations. HIV is driving the TB epidemic in many countries, especially those in sub-Saharan Africa. The aim of this study was to assess predictors of mortality among TB-HIV co-infected patients being treated for TB in Northwest Ethiopia.

Methods: An institution-based retrospective cohort study was conducted between April, 2009 and January, 2012. Based on TB, antiretroviral therapy (ART), and pre-ART registration records, TB-HIV co-infected patients were categorized into "On ART" and "Non-ART" cohorts. A Chi-square test and a *T*-test were used to compare categorical and continuous variables between the two groups, respectively. A Kaplan-Meier test was used to estimate the probability of death after TB diagnosis. A log-rank test was used to compare overall mortality between the two groups. A Cox proportional hazard model was used to determine factors associated with death after TB diagnosis.

Results: A total of 422 TB-HIV co-infected patients (i.e., 272 On ART and 150 Non-ART patients) were included for a median of 197 days. The inter-quartile range (IQR) for On ART patients was 140 to 221 days and the IQR for Non-ART patients was 65.5 to 209.5 days. In the Non-ART cohort, more TB-HIV co-infected patients died during TB treatment: 44 (29.3%) Non-ART patients died, as compared to 49 (18%) On ART patients died. Independent predictors of mortality during TB treatment included: receiving ART (Adjusted Hazard Ratio (AHR) =0.35 [0.19-0.64]); not having initiated cotrimoxazole prophylactic therapy (CPT) (AHR = 3.03 [1.58-5.79]); being ambulatory (AHR = 2.10 [1.22-3.62]); CD4 counts category being 0-75cells/micro liter, 75-150 cells/micro liter, or 150-250 cells/micro liter (AHR = 4.83 [1.98-11.77], 3.57 [1.48-8.61], and 3.07 [1.33-7.07], respectively); and treatment in a hospital (AHR = 2.64 [1.51-4.62]).

Conclusions: Despite the availability of free ART from health institutions in Northwest Ethiopia, mortality was high among TB-HIV co-infected patients, and strongly associated with the absence of ART during TB treatment. In addition cotrimoxazol prophylactic therapy remained important factor in reduction of mortality during TB treatment. The study also noted importance of early ART even at higher CD4 counts.

Keywords: Predictors, Mortality, TB-HIV, Co-infection

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Background

The human immunodeficiency virus (HIV) pandemic presents a massive challenge to the control of tuberculosis (TB) at all levels. The synergy between TB and HIV is strong; in high HIV prevalence population, TB is a leading cause of morbidity and mortality, and HIV is driving the TB epidemic in many countries, especially those in sub-Saharan Africa [1]. TB is often the first clinical indication that a person has an underlying HIV infection and, as a result, TB services can be a critical entry point for HIV prevention, care, and treatment [2].

The syndemic interaction between HIV and TB epidemics has had deadly consequences around the world, and disproportionately affects people in Africa [3].

In patients with advanced acquired immune deficiency syndrome (AIDS) and active TB, highly active antiretroviral therapy (HAART) may be administered concurrently with the TB treatment to prevent opportunistic infections which may superimpose and accelerate HIV disease progression [4]. The World Health Organization (WHO) currently recommends that ART should be initiated for all TB-HIV co-infected patients irrespective of their CD4 counts [5].

Despite international recommendations and the proven benefit of ART, physicians remain reluctant to prescribe ART to HIV-infected TB patients, due to concerns about overlapping toxicity, drug-drug interactions, pill burden, and immune reconstitution inflammatory syndrome (IRIS) [6].

Understanding the predictors of mortality for TB-HIV co-infected patients in the local context is critical for Ethiopia to improve TB-HIV co-infected patients' co-management. To date, there is inadequate data on predictors of mortality among TB-HIV co-infected patients in Ethiopia. To address this, the USAID-funded Help Ethiopia Address Low TB (HEAL TB) project conducted a retrospective study in Northwest Ethiopia to determine predictors of mortality among TB-HIV co-infected patients. The study also aimed to compare the survival rate between TB-HIV co-infected patients who received ART and did not receive ART. It is anticipated that findings from this study will contribute to the body of knowledge that informs TB-HIV program planers, decision makers, and project implementers by providing predictors of mortality among TB-HIV co-infected patients during TB treatment in Ethiopia.

Methods

Setting

We conducted a retrospective cohort study in governmental health institutions in Bahir Dar, Northwest Ethiopia, from August, 2011 to January, 2012. Bahir Dar is located in Northwest Ethiopia, 565 kilometers from Addis Ababa. In these health institutions, patients diagnosed as having HIV in any of HIV counseling and testing protocols (i.e., Voluntary counseling and testing, Provider initiated HIV counseling and testing units) are registered in Pre-ART and ART log books according to the status of disease progression. Patients are also referred to ART clinics for pre-ART and ART follow up from private health facilities within Bahir Dar and health facilities outside of Bahir Dar. Felege Hiwot Referral Hospital and Bahir Dar Health Center have provided pre-ART and ART services since 2005 and other health centers in the town began providing these services in 2009. Felege Hiwot Referral Hospital's 2011 annual report showed that the facility had detected 1,600 TB cases, enrolled 13,590 people living with HIV/AIDS (PLWHA) in ART clinic, and started 9,222 PLWHA on ART. As of 2011 annual report, there were 5,547 PLWHA taking ART at Felege Hiwot Referral Hospital. According to 2011/12 report of Bahir Dar Health Center, a total of 4, 420 PLWHA ever enrolled of which 1, 133 were currently on ART. In the same year the health center reported 135 TB patients. The 2011/12 report of Abay Health Center showed 756 PLWHA enrolled of which 326 were currently on ART. The health center also reported 162 TB patients. Han Health Center reported 1, 726 PLWHA were ever enrolled (407 currently on ART) and 112 TB patients were registered in the year 2011/12.

Participants

All TB-HIV co-infected patients who started ART before initiating TB treatment, and those who started ART while being treated for TB, were included in the "On ART" cohort. Patients who did not receive ART until completion of TB treatment were included in the "Non-ART" cohort. For both cohorts, inclusion criteria included TB-HIV co-infected patients, aged 15 years or older, who were diagnosed with TB at any time during pre-ART and or ART follow-up since April 2009, and who completed TB treatment before January 2012. Patients who had been diagnosed for both TB and HIV during their initial visit to the health facility were also included for the study.

Enrollment procedures for study subjects

Bahir Dar town was chosen purposely to get adequate number of sample with proper and complete patient record profile. In the town there are seven governmental health institutions, of which three were newly opened during data collection period. Therefore we included four health institutions (Felege Hiwot Refferal Hospital, Bahir Dar Health Center, Han Health Center and Abay Health Center) for the study which delivers TB service, Pre-ART and ART service for TB/HIV co-infected patients. During April 2009 – September 2011, 849 TB-HIV co-infected patients were registered in four

health institutions. A total of 422 TB-HIV co-infected patients (272 'On ART' and 150 'Non-ART' cohorts) were included for the study [Figure 1].

Data collection

Nurses who work in TB and ART clinics were selected to collect data from August, 2011 to January, 2012. Data was collected retrospectively by reviewing the files of TB-HIV co-infected patients in Bahir Dar. All profiles of TB-HIV co-infected patients between April 2009 and January 2012 were considered for data collection. Pre-ART registers, lab requests, follow-up forms, anti-TB record forms, ART intake forms, and patient cards were reviewed. The patients' date of death was extracted from TB registration log books. Data quality was assured by using a pre-tested data collection tool and trained data collectors. Two public health professionals (Master of public health) had provided continuous supervision and monitoring. Supervisors, data clerks and investigators had checked completeness and consistency of data before and after data entry.

Measurement of variables

Death from any cause during TB treatment was listed as "on-treatment TB death," according to the WHO's TB treatment outcomes definitions [7]. If the date of ART was more than one week before TB treatment initiation, that person was classified as "on ART prior to TB treatment". Patients who initiated ART at any time before TB treatment was completed were classified as "having received ART during TB treatment".

Patients were diagnosed with smear positive pulmonary tuberculosis (PTB+), if one of the sputum examinations was positive for acid fast bacilli (AFB). Patients were diagnosed with extra pulmonary tuberculosis (EPTB) if physicians suspected or observed that the TB infection had spread outside of the respiratory organs [5].

Functional status is measured at base line, and a person is categorized into working "able to perform usual work in or out of the house"; Ambulatory "able to perform activities of daily living" and Bedridden "not able to perform activities of daily living".

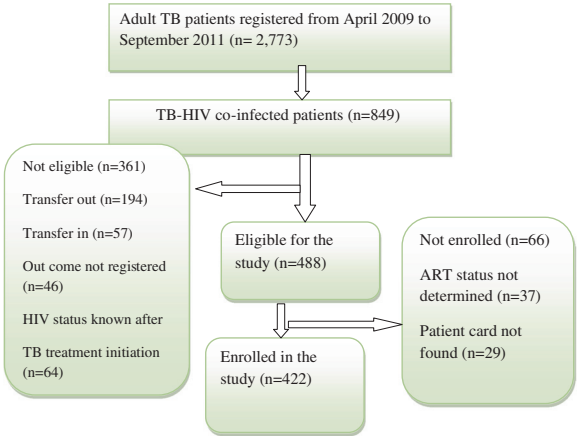

Figure 1 Enrollment of TB-HIV co-infected patients in the study, 2012.

Statistical analysis

Data was entered to EpiData 3.1[a] for Windows. Statistical package for social science (SPSS) version 16.0 for Windows and Stata version 11.0 were used for analysis. Data was cleaned and edited by simple frequencies and cross tabulation before analysis. The response variable was survival time, defined as "time in days transpired from the date of initial TB treatment to death" or, in the case of individuals who did not die (censored), "the time in days transpired to complete TB treatment".

Mean (with standard deviation), median (with inter quartile range [IQR]), and frequencies (as percentages) were used to describe patients' characteristics in each cohort. A Chi-square test and a *T*-test were used to compare categorical and continuous variables between the two cohorts, respectively. The Kaplan-Meier test was used to estimate the probability of death and the median time to death after TB diagnosis. The log-rank test was used to compare time to death between the two groups. The Cox proportional hazard model was used to determine predictors of death after TB diagnosis. All statistically significant ($p < 0.05$) factors in the bivariate analysis were included in the final model. The crude and adjusted hazard ratio (HR) and its 95% confidence interval (CI) were estimated.

Ethical issues

Ethical clearance for this study was obtained from the Review Ethics Committee of the School of Public Health at Addis Ababa University. To preserve patient confidentiality, nurses working in the ART clinics extracted the data from patients' medical records. Moreover, no personal identifiers were used on the data collection form.

Results

A total of 422 TB-HIV co-infected patients (272 On ART patients and 150 Non-ART patients) were included for the study and followed for a median of 197 days with an IQR of 140 to 221 days among On ART patients and 191 days among Non-ART patients with an IQR of 65.5 to 209.5 days.

Baseline socio-demographic characteristics of the study subjects

In this study, the two cohorts were not statistically different in any of the identified socio-demographic attributes.

The median age of study subjects in both cohorts was 30 years with an IQR of 27 to 37.5 years in the On ART cohort and 25 to 38 years in the Non-ART cohort. There were more female than male subjects in both cohorts, with 141 (53.4%) women in the On ART cohort and 83 (56.5%) women in the Non-ART cohort. More than one third of patients in both cohorts had completed secondary school with 93 (34.8%) in the On ART cohort and 50 (35.7%) in the Non-ART cohort (see Table 1).

Clinical characteristics of the study subjects

The clinical condition of study subjects within the two cohorts was not statistically different among any of the identified variables, except for history of prophylactic medication. In the On ART cohort, a higher proportion (51.6%) of patients had used prophylactic medication, as compared to patients in the Non-ART cohort (27.1%), (X^2 = 21.721; df (1); p = 0.000). Among all study subjects, more than one third had had at least one past opportunistic infection. In the On ART cohort, 58 (22.4%) study subjects had a history of past TB treatment, as compared to just 31 (21.7%) in the Non-ART cohorts. Data showed that the On ART and Non-ART cohorts had statistically different median CD4 counts (T = 10.305; p = 0.000): the On ART cohort had a much lower CD4 count with, a median of 114 cells/micro liter (μl) and an IQR of 58 to 185 cells/μl, as compared to the Non-ART cohort, which had a median of 291 cells/μl and an IQR of 183.5 to 448 cells/μl (see Table 2).

There was a statistically significant difference in the type of TB diagnosis between the cohorts. In the On ART group, 107 (39.3%) study subjects had smear negative PTB, whereas only 36 (24.0%) had smear negative PTB in the Non-ART group (X^2 =10.434; df = 2; p = 0.005). A higher proportion (93.3%) of study subjects in the On ART cohort had received CPT, as compared to those in the Non-ART cohort (77%) (see Table 2).

Comparison of mortality between the on ART and Non-ART cohorts

The 422 study subjects contributed a cumulative total of 2,274.4 person month observations (PMO) to this study; the On ART cohort contributed 1,545.03 PMO and the Non-ART cohort contributed 729.37 PMO. In the Non-ART cohort, 44 (29.3%) of TB-HIV co-infected patients died during TB treatment, which represented a higher percentage than the 49 patients (18%) who died in the On ART cohort. The incidence rate of mortality in the Non-ART cohort was 6.03 per 100 person months observations (PMO), (95% CI: 4.5, 8.1) and the mortality incidence in the

Table 1 Baseline socio-demographic characteristics of TB-HIV co- infected patients in Bahir Dar town, 2012

Base line variable	On ART (n = 272)	Non-ART (n = 150)	*X*2 Value (df)	P-Value
Residency (n = 407)				
Urban	235 (90.7%)	129 (87.2%)	1.271	0.260
Rural	24 (9.3%)	19 (12.8%)	(1)	
Age (n = 408)				
Mean ± SD	32.58 ± 9.123	31.98 ± 9.837	0.753♦	0.452
Median (IQR)	30 yrs (27-37.5)	30 yrs (25-38)		
Sex (n = 411)				
Male	123 (46.6%)	64 (43.5%)	0.355	0.551
Female	141 (53.4%)	83 (56.5%)	(1)	
Religion (n = 411)				
Orthodox	226 (85.3%)	117 (80.2%)	5.962	0.183
Muslim	26 (9.8%)	18 (12.3%)	(2)	
Others	13 (4.9%)	11 (7.5%)		
Marital status (n = 415)				
Single	76 (28.1%)	55 (37.9%)	7.901	0.131
Married	108 (40.0%)	57 (39.3%)	(3)	
Divorced	52 (19.2%)	24 (16.6%)		
Widowed	34 (12.6%)	9 (6.2%)		
Educational status (n = 407)				
Not educated	77 (28.8%)	40 (28.6%)	0.765	0.858
Primary	61 (22.8%)	35 (25.0%)	(3)	
Secondary	93 (34.8%)	50 (35.7%)		
Tertiary	36 (13.5%)	15 (10.7%)		

♦ = *T*-test Statistic for independent sample test used.

Table 2 Baseline clinical characteristics of TB-HIV co- infected patients in Bahir Dar town, 2012

Base line variable	On ART (n = 272)	Non-ART (n = 150)	X^2 Value (df)	P- Value
Past OIs (n = 366)				
Yes	105 (43.6%)	55 (44.0%)	0.006	0.937
No	136 (56.4%)	70 (56.0%)	(1)	
Past TB Treatment (n = 402)				
Yes	58 (22.4%)	31 (21.7%)	0.027	0.869
No	201 (77.6%)	112 (78.3%)	(1)	
Functional status (n = 397)				
Working	159 (60.9%)	80 (58.8%)	1.363	0.506
Ambulatory	72 (27.6%)	44 (32.4%)	(2)	
Bedridden	30 (11.5%)	12 (8.8%)		
CD4 count (n = 408)				
Mean ± SD	132.9 ± 94.42	312.78 ± 192.8	10.30♦	0.000*
Median (IQR)	114 (58-185)	291 (183.5-448)		
Hgb level (mmHg)(n = 357)				
Mean ± SD	11.36 ± 2.3	11.46 ± 1.83	0.063♦	0.95
Median (IQR)	11.3 (10.0-13.0)	12.0 (10.12-13.0)		
TB diagnosis				
Smear Positive PTB	53 (19.5%)	40 (26.7%)	10.434	0.005*
Smear Negative PTB	107 (39.3%)	36 (24.0%)	(2)	
Extra PTB	112 (41.2%)	74 (49.3%)		
CPT (n = 397)				
Prescribed	239 (93.0%)	109 (77.9%)	19.19	0.000*
Not Prescribed	18 (7.0%)	31 (22.1%)	(1)	
Outcome of TB Treatment (n = 417)				
Cure	37 (13.7%)	16 (11.0%)	8.039	0.045*
Treatment completed	167 (61.6%)	77 (52.7%)	(3)	
Defaulter	18 (6.6%)	9 (6.2%)		
Death	49 (18.1%)	44 (30.1%)		

* Significant at α = 0.05, ♦ = *T*-test Statistic for independent sample test used.

On-ART cohort was 3.2 per 100 PMO (95% CI: 2.40, 4.20). The overall incidence rate of mortality during TB treatment was 4.09 per 100 PMO (95% CI: 3.34, 5.01). Results from the On ART cohort showed that incidence of mortality in the first month of TB treatment was 5.4 per 100 PMO and, in the second month of TB treatment, was 4.8 per 100 PMO. The corresponding values in Non-ART cohort was 16.9 per 100 PMO and 5.9 per 100 PMO in the first and second months of TB treatment, respectively. The median time to death was 59 days in the On ART cohort and 29.5 days in the Non-ART cohort. The overall probability of survival in the On ART cohort was significantly greater than in the Non-ART cohort (log rank statistic = 8.93, df = 1, P = 0.003); (see Figure 2).

Predictors of mortality in TB-HIV Co-infected patients during TB treatment

The bivariate analysis showed that the risk of death decreased by 46% (HR = 0.54, 95% CI: 0.36-0.82) in the On-ART cohort. Compared to smear negative PTB patients, smear positive PTB patients had a 2.02 (95% CI: 1.07-3.83) times higher risk of death and EPTB patients had a 2.77 (95% CI: 1.61-4.75) times higher risk of death. In addition, patients who did not start CPT had a 3.15 times higher risk of mortality (95% CI: 1.95-5.11). Compared to the reference group, TB patients 45 years old or more (HR = 2.58, 95% CI: 1.34-4.92), patients with ambulatory and bedridden functional status (HR = 2.76, 95% CI: 1.71-4.47 and HR = 3.88, 95% CI: 2.15-7.02 respectively), and patients with CD4 count less than 75 cells/μl (HR = 2.08, 95% CI: 1.17- 3.70) had an increased risk of mortality during TB treatment. In the study, completing primary school -reduced risk of death by 55% (HR = 0.45, 95% CI: 0.22-0.90), compared to not educated TB-HIV co-infected patients (see Table 3).

ART status, CPT status, CD4 count, functional status, type of TB diagnosis, and type of health institution were independent predictors of mortality after controlling for

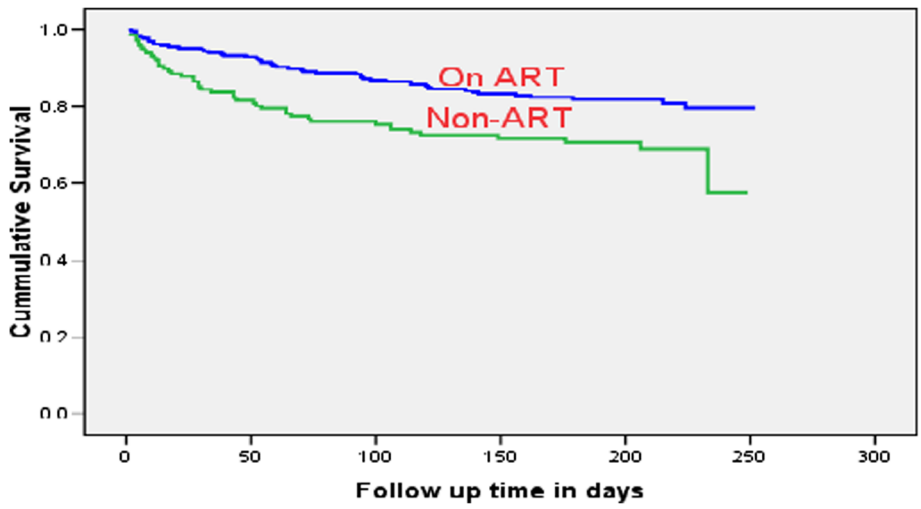

Figure 2 Kaplan-Meier estimate of survival among TB-HIV co-infected patients in Bahir Dar town, 2012.

the other factors. From these factors, receiving ART during TB treatment had decreased risk of mortality by 65% (AHR = 0.35, 95% CI: 0.19-0.64). In addition, CPT remained an important factor in reduction of mortality during TB treatment, in which patients without CPT were at a 3.03 times higher risk of mortality (95% CI: 1.58, 5.79). In this study CD4 count categories 0-75 cells/μl, 75-150 cells/μl, and 150-250 cells/μl; EPTB type; being ambulatory; and treatment in a hospital were independent predictors of increased risk of mortality during TB treatment (see Table 4).

Discussion

This study revealed the overwhelming problem of the high mortality of TB-HIV co-infected patients during TB treatment. More than 1 in 5 TB-HIV co-infected individuals died during TB treatment. Results from this study demonstrated that ART remained independently protective against mortality during TB treatment. In addition not having initiated cotrimoxazole prophylactic therapy; being ambulatory; CD4 count and treatment in a hospital were independent predictors of mortality during TB treatment.

In our study, the median CD4 count in the Non-ART cohort was twice as high as the median CD4 count in the On ART cohort. Non-ART cohorts may have been diagnosed as having HIV and TB, before their clinical and immunological conditions deteriorate. The median CD4 count among participants in this study was much higher than the median CD4 count among participants in other studies [8-15]. The difference may be due to the fact that researchers in our study took CD4 counts while the study subjects were being treated for TB or one month before they began TB treatment and, in most cases, these study subjects had started ART before TB diagnosis, which may have improved their immunological status. In addition, the results showed that 86.3% of study subjects had a CD4 count below 350 cells/μl. This is similar with a study conducted in Zimbabwe where 84.6% of study participants had a CD4 count below 350 cells/μl [16]. This showed that most study subjects were in progressive immunodeficiency condition.

There was no statistical difference in type of TB diagnosis between the two cohorts; 55.9% of study subjects were diagnosed with PTB and 44.1% were diagnosed with EPTB. This is in line with other studies [11,13,17] but the proportion of EPTB in this study is high compared to two studies conducted in India (22.9% and 31%) and one study conducted done in Thailand, which reported that 31% of study subjects had EPTB [10,12,18]. The variation could be a result of stage of HIV disease, difference in TB diagnosis or epidemiology of TB in different countries.

We found that mortality rate was high (22%) among TB-HIV co-infected patients during TB treatment. In line with this, previous studies have reported high mortality rates ranging from 8.5% to 30% among TB-HIV co-infected patients prior to successful completion of TB treatment [4,8-10,12,13,15,17-19]. In our study, death occurred in 49 of 272 patients (18%) exposed to ART during TB treatment, compared with 44 of 150 patients (29.3%) never exposed to ART. This finding is similar to a study conducted in India, where death occurred in 11.3% of patients exposed to ART during TB treatment and 24.6% of TB patients never exposed to ART [10]. However, results from a study conducted in Thailand showed 46% proportion of death among TB-HIV co-infected patients who did not start ART [13]. Another study in Thailand reported that 5 of 71 patients (7%) who received ART died, compared with 94 of 219 patients (43%) who did not receive ART (RR 0.2; 95%

Table 3 Predictors of mortality among TB-HIV co-infected patients in Bahir Dar town, 2012

Variable	Number at risk	Number of death	Incidence of mortality per 100 person month observation (95% CI)	Crude hazard ratio (95% CI)
ART				
Started	272	49	3.17 (2.39, 4.19)	**0.54 (0.36, 0.82)***
Not started	150	44	6.03 (4.49, 8.11)	1
CPT prophylaxis				
Prescribed	348	60	3.59 (2.66, 4.87)	1
Not prescribed	49	23	10.18 (6.77, 15.32)	**3.15 (1.95, 5.11)***
Type of TB				
Smear negative PTB	143	17	2.02 (1.26, 3.25)	1
Smear positive PTB	93	21	4.31 (2.81, 6.61)	**2.02 (1.07, 3.83)***
Extra PTB	186	55	5.81 (4.46, 7.57)	**2.77 (1.61, 4.78)***
Past OIs				
No	206	50	4.62 (3.50, 6.09)	1
Yes	160	31	3.53 (2.48, 5.02)	0.77 (0.49, 1.20)
Past TB treatment				
No	313	66	3.95 (3.10, 5.03)	1
Yes	89	18	3.58 (2.25, 5.68)	0.91 (0.54, 1.54)
Functional status				
Working	239	31	2.21 (1.55, 3.14)	1
Ambulatory	116	36	6.39 (4.61, 8.87)	**2.77 (1.71, 4.47)***
Bedridden	42	17	7.31 (3.81, 14.05)	**3.88 (2.15, 7.02)***
CD4 count				
< 75	107	33	6.22 (4.42, 8.75)	**2.08 (1.17, 3.30)***
75-150	91	21	4.44 (2.90, 6.81)	1.50 (0.80, 2.82)
150-250	95	19	3.57 (2.28, 5.59)	1.24 (0.65, 2.37)
> = 250	115	18	2.89 (1.82, 4.59)	1
Health institution				
Health center	226	34	2.67 (1.91, 3.72)	1
Hospital	196	59	5.89(4.57, 7.61)	**2.18 (1.43, 3.33)***
Age(n = 408)				
15-24	100	18	3.30 (2.08, 5.24)	1
25-34	193	40	3.79 (2.78, 5.17)	1.15 (0.66, 2.01)
35-44	69	16	4.40 (2.70, 7.18)	1.30 (0.66, 2.55)
> = 45	46	19	8.97 (5.72, 14.06)	**2.58 (1.34, 4.92)***
Sex				
Male	187	45	4.53 (3.36, 6.07)	1
Female	224	45	3.69 (2.75, 4.94)	0.82 (0.54, 1.24)
Educational status				
Not educated	117	26	4.47 (3.05, 6.57)	1
Primary	96	11	1.93 (1.07, 3.49)	**0.45 (0.22, 0.90)***
Secondary	143	37	4.82 (3.49, 6.66)	1.10 (0.66, 1.81)
Tertiary	51	13	4.48 (2.60, 7.72)	1.05 (0.54, 2.05)

*Significant at α = 0.05.

CI: 0.1–0.4) [18]. In Malawi, a total of 132 of 660 patients (20%) died during an eight-month course of anti-TBs treatment, which is consistent with our finding of 22% [20].

In this study, we have documented that the risk of mortality was high among subjects in the first month of TB treatment. This may be due to delayed presentation

Table 4 Multivariate predictors of mortality among TB-HIV co-infected patients in Bahir Dar town, 2012

Variable	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
ART		
Started	0.54 (0.36, 0.82)	**0.35 (0.19, 0.64)***
Not started	1	1
CPT prophylaxis		
Prescribed	1	1
Not prescribed	3.15 (1.95, 5.11)	**3.03 (1.58, 5.79)***
Type of TB		
Smear negative PTB	1	1
Smear positive PTB	2.02 (1.07, 3.83)	2.11 (0.95, 4.65)
Extra PTB	2.77 (1.61, 4.78)	**2.39 (1.23, 4.66)***
CD4 count		
< 75	2.08 (1.17, 3.30)	**4.83 (1.98, 11.78)***
75-150	1.50 (0.80, 2.82)	**3.57 (1.48, 8.61)***
150-250	1.24 (0.65, 2.37)	**3.07 (1.33, 7.07)***
> = 250	1	1
Functional status		
Working	1	1
Ambulatory	2.77 (1.71, 4.47)	**2.10 (1.22, 3.62)***
Bedridden	3.88 (2.15, 7.02)	2.11 (0.98, 4.53)
Health Institution		
Health center	1	1
Hospital	2.18 (1.43, 3.33)	**2.64 (1.51, 4.62)***
Age(n = 408)		
15-24	1	1
25-34	1.15 (0.66, 2.01)	1.17 (0.60, 2.29)
35-44	1.30 (0.66, 2.55)	0.98 (0.43, 2.23)
> = 45	2.58 (1.34, 4.92)	2.20 (0.97, 4.59)
Educational status		
Not educated	1	1
Primary	0.45 (0.22, 0.90)	0.49 (0.22, 1.12)
Secondary	1.10 (0.66, 1.81)	0.88 (0.49, 1.58)
Tertiary	1.05 (0.54, 2.05)	0.65 (0.29, 1.47)

*Significant at α = 0.05. ART status, health institution type, age, educational status, functional status, CD4 count, type of TB diagnosis, and CPT initiation were included in the model.

of patients and, thus, advanced TB and HIV/AIDS, late diagnosis of TB within health institutions, and the presence of life-threatening HIV related complications. These results are similar to results from a study conducted in Thailand which showed the first month of TB treatment is the time of the maximum number of deaths [21]. Another study conducted in sub-Saharan Africa concluded that ART should be started soon after TB diagnosis because the majority of deaths among TB-HIV patients in this study occurred during the patients' first two months of TB treatment [22].

In our retrospective, institution-based study, we found that TB-HIV co-infected patients who took ART during TB treatment had a lower risk of death. This is consistent with studies from several other settings [8-11,13,15,17-19,23,24] that demonstrate the positive impact of ART on the survival outcomes among TB-HIV co-infected patients, including successful immune restoration and reductions in morbidity and mortality.

In addition to ART, we found other immunological factors associated with mortality. For example, mortality rates increased in TB-HIV co-infected patients with

lower CD4 counts. This finding is consistent with a study in Zimbabwe, which showed that HIV-TB co-inflected patients with a CD4 count of <50 cells/micro litter had a 13 percent increased risk of death compared to patients with CD4 count greater or equal to 200 cells/micro litter [16]. Oppositely, a study conducted in southern India showed that a CD4 count below 200/mm3 was not associated with a higher rate of mortality [17]. The difference between our results and these others may be that we categorized CD4 counts into smaller intervals, which better enabled us to see the effect of CD4 counts on mortality.

The risk of death during TB treatment was higher in patients treated at a hospital compared to those treated at a health center. The reason could be that those who are taking care in hospitals might have advanced disease conditions. As a result, the severely ill hospitalized patients appeared to have a greater incidence of mortality, as compared to the less ill health center patients.

In this study TB-HIV co-infected patients with extra PTB were at increased risk of mortality during TB treatment compared to smear negative PTB patients. In other studies PTB is associated with high risk of mortality [10]. The possible reason may be HIV infected patients with extra PTB were highly immune-compromised.

In our study not initiating CPT was associated with high risk of mortality. In line with this, studies from South India and Sub-Saharan Africa showed that not taking CPT was significantly associated with mortality [17,22]. In our study, however, patients who died shortly after being diagnosed with TB and HIV may not have had the chance to initiate CPT. This may have led us to overestimate the benefit of CPT.

Our study was subject to several important limitations. All TB-HIV co-infected patients who started ART before initiating TB treatment, and those who started ART while being treated for TB, were included in the same group which may introduce bias. Information about other biomedical predictors for death that may have confounded this study, such as drug resistance, severity of immune suppression, or co-morbidities, adherence of medication were not available. We were also unable to collect adequate information about specific types of EPTB and patients' recent CD4 counts. Since most deaths in Ethiopia occur at home [25], it was difficult to trace all deaths. Exclusion of patients who transferred out of care may have also slightly confounded our results.

Conclusions

A significant difference was observed in the mortality rate during TB treatment between the On ART and Non-ART cohorts. Despite the fact that ART is available in most governmental health institutions throughout Ethiopia, death was strongly associated with the absence of ART during TB treatment. Risk of death was 65% lower in TB-HIV co-infected patients treated with ART, as compared to those not treated with ART. In addition cotrimoxazol prophylactic therapy remained important factor in reduction of mortality during TB treatment. The study also noted importance of early ART even at higher CD4 counts. To alleviate this, expanding ART use among TB-HIV co-infected patients is critical to improving the survival of these patients. Health institutions in Ethiopia should begin treating all TB-HIV co-infected patients with ART, irrespective of CD4count levels, as per the WHO recommendation.

Endnotes

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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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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.

1. Introduction

The Millennium Development Goals were established in the year 2000 to combat various dimensions of extreme poverty, including the sixth goal: "to combat HIV/AIDS, malaria, and other diseases." Since that time, new financing and delivery mechanisms for disease control have been introduced through the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), as well as the US President's Malaria Initiative (PMI) and the President's Emergency Plan for AIDS Relief (PEPFAR). To date, approximately USD $32 billion has been committed to the Global Fund,[1] USD $3 billion to PMI,[2] and USD $45 billion to PEPFAR.[3] Many billions of additional funding has made a huge difference in the lives of the world's poorest people. However, millions of people are still affected by these diseases, especially in the most remote and marginalized populations. Evidence suggests that co-infections between HIV, malaria, and TB exacerbate the individual diseases. Indeed, this is the reason that funding for the 'big three' is linked.[4,5] New research also suggests the highest-prevalence NTDs (soil transmitted helminths, schistosomiasis, onchocerciasis, lymphatic filariasis, and trachoma) result in increased susceptibility to and worsen the disease course for people infected with one or more of HIV, TB, and malaria. This paper summarizes the new evidence on how NTDs impact the progression and severity of HID/AIDS, TB, and malaria infections, and outlines priorities for future research.

2. Geographic overlap

Over the past several years, detailed mapping of NTDs has confirmed previous modeling based on statistical and spatial analyses,[6] and has demonstrated large degrees of geographical overlap between multiple NTDs and HIV and malaria.[7] For example, Sub-Saharan Africa has not only the world's highest incidence of HIV but also has more than 100 million people infected with soil-transmitted helminth infections and approximately 200 million people with schistosomiasis.[8] The geographical overlap is particularly prominent between urogenital schistosomiasis caused by *Schistosoma haematobium* and HIV and AIDS in the large southern and east African countries of Kenya, Mozambique, South Africa, Tanzania, Zambia, and Zimbabwe, and to some extent, Cameroon in West Africa.[9] Additionally, one-quarter of all schoolchildren in Sub-Saharan Africa are simultaneously at risk for both hookworm and malaria.[6] This pattern has also been noted between malaria and schistosomiasis.[10]

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3. Evidence on clinical links between NTDs and HIV

New research is beginning to suggest increased susceptibility and enhanced progression of HIV disease as a result of several helminthic, bacterial, and protozoan NTD co-infections. Soil-transmitted helminth infections have had a contributing, albeit largely hidden, impact on the AIDS epidemic.[6,10–12] In a study in Ethiopia, helminth co-infection was associated with increased T-cell activation; subsequent anti-helminthic treatment appeared to reduce the degree of T-cell activation, leading to a significant increase in absolute CD4 cell counts (192 vs. 279 cells/mm^3).[13] A systematic review of treatment of HIV-1 and helminthic co-infections found reductions in viral load following deworming, ranging from 0.17 $\log_{10}$ to 2.10 $\log_{10}$ copies/ml drop in plasma.[11] In addition, studies on the treatment of schistosomiasis and lymphatic filariasis in HIV-infected individuals have demonstrated a 0.39 $\log_{10}$ and 0.77 $\log_{10}$ reduction in viral load, respectively, noting that a 1.0 $\log_{10}$ viral load reduction corresponds to a halving of transmission risk and a 2-year delay in the development of AIDS.[12,14] The decreases they noted after treatment for helminth co-infection are comparable to decreases in viral load associated with the treatment of malaria and sexually transmitted diseases such as gonorrhea and syphilis.[11]

Although data conflict on the absolute impacts of treatment,[6,15,16] a Cochrane analysis of randomized clinical trials has demonstrated the benefits of deworming on HIV incidence and prevalence.[15] Evidence also suggests that maternal helminth infections increase the likelihood of mother-to-child transmission of HIV, possibly as a result of increased maternal HIV viral load.[6] A plausible mechanism suggests that helminth infections have an immunomodulatory effect, possibly diminishing host innate immunity to HIV, promoting viral replication and T-cell reduction.[11,12] Although the exact immunological mechanisms are yet to be elucidated, it is known that helminths skew the immune response toward Th2 (T helper cell) characterized by cytokines including interleukins IL-4, IL-5, and IL-13.[16]

Growing evidence from two studies in Zimbabwe demonstrates that female genital schistosomiasis occurs in up to 75% of women with *S. haematobium* infection and shows a threefold increase in the risk of women acquiring HIV infection.[17,18] Several reasons have been given to explain this increased correlation. Kjetland et al. suggest increased physical scarring on the vaginal walls of girls with female genital schistosomiasis that may increase transmission of the virus during intercourse.[19] Secor showed that patients with active schistosomiasis exhibit increased expression of the chemokine receptors and major HIV-1 co-receptors (CCR5 and CXCR4) on peripheral CD4 T-cells and monocytes.[20]

These associations are not unprecedented. Years of studies have demonstrated a large amount of evidence in the links between several protozoan diseases and HIV infection. The links between malaria and HIV have been well documented.[6,21,22] Patients with HIV infection frequently have a higher malaria parasite burden, more complications, and higher fatality rates than HIV-negative individuals.[23]

4. Evidence on clinical links between NTDs and malaria

Malaria is a leading cause of anemia in pregnant woman and young children. NTD co-infections have been shown to worsen anemia, potentially leading to large numbers of maternal deaths during pregnancy and to premature births.[7,24] Chronic anemia in young children is associated with reductions in physical growth and impaired cognition and school performance,[6,25] and many of the NTDs, but especially hookworm and schistosomiasis, cause anemia in low- and middle-income countries.[7,26] An estimated 7.5 million pregnant women (approximately one-third) living in Sub-Saharan Africa are infected with hookworm.[27] In Kenya, hemoglobin concentrations were found to be 4.2 g/l lower among children harboring hookworm and malaria co-infections than in children with only malaria infection.

Beyond the health improvements that would result from less anemia, some evidence indicates that selected NTDs may immunomodulate their host and promote increased susceptibility to malaria. To date, the data available on the effects of NTDs on malaria have been conflicting, especially in the older age groups. However, a study by Kirwan et al. demonstrated that repeated four-monthly anti-helminthic treatments for 14 months resulted in a significantly lower increase in prevalence of *Plasmodium falciparum* malaria infection in preschool children, coinciding with a reduction in the prevalence and intensity of ascariasis.[28] Research has also demonstrated that the use of an anti-helminthic reduces the clinically observable cases of malaria,[29] and ivermectin mass drug administration for onchocerciasis and lymphatic filariasis in humans has been shown to disrupt malaria parasite transmission in Senegalese villages.[30]

Additionally, research into social aspects of community health has demonstrated co-benefits between malaria and NTD prevention. Community-directed NTD treatments have increased the use of not only antimalarial bed-nets but also micronutrients and childhood immunizations.[31] The control of mosquito-borne diseases such as lymphatic filariasis can work in synergy with bed-net distributions and other disease control measures, such as intermittent preventive treatment and mosquito control, to reduce malaria incidence.[7,25] A study conducted in Nigeria demonstrated a nine-fold increase in households (with children under 5 years old, pregnant woman, or both) with more than one long-lasting insecticide-treated bed-net, when bed-net distribution was coupled with ivermectin and with albendazole treatment for lymphatic filariasis, onchocerciasis, and soil-transmitted helminths.[32] Other opportunities for integration with other diseases are currently being explored, such as combining malaria and trachoma treatments in Ethiopia.[33]

5. Evidence on clinical links between NTDs and TB

Soil-transmitted helminth infections have been evaluated as epidemiological risk factors for developing active TB. In one study, among 230 smear-positive TB patients and 510 healthy household contacts, an analysis showed a strong association between TB and intestinal helminth infection (odds ratio 4.2), and the odds of being a TB patient increased with the number of helminth species per person.[34]

TB patients with helminth infections present with more severe pulmonary disease, diminished anti-*Mycobacterium tuberculosis* immunity, and diminished responses to anti-TB chemotherapy.[31] Helminth infections also reduce the immunogenicity of bacille Calmette–Guérin (BCG) vaccine in humans,[35] and have been shown to interfere with diagnostic tests for TB.[36]

6. Need for further research

Even as NTD treatment programs scale up and the evidence base of the beneficial health effects of treatment is growing, the scientific knowledge of the health benefits of NTD treatment for HIV, TB, and malaria patients still needs more research. A recent study by Walson et al. noted that there were no significant increases in CD4 cell counts and no reductions in HIV RNA concentrations when people were treated presumptively for helminths.[37] However, they acknowledge that their study may not have been powered to detect the small differences in outcomes in individuals with helminth infection. Earlier work by Walson and

John-Stewart demonstrated that the treatment of known helminth-infected adults produced delayed HIV progression.[38] Such discrepancies between the studies may be explained by differences in the age groups studied, prevalence and intensity of helminth species, type and frequency of medication, and length of time post-treatment before the determination of viral load. Similar issues have been noted in research of NTDs with malaria, and several studies have demonstrated conflicting results. A recent review of these studies demonstrated a trend towards a protective effect of *Ascaris lumbricoides* and *S. haematobium* against severe malaria and a worsening effect of hookworm and *Schistosoma mansoni* on the pathogenesis and incidence of malaria, respectively.[39] The conflicting results listed above demonstrate the need for further studies on how individual NTDs affect the course of HIV and malaria infections and the immunological factors involved. Among the three diseases, scientific knowledge about the links with NTDs and TB remains the weakest.

The World Health Organization recently identified the need for further research into potential pharmacological interactions between antiretroviral and NTD drugs. This could be enhanced by conducting pharmaco-epidemiological studies to evaluate the safety of co-administration of such drugs and their therapeutic efficacy. Last but not least, further research will be required to address the social factors and logistical factors in implementation and operational challenges that arise from linking these programs.

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PLOS ONE

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.

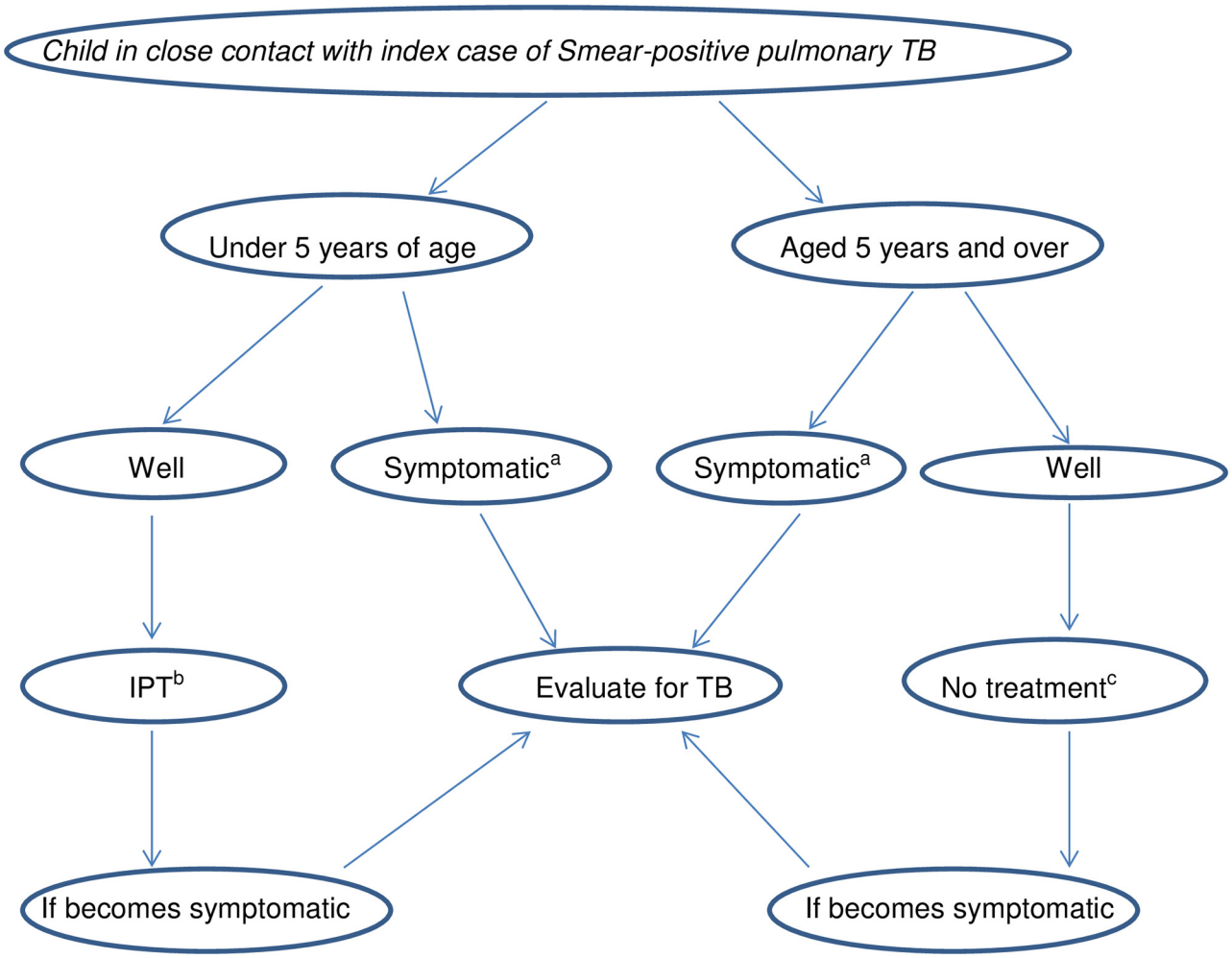
Data Analysis

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

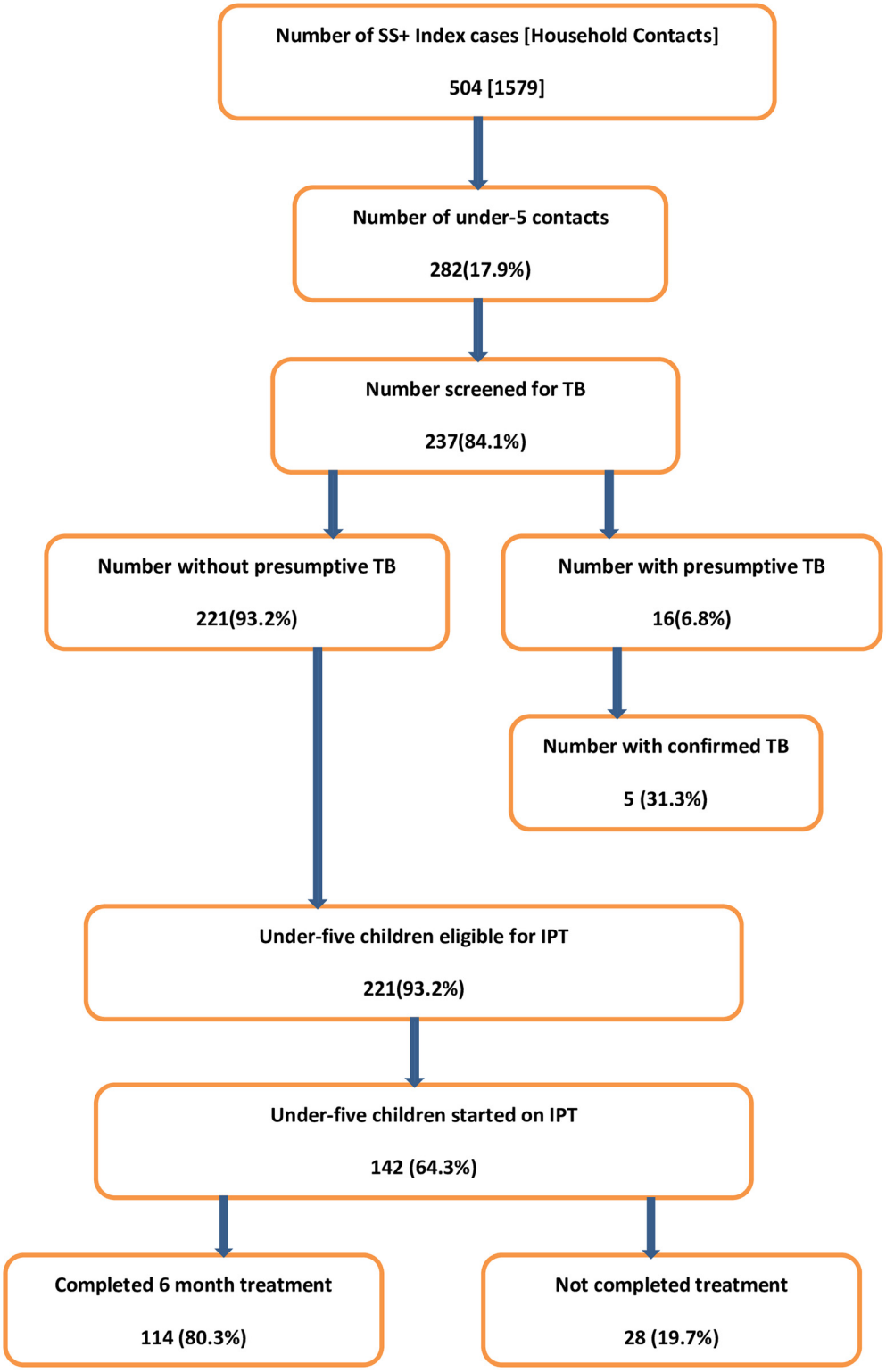

Fig 2. Contact screening and IPT among under-five children, Oct. 2013-June 2014, Ethiopia.

doi:10.1371/journal.pone.0155525.g002

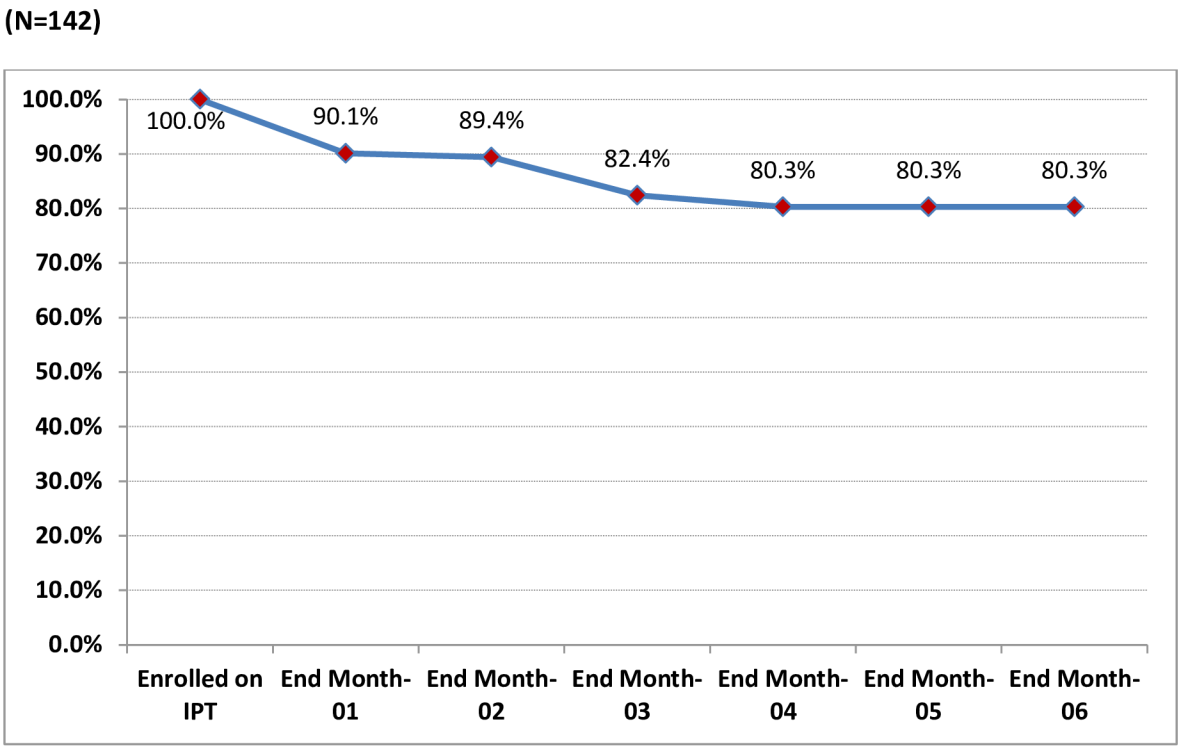

Fig 3. Percentage of under-five children retained on IPT during six-month follow-up.

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to 78.4% (34/40) at hospitals, but the difference was not statistically significant ($p > 0.05$) (Table 1).

Discussion

This study demonstrated the feasibility of providing a six-month course of IPT under routine program conditions to eligible under-five children who were in close contact with SS+ index

Table 1. Contact Screening and IPT among Under-five Children, by Health Facility Type.

Variables	Facility Type		
	Health center	Hospital	P- value [a]
Number of SS+ index cases	334	170	
Number of total household contacts	1036	543	
Ratio of index cases to household contacts	1:3	1:3	
Number (%) of under-five contacts	197 (19%)	85 (15.7%)	0.19
Number (%) of under-fives screened for TB	167 (85%)	70 (82%)	0.26
Number (%) of under-fives with presumptive TB	10 (6%)	6 (8.6%)	0.23
Number of under-fives diagnosed with TB and treated	2	3	
Number of children eligible for IPT	157	64	
Number (%) of children put on IPT	102 (64.9%)	40 (62.5%)	0.70
Number (%) of children who completed the six-month IPT	80 (78.4%)	34 (85%)	0.08

SS+, sputum-smear positive; IPT, isoniazid preventive therapy.

[a] Two-sample test for proportions using Stata.

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cases. We confirmed that contact investigation was an important entry point to identify under-five children with TB and those who needed preventive therapy against TB. The IPT completion rate was within a reasonable range, but the factors contributing to IPT interruption such as lack of leadership by national TB control programs (NTPs) of preventive interventions such as IPT, low awareness & experience of health care workers of the benefits of IPT, providers' perceived fear of toxicity of INH & generating drug resistance, lack of parent/caretaker knowledge as to benefits of IPT [15, 16] need to be addressed.

The WHO recommends clinical evaluation of household contacts of SS+ index cases for active TB. The two main purposes of contact screening and management are: first, to identify contacts of all ages with undiagnosed TB disease among the contacts of an index case, and second, to provide preventive therapy for contacts without TB disease who are susceptible to developing disease following recent infection [5].

The IPT initiation rate of 64.3% in our study is slightly lower than the 68% reported from South Africa [17]. However, it is higher than the 33% rate in southern India [12] and the 18% reported in Timor-Leste [9]. In addition, a study in Malawi showed that only 23 (6%) of 365 under-five child household contacts received IPT [18].

Even though the setting for IPT implementation among HIV infected populations is different from childhood IPT, the IPT initiation rate in the current study is much better than the 39% reported among a cohort of HIV-infected people in Southern Ethiopia [19], and 3.8% reported from Addis Ababa [20]. Uptake and adherence to IPT among HIV-infected people was difficult due to the use of multiple drugs at a time which is not the case for IPT among children [14, 15, 19].

In our study, over two-thirds of eligible children received IPT, with most of them successfully completing the recommended dose. The IPT completion rate of 80% in this study was much higher than the 23% reported from southern India, 24% reported among HIV-infected patients [18] and 12% reported from another study in southern Ethiopia [21. In Pakistan, of 184 under-five children enrolled in IPT, 60 (32.6%) completed six months of IPT [22]. But in the South African report [18], only 15% achieved four months of therapy. Hence, the higher IPT completion rate in our study is encouraging, but more effort is needed to ensure 100% adherence.

Achievement of a higher IPT completion rate in this study also demonstrates that IPT is feasible in a resource-limited setting and that contact investigation of index TB cases can be used as a core entry point for TB case detection and prevention in the childhood population in similar settings. With further strengthening of health workers' capacity, even higher rates of initiation and completion are within reach [23]

Of the total of 28 IPT interrupters, 25 (89%) children discontinued within the first three months after initiation of IPT. There was no interruption after completion of the fourth month of preventive treatment. The major reason for the high interruption rate in a study done in southern Ethiopia was families' refusal to have an otherwise healthy child treated for six months in a TB clinic (where TB treatment is provided) [21], similarly the long duration of treatment was a factor in 28% of cases in India [12]. Although 28 children interrupted preventive therapy in this study, evidence has shown that IPT is safe and well tolerated by children; major potential serious adverse events, including hepatotoxicity and pyridoxine deficiency, are rare in children [24–26]. As this was a routine reported data, there was no specific side effect related information. In a Kenyan study, among HIV-infected children below 14 years of age who were started on IPT, the main reasons for discontinuation of preventive therapy were developing active TB, frequent treatment interruptions, and being lost to follow-up [27].

It is encouraging to attain an overall IPT completion rate of 80%, but we still need to understand the factors contributing to IPT interruption early in the course of therapy and to address

the remaining 20% who interrupted IPT. Further studies are needed to provide evidence to improve completion rate and monitor adherence of IPT. Since IPT completion rather than initiation is the key protective indicator, studies on factors that contribute to completion of unsupervised IPT, such as parent/caretaker education, uninterrupted drug supply, and tracing of those lost to follow-up, should be emphasized. The effectiveness of delivering IPT in kits and directly observing parent-child pairs should be evaluated as there exists evidence showing that introduction of individualized TB treatment kit has beneficial effect in ensuring uninterrupted drug supply with fewer stock outs, minimizing lost to follow ups and building patient confidence with improved adherence to TB treatment [28].

Screening of contacts of TB cases helps to identify at-risk contacts, such as HIV-infected under-fives who require preventive therapy, and of any age who have active TB [29]. Contact screening also contributes significantly to identify children with active TB disease early to prevent childhood morbidity and mortality. In one study it was found that there is an eight-fold increased risk of TB mortality in children living in households with someone who has active TB [30]. Moreover, about 81% of missed opportunities for IPT in at-risk children who later presented with confirmed TB were under three years of age, 25% had disseminated TB, and 5% died [31]. Yet our study demonstrated that 45 (16%) children of index TB cases were not screened for TB. Another study in Malawi in 2006 reported that only 8% of parents with SS+ TB brought their children to a clinic for screening despite provision of clear information [32]. In Addis Ababa, only 23.6% of index cases reported that a health care worker instructed them to bring their child for TB screening [19]. These gaps could indicate that health care providers should also be equipped with the knowledge, skills, and tools to counsel parents or caregivers about the importance of screening children who are in contact with TB patients and about preventive treatment even for otherwise healthy children.

In terms of the capacity to initiate IPT for eligible children, 65% of eligible children at health centers were initiated on IPT, while 62.5% of eligible children at hospitals were initiated on IPT, which is not a statistically significant difference ($P > 0.05$). This indicates that mid-level health workers at peripheral health facilities can implement IPT and that IPT can be decentralized in order to make it more accessible to rural communities. The success can be attributed to capacity building of health care workers, especially at the primary health care level through training, mentorship, program monitoring, and supportive supervision. As reported elsewhere [33], provision of job aids (screening algorithms) and monitoring tools provided by the project were instrumental in improving the awareness of program managers and health care providers in implementing IPT as a childhood TB prevention strategy.

A review of clinical trials indicated that IPT reduces the risk of TB by about 60% among the infected contacts of all ages [34] and that the efficacy of IPT is even higher in children, at 80–90% [35]. The review also showed that 1 case of active TB (over the next five years) can be prevented for every 35 TB contacts who are prescribed INH for six months [35]. In the year of data collection, there were 38,403 registered cases of SS+ TB in the two regions support by the HEAL-TB Project (unpublished report). Extrapolating similar ratios of under-five contacts per index case and IPT completion rate in this analysis to the project regions, there would be 21,487 under-five contacts, of whom 8,686 had completed IPT. Accordingly, contact investigation and IPT intervention for the under-fives in the two largest regions of Ethiopia likely prevented about 248 cases of TB-related morbidity in under-five children (1 in 35 treated with IPT), provided that the findings in this analysis represent the overall project. If IPT had reached all under-five contacts without presumptive TB in the year, the corresponding number of children prevented from acquiring active TB in the two regions would have been 572.

The study has some limitations. Because we carried out the analysis in purposively selected health facilities, its findings might not be generalizable to the remaining health facilities. Also

unavailability of detailed data with respect to gender, age and smear positivity grading of the index case can be considered as limitations. However, the findings provided program-level evidence about the actual implementation of contact screening and IPT. Because contact screening and provision of IPT form part of regular program implementation, the development of TB among those who completed IPT was not assessed.

Conclusions

The findings demonstrated that tracing infants and young children who are contacts of infectious TB cases and offering them preventive therapy was feasible in the regular DOTS program setting. Services for IPT at health centers and at hospitals showed comparable IPT initiation and completion rates. Contact screening is a feasible entry point for IPT and the IPT completion rate was good, but the remaining gaps should be addressed. Comprehensive support provided by the project was instrumental in improving the awareness of program managers and health care providers in implementing IPT as a childhood TB prevention strategy.

Further studies are needed to better understand factors contributing to IPT interruption early in the course of therapy, the feasibility of delivering IPT in kit form, and the long-term benefits of IPT in terms of reducing TB-related morbidity and mortality among under-five child contacts of SS+ TB cases.

Supporting Information

S1 Table. List of Health Facilities.
(DOCX)

S1 Text. Ethical Approval from Amhara Regional Health Bureau.
(JPG)

S2 Text. Ethical Approval from Oromia Regional Health Bureau.
(PDF)

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Author Contributions

Conceived and designed the experiments: YT ZG DH NH SN KM DJ YKH YK MM. Analyzed the data: NG SD ZG PS. Wrote the paper: YT ZG DJ DH NH SN KM MM NG SD YKH YK PS.

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HIV and related infections in prisoners 5

HIV and tuberculosis in prisons in sub-Saharan Africa

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Given the dual epidemics of HIV and tuberculosis in sub-Saharan Africa and evidence suggesting a disproportionate burden of these diseases among detainees in the region, we aimed to investigate the epidemiology of HIV and tuberculosis in prison populations, describe services available and challenges to service delivery, and identify priority areas for programmatically relevant research in sub-Saharan African prisons. To this end, we reviewed literature on HIV and tuberculosis in sub-Saharan African prisons published between 2011 and 2015, and identified data from only 24 of the 49 countries in the region. Where data were available, they were frequently of poor quality and rarely nationally representative. Prevalence of HIV infection ranged from 2·3% to 34·9%, and of tuberculosis from 0·4 to 16·3%; detainees nearly always had a higher prevalence of both diseases than did the non-incarcerated population in the same country. We identified barriers to prevention, treatment, and care services in published work and through five case studies of prison health policies and services in Zambia, South Africa, Malawi, Nigeria, and Benin. These barriers included severe financial and human-resource limitations and fragmented referral systems that prevent continuity of care when detainees cycle into and out of prison, or move between prisons. These challenges are set against the backdrop of weak health and criminal-justice systems, high rates of pre-trial detention, and overcrowding. A few examples of promising practices exist, including routine voluntary testing for HIV and screening for tuberculosis upon entry to South African and the largest Zambian prisons, reforms to pre-trial detention in South Africa, integration of mental health services into a health package in selected Malawian prisons, and task sharing to include detainees in care provision through peer-educator programmes in Rwanda, Zimbabwe, Zambia, and South Africa. However, substantial additional investments are required throughout sub-Saharan Africa to develop country-level policy guidance, build human-resource capacity, and strengthen prison health systems to ensure universal access to HIV and tuberculsosis prevention, treatment, and care of a standard that meets international goals and human rights obligations.

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This is the fifth in a Series of six papers about HIV and related infections in prisoners

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Background

Countries in sub-Saharan Africa have borne the brunt of the generalised HIV and tuberculosis epidemics, which have strained health systems and devastated populations in the region.[1,2] As reported by Dolan and colleagues[3] in another paper in this Series, the prevalence of HIV infection among detainees was 15·6% (95% CI 11·8–19·8%) in east and southern Africa and 8·2% (6·2–10·5) in west and central Africa, suggesting a higher prevalence in prison populations than in non-incarcerated populations. Prevalence of tuberculosis was also extremely high: it was estimated at 5·3% (2·1–10·0) in east and southern Africa, and 2·9% (2·4–3·6) in west and central Africa.[3]

To control the HIV and tuberculosis epidemics and achieve ambitious international targets, countries are called upon to scale up prevention, testing, and treatment for vulnerable groups, including detainees.[4,5] Although incarceration necessarily restricts liberty, detainees have a right to a minimum standard of health care at least equivalent to that in the community,[6,7] including effective services along the entire continuum of HIV and tuberculosis prevention, treatment, and care.

In this Series paper, we provide a descriptive overview of prison populations in sub-Saharan Africa and the epidemiology of HIV and tuberculosis therein; discuss policies and interventions for the prevention, diagnosis, and treatment of HIV and tuberculosis within these

Key messages

- Despite global commitments to end HIV and tuberculosis, in the fourth decade of the HIV pandemic, most countries in sub-Saharan Africa do not collect or report comprehensive information about the incidence, prevalence, or clinical outcomes of HIV infection and tuberculosis in detainees, even though it is the region most affected by these diseases.
- Where data are available, the prevalences of HIV infection and tuberculosis in detainees in sub-Saharan Africa are almost always greater than those in non-incarcerated populations; detainees should be thought of as a priority population for HIV and tuberculosis interventions.
- Few countries have comprehensive prison HIV or tuberculosis policies or programmes, and, where programmes exist, they frequently cover only some detainees and provide inadequate services.
- Governments, donors, non-governmental organisations, and advocates urgently need to promote policy reform and guideline development to ensure the inclusion of incarcerated populations in national HIV/AIDS and tuberculosis programmes, with care provision and structured supervision consistent with community programmes. Specific requirements set by donors, regional governing bodies, and other multilateral organisations could contribute to advancement of both policy and service delivery to detainees.
- To ensure a data-driven and appropriate public health response, surveillance and quarterly monitoring systems, programme assessment, and operational research should be undertaken to ensure that the health needs of detainees are prioritised, ethically studied, and reported upon.
- Criminal-justice reform and conditions within prisons—including nutrition, substance use, mental health, infrastructure, and ventilation—should be prioritised by governments, donors, and human-rights advocates, and recognised as important areas of research, policy, and programme development.

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***Panel 1:* Limitations of the data presented**

The aim of this Series paper is to provide an overview of the epidemiology of HIV and tuberculosis in prison populations in sub-Saharan Africa, the services available and challenges to service delivery, and priority areas for programmatically relevant prisons research. We did not do a systematic review of all available information; rather, we summarise publicly available grey and peer-reviewed literature published in the past 5 years (but also include older work when data were limited or not available). To supplement this information, we sought additional data from experts, which yielded very limited information, did case studies in specifically selected countries, and investigated funding for HIV and tuberculosis programmes within prisons. Detailed epidemiological descriptions of HIV and tuberculosis in prisons in each country of sub-Saharan Africa, and detailed, contemporary information about prison populations, HIV and tuberculosis policies, funding, and services are beyond the scope of this Series paper.

The quality of the epidemiological data included is variable, and should be interpreted with caution. All data identified are presented (appendix) without exclusion. As a systematic review was not done, some data published between 2011 and 2015 might have been missed. For each study included, details about the study period, number of prisons included, sampling methods, screening or diagnostic procedures, and case definitions are in the appendix. When interpreting the data, the generalisability of findings, sample sizes, potential biases, confounding factors that might be unaccounted for, and the comparability of findings with non-incarcerated populations, other studies, and over time should all be considered.

Between 2011 and 2015, there were 48 publications from 24 (of 49) sub-Saharan African countries—19 in peer-reviewed journals, 26 in conference proceedings, and three in institutional reports. Eight studies included no information about when they were done and 12 were done before 2011 (one in 2007, two in 2008, four in 2009, and five in 2010). In the 40 studies in which time to publication of data could be determined, 32 were published within 2 years, seven within 3–5 years, and one within 7 years.

Nine studies aimed to provide nationally representative prison data; the remainder were subnational, with 13 focusing on individual prisons. Therefore most data cannot be generalised to the country's total prison population. Different methods and case definitions were used in each study, which prevents easy comparison. In several, inadequate information was provided about the sampling methods, which means that selection bias cannot be fully explored. Some studies were done in a convenience sample or had poor uptake, which could result in selection bias. Routine notification or programme data were used in some, which could have led to underestimation of prevalence, whereas others were done in purposively screened populations.

In most tuberculosis studies, a positive symptom screen was needed before participants underwent microbiological testing, which could have led to underestimated prevalence; diagnostic tests with sensitivities less than 100% were used in many, and thus the number of cases could have been under-ascertained. Concurrent sampling of prison and non-incarcerated populations to allow a direct and valid comparison of the prevalence of HIV infection and tuberculosis between these populations was not done in any study. Trends in prevalence cannot be ascertained from the data. These limitations should be considered when using and interpreting the epidemiological data presented in this Series paper.

populations, and the barriers to their implementation; and recommend a policy and service-delivery agenda for detainee health in sub-Saharan Africa, together with the associated research agenda.

Overview of methods

See Online for appendix

Full methods and a full list of search terms are detailed in the appendix. In brief, we reviewed grey and peer-reviewed literature published between Jan 1, 2011, and Dec 31, 2015, to identify available abstracts, publications, and other reports (published in English, French, or Portuguese) on HIV and tuberculosis epidemiology in prison populations in sub-Saharan Africa, and approaches to prevention, screening, diagnosis, and treatment of these diseases. When no data were available after 2011, the most recent literature before 2011 was included instead. We did case studies in five countries (Zambia, South Africa, Malawi, Nigeria, and Benin), which were purposively selected on the basis of regional spread and data availability to examine prison-specific HIV and tuberculosis policies and services in different regions of sub-Saharan Africa. Information about international donor funding between 2005 and 2015 was sought from four major international donors: the Global Fund Against AIDS, Tuberculosis and Malaria, the US President's Emergency Plan for AIDS Relief, the UK Department for International Development, and the European Union Funding Programme (panel 1).

In this paper, we use the term "detainee" to represent both people awaiting trial (on-remand detainees) and those who have been sentenced (convicted detainees). The term "prison" is used to represent facilities housing on-remand detainees (including jails, police holding cells, and other detention centres) and convicted detainees. We specify when data pertains to only one group or type of facility. This review does not include information about prison staff.

Prison populations in sub-Saharan Africa

Between 2011 and 2015, the estimated average daily census of detainees in sub-Saharan Africa was around

	Prison population (n)	Prisons (n)	Year	Source	Incarcerated per 100 000 population (n)	Pre-trial detainees (%)	Occupancy (%)	Estimated funding from Global Fund for prison HIV and tuberculosis programmes			
								Total budget (US$)	Proportion of total HIV and tuberculosis funding to the country (%)	Period	Annual funding per detainee (US$)
Angola	22 826	34	2014	Ministry of the Interior	106	47·1%	167%	$534 340	6%	November, 2011–August, 2016	$4·68
Benin	7247	9	2012	Government of Benin	77	74·9%	364%	$890 652	2%	October, 2010–September, 2015	$24·58
Botswana	3960	23	2015	Ministry of the President	192	24·5%	92%	..	..	..	..
Burkina Faso	6251	25	2014	US State Department	34	48·0%	171%	$47 547	1%	June, 2010–June, 2015	$1·52
Burundi	8646	11	2014	National prison administration	93	47·5%	214%	..	..	..	..
Cameroon	25 914	78	2013	Ministry of Justice	115	59·9%	138%	$4 835 690	20%	August, 2006–December, 2015	$20·73
Cape Verde	1434	5	2013	US State Department	286	29·6%	122%	..	..	..	..
Central African Republic	764	5	2015	UN mission	16	70·2%	..	$125 046	1%	December, 2011–May, 2014	$65·50
Chad	4831	45	2011	National prison administration	39	63·4%	232%	..	..	..	..
Comoros	233	3	2014	US State Department	31	55·8%	388%	..	..	..	..
Congo (Brazzaville)	1240	12	2014	US State Department	27	60·0%	483%	$702	<1%	January, 2011–December, 2015	$0·14
Democratic Republic of the Congo	21 711	120	2013	UN mission	32	82·0%	271%	..	..	..	..
Côte d'Ivoire	10 850	34	2014	US State Department	52	42·0%	218%	$4 163 261	3%	January, 2010–December, 2015	$63·95
Djibouti	600	2	2014	US State Department	68	50·0%	171%	$303 132	9%	October, 2013–September, 2015	$252·61
Equatorial Guinea	1000	15	2014	Estimate by Government officials	129	..	..	..	..	..	..
Eritrea	..	..	..	..	..	..	..	..	..	..	..
Ethiopia	111 050	126	2012	US State Department	128	14·0%	..	..	..	..	..
Gabon	3500	9	2013	US State Department	210	33·0%	..	..	..	..	..
The Gambia	1121	3	2014	UN Human Rights Rapporteurs	58	22·2%	173%	$90 008	3%	July, 2010–December, 2015	$16·06
Ghana	14 534	43	2016	National prison administration	53	18·7%	147%	$740 568	4%	May, 2006–April, 2011	$10·19
Guinea	3110	31	2014	Ministry of Justice	26	65·0%	175%	$4 493	<1%	February, 2007–January, 2012	$0·29
Guinea-Bissau	92	3	2013	US State Department	..	Vast majority*	102%	..	..	..	..
Kenya	54 154	108	2015	National prison administration	118	40·4%	202%	$434 360	4%	January, 2011–December, 2015	$1·60
Lesotho	2073	12	2014	National prison administration	92	19·5%	71%	$250 839	3%	October, 2010–March,2016	$24·16
Liberia	1719	15	2014	National prison administration	39	83·0%	138%	..	..	..	..
Madagascar	18 719	82	2013	US State Department	83	53·0%	181%	$203 431	1%	October, 2009–March,2016	$1·67
Malawi	12 156	30	2014	National prison administration	73	16·1%	174%	..	..	..	..
Mali	5209	58	2014	US State Department	33	52·8%	222%	..	..	..	..
Mauritania	1768	18	2014	Ministry of Justice	44	41·0%	102%	$1 290 980	15%	September, 2006–August, 2015	$81·08
Mauritius	2137	10	2016	National prison administration	159	41·1%	117%	$928 838	16%	January, 2010–June, 2015	$79·02
Mozambique	15 976	184	2015	Presidential quote	57	32·9%	195%	$1306	<1%	July, 2008–June, 2017	$0·01
Namibia	3560	13	2015	Ministry of Justice	144	6·6%	96%	$682 075	4%	October, 2011–September, 2016	$23·95
Niger	7424	38	2014	US State Department	39	53·4%	60%	..	..	..	..

(Table continues on next page)

	Prison population (n)	Prisons (n)	Year	Source	Incarcerated per 100 000 population (n)	Pre-trial detainees (%)	Occupancy (%)	Estimated funding from Global Fund for prison HIV and tuberculosis programmes			
								Total budget (US$)	Proportion of total HIV and tuberculosis funding to the country (%)	Period	Annual funding per detainee (US$)
(Continued from previous page)											
Nigeria	56 620	240	2014	US State Department	31	69·3%	114%	$4 090 276	7%	July, 2010–December, 2015	$13·38
Rwanda	54 279	14	2015	National prison administration	434	7·1%	96%	$21 232	<1%	January, 2005–June, 2010	$0·07
São Tomé and Príncipe	201	1	2014	US State Department	101	10·9%	77%	$165 582	16%	December, 2009–June, 2015	$147·11
Senegal	8630	37	2014	Groupe de Presse Walfadjri	62	41·4%	117%	$473 248	8%	January, 2012–December, 2016	$10·97
Seychelles	735	3	2014	US State Department	799	15·5%	143%†	..	..	..	..
Sierra Leone	3488	19	2015	National prison administration	55	54·3%	195%	$97 100	1%	November, 2008–October, 2015	$3·97
Somalia	3450‡	..	2012	US State Department	..	..	..	..	..	..	..
South Africa	159 563	236	2015	National prison administration	293	27·1%	133%	$4 963 001	31%	January, 2012–March, 2016	$7·76
South Sudan	6504	80	2015	National prison administration	52	28·9%	329%†	..	..	..	..
Sudan	19 101	125	2013	US State Department	50	20·4%	255%	..	..	..	..
Swaziland	3616	12	2014	National prison administration	289	18·1%	127%	..	..	..	..
Tanzania	34 196	126	2014	US State Department	69	50·1%	120%	..	..	..	..
Togo	4493	12	2014	US State Department	64	65·2%	165%	..	..	..	..
Uganda	45 092	247	2015	National prison administration	115	55·0%	273%	..	..	..	..
Zambia	18 560	88	2015	National prison administration	125	23·2%	229%	..	..	..	..
Zimbabwe	18 857	46	2015	National prison administration	145	17·1%	111%	..	..	..	..

Data are from the Institute for Criminal Policy Research[8,9] or the Global Fund, unless otherwise specified. The year column refers to the year in which the prison population estimate is from. Global Fund=Global Fund to Fight AIDS, Tuberculosis and Malaria. *Term used in the US State Department human rights report. †Based on occupancy at one prison.[8] ‡Estimate—no official figures available.

Table: **Overview of prison population in sub-Saharan Africa and estimated funding from the Global Fund to Fight AIDS, Tuberculosis and Malaria for prison HIV and tuberculosis programmes, by country**

600 000 (table, appendix).[9] On-remand detainees constitute 50% or more of the prison population in 40% of countries. 23 countries reported occupancy of more than 150%. Accounts of prison conditions are scarce and are likely to vary across countries. However, food rationing and poor-quality food (Mwapasa V, College of Medicine, Blantyre, Malawi, personal communication);[10,11] poor hygiene, water supply, and sanitation (Mwapasa V, College of Medicine, Blantyre, Malawi, personal communication);[10,11] frequent stockouts of basic drugs, including antibiotics (Mwapasa V, College of Medicine, Blantyre, Malawi, personal communication; unpublished UN Office on Drugs and Crime Data); and physical and psychological abuse[11] have all been reported. Such poor prison conditions—including overcrowding—are inconsistent with the basic principles set forth in the Mandela Rules, could constitute human rights violations, and pose serious risks to individual and public health (panel 2).[7]

Even among the prison population as a whole, access to health care, treatment of prisoners, and prison conditions differ substantially between specific groups. Ethnic minorities, migrants, poor people, foreigners, and socially marginalised populations such as sex workers, people who use drugs, lesbian, gay, bisexual, and transgender (LGBT) individuals, and on-remand detainees could be at increased risk of abuse, poor conditions, or lack of access to care.[6,16] Women and juvenile detainees, who have increased and distinct health needs, constitute 5% or less of the prison population in most countries, but often have poorer access to high-quality health care than do male detainees (panel 3).[18,19]

Epidemiology of HIV and tuberculosis among detainees in sub-Saharan Africa

Data for HIV or tuberculosis in prisons, published between 2011 and 2015, were identified from 24 of 49 sub-Saharan African countries (appendix). Data published before 2011 were available for three other countries. Studies were limited in number, varied in quality, and had differing methods (panel 1). Therefore caution is advised when comparing or generalising findings and making inferences from the data.

Most studies consistently showed a higher prevalence of HIV infection and tuberculosis among detainees than among unmatched non-incarcerated populations. Reported prevalence of HIV infection ranged from 2·3% to 34·9% (2·3%–10·8% in west Africa; 4·2%–23·0% in east Africa; and 7·2%–34·9% in southern Africa); tuberculosis prevalence ranged from 0·4% to 16·3% (1·2%–16·3% in west Africa; 0·5%–12·1% in east Africa; and 3·6%–7·6% in southern Africa).

Female sex was associated with prevalent HIV infection in prison; prevalence was also higher in women in prison than in those in the surrounding or non-incarcerated population. Although the reasons for this increased prevalence are unclear, the high background prevalence of HIV infection among younger women or behaviours associated with both incarceration and HIV, such as sex work, could have roles. One cross-sectional study[20] in Zambia showed a higher prevalence among already-incarcerated detainees than among those entering prison. Whether HIV transmission during incarceration or other epidemiological factors contributed to this difference is unclear.

When data were available, a large proportion of tuberculosis cases were in people with HIV (range 5–70%).[10,21–28] Overcrowding, incarceration in windowless cells, and sharing cells with patients with tuberculosis or a chronic cough were associated with increased tuberculosis prevalence among detainees in some studies. Furthermore, in a modelling study in a South African prison, annual tuberculosis transmission risk was estimated to be as high as 90%,[29] suggesting that prisons could be places of high transmission intensity.

The revolving-door effect (appendix)—as a result of detainees, prison personnel, and visitors cycling into and out of prisons—can result in the concentration of HIV and tuberculosis in prisons, and could amplify these diseases in the wider communities into which detainees are released and in which prison personnel live.[20,30] For example, in a study in Zambia,[20] the total prison population over 6 months was double the average static population (n=1300) for that period, and 24% of detainees entering prison had been previously incarcerated. Several other studies have also shown the high turnover of detainees.[10,21,31,32] Therefore, HIV and tuberculosis control in prisons benefits not only the individual and other detainees, but could also affect control in the community. Additionally, community and prison HIV and tuberculosis programmes face substantial challenges in ensuring appropriate services and continuity of care for detainees upon incarceration and release.

Understanding risk factors for HIV and tuberculosis in sub-Saharan African prisons is essential to the implementation of appropriate prevention interventions and services. The available empirical data do not allow determination of the relative contribution of transmission before and after incarceration to prevalence within prisons. The very limited data available suggest, however, that transmission during both periods might play a part.

Panel 2: Experience of detainees in sub-Saharan African prisons

Pre-trial detention

"I have stayed here for five years, and have not seen a plaintiff, and have not seen a judge. The court has not called the case."
Male detainee, South Sudan[12]

Sexual violence

"We called to the police and screamed for help, saying, 'These guys are forcing us to have sex with them.' But the police said, 'That is good, that's what you want.' So the police were encouraging the guys in there. There were about 50 other detainees, and five of them were raping us. Three of them raped me personally."
Male detainee, Tanzania[13]

Food

"Often there was no wood to cook, so [the deputised prisoner guards] would say, 'OK, spend the night without eating.' Once we went three days without eating. Even the children do not eat when there is no wood."
Male detainee, Rwanda[14]

Poor access to care

"There are delays in getting to the clinic. It depends on the officials, if they want to take you there or not. Sometimes you can go as long as a month waiting to go to the clinic.... They don't open the door in the cell at night for anything. There are no windows, no air. Someone who was 28 years old died at night in my cell and they didn't open the door until the morning."
Male detainee, Zambia[15]

Inadequate mental health care

"When I was brought here, I didn't believe I would come out of that place [Juba Central Prison]. At night, people fight themselves. Some use razor blades. Others they insult, others they cry. Others are innocent. Others are angry. Others laugh but are not happy. Others are quiet. Others do not wear clothes—they move naked."
Male detainee, South Sudan[12]

HIV care

"I normally get my medicine once a month and I take it each day. I started ARVs in 2006, but when I was in *Kwa Kabuga* I did not get them."
Female detainee, Rwanda[14]

"When I told the prison officer I was HIV positive, he said, 'Fight on, complete the sentence, go home, and get treatment.' It meant he can't do anything for me. There were wardens I informed. They said prison has nothing to offer me.'"
Female detainee, Uganda[11]

ARVs=antiretrovirals.

Panel 3: Experiences of children in adult prisons in Zambia

Zambia has no dedicated juvenile justice system, and children in conflict with the law face trial in the adult court system. Even after an initial appearance before a judge or magistrate, juvenile detainees can wait for lengthy periods while their cases are being concluded.

One 17-year-old detainee told researchers, "I am here on remand; I came in July, 2007. I am done with my trial, just waiting for judgment…The trial didn't take too long, it is only the judgment that has taken long. It's been a year and four months since my trial ended. I've been back to court four times just for the judgment but it never comes."

International law mandates that people who are charged with a criminal offence be informed of their right to have access to a lawyer. However, many juvenile detainees in Zambia report no legal representation. Even children appearing before the High Court were rarely represented by counsel. As one teenage detainee reported, "I had no representation, I stood on my own behalf. It was my first time in a police station or in court. I was just speaking, and I was scared. So I didn't know what I was saying… As young people, it is very threatening to see the inside of the court. Even if you are not guilty, you end up pleading guilty."

Children held with adults often face sexual violence. "By the time we are discharged, we will go out of here with disease", said another adolescent detainee. "Juveniles are either taken advantage of or enticed because of our vulnerability. We are young, we don't have people to bring us food and clothes. They make sure we consume what they give, then are unable to refuse."

Access to health care, which is often difficult for adults, can be especially difficult for children. "Sometimes it is difficult getting to the clinic, sometimes you may not get to go. We ask the cell leader—[and even if they agree] the guards might say no", said a third detainee. Another 16-year-old concluded, "If you are sick, then you can't go to the clinic."

Source: Todrys & Amon, 2011.[17]

Robust studies of the bio-behavioural, social, and structural factors underpinning the risk of HIV and tuberculosis among prison populations in sub-Saharan Africa are needed to answer these questions.

Tools, approaches, and structural interventions to prevention, screening, diagnosis, and treatment

International guidelines recommend a package of HIV and tuberculosis interventions for prisons in low-income and middle-income countries.[7,33] The recommended interventions can be organised into three categories: structural approaches to reduce overcrowding, improve tuberculosis infection control, and provide adequate nutrition; prevention and harm-reduction activities, including interventions to reduce transmission of HIV and tuberculosis; and HIV and tuberculosis diagnosis, treatment, and care, which should adhere to national guidelines and be linked operationally to national programmes.

Despite endorsement from regional and international governing bodies,[34,35] these interventions are rarely fully available in sub-Saharan African prisons because of a host of financial, policy, and systems-related barriers, including financial constraints,[36] inadequate infrastructure,[37] laws criminalising sex between men,[38] overcrowding,[39] absent health-information management systems,[39] inadequate infection-control procedures,[40] lack of transport to off-site clinics,[39] fragmented care due to facility transfers and release back to the community,[39] and scarce human resources for health.[39]

Prison overcrowding is a recognised problem globally,[36] and mathematical modelling suggests that implementation of internationally recommended cell-occupancy standards could reduce the annual risk of tuberculosis transmission by 50% in the specific case of South Africa.[29] However, there are limited data from sub-Saharan African countries describing the use of structural or criminal-justice interventions to mitigate overcrowding.[39] South Africa provides a counter-example: reforms to the pre-trial detention system have helped to reduce overcrowding by creating alternatives to detention for on-remand detainees unable to post bail, including release on warning and the use of electronic monitors.[41–43] Partly as a result of these reforms, the South African prison population declined between 2004 and 2014, from 187 036 to 157 170 detainees.[44] Another policy change identified in one prison was increasing food rations, which correlated with a reduction in reported tuberculosis incidence and all-cause mortality.[45]

In some cases, better service delivery for HIV and tuberculosis prevention and treatment could be politically and logistically more feasible than structural changes as a first step towards improvement of detainees' health. With respect to HIV prevention, behaviour-change communication and educational interventions have been implemented in some prisons, although their reach and effectiveness are unknown.[37,46–48] Crucial concerns, such as mitigation of sexual violence and coerced sex,[49] appear to be minimally addressed, with no reports of clearly effective strategies.[50,51] Provision of condoms, post-exposure prophylaxis, and pre-exposure prophylaxis could reduce HIV transmission in facilities. Condoms are available in prisons in Burundi, Lesotho, and South Africa;[38] non-occupational post-exposure prophylaxis is reported to be available only in South Africa. Data for uptake (how often, when, and by which detainees) or effectiveness of these preventive measures are unavailable. Condom provision is illegal in prisons in many countries, including Ethiopia,

Malawi, Namibia, Rwanda, Senegal, Swaziland, Tanzania, Uganda, Zambia, and Zimbabwe. We identified no reports suggesting that pre-exposure prophylaxis is being prepared for implementation in sub-Saharan African prisons at present.

International guidelines state that mandatory HIV testing is a violation of human rights and endorse the availability of voluntary, confidential, on-site HIV counselling and testing for all people within closed settings.[52] Despite potential concerns about stigma, voluntary HIV counselling and testing seems to be accepted by detainees, as shown by several reports of uptake and a study of detainee satisfaction.[10,20,32,53–55] It is available in prisons in some countries, including Cameroon,[56] Côte d'Ivoire,[10] Democratic Republic of the Congo,[53] Kenya,[46,57] Malawi,[58] South Africa,[31] Uganda,[37] and Zambia.[59]

Although the availability of antiretroviral therapy (ART) in prisons in sub-Saharan Africa is limited,[30,31,60] when combined with comprehensive, voluntary HIV counselling and testing, initiation of ART can, in some cases, occur earlier in prisons than in the community. For example, the median CD4 cell count among male detainees initiating ART in South Africa appears higher than that among men in neighbouring community programmes.[31,61,62] Once in care, people who remain in prison can achieve excellent clinical outcomes: viral-load suppression was 93% at 12 months at an on-site treatment clinic[31] and 92% at 96 weeks at an off-site HIV clinic.[60] A description of the HIV treatment continuum in Kenyan prisons suggests that service uptake along the cascade might be similar to that in the community, and is in need of strengthening: 48 535 detainees received HIV counselling and testing and 2782 (5·7%) received a diagnosis of HIV, of whom 1493 (53·7%) enrolled into HIV care and 505 initiated ART (18·2%).[46,63]

Frequently set apart from HIV services, tuberculosis prevention activities in prisons have historically involved passive approaches to case detection.[29,64] By contrast, active case-finding—the aims of which are to systematically screen, diagnose, and treat detainees with tuberculosis early, with the goal of interrupting transmission—has been reported in prisons in Cameroon,[32] Malawi,[65] Nigeria,[66] South Africa,[67] Tanzania,[68] and Zambia.[59] Evidence shows that, with support and funding from implementing partners, mass and at-entry screening for tuberculosis—frequently integrated with HIV counselling and testing—is feasible, acceptable, and results in high uptake.[20,59,69] In Zambia in 2010, through a collaboration between the Zambia Correctional Service, Ministry of Health, and a Zambian non-governmental organisation (NGO), 4879 detainees and neighbouring community members were screened for HIV, and 7638 for tuberculosis;[59] 564 individuals were newly diagnosed with HIV and linked to care, and 409 were diagnosed with tuberculosis, with 372 (91%) initiating treatment. These results demonstrate what can be achieved when prison leadership, donor funding, and NGOs align to support implementation of tuberculosis programmes in prisons. Nonetheless, solutions embedded within and linking prisons and mainstream health systems will be required to achieve sustained screening, service-delivery, and health improvements.

To maximise efficiency and control costs, evidence-based screening tools are needed,[70] but few reports from sub-Saharan Africa have been published to guide how to screen detainees for tuberculosis. The sensitivity and specificity of symptom screening varies depending on the number of symptoms included.[27,70] In Zambian detainees, low body-mass index and HIV infection had moderate sensitivity (60%) for tuberculosis.[70] Among South African detainees, the use of chest radiography in addition to symptoms improved screening sensitivity from 24–38% to 70–80%.[27] These results are in keeping with findings from other continents,[71,72] which suggests that use of chest radiography is beneficial among prison populations. However, chest radiography necessitates resources, including health-care workers or computer-aided diagnostic algorithms to interpret or score radiographs, respectively.

Tuberculosis diagnosis in sub-Saharan African prisons often relies on sputum smear microscopy, (usually performed off site),[28] which misses about half of all cases.[73] Improving access to tuberculosis culture, chest radiography, and newer nucleic acid amplification tests could increase diagnostic yield in prisons and allow for earlier detection of multidrug-resistant tuberculosis. In South Africa, testing symptomatic on-remand and convicted detainees (both new entrants and those incarcerated) identified by the WHO symptom screen[74] with on-site nucleic acid amplification was feasible and affordable: 87% of all new entrants and 23% of incarcerated detainees were reached, and costs were similar to those of other screening modalities (US$1513 per case of tuberculosis identified).[67]

Some evidence suggests that detainees in sub-Saharan Africa might experience suboptimal retention along the tuberculosis care continuum. Among 466 detainees beginning tuberculosis treatment at ten regional Ugandan prison health centres, only 222 (48%) completed treatment (202 [43%] were lost to follow-up and 22 [5%] died).[22] A chart review[75] of 202 detainees initiating tuberculosis treatment at one South African prison showed similar challenges: 92 (46%) patients were cured, but 103 (51%) had no ascertainable outcome because they were transferred before treatment completion. Findings that less than 50% of patients completed treatment or had documented cure are concerning, and have implications for the health of detainees and the potential development of drug-resistant tuberculosis. Early reports suggested a high prevalence (9·5%) of multidrug-resistant tuberculosis in one Zambian prison.[76] However, subsequent studies in Zambia[20] and South Africa[67] have shown a much lower prevalence (1·1% and 1·0%, respectively) similar to general population estimates in sub-Saharan Africa (1·5% prevalence among treatment-naive patients with tuberculosis),[77] suggesting that

Panel 4: South Africa and Malawi—strong policies, but work still to do

South Africa's prison system serves a prison population larger than any other African country and is administrated by a dedicated government ministry (table). Unusually in the African context, South Africa has both policy and stand-alone guidelines outlining a comprehensive package of HIV and tuberculosis prevention, diagnosis, care, and treatment actions (appendix). Malawi also has strong policies addressing prison tuberculosis services. The publication of the Malawi Policy on Tuberculosis Control in Prisons,[100] which incorporates some actions on HIV, demonstrated unusual alignment of political and technical commitment, by recommending provision of entry screening, active case-finding, HIV testing, DOTS, antiretroviral therapy, and treatment follow-up for all post-release detainees with tuberculosis. The National Strategic Plan for Prevention and Control of TB 2015–2020 additionally articulated plans to align tuberculosis registration in Malawi's five largest prisons with Ministry of Health and National Tuberculosis Control Programme protocols, and to provide tuberculosis and HIV training for prison officers.[101]

Policies and guidelines provide an important framework for planning, financing, and implementation of HIV, tuberculosis, and other essential prison services, yet by themselves are insufficient. In South Africa, despite a well defined package of HIV and tuberculosis service entitlements and comparatively high levels of funding, key informants noted that prison health care remains suboptimal. All South African prisons have internal clinics but these clinics are understaffed. Lack of medical doctors (eight of 48 prison doctors' posts were filled in June, 2014) and a nursing act that prevents nurses prescribing without authorisation contribute to timelags and bottlenecks in chronic-disease management and increase dependence on non-governmental organisations to deliver tuberculosis and HIV testing and treatment. Prevention services are weak because nurses frequently are not adequately trained in primary care or preventive health. Infrastructural issues also limit tuberculosis infection control because prisons were not built to allow adequate airflow, and there is a high demand for isolation cells for purposes other than infection control (eg, for so-called trouble makers). High levels of stigma for HIV and a reluctance to report sexual abuse limit access to HIV preventive and treatment services. Continued treatment once detainees are released from prison has also proved problematic, and is exacerbated by inconsistent referral practices, reluctance of detainees to access services once released, and reported maltreatment of former prisoners in public health services.

Key informants noted that Malawi, too, is facing systemic barriers to realising its far-reaching tuberculosis and HIV prison policies. Although the four largest prisons have static antiretroviral therapy clinics (registering around 600 detainees annually), the prison system struggles with human-resource capacity: only 20 health-care professionals are employed (one medical doctor, five clinical officers, five medical assistants, five nurses, and four microscopy technicians), with support from 30 patient-attendants. Challenges with supervision, supply chain, and disease notification are ongoing. In several smaller prisons, health services—including HIV and tuberculosis testing and treatment—are provided by visiting Ministry of Health staff, with occasional support from local or international non-governmental organisations. In many smaller sites, however, detainees must continue to be accompanied to external health centres.

detainees might not be disproportionately affected by multidrug-resistant disease. Screening, diagnosis, and effective treatment should be linked to preventive therapy (ie, isoniazid preventive therapy and ART) to control tuberculosis in high-risk populations such as detainees.[78] No published reports from sub-Saharan African prisons include descriptions of initiation or completion of isoniazid preventive therapy, or associated adverse events.[79] There was a notable dearth of sex-disaggregated and age-disaggregated data describing HIV or tuberculosis treatment outcomes for women and children within sub-Saharan African prisons.[19]

The breakdown of continuity of care for HIV and tuberculosis as a result of inter-facility transfer and release have been frequently noted.[31,60] The transition into detention often starts in police detention facilities or holding cells within police stations—facilities that generally lack health services.[80,81] For individuals already on ART or tuberculosis treatment, or both, who transition into prison, breaks in treatment of as little as several days can have serious adverse consequences, including the development of drug resistance.[82] Within prison and after release from prison, continuation of ART and tuberculosis treatment is essential for sustainment of individual health, prevention of development of drug resistance, and reduction of the risk of transmission to other detainees and the communities into which detainees are released. On the basis of data largely from Europe and North America,[83–85] retention in HIV or tuberculosis care, or both, after release from prison is thought to be challenging for various psychosocial, health-systems, and structural reasons. In the only sub-Saharan African study[60] in which retention in HIV care after release is discussed, 23 (68%) of 34 detainees visited the same South African HIV clinic at which they received care during incarceration at least once after release.

Prison populations are likely to have a higher prevalence of substance-use and mental health problems than the general population. These issues can compromise HIV and tuberculosis prevention, treatment, and care efforts within prisons through poor adherence to treatment, transactional sex for drugs, and high-risk sexual behaviours.[55,86,87] However, data for

prevalence and strategies to address these issues are scarce. Substance use in the past month (mostly cannabis or alcohol) has been reported by about 5% of detainees in Nigeria[88] and Kenya.[89] In a South African study[90] in which urine testing was done, either cannabis or methaqualone was detected among 45% of detainees at the time of police arrest. Although anecdotal reports describe the use of injection drugs in sub-Saharan African prisons, the frequency is unknown, but appears low.[89] Depressive and anxiety disorders have been reported in a large proportion of detainees in several studies.[91,92] Despite the probable burden of these comorbidities, we identified only one description of mental health activities (in Malawi)[93] and one drug harm-reduction programme (in Mauritius) in prisons.[94]

The lack of sufficient numbers of health workers and training[95] to provide HIV and tuberculosis treatment and other services[95] is a severe constraint on delivering care in sub-Saharan African prisons. Task-sharing and involving detainees themselves in health-service delivery could help to overcome some gaps in the system.[59,96] Reports from Rwanda, South Africa, Zambia, and Zimbabwe highlight the role of inmate peer educators in the provision of a host of services, including health education, psychosocial support, symptom screening and sputum collection for tuberculosis, referral for HIV testing, and social mobilisation for uptake of health services.[48,97–99] Sustainment of these programmes necessitates dedicated financing, ongoing training and peer-to-peer mentoring to maintain the cadre, and training of prison personnel to supervise and support peer educators.[59,97]

HIV and tuberculosis prevention, care, and treatment policies, and availability of services

Few sub-Saharan African countries have comprehensive policies in place guiding the implementation of HIV and tuberculosis prevention, care, and treatment activities in prisons. The appendix shows differing progress in this field, with summaries of the state of HIV and tuberculosis policies for detainees in five countries. Whereas South Africa has fully developed prison guidelines for tuberculosis, HIV, and sexually transmitted infections that outline a comprehensive package of interventions specific to detainees, prisons in Benin, Zambia, and Nigeria remain dependent on guidelines developed for the general community, with little or no reference to the epidemiological or structural particularities of prison populations. Malawi has a specific policy for tuberculosis management in prisons, but not for HIV or other sexually transmitted infections.

Policies provide clarity, direction, and normative standards to guide planning and service implementation and help to hold government institutions accountable. But, as shown by experiences in South Africa and Malawi (panel 4), comprehensive policies are not a guarantee of service implementation or operational efficacy (appendix). As demonstrated by Zambia and Benin (panel 5), innovations to improve HIV and tuberculosis care in prisons are possible despite weak or absent policies, but will probably remain limited in their sustainability and strategic impact (appendix). In many countries, NGOs often make a large and unmeasured contribution to essential services.[102]

Panel 5: Zambia and Benin—working outside the box

Benin and Zambia have small absolute numbers of detainees by international standards but their prisons are severely overcrowded (table). Such conditions pose particular risks in relation to the spread of tuberculosis and HIV, and, in the absence of prison-specific policies, the evolution of HIV and tuberculosis care in prisons in these countries has been iterative (appendix).

Key informants report that health care in Benin's nine prisons is delivered by a small team of under-resourced nurses employed by the prison authority, *La Direction de l'Administration Pénitentiaire et de l'Assistant Social* (DPAS). In recognition of the potential health threat posed by overcrowding in 2010, the country's national tuberculosis programme, *Programme National contre la Tuberculose, Bénin* (PNT, Bénin), recruited five new nurses, one at each of the five largest prisons. The nurses were tasked with providing HIV and tuberculosis counselling, conducting tuberculosis case-finding, collecting sputum samples, recording results, and overseeing referrals to PNT-run basic management units. Detainees with confirmed tuberculosis were also tested and treated for HIV. The nurses additionally provided general support to DPAS health staff.

In December, 2014, all five PNT-recruited nurses were absorbed (ie, employed and deployed by the Ministry of Health) in a national recruiting round, and, because of cost and supervisory complications, not replaced. In 2015, the PNT, Bénin announced a new policy to train DPAS nurses to do the same tasks. According to key informants, however, the capacity of existing staff to absorb the full suite of HIV and tuberculosis activities in prisons remains limited. So far, no specific policies for prison health, or prison HIV and tuberculosis services are being developed.

17 of Zambia's 87 prisons have internal health clinics. With only 34 health professionals employed (as of January, 2015), these clinics remain poorly staffed and resourced. At the central level, inadequate prison-health financing hampers implementation of health-workforce planning and limits health surveillance and monitoring.

Despite these and other policy barriers, Zambia has made some gains in prison-based HIV and tuberculosis care and treatment. Funded by the TB Reach initiative of the Stop TB Partnership, the Zambia Correctional Service and the national tuberculosis programme in 2011 worked with non-governmental organisations to optimise HIV and tuberculosis detection among detainees, prison staff, and the communities in and around six of the prisons with the heaviest tuberculosis burdens. The same project also reinvigorated efforts to institute routine tuberculosis screening at entry and train a cadre of prison peer educators in several facilities. Under one partner-supported project, testing for tuberculosis with Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) has been introduced in five Zambian prison clinics, along with protocols and training for staff. Concurrently, a second partner project supported the Zambia Correctional Service to form the first 11 prison health committees, comprising both officers and detainees, with a mandate to do facility-based needs assessments, basic service planning, and data collection.

International donor funding for HIV and tuberculosis services within prisons

Estimation of total national funding for prevention and treatment services for HIV and tuberculosis in prisons is complicated by multiple funding sources and frequent lack of transparency in the reporting of funding. Funding can

come from domestic government, NGOs, and international donor sources, and could be channelled through health, justice, or interior ministries, or through NGO interventions. Available data for domestic funding, although sought, were not comprehensive and therefore are not presented. We also sought information about international donor funding from four major funders, which is presented.

Among the Global Fund to Fight AIDS, Tuberculosis and Malaria's grant agreements to 49 sub-Saharan African countries between 2005 and 2015, only 24 included indicators of prison-related HIV or tuberculosis initiatives. Total funding for these activities was less than $100 000 in seven countries; another five countries reported more than $1 000 000 in prison-related funding (table). In 15 countries, less than 5% of the total budget for HIV and tuberculosis programmes was allocated to interventions in prisons.

Planning and budgeting documents for 2007–14 for the 21 sub-Saharan African countries that are part of the US President's Emergency Plan for AIDS Relief included references to HIV or tuberculosis programmes, or both, addressing prisoners in all countries, except South Sudan. The most frequently proposed intervention was HIV testing (16 [80%] of 20 countries). Other frequently proposed programmes mentioning prisons included HIV treatment, technical assistance, and research (11 countries [55%]); tuberculosis case-finding, abstinence, and general education about HIV prevention (eight countries [40%]); programmes for prison staff (six countries [30%]); and tuberculosis treatment (five countries [25%]). With the exception of Ethiopia and Kenya, prison-related funding for HIV and tuberculosis was rarely continuous (data not shown). Many of the interventions in which detainees were mentioned were part of larger programmes targeting most-at-risk populations, making it difficult to determine if—and the extent to which—programme activities actually included prison-specific activities.

Only one prison-related programme supported by the UK Department for International Development was identified: the Evidence for HIV Prevention in Southern Africa project. This initiative provides funding for research into HIV prevention in key populations, including detainees, in sub-Saharan Africa, with two research projects funded in 2015. Although the European Union did not provide information about prison programmes funded in sub-Saharan Africa, experts in the field report two projects funded by them—a 3 year project targeting health-systems strengthening in Zambian prisons, which began in February, 2013, and a multi-year project to build prison-service capacity to protect detainees' human rights in Uganda.[103,104]

A policy, service-delivery, and research agenda for detainee health in sub-Saharan African prisons

Provision of HIV and tuberculosis prevention and care services for detained populations is not only a human right, but also crucial for overall disease prevention and improved population health. To understand and address the gaps in HIV and tuberculosis services in prisons, political will, leadership, operationally relevant research, and long-term funding are needed to enable implementation of crucial programmes. Greater transparency and accountability are also needed to ensure that interventions and reforms are properly implemented and detainee rights are respected.

Reflecting the low political priority of detainees as a group, prison-specific policy guidance and adequate sustained funding for health-service delivery in prisons are absent in many sub-Saharan African countries—an issue that needs to be urgently addressed. Additionally, donors and governments have an obligation to report funding transparently, and should support efforts to track detainee health funding from domestic and international sources to ensure comprehensive coverage of prevention and treatment programmes.

Although specific interventions for HIV and tuberculosis are important, an overall health-systems-strengthening approach is required in prisons to address the pervasive barriers of poor infrastructure, shortages of human resources for health, scarce medical supplies, and inadequate information systems. Specific reforms include the adoption of a harmonised, intersectoral approach to recruitment, supervision, and remuneration of prison health professionals and the inclusion of prisons in quarterly facility-based reviews by community HIV and tuberculosis programmes. Such actions could form the basis for implementation of comprehensive, integrated screening, diagnosis, and treatment services for HIV and tuberculosis—as well as nutrition, substance-use, and mental health services—within a primary care framework, tailored to the prison context, and linked to community services. Services provided by NGOs should also be integrated into, and aligned with, prison and mainstream health systems to promote local ownership and ensure a continuum of care.

Criminal-justice reforms that address policies or practices that limit bail and reduce long delays in access to courts would probably reduce exposure to, and incidence of, disease. Limitation of arbitrary and extended pre-trial detention is a cost-effective criminal justice measure, as are large-scale interventions such as release of people detained for minor, non-violent offences. Interventions such as reformation of bail guidelines, restriction of overly broad police authority to detain so-called co-conspirators with no evidence, expansion of community service and parole programmes, increasing the numbers of judges, and improvement of access to legal representation, could all contribute to the reduction of prison populations in a sustained manner.[39] These interventions would probably reduce the risk of acquiring HIV and tuberculosis and recidivism, facilitate access to care, and ensure respect for international laws requiring prompt access to justice and freedom from pre-trial detention except in exceptional circumstances.

Strengthening of prison health and criminal-justice systems will require engagement by advocacy groups and

civil society to raise attention and apply political pressure for reform. Where improvements in prevention and treatment services have occurred, advocacy or legal action, or both, have frequently been instrumental (eg, Botswana withheld ART from non-citizen detainees until a constitutional court overturned this policy,[105] South Africa expanded HIV and tuberculosis services in prisons in response to legal action).

Optimal prevention and treatment strategies are best implemented when informed by regularly updated epidemiological and programmatic data. These data should inform priority health-service needs, service-implementation strategies, and guidelines within countries. The transparency of these data will enable best practices in the region to be shared. Priority programme and research questions that could guide the evidence-based implementation of services within prisons include sensitive entry and mass-screening algorithms for tuberculosis with universal access to diagnostic testing; the feasibility, uptake, and completion of isoniazid preventive therapy with or without ART and effects on tuberculosis epidemiology; and the burden and causes of mental health and substance-use problems and their association with HIV and tuberculosis epidemiology and clinical outcomes. Additional robust evidence of longitudinal clinical outcomes and linkage to and retention in high-quality treatment services for HIV and tuberculosis for prison populations was notably lacking. Implementation and assessment of new strategies are urgently needed to reinforce a continuum of care for detainees at incarceration, during inter-facility transfer, and after release. Additionally, it is important to understand the differing needs of ethnic minorities, children, migrants, LGBT people, people with disabilities, and people who use drugs in prisons, and to ensure effective and tailored services.

Conclusion

Good-quality data for HIV and tuberculosis in prisons in sub-Saharan Africa are rare; recent (ie, in the past 5 years) research is lacking in more than half the countries, and capacity to determine national estimates or monitor trends is limited. Available data suggest inadequate health services incommensurate with high disease burden. Funding is minimal, and policies guiding service implementation are often missing. Although some promising practices exist, increased political commitment and dedicated resources are needed to ensure universal access to high-quality prevention, treatment, and care of HIV and tuberculosis for detainees in sub-Saharan Africa.

Contributors

All authors contributed to the design of the study. LT, SC, SMT, MEH, CJH, and JJA undertook the searches and case studies, interpreted the findings, and wrote the Series paper. EJS, RZ, and ADH provided data or information for the study. All authors reviewed and edited the final paper.

Declaration of interests

We declare no competing interests.

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The yield of screening symptomatic contacts of multidrug-resistant tuberculosis cases at a tertiary hospital in Addis Ababa, Ethiopia

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Abstract

Background: Early detection and treatment of multidrug-resistant tuberculosis (MDR-TB, resistant to isoniazid and rifampicin) is an urgent global priority. Identifying and tracing close contacts of patients with MDR-TB could be a feasible strategy to achieve this goal. However, there is limited experience with contact tracing among patients with drug-resistant tuberculosis both globally and in Ethiopia. Here we present our findings on the extent of screening symptomatic contacts and its yield in a tertiary hospital in a major urban setting in Ethiopia.

Results: Symptomatic household contacts were identified in 29 (5.7 %) of 508 index cases treated at the hospital. There were a total of 155 family members in the households traced of whom 16 (10 %) had confirmed MDR-TB. At least one confirmed MDR-TB cases was identified in 15 (51.7 %) of the 29 traced households.

Conclusions: Tracing symptomatic contacts of MDR-TB cases could be a high yield strategy for early detection and treatment of MDR-TB cases in the community. The approach should be promoted for wider adoption and dissemination. Larger scale studies should be done to determine its effectiveness and sustainability in similar settings.

Keywords: Contact tracing, MDR-TB, Ethiopia

Background

Multidrug-resistant tuberculosis (MDR-TB, resistant to isoniazid and refampicin) like drug-sensitive tuberculosis (TB) is transmitted through air droplets from infected person and they have a high potential to spread within people who have close contact with infected persons. Close contacts of MDR-TB patients are defined as people living in the same household, or spending long hours a day together with the patient in the same indoor living space. According to the World Health Organization (WHO), the International Union Against Tuberculosis and Lung Disease (IUATLD) and the International Standards of TB Care (ISTC), contacts of patients with multi or extensively drug-resistant TB (MDR/XDR-TB, XDR-TB is MDR-TB and have additional resistance to one of fluoroquinolones and any of the second-line injectables which include kanamycin, amikacin and capreomycin) should be closely followed up to prevent further spread of the bacteria [1, 2]. Close contacts of tuberculosis cases, such as household members, are the most likely to become infected due to intense and/or prolonged exposure to index cases in the weeks to months before diagnosis and treatment initiation [3].

In the absence of molecular epidemiologic data, secondary cases of MDR-TB within a household in an area with increasing incidence of MDR-TB are generally assumed to be the result of within-household transmission [4]. The spread of tuberculosis occurs mainly in settings where prolonged contact between people promotes the transmission from an infectious 'index case' with TB disease to one or several 'contacts'. Contact tracing in general is believed to serve two functions: (1)

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identifies contacts with TB disease so that treatment can be initiated early when disease is more limited—this also serves to reduce transmission and (2) identifies high risk infected contacts who might benefit from either preventive therapy or close observation [5].

As is in many high MDR-TB burden countries, there is little experience with contact tracing of MDR-TB patients in Ethiopia. The main objective of this study was to assess the extent of screening symptomatic contacts in specialized tuberculosis treatment center in Addis Ababa. In this report, we present data on screening symptomatic contacts and its yield at a tertiary TB care center in Addis Ababa. The findings from this study are believed to inform the national MDR-TB treatment implementation plan as well as other similar countries in their effort to roll out MDR-TB treatment services.

Methods

Setting and study design

We conducted this study at St. Peter Tuberculosis Specialized Hospital (SPTSH) from February 2013 to April 2013 in Addis Ababa, Ethiopia. SPTSH was the first hospital to start MDR-TB treatment in 2009. The program was initiated as part of a pilot program with the Green Light Committee (GLC) approval to treat 45 patients. As of November 2012 there were over 508 patients enrolled in the MDR-TB care unit of the hospital [6]. Considering the total treatment period and to see the treatment out-come, we carried out retrospective chart and register review of patients enrolled and treated at SPTSH during the period February 2009–December 2012 to determine the yield and extent of household contact investigation.

Screening contact practice at the hospital

In the hospital, it was a routine work practice to ask all index cases if any household member had respiratory symptoms suggestive of TB. If any symptomatic household members were identified, the index case was encouraged to bring the household member for further evaluation at the hospital. The clinic staff did thorough clinical evaluation of the symptomatic household member including detailed history, physical examination, and laboratory work up as per the national algorithm. Close contacts with no active TB disease were monitored carefully for at least 2 years. In particular, careful and close follow-up was encouraged for infants and children under 5 years of age. Those contacts with no signs and symptoms suggestive of active TB were educated about the signs and symptoms of TB, about their contact with an MDR-TB index case and about the importance of seeking treatment urgently if they develop signs and symptoms of TB disease. Follow up monitoring was done every 1–2 months. For contacts from Addis Ababa and nearby towns, community team members composed of a health officer and a nurse did 1–2 monthly home visits. Those contacts who came from outside Addis Ababa were encouraged to visit the clinic every 1–2 months.

Data collection

We used secondary data abstraction form for data collection. We did data collection at two stages—first for the index cases and then for the contacts. For each index case we used the MDR-TB register as data source. The register contained the following variables: age, gender, marital status, employment status, whether the patient had MDR or XDR-TB, vital status within the last 24 months (as alive or dead), HIV status, and whether contacts were traced/screened. For contacts who were screened, detailed information was recorded in a separate Contact Tracing Form. Data recorded in the Contact Tracing Form included a list of all household members and their age, sex, symptoms, physical findings, HIV status, sputum microscopy, chest X-ray, and actions taken. Two health officers and four nurses who were working at the MDR-TB care unit collected the data by reviewing each patient's chart and register of patient files at the MDR-TB centers. A two-day training was given for all data collectors. Data quality was controlled through continuous supervision by one of the authors (AT) during data collection. All completed data collection forms were examined for completeness and consistency during data management, storage and analysis.

Data entry and analysis

We used EPI-INFO version 3.3.1 and SPSS version 16.0 for data entry and analysis respectively. A descriptive analysis was performed by calculating proportions. The median and inter-quartile- range were calculated to measure variability of quantitative variables. Results were analyzed with the outcome being whether contact tracing was performed. Categorical variables were compared using the χ^2 test. *Odds ratios* (OR) and confidence intervals to 95 % (CI) were calculated as a measure of association. The variables found to have a p value ≤ 0.2 on a bivariate analyses were further analyzed using the logistic regression, step wise technique. A p-value of <0.05 was considered statistically significant.

Ethical considerations

The study was approved by the Institutional Review Board (IRB) of the College of Health Sciences, Addis Ababa University. Following the approval, official letter of co-operation was written to St. Peter TB specialized hospital by the School of Public Health. The ethical committee of St. Peter TB specialized Hospital reviewed the protocol and agreed on the study. Since the study was

conducted through review of medical records, no invasive procedures were involved. To preserve the confidentiality, nurses and health officers working in MDR-TB clinic of the hospital extracted the data from the medical records. Moreover, no personal identifiers were used on data collection form. The recorded data was not accessed by a third person.

Operational definitions

Index case—the initially identified case of MDR-TB.

Contact case—a person who shared the same enclosed living space.

Results

Baseline information

We reviewed the records of 508 index cases. Their median age (interquartile range, IQR) was 27 years (23–35). Over a half (52 %) were men, 54 % were married and 41 % had secondary level of education. Only four (0.8 %) out of 508 index cases had history of previous exposure to confirmed MDR-TB or TB patient and majority of index cases were retreatment patients that received treatment either of first line anti TB drugs of WHO treatment category regimen previously. In the study population, 410 (80.7 %) were HIV negative, ninety eight (19.3 %) of confirmed MDR-TB index cases were also HIV positive, 87 (88.8 %) of whom started ART including four on second line ART regimens (Table 1).

Table 1 Baseline and socio demographic characteristics of index cases, St. Peter TB Specialized Hospital, 2013

Characteristics	Number (n = 508)	%
Age group		
<15	10	2
15–24	162	31.9
25–34	198	39
35–44	70	15.6
45+	59	11.7
Sex		
Female	244	48
Male	264	52
Marital status		
Single	287	56.5
Married	200	39.4
Undocumented	21	4.1
Educational level		
No formal education	44	8.7
Formal education	380	84.7
Undocumented	34	6.7
Exposure to MDR-TB patient		
Yes	4	0.8
No	504	99.2
Events		
Cured	93	18.3
On follow up	321	63.2
Drop	20	3.9
Died	53	10.4
Undocumented	21	4.1
HIV status		
Positive	98	19.3
Negative	410	80.7
Index cases traced		
Yes	29	5.7
No	479	94.3

Characteristics and yield of contacts screened in the household

A symptomatic household contact was identified in 29 of 508 (5.7 %) index cases. Household screening and follow up was undertaken in these 29 symptomatic contacts. At least one confirmed MDR-TB case was identified in 15 of the 29 symptomatic contact traced households. The household contacts of the index cases were identified via the medical records of the index cases and through interviews; symptomatic contacts or family members identified on the screening form and attached with the respective index case file. Of 155 household contacts screened, 16 (10.3 %) were found to have MDR-TB. Of the 16 confirmed cases, 15 had already been started on treatment at the time of chart review; eight have shown improvement, three died, two of them were HIV positive and the outcome of five patients were not documented. The family size in the traced households ranged from 2 to 14. Nine (6 %) of the screened household contacts had previous history of TB treatment and four of the sixteen confirmed MDR-TB contact cases had previous history of TB treatment. From the sixteen confirmed MDR-TB contact cases, 13 (81.25 %) were also diagnosed for pulmonary TB (Table 2).

Factors associated with developing MDR-TB

The number of contacts traced for MDR-TB was too small to identify associated factors. However, we identified some degree of associations on univariate analyses. The odds of developing MDR-TB was five times [OR: 5, 95 % CI: 1.03, 24.279], higher among contacts from Addis Ababa as compared to the odds of contacts from other regional towns. Similarly the odds of developing MDR-TB was five times higher among contacts that received previous TB treatment [OR: 5.3, 95 % CI: 0.86, 32.02] as compared to those who didn't receive previous TB treatment. From the confirmed contacts of MDR-TB, the odds of developing MDR-TB was 0.33 less likely among HIV positive contacts as compared to HIV negative [OR: 0.33,

Table 2 Characteristics of index cases for whom contacts were identified, St. Peter TB Specialized Hospital, 2013

Characteristic	Number (n = 29)	%
Age group		
14–24	16	55.2
25–34	9	31
35–44	3	10.3
45+	1	3.4
Sex		
Female	20	69
Male	9	31
Familial position of the index case		
Mother/father	2	6.9
Sister/brother	12	41.4
Wife/husband	7	24.1
Child	4	13.8
Cousin	4	13.8
Place of living		
Addis Ababa	14	48.3
Out of Addis Ababa	15	51.7
Number of MDR-TB cases per household		
One	14	48.3
Two	12	41.4
Three	3	10.3
Number of symptomatic contacts who developed MDR-TB per household		
One	14	44.8
Two	1	3.4
None	14	44.8

95 % CI: 0.06, 1.74]. Sex of contacts compared on bi varate among contacts confirmed MDR-TB and the odds of female was three times higher compared to the odds of male [OR:3, 95 % CI: 0.58, 15.61].

On multivariate analyses none of the variables found to be statistically significant.

Discussion

In this study, we found a high rate of confirmed MDR-TB cases among symptomatic household contacts of MDR-TB index cases. ONE IN TEN of the family members in the traced households had MDR-TB. The overall rate of contact tracing, however, was low and it focused on the symptomatic ones only. The study suggests that active tracing of symptomatic contacts of index MDR-TB cases could contribute to prompt identification and treatment of MDR-TB cases. This could be a highly effective strategy in saving more lives as well as in cutting the chain of the transmission in the community. Many risk factors for the development of MDR-TB have been reported among contacts. In our study, we considered variables such as place of living, previous history of TB treatment, HIV status, sex, age, number of confirmed MDR-TB in the house, and number of family traced.

As genetic studies were not performed, this study could not ascertain whether or not the source of infection was the index case. However, there is considerable evidence to support human-to-human MDR-TB strain transmission. Indeed over half of global MDR-TB cases are thought to result from primary transmission [7]. Moreover, our finding is similar to findings from a cross sectional study conducted in India among contacts of MDR-TB patients which showed high proportion of MDR-TB cases among contacts of MDR-TB index cases [8].

Although studies have shown that household contacts with TB are likely to have acquired infection independently in high-incidence settings, there are no published estimates of the probability that two household members with multidrug-resistant TB share a similar genotype and are members of the same transmission chain. Molecular epidemiologic data from households with more than one MDR-TB case can help shed light on the transmissibility of highly drug-resistant disease and also help guide public health policy. For example, international guidelines for the management of known contacts of MDR-TB patients recommend an empirical drug regimen based either on the drug-resistance profile of an isolate from the suspected index MDR-TB case-patient or on the most common drug-resistance pattern in the community while drug sensitivity tests are pending [9, 10]. Since this is the first report of the yield of MDR-TB contact investigation from Ethiopia and among few from the developing world, it provides useful information that can serve us input for planning contact investigation at larger scale.

The high rate of MDR-TB cases among traced household contacts suggests the need for improved TB control measures. The data calls for improved infection control measures, implementation of rapid diagnostics, and enhanced active screening strategies. This was suggested by others as well. A cross sectional study conducted in India among contacts of MDR-TB patients, for examples, showed from the total 302 contacts of 58 index MDR-TB patients traced 16 (5.29 %) developed TB and two (0.66 %) had MDR-TB. The study concluded that evaluation of contacts of MDR-TB case may lead to early diagnosis and prevention of tuberculosis [11].

Few studies have examined the burden of active disease in close contacts of MDR-TB patients [12–14]. A Brazilian study reported that the prevalence of TB infection and progression to active TB was comparable in close contacts of MDR-TB and drug-susceptible TB patients, despite the longer duration of exposure of contacts in patients with MDR-TB. Another study by Ottmani S et al. showed high proportion of index case contacts developed

tuberculosis and the authors concluded that performing contact investigation as a routine activity of the national TB programme was feasible and useful in low–middle-income countries [15].

Whether only symptomatic contacts could be screened as a first stage in scaling up contact tracing in low and middle income countries is an possible consideration arising from our study. This would make contact tracing more feasible in resource limited settings given the burden of disease. In the systematic review by Shah et al. 8 % of household MDR-TB contacts were found to have MDR-TB. In our study 10 % of symptomatic contacts had MDR-TB. These figures are comparable but have different entry points as most of the studies included in the systematic review/meta analysis included screening of all MDR-TB contacts, not just those with symptoms. It may be that it is only necessary to screen symptomatic contacts [16].

Earlier diagnosis of MDR-TB remains a significant programmatic objective because of in this setting where close contacts of MDR-TB cases, such as household members, are the most likely to become infected, due to intense and/or prolonged exposure to index cases in the weeks to months before diagnosis and treatment initiation. Our study highlights the high proportion of MDR-TB in household contacts of MDR-TB cases. Dhingra et al. reported a 53.5 % prevalence of TB infection of disease in household contacts in their study group compared to 44 % in the general population [17]. A better understanding of the relative importance of intra household or community transmission may help to inform the choice of empirical regimens [18].

There are several limitations in the study. First, the small sample size of drug-resistant contact cases available for analysis of associated factors and contacts with active TB (only with cough symptom) did not allow for making valid conclusions as to factors associated with MDR-TB among household contacts. Second, data on several determinants for MDR-TB disease were absent from analysis because they were not in the routine registers and charts of the patients. Third, we considered only household contacts and not other casual or close contacts. Fourth, the investigation considered only recorded household contacts, were not able to find each household contact. Finally, the lack of molecular typing data which could help determine whether the drug susceptibility profiles between index and contact cases were from strains with the same genotype or not.

Conclusions

Tracing symptomatic close contacts of MDR-TB cases could be a high yield strategy for early detection and treatment of MDR-TB cases in the community. The approach should be promoted for wider adoption and dissemination. Larger scale studies should be done to determine its effectiveness and sustainability in similar settings.

Authors' contributions

AT carried out the conception and design, or acquisition of data, or analysis and interpretation of data and also drafting the manuscript. DJ reviewed the manuscript for important intellectual content, participated in the design of the study and helped to draft the manuscript. FE reviewed the manuscript for important intellectual content, participated in the design of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical guidelines

Competing interests

The authors declare that they have no competing interest.

Financial competing interests

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NOTES FROM THE FIELD

The role of technical assistance in expanding access to Xpert® MTB/RIF: experience in sub-Saharan Africa

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To improve tuberculosis (TB) diagnosis, many national TB programmes have committed to deploying Xpert® MTB/RIF. Implementation of this relatively new technology has suffered from a lack of comprehensive technical assistance, however, including the formulation of policies and plans to address operational issues. While providing technical assistance, we observed numerous operational challenges in the implementation and scale-up of Xpert in five sub-Saharan African countries: low coverage, poor laboratory infrastructure, limited access, poor linkages to treatment, inadequate data on outcomes, problems with specimen transport, diagnostic algorithms that are not aligned with updated World Health Organization recommendations on target patient groups and financing challenges. We recommend better country preparedness and training, laboratory information and quality systems, supply management and referral mechanisms.

An estimated 9.6 million people worldwide develop tuberculosis (TB) each year, yet only 6.3 million cases are reported and treated.[1,2] Limited availability of sensitive, rapid TB diagnostics impedes case detection for both drug-susceptible and drug-resistant (DR) TB.

In 2010, the World Health Organization (WHO) endorsed the use of Xpert® MTB/RIF (Cepheid, Inc, Sunnyvale, CA, USA), a rapid diagnostic assay that can identify *Mycobacterium tuberculosis* and resistance to rifampicin (RMP).[3] Its availability at lower-level health facilities is an added benefit to improving access to testing. The WHO recommends using Xpert as a primary diagnostic test for adults with suspected DR-TB, for children and adults with human immunodeficiency virus (HIV) with suspected TB in settings with high HIV prevalence, for children with suspected TB and for the detection of extra-pulmonary TB. Resources permitting, Xpert may also be used as an initial diagnostic test for all patients with suspected TB or as a follow-on test to microscopy for adults with smear-negative results. Such an algorithm may require additional screening, using either chest X-ray or further clinical assessment as a pre-test screening tool, to reduce the numbers of individuals to be tested.[4,5]

Globally, the scale-up of Xpert remains the most important change in the TB diagnostics landscape, with over 4.8 million Xpert cartridges procured in the public sector in 116 of the 145 countries eligible for concessional pricing in 2014.[6] Studies have documented the effectiveness of Xpert for detecting *M. tuberculosis* in clinical specimens[7–12] and for detecting RMP resistance.[8] Commentaries, studies and models have presented potential uses and impacts of the test,[4] but few results have been published on the programmatic implementation of large Xpert networks.

Implementers, policy makers and donors need information about real-world implementation. This paper presents the challenges, lessons and recommendations from our experiences in providing technical assistance in five countries.

INTERVENTION

National policy reform and strengthened laboratory capacity are vital for country uptake of new TB diagnostic technologies. The WHO has established a process to rapidly review the evidence base for new TB diagnostics and ensure that new tools meet performance standards. In parallel, the environment in which new diagnostic devices are being implemented is important. All the essential elements of laboratory services must be addressed, including laboratory infrastructure, biosafety measures and maintenance, equipment validation and maintenance, specimen transport and referral mechanisms, management of laboratory commodities and supplies, information and data management systems, quality management systems, strategies and funding for development of laboratory human resources and integration of diagnostic algorithms into laboratory strengthening plans.

To fulfil these requirements, countries must coordinate the support of donors and partners and propose a budget and plan that covers technical assistance needs, the development of a TB laboratory strategic plan—including the roll-out of Xpert—and the coordination of support from donors and partners.

Specific intervention

Management Sciences for Health (Arlington, VA, USA) has provided south-to-south technical assistance for the implementation of Xpert in five sub-Saharan African countries—the Republic of Congo, Eritrea, Ethiopia, Ghana and Kenya—in collaboration with the US Agency for International Development, the African Society of Laboratory Medicine, the WHO and the Global Fund to Fight AIDS, Tuberculosis and Malaria. This assistance has included support to develop scale-up plans, increase awareness of global policy guidance, train hundreds of technicians and clinicians

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KEY WORDS
TB diagnostic technology; Xpert; TB laboratory services; technical assistance; implementation of innovations

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and install 55 Xpert GX4 machines in collaboration with Cepheid between July 2013 and March 2015.

The technical assistance provided to countries included, to varying extents, the following interventions:

- Inform countries about the availability of the WHO checklist to assess the readiness and appropriateness of sites. Recommendations relate to optimising the placement and use of machines, aligning clinicians' case-finding practices to the recommended use of Xpert and supporting supply and specimen referral systems.
- Improve coordination between donors and partners to ensure that the purchase of equipment and reagents is in alignment with a national implementation plan and budget that follows WHO policies.
- Improve the linkage between Xpert test results and the comprehensive management of patients, including confirmatory testing and linkages to care and patient outcomes.

Results from two countries illustrate the direct impact of these interventions: in Kenya, 8221 Xpert tests were conducted during the first quarter of 2015, of which 1830 (22.3%) were positive for *M. tuberculosis* and 81 (4.4%) were RMP-resistant. In Ethiopia, an evaluation after the first year of implementation (July 2013–December 2014) showed a 22% increase in the number of DR-TB cases detected, while total TB cases detected rose from 58 802 to 63 168 (7.5%). The contribution of Xpert to TB case detection was 2% (source: Ethiopia National TB Programme, 2015).

RESULTS

Integration of Xpert as a point-of-care test into national policies

In most countries, Xpert is not used as a point-of-care test, and the status of integration of this novel diagnostic tool into national algorithms varies among countries.

Impact of Xpert on case notification

In all countries, we observed an increased number of bacteriologically confirmed cases. This observation was counterbalanced by an irregular impact on the total number of cases notified. Generally, Xpert allowed more rapid diagnosis for HIV-TB co-infected patients and notification of RMP-resistant cases.

Impact of Xpert on patient care

There were no significant or systematic improvements in the linkage of diagnosed patients to treatment or in terms of mortality. Empirical treatment generally remains the rule, despite the availability of additional information about drug resistance, for example, with Xpert testing. The utilisation of the Xpert machines is at 15% of full capacity overall, representing a missed opportunity to diagnose potential TB and DR-TB cases due to poor referral and transport systems.

Linkages between Xpert assay results and other technologies and treatment are weak. Follow-up cultures and drug susceptibility testing (DST) may not be undertaken, mainly due to a lack of capacity for DST.

LESSONS LEARNT

Although Xpert is a diagnostic device with demonstrated performance in research environments, the literature is equivocal about its impact in programmatic conditions. Impacts on case notification or measurable patient outcomes should be considered the main indicators of success.

To increase the chances of achieving these results, the introduction of Xpert or any novel tool requires not only funding but also technical support for the revision of diagnostic and treatment guidelines. Furthermore, monitoring the progress and constantly evaluating the impact of new policies on indicators such as case detection, programmatic management of DR-TB and integration of TB-HIV activities are essential.

CONCLUSION

Realising the potential of WHO-recommended technologies such as Xpert to reduce the burden of TB depends on the behaviour of patients and providers, access to new tools, and the quality of TB treatment following diagnosis. Any Xpert roll-out strategy must balance the need to accelerate implementation with overall health systems strengthening. To achieve the maximum impact from novel diagnostics, countries should improve the quality of health care, commit the resources needed to develop and implement a strategic plan for laboratory services and involve laboratory experts to guide implementation.

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De nombreux programmes nationaux tuberculose (TB) se sont engagés à déployer le Xpert® MTB/RIF afin d'améliorer le diagnostic de la TB. La mise en oeuvre de cette technique relativement nouvelle a cependant souffert d'un manque d'assistance technique d'ensemble, notamment la formulation de politiques et de plans destinés à prendre en compte les problèmes opérationnels. Lorsque nous avons fourni cette assistance technique, nous avons observé de nombreux défis opérationnels dans la mise en oeuvre et l'expansion du Xpert dans cinq pays d'Afrique sub-saharienne : une faible couverture, une infrastructure de laboratoire limitée, un accès limité, des liens médiocres avec la prise en charge thérapeutique, des données insuffisantes sur les résultats, des problèmes de transport des échantillons, des algorithmes de diagnostic qui ne sont pas en accord avec les dernières recommandations de l'Organisation Mondiale de la Santé relatives aux groupes cibles de patients et des défis financiers. Nous recommandons une meilleure préparation et formation des pays, une information des laboratoires et des systèmes de contrôle de qualité, une gestion des stocks et des mécanismes de référence.

Con el propósito de mejorar el diagnóstico de la tuberculosis, muchos programas nacionales han decidido generalizar la práctica de la prueba Xpert® MTB/RIF. Sin embargo, la introducción de esta técnica relativamente nueva se ha dificultado debido a una falta de asistencia técnica integral, que comprenda la formulación de normas y de planes que aborden los aspectos operativos. Durante la experiencia de prestación de asistencia técnica, se observaron múltiples dificultades operativas en la ejecución y en la ampliación de escala de la técnica Xpert en cinco países de África subsahariana, a saber: la baja cobertura, la insuficiencia de las infraestructuras de laboratorio, el acceso limitado, la escasa vinculación con el tratamiento, la deficiencia de los datos sobre los desenlaces, los problemas relacionados con el transporte de las muestras, los algoritmos diagnósticos que no corresponden a las recomendaciones actualizadas de la Organización Mundial de la Salud en materia de grupos destinatarios de pacientes y las dificultades de financiamiento. Se recomienda procurar una mejor preparación y una mayor capacitación en el país, perfeccionar los sistemas de información y control de calidad de los laboratorios y poner en práctica procedimientos de gestión de los suministros y mecanismos de remisión.

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RESEARCH ARTICLE Open Access

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

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Abstract

Background: One of the main goals of the post-2015 global tuberculosis (TB) strategy is that no families affected by TB face catastrophic costs. We revised an existing TB patient cost measurement tool to specifically also measure multi-drug resistant (MDR) TB patients' costs and applied it in Ethiopia, Indonesia and Kazakhstan.

Methods: Through structured interviews with TB and MDR-TB patients in different stages of treatment, we collected data on the direct (out of pocket) and indirect (loss of income) costs of patients and their families related to the diagnosis and treatment of TB and MDR-TB. Direct costs included costs for hospitalization, follow-up tests, transport costs for health care visits, and food supplements. Calculation of indirect costs was based on time needed for diagnosis and treatment. Costs were extrapolated over the patient's total treatment phase.

Results: In total 406 MDR-TB patients and 197 other TB patients were included in the survey: 169 MDR-TB patients and 25 other TB patients in Ethiopia; 143 MDR-TB patients and 118 TB patients in Indonesia; and 94 MDR-TB patients and 54 other TB patients in Kazakhstan. Total costs for diagnosis and current treatment episode for TB patients were estimated to be USD 260 in Ethiopia, USD 169 in Indonesia, and USD 929 in Kazakhstan, compared to USD 1838, USD 2342, and USD 3125 for MDR-TB patients, respectively. These costs represented 0.82–4.6 months of pre-treatment household income for TB patients and 9.3–24.9 months for MDR-TB patients. Importantly, 38–92 % reported income loss and 26–76 % of TB patients lost their jobs due to (MDR) TB illness, further aggravating the financial burden.

Conclusions: The financial burden of MDR-TB is alarming, although all TB patients experienced substantial socioeconomic impact of the disease. If the patient is the breadwinner of the family, the combination of lost income and extra costs is generally catastrophic. Therefore, it should be a priority of the government to relieve the financial burden based on the cost mitigation options identified.

Keywords: Tuberculosis, Multi-drug resistance, Patient costs, Cross-sectional survey, Ethiopia, Indonesia, Kazakhstan

Abbreviations: AHRI, Armauer Hansen Research Institute; CSO, Civil society organization; DOT, Directly observed therapy (for (MDR)TB); HIDN, Office of Health Infectious Disease and Nutrition; IQR, Interquartile range; MDR, Multi-drug resistance (i.e. resistance to rifampicin and isoniazid); NGO, Non-governmental organizations; NTP, National Tuberculosis Program; TB, Tuberculosis; TORG, Tuberculosis Operational Research Group; USAID, United States Agency for International Development; USD, United States dollar; WHO, World Health Organization

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Background

One of the main goals of the post-2015 global tuberculosis (TB) strategy is that no families affected by TB face catastrophic costs [1]. There is no universal definition of catastrophic costs and a threshold for TB-related catastrophic costs still needs to be defined [2]. Although drugs for TB treatment are free in most high TB-burden countries, TB patients face costs due to charges for related health services, costs for transport, accommodation, nutrition and suffer lost income. A recent systematic review showed that the financial burden of both diagnosis and treatment was high and varied widely across settings, the total costs amounting to 58 % (range 5–306 %) of annual patient income [2]. These costs are expected to be higher for patients with multidrug resistant (MDR) TB than for other TB patients given the three to four times' longer treatment period. Although there is a paucity of data, the data at hand indicate that, during treatment, patients with MDR-TB face 5–20 times higher costs than patients with drug-susceptible TB, due to relocation costs and longer pre-diagnosis and treatment periods involving more visits and procedures and inability to work [3, 4]. Patients who cannot afford to start or continue treatment will suffer from more extensive morbidity [5]. This may result in higher health system costs, and is likely to result in continued transmission [6].

Policy makers need to understand patient costs to assess how many families face catastrophic costs, to identify the main cost components in TB diagnosis and treatment that lead to catastrophic costs, to develop mitigation policies and to identify and tackle bottlenecks in access to and continuation of TB and MDR-TB treatment. Thus, measurement of financial burden and the main cost drivers for TB and MDR-TB diagnosis and treatment is needed. We conducted such a survey in three different settings; in Ethiopia, Indonesia, and Kazakhstan. We adapted a previously developed tool to estimate TB patients' costs that has been implemented in several countries. That work had a positive impact resulting in improvements in access, nutrition support, adoption of a shorter treatment regimes, and the inclusion of TB services under insurance [7–9]. However, this tool was not meant to include both TB and MDR-TB patients and compare costs between both patient groups. The tool was, therefore, adapted for inclusion of MDR-TB patients' costs to determine the main cost drivers for TB and MDR-TB diagnosis and treatment. The results observed in the three study countries were presented and discussed in in-country workshops for policy makers, focusing on ways to relieve the financial burden of diagnosis and treatment for TB and MDR-TB patients. The results from the surveys in Ethiopia, Indonesia, and Kazakhstan are described here together with identified mitigation strategies.

Methods

Study design

We conducted a cross-sectional survey in six public hospitals (and their satellite clinics) providing TB and MDR-TB (from now on referred to as (MDR)TB) services in Ethiopia, Indonesia, and Kazakhstan. These three countries were selected purposefully as to have representation from three different settings: one in Africa, one in South-Asia and one in Central Asia. Details on methods and results per country are available in the individual country reports and a summary report [10–13].

The (MDR)TB patients were interviewed once, at the health facility. In Ethiopia patients were interviewed at all three MDR-TB hospitals (St. Peters and ALERT in Addis Ababa and University of Gondar Hospital in Gondar). In Indonesia patients were interviewed at two MDR-TB referral hospitals on Java Island (Persahabatan hospital in Jakarta and Dr Moewardi hospital in Solo) and five satellite sites. In Kazakhstan patients were interviewed at one MDR-TB hospital caring for MDR-TB patients from Akmola oblast and its satellite sites providing directly observed therapy (DOT) for (MDR)TB patients in Kokshetau city.

The previous version of the questionnaire [7] was used as the basis for a new generic questionnaire. It was shortened to exclude questions not informative with respect to TB costs (on delays in health seeking behavior, on additional costs for other illnesses, and on impact of disease on social life). Included were some questions expected to be applicable mostly for MDR-TB patients; on adverse effects of treatment and related costs, relocation costs, and on receiving incentives and enablers (e.g. transport or food vouchers).

We did not aim to collect longitudinal data of patients covering the full pathway of diagnosis and treatment, since this would make data collection a lengthy and complicated undertaking when done prospectively. Retrospective data collection over a prolonged period of time would yield unreliable results [9], especially for MDR-TB patients, probably leading to underestimation of costs. To get insight in costs of the different phases of diagnosis and treatment of (MDR) TB, we included patients in different phases of treatment.

Study population

We categorized and selected patients from five groups of TB and MDR-TB patients, representing different phases of diagnosis and treatment:

1. TB patients who completed at least 1 month of treatment and were within last month of the intensive phase of drug-susceptible TB treatment;

2. TB patients who started at least 3 months previously with the continuation phase of drug-susceptible TB treatment;
3. Patients diagnosed with MDR-TB within the month before the interview;
4. MDR-TB patients who started at least 3 months previously with the intensive phase of MDR-TB treatment;
5. MDR-TB patients who started at least 3 months previously with the continuation phase of MDR-TB treatment.

We excluded patients not consenting to the study, those not able to answer the questions in the interview, and those younger than 21 years of age since most of those below the age of 21 are not economically independent and still mainly live on their parent's earnings. Also, we excluded patients who died or transferred out while on treatment because of logistic difficulties of reaching them or family members for reliable information. In Indonesia, bedridden patients were also excluded as these could not be interviewed in a private environment. In Kazakhstan, two additional exclusion criteria were applied: 1. patients diagnosed by Xpert MTB/RIF were excluded as this diagnostic tool only very recently had been introduced and only small numbers of patients had been diagnosed with it, and 2. patients who receive home-based care, as they are a small group with very distinct costs compared to other patients.

Sampling

We aimed to include 50 patients per group in each of the three countries. We applied consecutive sampling, inviting all patients coming to the included health facilities to participate in the study until the target sample size was reached or until the end of the study period, whichever came first.

Data collection

Structured interviews were conducted by trained interviewers with (MDR)TB patients in different stages of treatment. Eligible patients were invited to participate in the interview by the doctor or nurse they were seeing during their scheduled visit to the health care facility. After this visit, those patients wishing to participate in the study were sent to a separate room where they were interviewed by the study staff, i.e. not involved in the patients' care. Before the start of the interview, written informed consent was obtained. Through a structured questionnaire we collected data on costs related to the diagnosis and treatment of (MDR)TB patients, as well as background information of the patients (age, sex, treatment type and phase, socio-economic status, ethnicity and distance to health facilities). To minimize recall bias [9], we restricted collection of most cost data to the last 3 months; but major coping costs were not restricted to this period.

In each country, the structured questionnaire was translated from English to the local language, adapted to the local context for some questions (e.g. insurance types, type of health care facility, reimbursement schemes), and translated back into English by another individual to check for translation and interpretation errors. The questionnaire was pretested to check for clarity on 3–5 patients per country before it was finalized. Face-to-face interviews were conducted in March 2013 (Ethiopia), February-March 2013 (Indonesia), and September-October 2012 (Kazakhstan) at the selected health care facilities. The questionnaire included cross-checks and the interviewers were trained to double-check unusually high costs when reported by the patients. Data on costs were collected in the local currency.

Data analysis

For each country, data were entered in a separate pre-designed data entry file (Microsoft Excel for Ethiopia; EpiData (www.epidata.dk) for Indonesia and Kazakhstan) and analyzed (Microsoft Excel for Ethiopia; STATA/SE 11.1 for Windows (Stata Corp., College Station, Texas, USA) for Indonesia, SPSS v20 IBM, New York, USA) for Kazakhstan).

We calculated costs of getting a (MDR)TB diagnosis, costs of treatment (in the intensive and continuation phase of (MDR)TB treatment) and financial values involved in coping as explained below and summarized in Table 1.

Costs for (MDR) TB diagnosis

Costs were obtained per diagnostic visit. Direct costs included all out-of-pocket payments that the patient had to make, such as paying administration fees, paying for laboratory tests, X-ray, and drugs, for food and accommodation, and for transportation to and from the hospital. Direct costs were summed up per cost item over all visits, after which the sums of the cost items were summed up in a total of direct costs per patient. Indirect costs (loss of income) were calculated by multiplying the total number of minutes spent on diagnostic visits with the patient's income per minute before diagnosis of TB.

Costs for (MDR) TB treatment

Cost items for (MDR) TB treatment included costs made because of taking or picking up drugs at the clinic, costs for follow-up tests, supplements, hospitalization, and treatment of adverse events. Costs for taking or picking up drugs were reported for a typical visit to take or pick up drugs. To get the total costs per month, individual cost items per visit were summed up and the total costs per month were calculated by multiplying these costs with the number of times per week that drugs were taken/picked up and the number

Table 1 Methods used to estimate different types of costs for TB diagnosis and treatment

Type of cost	Elements included in cost type	Methods used to calculate costs
Diagnostic (for those in intensive phase)	Food, travel, accommodation, medical costs, and loss of income during visits	Summed direct and indirect costs of visits
		Indirect costs (income loss) as calculated from total time spent x income/time
Treatment (excluding for those just diagnosed with MDR-TB)	DOT and drug collection visits, follow-up tests, food, travel, treatment of adverse events[a], supplements[b], hospitalization[c], and loss of income	Summed direct and indirect costs, multiplied by number visits/week, weeks/ month, and internationally defined duration of treatment phase
		Indirect costs (income loss) for DOT as calculated from total time spent x income/time
Other Costs	Direct and indirect costs of accompanying persons/attendants	Summed costs related to diagnosis or treatment visits
Coping strategies	Amount borrowed, assets sold	Summed costs

[a]Assuming that all costs for these elements had been made before the time of the interview (hence, costs were not extrapolated to the treatment phase)
[b]Summed direct costs over last month *x* internationally defined duration of treatment phase
[c]In Ethiopia and Indonesia: costs reported up until time of interview. For Kazakhstan, summed direct costs over last month *x* internationally defined duration of treatment phase; summed indirect costs (income loss) for hospitalization as calculated based on internationally defined duration of intensive phase *x* income/time

of weeks per month (4.3). Indirect costs were calculated by multiplying the turn-around-time in minutes for a typical visit with the number of times per week that drugs were taken/picked up, the patients' income per minute, and 4.3 weeks per month. These monthly costs were subsequently extrapolated over the complete treatment phase using the internationally defined durations of the different treatment phases: 2 months of intensive phase and 4 months of continuation phase for new TB patients, 3 and 5 months for retreatment patients and 8 and 12 months for MDR-TB patients [14, 15]. If patient had been longer in their treatment phase at the time of the interview, we assumed they were in the last month of the respective phase during the interview. The main outcomes therefore were total costs incurred by the patient during the phase (intensive or continuation) of treatment they were in.

Costs for follow-up tests were reported from the start of TB treatment till the interview. Since it was assumed that in a typical TB treatment phase, only one or two follow-up tests would be needed, no extrapolation was applied to obtain the costs per treatment phase for patients being treated with TB regimens. To calculate the costs per treatment phase for MDR TB patients, the total costs were multiplied by the internationally defined duration of the treatment phase of the patient, divided by the number of months that the patient had been in that treatment phase.

Costs for supplements were reported over the past month. To obtain the total cost per month, individual cost items were summed up and extrapolated to the total treatment phase. We considered adverse events needing treatment unlikely to occur and did not apply extrapolation of the costs reported to the complete treatment phase.

In Ethiopia and Indonesia most TB and MDR-TB patients are not hospitalized, unless cases are severe or experience serious side effects from treatment. In these two countries we therefore assumed that hospitalization did not occur after the interview and we did not extrapolate the costs of hospitalization to the complete treatment phase. In Kazakhstan however, most patients are hospitalized during the full intensive phase of treatment. As patients are not able to work when hospitalized, loss of income in Kazakhstan was calculated assuming hospitalization for the duration of the intensive phase.

Coping costs

Coping with the financial impact of TB treatment involves multiple strategies, such as borrowing money, asking for donations from family and friends, using savings, selling assets costs and cutting down other expenses. We asked patients for the financial impact of their disease on their family and the coping strategies used. Costs were defined as loss of household income after TB diagnosis (indirect costs), amounts borrowed, and market value of assets sold (both defined as direct costs). We did not extrapolate any of these costs since reduction in household income was reported as monthly reduction in income and it remained unknown when the income had changed. Besides, we assumed that borrowing money and selling assets were one-off actions.

Since the distributions of almost all costs were highly skewed towards higher values, we chose to present median values with 25th and 75th percentiles (also called the interquartile range (IQR)). The total financial value for coping strategies reported by the patient was calculated.

We converted all costs into US Dollar using the average daily midpoint exchange rate over the data collection period [16]. Over this period, the average exchange rates for 1 USD were 18.60 Ethiopian Birr, 9689.86 Indonesian Rupiah, and 148.35 Kazakh Tenge.

Results

In total 197 TB patients and 406 MDR-TB patients participated in the three countries: 25 TB patients and 169 MDR-

TB patients in Ethiopia; 118 TB patients and 143 MDR-TB patients in Indonesia; plus 54 TB patients and 94 MDR-TB patients in Kazakhstan (Table 2). In Ethiopia, the time period allocated for data collection turned out to be too short and it was decided to focus on reaching the targets for the number of MDR-TB patients. In Kazakhstan, the number of eligible TB patients treated at the selected healthcare facilities was below 50 during the period of data collection. In all three countries, the majority of patients were pulmonary sputum smear positive patients.

The median (IQR) number of visits needed for a TB diagnosis was three (2–5) in Ethiopia, three (2–4) in Indonesia, and two (2–3) in Kazakhstan. For Ethiopia, the number of respondents on TB diagnosis was small, and four out of five were from Gondar with a large and remote catchment area. The median time spent per visit for those patients was 43 h for a total median time spent for diagnostic visits of 144 h. The median (IQR) total time in minutes needed for diagnostic visits was 355 (130–600) in Indonesia and 120 (78–273) in Kazakhstan.

TB illness related costs

The median costs (with IQR) for patients in the three countries are shown in Table 3. Costs are separated for diagnostic and treatment expenditure. Also, we show direct (out of pocket) and indirect (foregone income) costs separately. The median estimated total costs for diagnosis and treatment during the current TB treatment episode was USD 260 in Ethiopia, USD 169 in Indonesia, and USD 929 in Kazakhstan, respectively. The median estimated costs for MDR-TB patients were 7.1, 13.9 and 3.4 times higher: USD 1838 in Ethiopia, USD 2342 in Indonesia, and USD 3125 in Kazakhstan, respectively.

Treatment costs were much higher than diagnostic costs in all countries, both for TB and for MDR-TB patients, with median diagnostic costs ranging between USD 9 and USD 75 (Table 3). In Ethiopia and Indonesia but not in Kazakhstan, direct costs for treatment where higher than indirect costs related to treatment. In Kazakhstan, estimated indirect costs were high because of hospitalization in the intensive phase.

Table 2 Patient characteristics

	Ethiopia		Indonesia		Kazakhstan	
	n	(%)	*n*	(%)	*n*	(%)
Patient group						
Intensive phase of standard (re)treatment regimen	12	(6.2)	62	(23.8)	41	(27.3)
Continuation phase of standard (re)treatment regimen	13	(6.7)	56	(21.5)	13	(8.7)
Just diagnosed with MDR-TB	21	(10.8)	29	(11.1)	2	(1.3)
Intensive phase of MDR-TB treatment	85	(43.8)	55	(21.1)	62	(41.3)
Continuation phase of MDR-TB treatment	63	(32.5)	59	(22.6)	32	(21.3)
Type of TB						
Pulmonary smear positive	176	(91.2)	166	(63.6)	121	(80.7)
Pulmonary smear negative	4	(2.1)	72	(27.6)	27	(18.0)
Extrapulmonary	13	(6.7)	16	(6.1)	2	(1.3)
No information	1	(0.5)	7	(2.7)	0	(0.0)
Gender						
Male	107	(55.2)	138	(52.9)	100	(66.7)
Female	87	(44.8)	120	(46.0)	50	(33.3)
No information			3	(1.2)		
Age (years)						
21–29	110	(56.7)	62	(23.8)	47	(31.3)
30–39	49	(25.3)	71	(27.2)	43	(28.7)
40–49	20	(10.3)	66	(25.3)	42	(28.0)
50+	15	(7.7)	61	(23.4)	18	(12.0)
No information			1	(0.4)		
HIV						
Positive	41	(21.1)	8	(3.1)	0	(0.0)
Negative	146	(75.3)	128	(49.0)	150	(100)
not tested/unknown	7	(3.6)	125	(47.9)	0	(0.0)

Table 3 Summary table on median costs (interquartile ranges) in US dollars for TB and MDR-TB patients in the three study countries, related to costs for diagnosis, and treatment in the intensive phase and continuation phase

	TB			MDR-TB		
	Ethiopia	Indonesia	Kazakhstan	Ethiopia	Indonesia	Kazakhstan
Direct pre(diagnosis) costs (costs in last 3 months)	14 (4–109)	33 (9–64)	5 (1–13)	68 (35–191)	39 (12–63)	N.A.[b]
Indirect pre(diagnosis) costs (costs in last 3 months)	0 (0–30)	4 (0–9)	3 (1–5)	0 (0–8)	3 (1–6)	N.A.[b]
Total pre(diagnosis) costs (costs in last 3 months)	14 (6–129)	35 (16–69)	9 (4–19)	75 (40–191)	46 (16–82)	N.A.[b]
Direct treatment costs						
Subtotal for intensive phase	104 (10–231)	41 (8–108)	0 (0–74)	639 (259–968)	596 (342–1035)	165 (0–541)
Subtotal for continuation phase	80 (34–156)	59 (17–224)	179 (90–328)	634 (458–1048)	976 (558–1584)	754 (344–2022)
Indirect treatment costs						
Intensive phase	0 (0–34)	10 (0–40)	404 (303–674)	220 (89–374)	315 (153–848)	1537 (0–2696)
Continuation phase	0 (0–4)	9 (0–57)	104 (70–159)	73 (1–375)	254 (0–504)	227 (0–300)
Total treatment costs						
Intensive phase	119 (19–260)	52 (17–134)	607 (317–809)	831 (462–1525)	1079 (600–2299)	1914 (175–3370)
Continuation phase	128 (34–177)	82 (26–286)	319 (236–702)	931 (494–1296	1227 (730–1846)	1202 (657–2245)
Total (pre)diagnosis and treatment costs[a]	260	169	929	1838	2342	3125

[a]Sums are based on adding up medians from different groups of patients, and therefore must be interpreted with caution
[b]Not available as only two patients were interviewed with a diagnosis of MDR-TB in the last month

The main cost components related to (MDR) TB diagnosis and treatment varied between countries.

In Ethiopia the highest cost element in the diagnostic phase was for food expenditure and for food supplements during treatment, both for TB and MDR-TB patients. In Indonesia the largest cost share during diagnosis was for travel and food for TB patients, and for laboratory tests and administration fees for MDR-TB patients. For both TB and MDR-TB patients, travel expenditure was the highest cost element during treatment. In Kazakhstan, transport expenditure was responsible for most costs during diagnosis, and indirect costs of hospitalization and direct costs related to food supplements and travel for DOT visits during treatment.

Socio-economic impact of TB illness related costs

Table 4 shows the main indicators of the socioeconomic impact of MDR-TB disease in the three countries. Most patients reported income loss due to TB illness, ranging from 33 % of TB patients in Ethiopia to 100 % for MDR-TB patients in Kazakhstan (where no outpatient treatment during the intensive phase was available at the time of the data collection). The median value of this reduction in income was 100 % except for TB patients in Indonesia 25 %). A highly varying proportion of patients received assistance, ranging from 17 % of TB patients in Kazakhstan to 73 % of MDR-TB patients in Ethiopia. However, in all countries the amount of financial assistance received in general was low, including through health insurance. The proportion of patients who sold property or took out loans to cope with TB related costs, was especially high in Ethiopia: 56 % of TB patients and 41 % of MDR-TB patients took out loans.

Figure 1 shows patient and household income before TB illness and at the time of interview. Mean incomes were much higher than median incomes, especially in Indonesia and to a lesser extent in Ethiopia, representing the highly skewed distributions with a few patients have relatively much higher incomes than the rest.

In Ethiopia the median TB and MDR-TB patient income fell from USD 43 and USD 54 to before TB illness, respectively, to zero at the time of the interview. The fast majority (88 % of TB patients and 76 % of MDR-TB patients) did not have any income after (MDR) TB diagnosis, compared to 8 and 14 % before (MDR)TB diagnosis. The median monthly household income of TB patients dropped by 50 % (from USD 75 to USD 38), and by 33 % (from USD 81 to USD 54, respectively). Although many patients were primary income earners before TB diagnosis, household members started to work more to compensate for lost income. The total costs of TB and MDR-TB diagnosis and treatment equaled 4.6 and 24.9 months of pre-diagnosis household income.

In Indonesia, the median TB and MDR-TB patient income dropped from 134 and 103, respectively, to zero. The proportion of TB patients with no formal income increased from 29 % before diagnosis to 52 % at the time of the interview, and from 22 to 74 % for MDR-TB patients. The median household income dropped by 10 % (from USD 206 to 186) and 40 % (from USD 206 to

Table 4 The main indicators of financial impact of TB illness experienced by the (MDR) TB patients in the three countries

	Ethiopia		Indonesia		Kazakhstan	
	TB	MDR-TB	TB	MDR-TB	TB	MDR-TB
Patients who were primary income earner before TB illness	N.A.[b]	N.A.[b]	44 %	24 %	61 %	53 %
Patients who lost their job	76 %	72 %	26 %	53 %	31 %	41 %
% of patients reporting income loss due to TB	92 %	79 %	38 %	70 %	67 %	56 %
% reduction in median income *(for those reporting an income change)*	100 %	100 %	25 %	100 %	100 %	100 %
Patients hospitalized for TB	36 %	82 %	33 %	62 %	98 %	100 %
median duration of hospitalization (days)[a]	40	80	7.5	10	90	195
Patients who received assistance from government or other organizations	24 %	73 %	22 %	34 %	17 %	27 %
median value of assistance in last 3 months (USD)[c]	76	33	0	41	88	31
Coping costs						
patients who sold property	24 %	38 %	3 %	21 %	0 %	1 %
patients who took out loans	56 %	41 %	9 %	27 %	0 %	4 %
patients who received donations from family/friends	N.A.	N.A.	32 %	43 %	57 %	66 %
Patients with health insurance	0 %	1 %	22 %	25 %	0 %	1 %
Of those, patients who received reimbursements	0 %	0 %	N.A.[d]	N.A.[d]	0 %	0 %

[a]For those patients in hospitalized at time of interview, assuming hospitalization for patients during standard duration of intensive phase
[b]Not available as this question was taken out of the locally used questionnaire
[c]For Ethiopia and Kazakhstan, this includes the value of vouchers; for Indonesia it only includes cash assistance
[d]In principle, insured patients receive specified services for free. However, not all services provided are necessarily included

124), respectively. The total costs of TB and MDR-TB diagnosis and treatment equaled 0.82 and 11.4 months of pre-diagnosis household income.

In Kazakhstan, the median TB and MDR-TB patient income dropped from USD 236 and 202 USD to zero, respectively. Fifty-nine percent and 67 % of TB and MDR-TB patients, respectively, did not have any income at the time of interview, compared to 13 and 36 % before diagnosis. The median household income of TB and MDR-TB patients dropped by 20 % (from 708 to 566 USD), and 31 % (from 489 to 337 USD), respectively. As in Ethiopia, many patients were primary income earners before TB diagnosis, and household members started to work more to compensate for lost income. In Kazakhstan, the median household income dropped by 31 % both among TB and MDR-TB patients, and the total costs of TB and MDR-TB treatment equaled 2.8 and 9.3 months of median pre-diagnosis household income.

Mitigation policy options

Policy options for mitigating patient costs due to (MDR) TB were listed during national workshops with participants representing different Ministries, Universities, hospitals, non-governmental organizations (NGOs), civil society organizations (CSOs), and patients. Options related to TB service improvements prioritized in all three countries were 1) to ensure that the policy of free care for all (MDR) TB services is fully implemented and 2) that services are brought closer to patients, followed by social service improvements related to 3) inclusion of direct (transport, food support) costs in social support schemes provided through TB services, 4) inclusion of indirect (sick leave allowance) costs in social protection schemes, and 5) improvements of employment protection. Note that these recommendations are not mutually exclusive – to improve the situation of especially MDR-TB patients, it may be necessary to apply more than one strategy at the same time.

Discussion

The findings from all three countries showed that, although MDR-TB diagnosis and treatment services are supposed to be free for patients, patients have other direct and indirect costs and the financial impact was significant for most patients. For most respondents, direct and indirect costs increased while income decreased. The estimated costs of MDR-TB patient diagnosis and treatment were 3.4–13.9 times greater than those for other TB patients, mainly due to the longer time period for treatment. Aggravating this situation, MDR-TB patients more often lost their jobs.

We probably underestimated direct and indirect costs in our study. Firstly, costs for the pre-diagnosis period may have been underestimated as patients may spend a long time getting an accurate diagnosis, making full recall difficult. Secondly, for some patients treatment duration may be prolonged, e.g. due to missed doses during TB treatment or lack of culture conversion during the intensive phase of

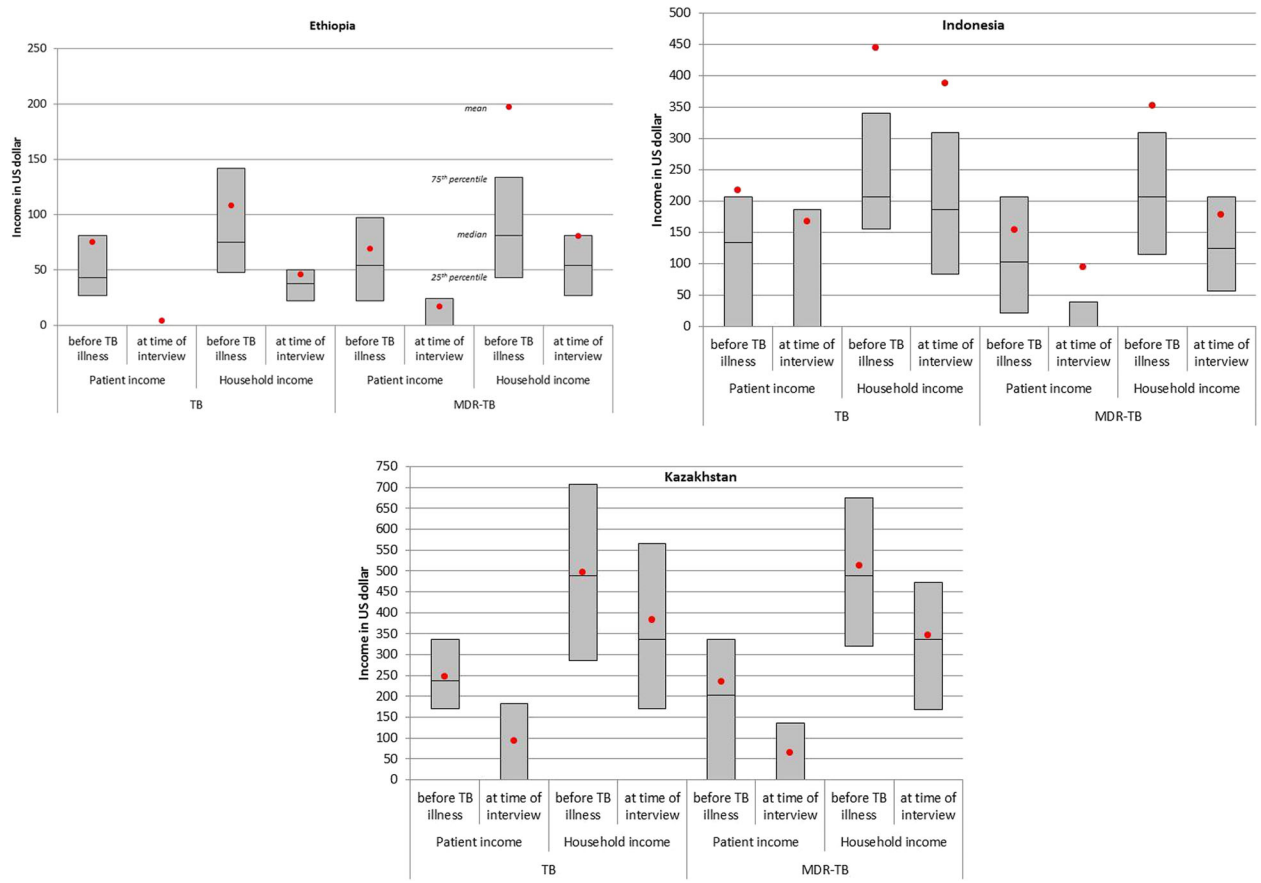

Fig. 1 Box plots showing mean, median and interquartile range of patient and household income before TB illness and at the time of the interview, stratified for TB and MDR-TB patients. Plots are provided separately for patients interviewed in Ethiopia, Indonesia and Kazakhstan. Note the different y-axis scales used. Whiskers are not included as distributions are highly skewed to high incomes, with some patients and household having an income far above the 75th percentile

MDR-TB treatment. Thirdly, we only included costs of the current treatment episode while especially MDR-TB patients may have been treated previously. Fourthly, indirect costs presented here do not include costs after the end of treatment, especially further loss of income for those who have lost their jobs or who have developed disabilities not allowing them to do the work they did before. Fifthly, loss of income was estimated only as a result of time spent obtaining diagnosis and for getting treatment. In reality, some patients may not work at all because they are not feeling well, because they lost their job, or because they are not allowed to work (i.e. in Kazakhstan). This may be the reason why we found a smaller proportion of costs incurred before TB diagnosis than the 50 % estimated in a recent systematic review [2]. That is why the updated version of the questionnaire –currently applied in several countries under leadership of WHO- also collects information on time off work. Of note, we did not discount financial assistance that patients had received. Although a substantial proportion of patients did report to receive financial assistance from the government or other organizations, the majority of patients received only incident and little to no actual reimbursements. So this would far from compensate patients' actual costs including reduced income.

This study has several other limitations. Most importantly, due to limitations in time and budget, only patients being under care at health facilities were interviewed. It was not feasible to conduct interviews to collect data from people who did not attend a facility during the period of the study. Such people may have been too poor to seek diagnosis and treatment. Among those who initiated treatment, some stopped treatment – an unknown proportion because of associated costs - or died during treatment – the impact on family income would be greatest for those households. Therefore, the study population may have been biased against the less socio-economically vulnerable groups [17]. Globally, 16 % of MDR TB patients are lost to follow-up and another 16 % die during treatment [18]. Their families lose the income of the deceased household member. A substantial but unknown proportion of patients die before accessing appropriate diagnosis and treatment.

A consequence of our study design is that we did not collect total costs of (MDR) TB treatment per patient – which would have required longitudinal follow-up - but instead extrapolated costs per stage and to the total (MDR) TB episode. Also, the study was limited to a few public health facilities in Indonesia and Kazakhstan – all three MDR-TB treatment centers in Ethiopia were included - and thus, rather than providing an estimate of the costs incurred by the average (MDR) TB patient in those countries, it does give insight into the major cost components and it provides an idea of the financial burden that a free public health program poses on its patients.

Although many patients were primary income earners before TB diagnosis in Indonesia and Kazakhstan (results not available for Ethiopia), household members started to work more to compensate for lost income. Less MDR-TB than TB patients were primary income earners and on average they earned less than TB patients; this may be explained by the fact that most already were being treated for TB at the time of MDR diagnosis.

Transport costs to reach the DOT facility may be small, but may add up to a substantial amount if made every day during ambulatory treatment. For some patients, these costs can be brought down by bringing DOT facilities closer to the patients' homes. It is important that the facility staff or community health workers do have sufficient expertise to manage MDR-TB patients, including those needed to recognize treatment failure and adverse drug reactions at an early stage to ensure patients can access clinical services when necessary and will not stop treatment [16]. Several reviews concluded that ambulatory and community-based MDR-TB models of care are equally or more effective than hospital-based models in treatment outcomes and may be more cost-effective 19–23]. However, even community-based treatment models may face high proportions of patients lost to follow-up [24] and economic support may still be required [25].

Only a few studies collected patient cost data specifically both for TB and MDR-TB patients and numbers of patients usually were small [2]. In Ecuador, average patient costs were estimated at USD 960 among 104 TB patients compared to USD 6880 for 14 MDR-TB patients [4]. In Cambodia, total household costs for eight MDR-TB patients was USD 1525 compared to USD 477 for 261 HIV-negative TB patients and USD 555 for eight HIV-positive TB patients [26]. Only in Brazil, patient costs were not very different for MDR-TB patients, although health service costs were 37 times higher: total household costs were estimated to be USD 266 for new TB patients compared to USD 333 for MDR-TB patients [27]. In the Dominican Republic, 20 out of 198 TB patients had MDR-TB. Total costs were estimated at UDS 3557 for MDR-TB patients compared to USD 908 for new patients [8]. Our study confirmed previous findings that in general MDR-TB patients face much higher costs than other TB patients as a result of longer duration of treatment, more adverse drug reactions due to the more toxic drugs used in MDR-TB treatment, and related need for (additional) hospitalization.

Policy implications

The recommendations we made were similar to the ones based on studies with the previous version of the questionnaire, not specifically including MDR-TB patients [7]: bringing services closer to patients, reducing expenditures on transport and invested time, increasing efforts to find cases early to reduce indirect costs related to inability to work, informing health care workers and the public about TB diagnosis and treatment to reduce costs unrelated to TB, and including TB-related out-patient costs in social protection schemes (Table 5 and Table 6 in Appendix). Indonesia is rapidly expanding the number of satellite sites. All three countries are moving towards outpatient care, with expansion of DOT services in primary health care services. This study shows the importance of using freed up resources from hospital-based care to support patients during treatment.

Based on results from the previous version of the tool, several countries took action to implement one or more of the identified solutions for TB patients [7]. For example, policy makers in Ghana agreed to include TB care interventions as part of its pro-poor strategies in the delivery of health care and nutrition guidelines were developed to address the specific needs of TB patients. Given the identified high burden for female TB patients in Ghana, the national tuberculosis program (NTP) focused on addressing gender-sensitive challenges of poor TB patients. Also the insurance coverage for all TB patients was increased to also cover health-related costs other than anti-tuberculosis treatment. In Vietnam, the NTP decided to increase the involvement of the private sector in public-private-mix projects focusing on reducing travel, accommodation and hospitalization costs for TB patients and guardians. Also, the NTP worked on the expansion of its NTP network to provide TB services at more public and private hospitals. In the Dominican Republic the Ministry of Health decided to move forward with allocating public funds for food supplements for TB patients and including in- and outpatient TB services in the national health insurance schemes. In Kenya, TB treatment services were decentralized, local partners were approached for sputum sample transport reduce patients' transport costs and time spent on the road, and other health programs were approached for nutritional support of TB patients. A TB and poverty subcommittee was convened to develop a comprehensive pro-poor approach within the routine TB program [9].

Table 5 Summary of policy options to mitigate (MDR) TB patients' costs considered per country

	Ethiopia	Indonesia	Kazakhstan
TB service improvements			
Ensure that policy of free care for all (MDR) TB services is fully implemented	X	X	X
Bring services closer to patients	X	X	X
Detect and treat MDR-TB cases earlier	X	X	X
Raise the awareness of health workers	X	X	X
Involve local NGO's and civil society organizations		X	X
Reduce hospitalization			X
No unnecessary or substandard tests		X	
Obligatory treatment for MDR-TB patients		X	
Social protection improvements			
Include direct (transport, food support) costs in social support schemes provided through TB services	X	X	X
Include indirect (sick leave allowance) costs in social protection schemes	X	X	X
Improve employment protection	X	X	X
Reduce stigma and acceptance of outpatient treatment	X	X	X
Increase re-socialization and employment possibilities	X	X	X
Use social health insurance	X	X	
Consistency across social assistance programs and over time	X		
Assure continuation of education			X
Involve local NGO's and civil society organizations		X	
Provide convenient lodging		X	
Empower patient groups that can support MDR-TB patients		X	

This shows that action may be taken only after studies can show policy makers what the issues are.

Both in Ethiopia and Indonesia, a considerable proportion of MDR-TB patients may not start treatment after diagnosis and another considerable proportion is lost to follow-up before completion of treatment. We do not know in how far economic consequences are a key reason for this but they may be a relevant contributor. In Ethiopia as many as 29 % of patients diagnosed with MDR-TB may not have started second-line drug treatment and 3 % are lost to follow-up during treatment (unpublished data: Ministry of Health progress report to the Green Light Committee, April 2013). In Indonesia around one-third of diagnosed MDR-TB patients is not started on MDR-TB treatment, whereas up to one-third of those starting treatment is lost to follow-up during treatment (unpublished NTP data, Indonesia).

Treatment cost data were collected during a single interview and extrapolated over the treatment phase the patient was in during the interview, i.e. intensive or continuation phase. As costs were estimated per treatment phase and not per patient, it means that this study did not yield total costs of (MDR) TB treatment incurred per patient. To give an idea of the costs of a total episode of (MDR) TB, we did add median costs per stage, thus assuming that patients interviewed per stage were representative of all patients. These summed medians must therefore be interpreted as crude estimates, meant to indicate what were the main cost drivers. With this cross-sectional method we were able to capture the major cost components in a relatively short timeframe. Capturing the total costs per patient requires follow-up of a sample of patients during their treatment, which may take more than 2 years for MDR-TB patients and takes at least 6 months for TB patients. To get an exact estimate of total costs incurred, other methods than (repeated) interviews would have been required, such as patient diaries. However, it is known that it is difficult to motivate patients to keep diaries for a longer time period and this may lead to selective dropout of the less well educated and socially engaged patients.

Conclusions

In conclusion, while the financial burden of MDR-TB patients was (much) higher than that of TB patients in all three countries, all patients experienced substantial socioeconomic impact of TB disease, most importantly due to inability to work and job loss. If the patient is the breadwinner of the family, the combination of lost income and extra costs generally is catastrophic. A too high financial burden may cause patients to not get diagnosed, to not start treatment, or to stop treatment, leading to prolonged transmission of the disease to others. Patients stopping treatment as soon as they feel better may need retreatment, which is more expensive, takes longer and is more toxic than initial treatment. Therefore, it should be a priority of governments to relieve the financial burden especially for MDR-TB patients. The cost mitigation options in all three countries should be used to prepare an action plan for mitigating patient costs under the guidance of NTP, indicating main stakeholders, and with whom, how and when the option can be worked out into a strategy, and when and how this strategy can be implemented. However, the effectiveness of such strategies will depend on the countries' willingness and ability to address these problems.

Appendix

Table 6 Policy options to mitigate (MDR)TB patients' costs considered per country (expansion of Table 5 in manuscript)

	Ethiopia	Indonesia	Kazakhstan
TB service improvements			
Ensure that policy of free care for all (MDR) TB services is fully implemented. Agreements need to be in place so that presumed TB patients can make use of the necessary diagnostic tools for free.	X	X	X
Bring services closer to patients. Further decentralization should reduce patient expenditures on transport and patient time and should reduce detection and treatment delays, especially for MDR-TB patients. For areas where there is no public transport, transport for patients or home visits should be arranged. This includes improving downward referral from national or provincial MDR-TB treatment centers to local community health centers.	X	X	X
Detect and treat MDR-TB cases earlier. Especially detection of drug-resistant TB should reduce the time to appropriate treatment, and thus reduce direct and indirect treatment costs for patients, especially the amount of income lost due to inability to work during initial first-line drug treatment. Full implementation of new diagnostics such as Xpert MTB/RIF should reduce time to diagnosis and thus patient costs.	X	X	X
Raise the awareness of health workers. Provide education and training of primary level health workers to recognize suspects and ensure speedy diagnosis, and to follow up on cases and contact tracing.	X	X	X
Involve local NGO's and civil society organizations to support patients and hereby improve (MDR) TB treatment adherence.		X	X
Reduce hospitalization. Kazakhstan has moved in recent years from full in-patient treatment to partial outpatient treatment, usually in the continuation phase. The country plans to move towards full outpatient care. This has the potential to greatly reduce indirect patient costs.			X
No unnecessary or substandard tests. Sometimes, tests are being prescribed by physicians that are not needed (e.g., X-ray for diagnosis of smear-positive TB patients). Private laboratories sometimes use substandard tests (e.g., IS*6110* based PCR for detection of *Mycobacterium tuberculosis*) and serological tests. Such tests are not only unnecessary, but also may importantly increase the costs of (MDR) TB diagnosis.		X	
Obligatory treatment for MDR-TB patients may be needed in parts of the country where a large proportion of MDR-TB patients refuses MDR-TB treatment, due to lack of knowledge or support, to protect the community against the spread of MDR-TB. MDR-TB patients may fear the costs and side effects related to MDR-TB treatment. Patient education, installation of patient organizations (as is starting up now in different hospitals), and provision of living allowances may help to remove some of these obstacles.		X	
Social protection improvements			
Include direct (transport, food support) costs in social support schemes provided through TB services. Such incentives and enablers should reduce direct costs associated with TB treatment and improve treatment adherence.	X	X	X
Include indirect (sick leave allowance) costs in social protection schemes. Review, standardize and expand current social protection mechanisms and schemes by the government. Social protection schemes, including temporary disability allowances, should be made available to those (MDR) TB patients who need it, from the moment they are diagnosed. Include social protection for (MDR) TB under disability policy strategies while ensuring that the protection is provided from the time of confirmed diagnosis to those who are at risk of becoming poor or not seeking or completing treatment. Professional guidance by health care workers or social workers for submitting applications for social support is needed for many patients. Possibilities for agreements on delaying or waiving payments (e.g. mortgage loans, school fees) are to be investigated.	X	X	X
Improve employment protection. Advocate for regulations and policies that mandate that both public and private employers pay employees (a portion of) their salary while they are unable to work. Also advocate for patients to be able to return to previous positions once they are fully cured and clinically fit to perform their assignments.	X	X	X
Reduce stigma and acceptance of outpatient treatment. Improve education to the public on TB and MDR-TB, e.g. through primary level services, in order to reduce stigma of (MDR) TB and reduce fear of transmission during outpatient treatment.	X	X	X
Increase re-socialization and employment possibilities. Develop mechanisms to involve socially vulnerable patients in different re-socialization activities provided e.g. through temporary, assisted living facilities. Develop mechanisms to involve patients in income generating activities and advocate government to support this, for example through microfinance.	X	X	X

Table 6 Policy options to mitigate (MDR)TB patients' costs considered per country (expansion of Table 5 in manuscript) *(Continued)*

Use social health insurance. Advocate with government to incorporate TB services in the future social health insurance system to provide sustainable financing. Also advocate for social protection to be included in the benefits package on the grounds that this will reduce severity of illness and transmission and thus save on treatment costs.	X	X	
Consistency across social assistance programs and over time. The data collected on vouchers indicates that the amounts provided are very low compared with the patient costs and taking into account reductions in income. In addition there may be inconsistency in the amounts provided across facilities and over time. It is recommended that the government develops a standard.	X		
Assure continuation of education. When rendered non-infectious, children and students need to be able to continue their education.			X
Involve local NGO's and civil society organizations and empower community health workers in provision of (MDR) TB drugs to improve (MDR) TB treatment adherence, since this will increase the population that can be targeted.		X	
Provide convenient lodging to those MDR-TB patients who cannot travel back and forth for receiving DOT. Since MDR-TB treatment roll out is still ongoing distances that MDR-TB patients have to travel for receiving DOT can be long in Indonesia and this may mean that patients need to move to a shelter close to the PMDT site. It is expected that the number of patients needing such housing will decrease with the roll out of the PMDT program.		X	
Empower patient groups that can support MDR-TB patients in a practical way during MDR-TB treatment. Being a new development in Indonesia, MDR-TB peer educator groups are being set up by ex MDR-TB patients. MDR-TB patient support groups provide information to MDR-TB patients regarding side effects, reimbursements systems, etc., and thus serve as a valuable and easily accessible information point to MDR-TB patients.		X	

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Availability of data and materials
The datasets supporting the conclusions of this article are available on request from the authors.

Authors' contributions
SvdH, DC and ET designed and coordinated the study, supervised data collection, performed the statistical analysis, and drafted the manuscript. FH, DB, and AT supported the design, coordinated the data collection in their respective countries and helped to revise the draft manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
Ethics approval was sought and received from Armauer Hansen Research Institute (AHRI)/ALERT ethics review committee in Ethiopia, the institutional review board of Gadjah Mada University in Yogyakarta and the ethical review boards of Persahabatan and Dr Moewardi hospital in Indonesia, and the National Center for Problems of Tuberculosis and the Akmola oblast tuberculosis dispensary in Kazakhstan. Written informed consent was obtained before patients were interviewed. The interviewers wore N95 respirators when interviewing smear-positive TB patients and culture-positive MDR-TB patients. Interviews were done in separate rooms to ensure confidentiality, or outside if such a room was (temporarily) not available. In Indonesia, patients received a free hygiene kit after the interviews. Data were stored and analyzed without personal identifiers.

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PLOS ONE

RESEARCH ARTICLE

The Effects of Psycho-Emotional and Socio-Economic Support for Tuberculosis Patients on Treatment Adherence and Treatment Outcomes – A Systematic Review and Meta-Analysis

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Abstract

Background

There is uncertainty about the contribution that social support interventions (SSI) can have in mitigating the personal, social and economic costs of tuberculosis (TB) treatment on patients, and improving treatment outcomes.

Objective

To identify psycho-emotional (PE) and socio-economic (SE) interventions provided to TB patients and to assess the effects of these interventions on treatment adherence and treatment outcomes.

Search strategy

We searched PubMed and Embase from 1 January 1990–15 March 2015 and abstracts of the Union World Conference on Lung Health from 2010–2014 for studies reporting TB treatment adherence and treatment outcomes following SSI.

Selection criteria

Studies measuring the effects of PE or SE interventions on TB treatment adherence, treatment outcomes, and/or financial burden.

Data collection and analysis

Two reviewers independently assessed titles and abstracts for inclusion of articles. One reviewer reviewed full text articles and the reference list of selected studies. A second reviewer double checked all extracted information against the articles.

reflect the views of USAID or the United States Government. The funder was not involved in conception of the study, study design, data collection and analysis and preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

Main results

Twenty-five studies were included in the qualitative analysis; of which eighteen were included in the meta-analysis. Effects were pooled from 11 Randomized Controlled Trials (RCTs), including 9,655 participants with active TB. Meta-analysis showed that PE support (RR 1.37; CI 1.08–1.73), SE support (RR 1.08; CI 1.03–1.13) and combined PE and SE support (RR 1.17; CI 1.12–1.22) were associated with a significant improvement of successful treatment outcomes. Also PE support, SE support and a combination of these types of support were associated with reductions in unsuccessful treatment outcomes (PE: RR 0.46; CI 0.22–0.96, SE: RR 0.78; CI 0.69–0.88 and Combined PE and SE: RR 0.42; CI 0.23–0.75). Evidence on the effect of PE and SE interventions on treatment adherence were not meta-analysed because the interventions were too heterogeneous to pool. No evidence was found to show whether SE reduced the financial burden for TB patients.

Discussion and Conclusions

Our review and meta-analysis concluded that PE and SE interventions are associated with beneficial effects on TB treatment outcomes. However, the quality of evidence is very low and future well-designed evaluation studies are needed.

Background

In 2013, 9 million people developed TB and 1.5 million died from this disease [1,2]. TB is the most common cause of death in people with HIV [1]. The treatment duration for TB is long, at least 6 months for drug-susceptible TB and 18–24 months for multidrug-resistant tuberculosis (MDR-TB) that does not respond to the two most effective anti-TB drugs isoniazid and rifampicin. The long treatment, adverse drug reactions during treatment, stigma and financial burden of TB contribute to non-adherence to treatment and unsuccessful treatment outcomes [3–8]. In addition, ensuring patient adherence to treatment through facility-based directly observed therapy (DOT) competes with work related priorities of patients, adding to the financial burden coming from out-of-pocket and indirect costs related to treatment [7,9], even though anti-TB drugs are provided free of charge in most countries [1,10]. The quick improvement of TB symptoms early in treatment also contributes to patients' stopping treatment prematurely (i.e. loss to follow-up) as competing interests take priority [9,11]. Poor treatment adherence and loss to follow-up increase morbidity, mortality, and the risk of drug resistance development, and can lead to prolonged transmission of TB [12–17].

Adherence to tuberculosis treatment improves the chance of cure and reduces acquisition of drug resistance and ongoing transmission of TB. The use of DOT through a patient-centered approach, which often requires enablers, is recommended to encourage adherence to TB treatment [18,19]. In some settings and circumstances, incentives alone or in addition to enablers are used to motivate patients to adhere to and complete their full course of treatment [9,16,20–22]. Social support through various educational, emotional, and/or material (in-kind or services) interventions are being provided by numerous TB programmes to remove or alleviate barriers to treatment adherence [9,20,23–25], including the financial burden associated with TB illness and its treatment. Despite the fact that different types of social support interventions (SSI) are implemented, countries still struggle to develop systems that are able to provide SSI in an efficient, effective and sustainable way [26]. WHO guidelines for the programmatic

management of drug resistant TB and the new End TB Strategy recommend the use of SSI in TB patients, though WHO has not yet systematically assessed the evidence to support such a recommendation [2,19,27]. Hence, a systematic review of relevant literature on the effects of SSI on TB treatment adherence, treatment outcomes, and financial burden will be informative for national and global policy making.

The primary aim of this systematic review was to identify SSI provided to TB and MDR-TB patients and assess the evidence of their effects on treatment adherence, treatment outcomes and financial burden related to TB illness. The secondary aim was to describe the funding sources for and ownership of local organizations in the identified interventions.

Methods

This review followed standard methods as defined by the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [28,29]. The PRISMA checklist is enclosed in the supporting information (S1 PRISMA Checklist).

Literature search

In this review we searched for two main categories of SSI, namely PE support and SE support. PE support includes both emotional support through psychological interventions (e.g. counseling by health care workers) and companionship support through provision of help for patients to participate in a social network (e.g. peer counseling for patients and their support network) [19]. We did not consider interventions aimed only at providing improved information or education to TB patients, given the recent systematic review showing a lack of evidence related to TB treatment [17]. In addition, reminder systems were not considered social support interventions [30]. SE support entails delivering services, material goods and/or financial assistance [19,31,32]. Financial assistance was categorized according to Richter et al. [7] as"direct transfers of money, such as cash paid as part of a social security system or a program incentive, transport reimbursements, treatment allowances, and the like that are paid directly to affected individuals". Indirect assistance was defined as: "indirect transfers through, for example, food packages or vouchers, travel vouchers, and payment of health insurance for individuals, households or families". Some forms of indirect assistance may also be converted into cash. We included tax exemption under indirect assistance. Enterprise assistance was defined as"training programs or microcredit that aim to assist individuals or families to generate income" [7]. We searched for studies assessing the effects of socio-economic and/or psycho-emotional interventions on treatment adherence and/or treatment outcomes and/or financial burden. The study population consisted of patients initiated on anti-TB treatment, including treatment for MDR-TB.

Outcome measures

Treatment adherence, treatment outcomes and financial burden were considered as the primary outcome measures. Adherence was calculated as the percentage of prescribed doses actually taken. Treatment outcomes were defined according to WHO definitions, where cure and completed treatment are defined as successful treatment outcomes [1]. Unsuccessful treatment outcomes for active TB treatment included death, treatment failure and loss to follow-up (previously named default). Patients with transfer-out or missing treatment outcomes were excluded from the analysis. As timing of loss to follow-up per individual was not available for studies reporting on treatment outcomes but not treatment adherence, for these studies loss to follow-up was not included in calculation of treatment adherence. Financial burden was

reported according to the definitions used in the individual studies. We also extracted information about how the SSI were financed and organized.

Search strategy

We systematically searched PubMed and Embase for primary articles and reviews reporting on SSI and tuberculosis treatment for human subjects, published from 01 January 1990–15 March 2015, on the grounds that relevant old information would emerge from previous reviews and references lists. We reviewed the reference lists of identified articles, editorials and reviews. Additionally, we hand searched the 2010–2014 abstract books of the Union World Conference on Lung Health to identify recent studies that were not published in the literature yet. Databases were searched using the full text search strategy as described in S1 Web annex. We contacted authors when we were not able to extract required information from the identified publication on the SSI provided and its effects.

Eligibility criteria

Eligibility of studies was based on predetermined inclusion criteria. Original studies including a description of SSI had to be in place, as well as an evaluation of the association of SSI on treatment adherence, treatment outcome and/or financial burden. This was evaluated either by means of a comparison between outcomes of an intervention group and a group receiving standard support (which could be none or a more limited package), or by means of a comparison of the occurrence of interventions in those with positive and negative outcomes (case-control studies). The search strategy was restricted to certain languages including publications in Dutch, English, French, German, Portuguese, Russian and Spanish. No age restriction was applied. We chose not to exclude studies that did not provide DOT to their patients as there is no hard evidence that DOT in a strict sense (i.e. direct observation of medication ingestion) without the DOT provider supporting the patient through education and counseling improves treatment outcome under programmatic conditions [22,33].

Data collection and analysis

Selection of studies and data extraction. One reviewer conducted the literature search (RH) based on the search strategy developed by all authors. Subsequently, two reviewers (SH, RH) independently examined titles and abstracts retrieved by the search. One reviewer (RH) reviewed full texts and the reference lists of selected articles, and extracted study data, which were then verified by a second reviewer (SH). For data extraction and management, a pre-piloted form was developed to list study characteristics including: study design and study aim, type(s) of patients, type(s) of TB treatment, descriptions of intervention and control group, descriptions of intervention and routine support, coverage of patients that received the intervention, results of the intervention and control group and differences between these groups. Duplicate publications of included studies were taken into account if they provided additional information. When disagreements occurred, a third independent reviewer was consulted and discrepancies were resolved by consensus among the three.

Risk of bias and quality of evidence. Risk of bias was assessed separately for Randomized Controlled Trial (RCTs) and Non Randomized Studies (NRS). We used the Newcastle Ottawa Scale for NRS [34] and The Cochrane Collaboration's Tool for RCTs [35]. Furthermore, an additional assessment was made for Cluster Randomized Trials on recruitment bias, baseline imbalance and loss of clusters [36]. For NRS, we considered $<10\%$ of subjects lost as indicative of low risk of bias. The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool [37–40].

Data analysis. All SSI were described, irrespective of inclusion in the meta-analysis. We analyzed the dichotomous outcomes using Risk Ratios (RR) for RCTs and cohort studies, and Odds Ratios (OR) for case-control studies, together with corresponding 95% confidence intervals. Ratios were (re)calculated from the data provided in the publications. Subsequently, the (calculated) intervention effects were combined in the meta-analysis. Studies were assessed on clinical diversity (e.g. differences in patient spectrum, type and dose of treatment) and methodological diversity (e.g. differences in methods: blinding of patients, concealment and randomization). Additionally, (statistical) heterogeneity was examined with the I^2 test along with the visual assessment of the forest plots [28,41]. An I^2 of 0–40% was considered as low heterogeneity, 30–60% was defined as moderate heterogeneity, 50–90% substantial heterogeneity and 75–100% as high heterogeneity [42]. Furthermore, the I^2 was interpreted along with the directions and magnitudes of the different studies observed in the forest plots. A p-value for the Chi^2 test of ≤ 0.10 was considered as a cut-off point for statistically significant heterogeneity. In case of statistically significant heterogeneity, sensitivity analysis were performed based on patient type (e.g. MDR-TB or not) and risk of bias (e.g. low vs. high risk of bias)[42]. Funnel plots were created to assess for publication bias. To execute the meta-analysis, a random effects model was used, considering the diversity in participants (e.g., susceptible TB-patients and MDR-patients) and interventions (e.g. self-help groups and counseling). The DerSimonian Laird method is based on the inverse-variance approach [42]. Due to the potential heterogeneity of the interventions (PE support, SE support and combined PE and SE support) also stratified analyses were performed [43]. Stata (STATA/SE 13.1) was used to perform the meta-analysis. To visualize the risk of bias assessment, Review Manager (Review Manager (RevMan) 5.3, The Nordic Cochrane Centre, Copenhagen) was used.

Results

In total, we identified 2443 articles. After removal of 694 duplicates, two reviewers screened titles and abstracts of the 1752 citations. Twenty-five articles were eligible for inclusion in the description of included studies (Fig 1).

Description of included studies

Fourteen NRS and eleven RCTs were included in the description of interventions from 15 different countries. Study populations ranged from 46 to 4,091 participants. Eight studies included both children and adults [44–51]. Three studies explicitly included adults [52–54]. For the other studies the age range was not reported, however mean age was provided frequently [20,55–64]. Most studies were conducted in middle income countries, 9 in upper middle income countries and 7 in lower middle income countries [65]. Six studies were performed in high income countries and the remaining three studies in low income countries. Eleven studies provided SE support only, seven studies provided only PE support, while the remaining seven studies provided a combination of PE and SE support [44,52,56,57,61,66,67] (Table 1). Table 2 includes a comprehensive summary of studies including the frequency of the intervention provided and sustainability of the below described interventions.

Psycho-emotional support. Seven studies provided counseling, exclusively [46,53] or in combination with other PE and or SE interventions [44,51,52,61,67]. The scope of the additional interventions varied from food supplementation [44] combined with home visits [67], direct economic support constituted after an exploratory quality study [52], cash coupons at every monthly visit and at the end of treatment [61], arrangement of a self-chosen treatment supporter [51]. See Table 2 for details.

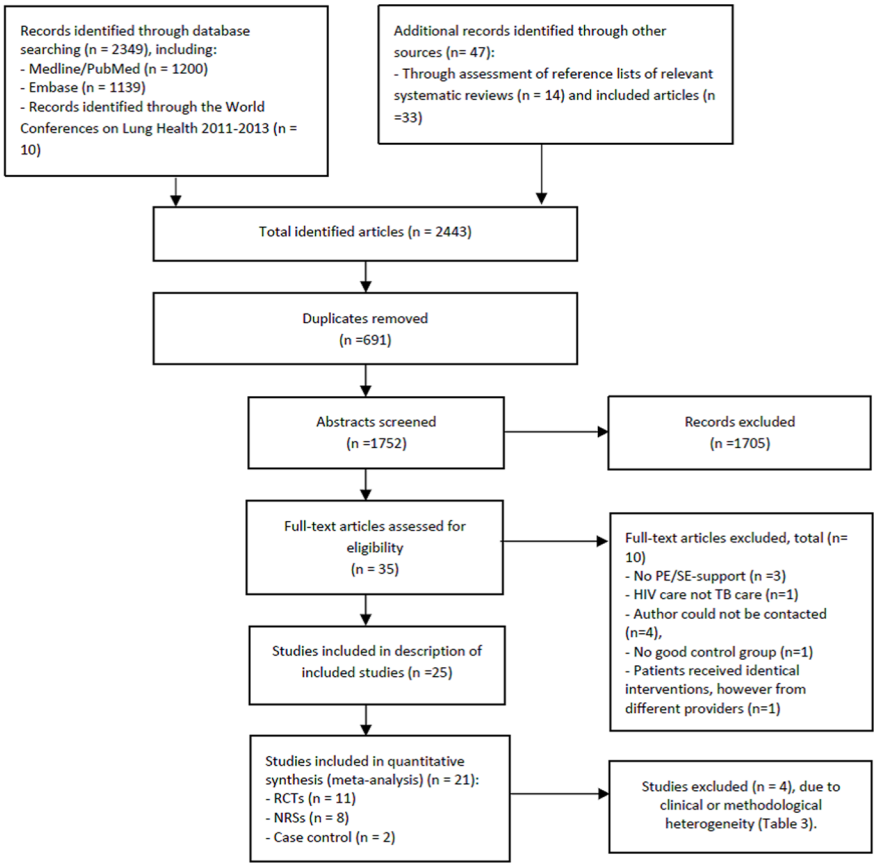

Fig 1. Flow diagram for review and meta-analysis.

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Furthermore, 2 studies organized self-help groups [50,59], one of these studies along with stigma reduction and home visits [59]. TB clubs were raised in the form of self-help groups in combination with support to reduce stigma and home visits to get insight in the social network of the patients and to plan activities to support the patient [59]. In the second study, the patients could choose the number of meetings and the topics discussed [50]. Another 6 studies arranged home visits together with other interventions [51,57,59,66–68].

Socio-economic support. Eight studies provided food supplementation consisting of fresh food supplies [58,60], hot meals [44] and/or food packages [44,45,49,54,60,67,68]. Four of them exclusively provided food supplementation [45,49,58,60]. Other studies also provided food supplementation, in combination with direct economic support and/or other material support through provision of e.g. clothing and legal support [44], assistance in providing documentation for health care access and social security [54], or establishing a supportive social network of organizations that could provide support to the local community, such as public day care centers and employment agencies [68]. One study additionally provided PE support [67].

Four studies provided indirect economic support including food and transport vouchers [20,47,56,61]. Coupons varying from 5 to 15 US$ were given when attending each appointment or at drug collection each month. Some studies provided additional coupons varying from 40 to 60 US$ after completion of 3 months of treatment or at the end of treatment [56,61]. Seven studies granted direct economic support, mainly financial support varying from 19 to 240 US$

Table 1. Overview on types of support and inclusion in the quantitative analysis.

	Counseling	Self-help groups	Stigma reduction	Psychotherapy	Involvement of a treatment supporter	Home visits	Other psycho-emotional support	Food supplementation	Other material support	Direct economic support	Indirect economic support	Included in quantitative analysis?
	PSYCHO-EMOTIONAL SUPPORT							SOCIO-ECONOMIC SUPPORT				
Non-Randomized Studies												
Bock et al. 2001 [20]											X	
Cantalice Filho 2009 [45]								X				**X**
Davidson et al. 2000 [56]											X	
Farmer et al. 1991 [57]						X				X		**X**
Finlay et al. 2012 [53]	X											**X**
Garden et al. 2013 [54]								X	X			**X**
Gelmanova et al. 2011 [66]						X	X		X			
Jakubowiak et al. 2007 [44]	X							X	X	X		**X**
Lu et al. 2013 [48]										X		**X**
Macq et al. 2008 [59]		X	X		X	X						**X**
Soares et al. 2013 [68]						X		X	X			
Sripad et al. 2014 [62]										X		**X**
Wei et al. 2012 [63]										X		
Zou et al. 2013 [64]										X		**X**
Randomized Controlled Trials												
Alvarez et al. 2003 [50]		X										**X**
Baral et al .2014 [52]	X									X		**X**
Drabo et al. 2009 [67]	X					X		X				**X**
Jahnavi & Sudha 2010 [58]								X				**X**
Janmeja et al. 2005 [55]				X								**X**
Liefooghe et al. 1999 [46]	X											**X**
Lutge et al. 2013 [47]											X	**X**
Martins et al. 2009 [60]								X				**X**
Morisky et al. 1990 [61]	X										X	**X**
Sudarsanam et al. 2011 [49]								X				**X**
Thiam et al. 2007 [51]	X				X	X						**X**

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

Study	Country income*	Study type	Enrolment period	N*	Population	Comparison	Intervention(s)	Funding source and organization	Outcome(s)	Other
Alvarez Gordillo et al. 2003 [50]	Chiapas, Mexico,UMIC.	Parallel cluster-randomized study (23 intervention and 25 control health centers).	Febr 2001-Jan 2002.	87 (I: 44, C: 43).	Smear positive pulmonary TB patients 15–89 years, 51% male. Patients with documented resistance were excluded.	Self-help groups vs no support.	Self-help groups. Monthly meetings under coordination of doctors from the specific health unit where the patients received treatment.	Funded by the System Research Benito Juárez, System SEP / CONACYT of Oaxaca, Mexico.	Adherence, defined as Minimal 75% of prescribed dosages taken; treatment completion was defined as 100% of the dosages taken; cure according to the WHO definitions.	Patients could choose the number of meetings and the topics discussed. The health personnel (staff doctors, nurses and social health workers) were trained; they had 6 multidisciplinary workshop days in total. Topics discussed: health, social-economic and cultural aspects of tuberculosis. Theory and practice of diagnosis and treatment of TB and formation of self-help groups.
Baral et al. 2014 [52]	Kathmandu Valley, Nepal, LIC.	Parallel cluster-randomized study.	Jan-Dec 2008.	156 (I1: 33, I2; 42, C: 81).	MDR-TB patients. 83% 21–60 years; 65% male.	1) Counseling only 2) counseling and financial support vs 3) usual care. 7 DOTS plus centers (3:2:2).	1) Counselling on individual level and in small groups, every 2–3 weeks. Or 2) counselling on individual level and in small groups, every 2–3 weeks and US$ 28 per month meant to cover local transport, food and rental costs, but free to use as they chose.	Funded by UK Aid from DFID. Patients receiving financial support were given Nepali Rupees (NRs) 2000 (US$ 28) per month.	Cure, as internationally defined (treatment success).	The intervention was designed after exploratory qualitative study. No adequate sample size calculation (not taking into account clustering), and sample size was smaller than anticipated (partially compensated by including larger number of control patients).
Bock et al. 2001 [20]	Fulton County, Georgia, USA, HIC.	Historically controlled study.	I: Nov 1996—Oct 1997; C: April 1995 -March 1996.	107 (I: 55, C: 52).	TB patients who demonstrated non-adherence by missing at least 25% of DOT doses over a 4-week period. Mean age: 36–38 years; 58% male; HIV infected 34%; alcohol or injection or non-injection drug abusers 56%. Patients, who died, transferred out, lost or uncooperative, were excluded.	Incentive program vs historical controls in the same county. =, who would have been eligible for the incentive under the incentive program.	A coupon redeemable for five dollars in merchandise at a regional chain of grocery stores was given to the patient (or parent/guardian) at each DOT and physician appointment after enrolment. Frequency is unknown.	Partial funding was provided by the Georgia Chapter of the American Lung Association. The cost of incentives for 55 patients was approximately US$ 10.000, less than the cost of treating 1 TB case.	Treatment completion, not defined.	.
Cantalice Filho 2009 [45]	Duque de Caxias, Brazil, UMIC.	Historically controlled study	I:2004 –Jul 2006; C: Sept 2001 – Dec 2003	142 (I: 74, C: 68)	TB patients > 15 years old with confirmed TB. Mean age: 37 years; 59% male; 20% patients with a history of TB; 2% HIV positive.	Treatment and provision of food baskets vs treatment only. Historical controls.	Provision of food baskets on a monthly basis (non-perishable food, the content of the food baskets was not further described).	Funding source is not reported.	Cure, loss-to-follow up, failure and death are not defined.	.
Davidson et al. 2000 [56]	New York City, United States of America, HIC.	Case-control study.	Oct 1992—March 1996.	365 (Cases: 147, controls: 218).	TB patients. Mean age: 40 years; 75% male. 84% were currently unemployed, 74% had no income at the time of the study. 58% was in prison in the past year.	Adherent (attending 80% of the prescribed visits) vs non-adherent patients. Comparison within the same time range. From 6 DOT programs from different city-districts.	10 subway tokens (cash value 15 US$) for attendance at all scheduled appointments each week throughout the course of treatment. Later it changed to 20 tokens a month (cash value 30 US $) at the end of each of the first 2 months and a bonus of 40 tokens at the end of the 3rd month. The 3-month cycles were repeated until treatment ended.	Funded by grants from the Aaron Diamond Foundation and the New York State Department of Health.	Adherence, defined according to a 1990 USPHS report that has been widely cited as a standard for TB treatment. Patients were considered adherent if they attended 80% of their prescribed visits every month of their treatment during the study period.	Not clear what the coverage of support was in the adherent and non-adherent group.

(*Continued*)

Table 2. (*Continued*)

Study	Country income*	Study type	Enrolment period	N*	Population	Comparison	Intervention(s)	Funding source and organization	Outcome(s)	Other
Drabo et al. 2009 [67]	Burkina Faso, LIC.	Parallel cluster-randomized study	Oct 2005-Dec 2007.	333 (I: 178, C: 155).	Smear positive TB patients, further characteristics unknown.	3 intervention vs 3 control districts.	Community groups were raised. Material (food), home visits and psychosocial support was provided to patients. Support was partially provided when needed and educational information was given to the community.	The organizational costs for support committees were included in the annual budgets of respective health districts.	Loss to follow-up, cure and death are not defined.	The community group included 14 people. 2–3 traditional healers, 2 former TB patients, 1–2 community health care workers, 3–4 religious leaders, 2–3 people from community associations and 2 nurses.
Farmer et al. 1991 [57]	Haiti's central plateau, Haiti, LIC.	Non-randomized controlled study.	Febr 1989—June 1990.	60 (I: 30, C: 30).	(Extra) pulmonary TB (mostly rural) patients. Mean age: 45 years; 33% male; 5% HIV infected patients.	Intervention vs free usual medical care, comparison within the same time frame. Two districts geographically distinct, but are contiguous to each other.	Daily home visits during first month and-, a monthly reminder for clinic visits by the community health worker, and no-show home visits by clinic staff, for food supplements 30 US$ per month for the first 3 months and 5 US$ for travel expenses per month.	Funding source is not reported., however, support was organized by 'Proje Veye Sant'.	Cure: negative sputum smear at the end of treatment (treatment success).	Other support: nutritional supplementation.
Finlay et al. 2012 [53]	8 out of 9 provinces, South Africa, UMIC.	Case-control study.	Jan 1—Dec 31 2002.	1164 (I: 232, C: 932).	TB patients > 18 years old from facility-based national TB registers. HIV rate is unknown. Median age new cases, I: 30 years C: 34 years; median age re-treatment patients, I: 33 C: 39; 58% male.	Patients that were lost to follow-up vs patients that cured, completed or failed treatment. Comparison within a similar time range and geographical location.	Given adequate counselling or information.	Funding source is not reported.	Loss to follow-up is defined as interrupting treatment for two or more consecutive months during treatment.	Also information on TB treatment was measured. Sample selection was conducted by multistage sampling of urban and rural sub-samples.
Garden et al. 2012 [54]	Saint Petersburg, Russia, HIC.	Non-randomized controlled study.	I: 2001–2004, C: 1998–1999.	518 (I:142, C:376).	Homeless TB patients. Age range 23–70. 94% male; 77% has been treated previously for TB; 45% was registered as alcoholics and for 38% no information on this topic was available.	Intervention vs historical controls (no DOT was provided to the controls).	Food incentives, and assistance in providing documentation for health care access and social security	Two Swedish governmental organizations (Swedish East Europe Committee (SEEC) and the Swedish International Development Cooperation Agency (SIDA): Stockholm Sweden).	Loss to follow-up is defined as: when not turning up at the dispensary during three consecutive days. Completion: not interrupting treatment.	.
Gelmanova et al. 2011 [66]	Tomsk City, metropolitan region, Russian Federation, HIC.	Case series (uncontrolled longitudinal study).	17 Dec 2006–30 Nov 2008.	46.	TB patients that participated in at least one intervention to improve adherence before referral to the Sputnik program.68% aged < 38 years; 76% male, 79% was unemployed, 83% had chronic alcoholism, and 72% had MDR-TB.	Before and after the referral to Sputnik's program. Participants came from all over the Tomsk City region.	More attention and care by health staff, psychological and social assistance (e.g. clothing and assistance with procuring documentation required to access state social service).	Funding source is unknown. The 'Sputnik' program was implemented as a joint program by the Tomsk Oblast Tuberculosis Services (TOTBS) and Partners in Health (PIH).	Adherence: the proportion of doses taken over the total prescribed. Loss to follow-up if they missed all doses for 2 consecutive months. Cure, death and failure according to international consensus definitions	Sputnik' has a high nurse to patient ratio (2:15), more staff time per patient, provision of cellular telephones to nursing staff (which increases flexibility and easier access to specialists and expanded social and psychological support). Program nurses had training on how to care for patients facing myriad bio-social challenges).

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Table 2. (*Continued*)

Study	Country income*	Study type	Enrolment period	N*	Population	Comparison	Intervention(s)	Funding source and organization	Outcome(s)	Other
Jahnavi& Sudha 2010 [58]	16, villages in India, LMIC	Randomized controlled study.	Aug–Dec 2005	100 (I: 50, C: 50)	TB cases, culture or sputum positive; BMI < 20. 89% aged 18–65 years old; mean age 37; 74% male; Patient with HIV, DM or other severe underlying diseases were excluded.	Food supplementation and dietary plan vs only general advice and instructions to increase food intake.	Advice on dietary intake with locally available foods was provided to the patient, to meet the target intake of 35 kcal /day/kg body weight. Every day, the patients also received sweet balls made from wheat flour, caramel, groundnuts and vegetable ghee (6 grams protein and 600 kcal of energy), and 100 grams of sprouted grams and nuts for vitamins and minerals), to be consumed in presence of community worker.	Funded by the Padova University, Italy.	Cure: when initially smear-positive who completed treatment had negative smear results on at least two occasions. Completed: When an initially smear-negative patient received the full course of treatment. Death: patients who died during the course of the treatment regardless of the cause.	The community worker ensured that these supplements were collected and distributed to the patients, and consumed.
Jakubowiak et al. 2007 [44]	Six different regions, Russian Federation, HIC.	Case-control study.	March-Sept 2003.	1527 (I: 1444, C: 84)	New pulmonary smear positive and smear-negative TB patients 16–86 years old. Mean age: 43 years; 73% male; 37% was unemployed; 13% imprisonment history; 24% alcohol abuse.	Success vs default, measured in the same time range, from six different regions.	Varying daily to monthly social and economic support (cost 5–30 US$ per package provided): protein food parcels, food supplementation, hot meal, hygiene kits, clothing and/or footwear, newspapers, board games, reimbursement of travel, legal support, household goods on treatment completion. Psychological support (counselling).	Funded by the WHO, IFRC and local authorities. Now already 20 regions are implementing joint social support programs to motivate patients to adhere to treatment.	Treatment success and loss to follow up are according to the WHO definitions.	Social support was organized and implemented by regional TB services, social welfare services, and the local International Federation of the Red Cross and Crescent Societies (IFRC). The support differed intensely per region. 43.3% of the success group did not received social support. 12.1% of the lost to follow-up group received social support
Janmeja et al. 2005 [55]	Chandigarh, India, LMIC.	Non-randomized controlled study.	2001	200 (I: 100, C: 100)	Confirmed new adult cases of pulmonary and extra pulmonary TB patients. Mean age approximately 31 years; 75% male; 38% illiterate.	NTP program + intervention vs usual NTP program care (routine motivation and education). Measured in the same time range and at the same location.	Psychotherapy (8 sessions combined with drug-collection visits), biweekly during the first two months, then monthly.	Funding source is not reported.	Successful treatment: cure and completed. Cured: 6 months of treatment and negative sputum smear at the end of treatment. Completed: negative sputum smear at 2–6 months, without sputum results at completion. Treatment failure: positive sputum smear or culture at 5 months. Loss to follow-up: stopped taking treatment for 2 months or more.	The themes for psychotherapy sessions were structured according to the conceptual understanding of an individual patient obtained from pretreatment psychological assessment. Costs: 12 US $ per patient.

(*Continued*)

Table 2. (*Continued*)

Study	Country income*	Study type	Enrolment period	N*	Population	Comparison	Intervention(s)	Funding source and organization	Outcome(s)	Other
Liefooghe et al. 1999 [46]	Sialkot, Pakistan, LMIC	Randomized controlled trial.	1 Jan—30 Nov 1995	1019 (I: 504, C: 515)	Adult TB patients, age: 15–45+ years; 42% male; 81% new cases; 40% had a low income job.	Intervention vs. usual explanations and treatment by medical staff. Measurements at one hospital.	Counseling. Patients received individual counseling each time they attended for follow-up assessment, and admitted patients received weekly counselling in the tuberculosis ward. Counseling was combined with health education.	Funded by the Vlaamse Interuniversitaire Raad, the Belgian co-operation and the Damien Foundation. The intervention was conceived within the framework of Bandura's social-cognitive learning theory.	Adherence: drug collection at the drug s at the scheduled appointments. Loss to follow-up: no drug collection for 2 months or more.	The social counsellors had several tasks: verify correct understanding of drug intake, to increase the patients' motivation, anticipate problems and/or critical moments, to activate a social network and involve family members and to act ombudsperson between the hospital/paramedical team and the patient. Two male and two female para-medics received a 2-week training course in counselling. They belonged to the same socio-economic background as the majority of the patients, and were fluent in the different local vernaculars.
Lu et al. 2013 [48]	Shanghai, China, UMIC.	Controlled before-and-after study.	Baseline 2006 and Intervention 2010	1935 (I: 2006: 961, 2010: 734, C: 2006: 281, 2010: 229)	Migrant active TB cases; 59% male, 64% aged 15–34; 86% new cases.	Intervention group vs control group without support in 2006 and 2010. Both groups consisted of 3 districts that have the same geographical characteristics.	Transportation subsidies of US$ 14.63 a month and living allowances of US$ 4.39 a month.	The initial project was made possible through a governmental special financing program (WHO Regional Office for the Western Pacific)	Treatment success: cure (with bacteriologic evidence of success), or completion (without bacteriologic evidence of success).	.
Lutge et al. 2013 [47]	KwaZulu-Natal, South Africa, UMIC.	Randomized controlled trial.	July 2009—March 2010	4091 (I: 2107, C: 1984)	Adults and children diagnosed with pulmonary, drug-sensitive TB, mean age: 31 years; 52% male; 49% HIV positive patients; 56% unemployed.	Incentive treatment vs usual care. 20 public sector clinics were enrolled in rural and urban districts (10:10)	15 US$ voucher was offered to patients every month on collection of their treatment, to a maximum of eight months. Vouchers were redeemed at local shops	Governmental funding.	Successful treatment, the sum of those patients cured and completing treatment. Loss to follow-up and failure was a secondary outcome, however not defined.	In many cases nurses withheld vouchers from eligible patients whom they felt were relatively better off financially.
Macq et al. 2008 [59]	9 rural municipalities, Nicaragua, LMIC.	Non-randomized controlled study.	Diagnosed between March 2004 and July 2005	286 (I: 122, C: 146)	New AFB positive TB patients. Average age: 35 years; 73% male; 49% without declared income.	5 intervention municipalities vs 4 control municipalities (these are the municipalities were the intervention was not effectively implemented).	Strengthening the TB patients through TB clubs taking the form of self-help groups. Additionally arranged home visits, reduce stigma and choice of DOT supporter. At least home visits and TB clubs were implemented in de intervention municipalities	TB clubs were chaired by TB patients and appointed an executive board. A local NGO supported this. The project influenced the National policies about the care of TB in government health services. The National TB program of the Nicaraguan Ministry of Health, the administer of the Global Fund (the NGO NICASALUD), the Damian Foundation (Belgian NGO) and a public health school were involved	Treatment success and loss to follow-up (and stigma reduction), no definition(s) available.	The aim was to increase the relationship between health personnel and TB patients and their realities through performing patient centered home visits to support the patient. And also plan social network activities the patient during the treatment. The interventions received full participation of MOH authorities. And TB clubs had been included in the 2005 Global Fund grant for Nicaragua.

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Table 2. (*Continued*)

Study	Country income*	Study type	Enrolment period	N*	Population	Comparison	Intervention(s)	Funding source and organization	Outcome(s)	Other
Martins et al. 2009 [60]	Dili, Timor-Leste, LMIC.	Randomized controlled trial.	March 2005—Nov 2005	270 (I: 137, C: 133)	Outpatient participants with newly diagnosed pulmonary tuberculosis. Mean age: 33 years; 65% male; 43% unemployed.	Routine care and nutritional support vs routine care and nutritional advice. The moment of measurement differed between the two groups. From 3 community districts, geographically distinct zones.	Food provision. The participants received food every time they attended the clinic. In the intensive phase, each day they were provided with one bowl food. During the continuation phase, patients were given a food parcel containing unprepared food to take home; quantities were for one meal per day.	Funded by Unicef/UNDP/ World Bank/WHO Special program for research and training in tropical diseases	Adherence: not defined. Completion: the clearance of acid fast bacilli from the sputum after treatment or the completion of eight months of treatment, or both, including cure.	.
Morisky et al. 1990 [61]	California, United States of America, HIC.	Randomized controlled trial.	Nov 1985—March 1987	88 (I: 43, C: 45)	Subjects receiving preventive therapy and subjects receiving treatment for active TB (divided into two subgroups). Mean age: 35 years; 55% male.	Intervention vs standard clinic treatment including the use of community workers. Interventions and control came from the same 2 districts.	Health education counselling for 5–10 minutes and 10 US$ (in coupons) at every monthly visit and 40 US$ at the end of treatment (in coupons). (An incentive scheme to reward positive health behaviors plus targeted educational counseling session).	Funded by centers for Disease control. Assistance of the project 'Clerk', the project health educators and clinical staff	Treatment adherence: 95% of prescribed medicines taken. And the extent to which a person's behavior (in terms of keeping appointments, taking medications, and executing life-style changes) coincides with medical advice. Loss to follow-up was not defined.	When an active case missed a clinic appointment (interventions and controls), clinical personnel contacted that individual by phone or by home visit to reschedule a new appointment. Intervention subjects were questioned about their specific regimen, and any misunderstandings concerning their medical treatment program were clarified.
Soares et al. 2013 [68]	Rio de Janeiro, Brazil, UMIC	Historically controlled study.	Controls: 2001–2003 and intervention: 2003—Jun 2008	2623 (I: 1771, C: 852)	TB cases from an urban slum	Intervention group vs historical control group without support. Similar geographical location. No DOT provided in control group	DOT, establishment of community health care workers (CHWs) who, led by nurses, established a supportive social network, through this activity the team managed useful services such as transport to TB clinics and donation of food baskets. Also, they and carried out educational activities to enhance TB awareness and promoted breakfasts for patients and their families. The CHWs also collected sputum at home, monitored medical appointment attendance, sent contacts for evaluation and made home visits to supervise treatment	Funded by United States Agency for International Development through the Johns Hopkins University and the US National Institutes of Health Fogarty International Center, Bethesda USA	Treatment outcome (and TB notification rates).	Additionally educational activities were supported. The program was an ongoing training program based on regular feedback of the results of the local team and an on-site supervision scheme implemented by the City TB Program staff. The CHW's have contact with the municipal government, which minimizes employee turnover, making the team stable and avoiding the need for constant training. Regimen was intermittent (twice weekly) in continuation phase during intervention.

(*Continued*)

Table 2. (*Continued*)

Study	Country income*	Study type	Enrolment period	N*	Population	Comparison	Intervention(s)	Funding source and organization	Outcome(s)	Other
Sripad et al. 2014 [62]	Four regions, Ecuador, UMIC.	Historically controlled study.	Jan 2010-Aug 2010, and from Aug 2011-Jan 2012	191 (I: 105, C: 86)	DR-TB patients [resistance to at least one FLD] that received in-patient care for three months and then outpatient care. Mean age: 38 years; 73% male; 63% MDR TB.	Intervention group vs historical control group without support. 3 different regions vs whole Ecuador.	All DR-patients received a US$240 bonus after each month of adherence, defined as taking medications on 26 days per month for up to 24months. They can spend their bonuses according to their needs. They planned to spend their money on food, vitamins, rent, transportation, children's needs and medicine mainly.	The program was covered by governmental funds. Payments were arranged by the Central Bank of Ecuador, the Ministry of Economic and Social Inclusion and the NTP.	Loss to follow-up rate, not defined.	The program is part of the Ecuador's National Tuberculosis Program (NTP) NTP is a branch of the Ministry of Public Health, is a DOTS-based program with its headquarters in Quito
Sudarsanam et al. 2011 [49]	Southern Indian state of Tamil Nadu, India, LMIC	Randomized controlled trial.	Jan 2005 – Nov 2005	97 (I: 48, C: 49)	Newly diagnosed TB patients. Age: >12 years; 61.2% male; 20.6% HIV positive	Supplementation vs non-supplementation group	The supplementation group received a mixture of cereal and lentil. Three servings a day were provided (930 kcal and 31.5 g protein) and an one-a-day multivitamin tablet.	Funded by the Fogarty AIDS International Research and Training Program and the Global Infectious Disease Research Training grant	Cure: pulmonary smear-positive, completed treatment and had negative smear results on two occasions, one of which is at the end of treatment. Completion: Either pulmonary smear positive, completed treatment with negative smears at the end of the intensive phase but none at the end of treatment or pulmonary smear-negative or extra pulmonary and completed treatment. Unsuccessful: failure, death and loss to follow-up	.
Thiam et al. 2007 [51]	Senegal, LMIC.	Randomized controlled trial.	June 2003—May 2004	1522 (I: 778, C: 744)	Newly diagnosed smear positive pulmonary TB. 88% between 15–49 years; 67% male.	Intervention vs usual NTCP care. Geographical locations of the groups differed. Participants from 16 government districts in Senegal (8:8).	Reinforced counseling and communication between health personnel and patients, involving community health workers, choice of DOT supporter and reinforcement activities.	Funded through a special program from the French Ministry of research, called PAL, which was granted in September 2000.	Cure: negative sputum smear at 8 months and on at least 1 previous occasion. Completion: missing smear results but who had finished their treatment regimen. Loss to follow-up: definitely stopped treatment before completion.	The total support was divided into four components: improving counseling and communication between health personnel and patients through appropriate training, decentralizing treatment to remote health posts and involving community health workers, strengthening the DOT strategy by giving patients the opportunity to choose their treatment.

(*Continued*)

Table 2. (*Continued*)

Study	Country income*	Study type	Enrolment period	N*	Population	Comparison	Intervention(s)	Funding source and organization	Outcome(s)	Other
Wei et al. 2012 [63]	Shanghai, China, UMIC.	Controlled before-and-after study.	Baseline: July 2006—Sept 2007, intervention period: Oct 2007 –Dec 2008	183 (I: 90, C: 93)	Migrant pulmonary TB cases. Average age approx. 33 years; 9% male; 13% illiterate or semi-illiterate. 83% employed.	Intervention group vs control group without support. The two district names were anonymous to protect the patient's identities.	2 US$ per month for transportation for all migrants, and for all poor migrants (after assessment of poverty) a living allowance of 157 US $ was provided (in four installments 47 US$ at the time of diagnosis, 47 US$ at the end of the second month of treatment, 31 US $ at the end of the fourth month of treatment and 31 US$ at the end of the treatment). 78% and 60% of I and C were assessed to live in poverty; 60% of those in I received a living allowance and the transport subsidy.	Funded by the government. The intervention was designed to fit into the routine practices and job descriptions of the health providers from the CDC, TB clinic in the designated hospitals, and CHCs.	Loss to follow-up: the proportion of migrant TB patients who defaulted from treatment. Completion: the proportion of TB patients who have successfully completed treatment among all the migrant TB patients (treatment success). Financial burden: Percentage of total costs.	Incremental cost-effectiveness analysis. In total, this project involved an investment of RMB 52,400, which consisted of RMB 46,000 of financial subsidy and RMB 6,400 of transport incentives. This additional cost prompted an increase of 8% in treatment completion rate in the intervention district as compared to the control district. This suggests that for each percent increase in treatment completion, an additional cost of RMB 6,550 (US$ 1301) was invested in the intervention district. Similarly, this additional cost delivered a reduction of 10% in the default rate in the intervention district compared with the control district, showing that an additional cost of RMB 5,240 (US$825) was needed to reduce each percent in default rates.
Zou et al. 2013 [64]	Shanghai, China, UMIC.	Controlled before-and-after study.	For baseline: July 2006—Sept 2007. For intervention: Oct 2007—Dec 2008	787 (I1: 90, baseline: 143. I2: 173, baseline: 155. C:93, baseline 133)	Rural to urban migrant active TB cases. Average age, I1: 30, I2: 33, C: 35 years; more patients from I1 and I2 came to Shanghai alone (65% and 47% compared to 30%) other characteristics for the whole population are unclear.	Intervention 1 or intervention 2 vs control group without support. Participants came from 3 districts in downtown Shanghai (1:1:1)	1: A living subsidy of US$ 146 was provided to each poor migrant TB patients (after financial assessment) in four instalments. Every migrant also received US$ 1.50 per month as a transportation incentive. 2: All TB patients, regardless of economic status received a living subsidy of US$ 114 (US$ 19 per month over 6 months) and a transportation incentive of 4.4 US$.	Intervention 1 funded by the Communicable Disease Research Consortium (COMDIS) for the UK Aid Program. Intervention 2 was funded by the Global Fund. The COMDIS approach did not require extra investment from the health provider as the Global Fund approach did. The COMDIS approach might achieve better cost savings as it focused on providing financial incentives only to poor migrant TB patients	Treatment success (completion and cure), loss to follow-up and death. Nod definitions available. Financial burden was described as: cost-effectiveness.	For each percent increase in treatment completion, an additional cost of US$ 1301 was invested in the intervention district. For each percent decrease in loss to follow-up additional costs of US$ 825 was needed.

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per month [44,48,52,57,62–64]. Four studies provided direct economic support exclusively [48,62–64]. Other studies only provided economic support for the first three months and 5 US $ per month for travel expenses [57] or arranged reimbursement of travel for an unknown amount of money, combined with food supplementation, other material support and psycho-emotional support [44]. The remaining three studies also combined socio-economic support with psycho-emotional support. No studies on 'enterprise assistance' were found. Details on economic support provided per study are retrievable in Table 2.

Funding sources and organization. Information on funding sources and involvement of local bodies in the organization of the interventions can be found in Table 2. Seven SSIs were financed through governmental funding or local authorities. Another nine interventions were funded by foreign donor assistance (e.g. WHO, Unicef). Three interventions received combined funding (local and foreign donor assistance). For the remaining five interventions the funding source was unknown.

In total nine studies provided information on the organization of interventions, including six RCTs [46,50–52,55,67] and three NRS [44,59,66]. A study from Russia organized and implemented support by regional TB services and a local international organization[23] and a study from Nicaragua raised TB clubs organized by TB patients, with the help of local non-governmental organizations [59]. Community involvement was integrated into regular patient management in Burkina Faso [44,59,67]. The remaining studies reported very limited information on organizational sustainability.

Incentives and enablers. All the RCTs defined their support as incentives. Incentives are rewards for adherence while enablers assist patients to overcome barriers to treatment adherence. Most studies provided support to all TB patients. In studies where only poor patients were supported [64]; it may be that the support in fact was in the form of enablers.

Risk of bias and quality of evidence

Risk of bias was assessed for all included RCTs, including six Cluster Randomized Trials [47,50–52,60,67]. Only five out of eleven RCTs described an adequate randomization approach [50–52,58,60]. For the majority of the studies it was not described whether investigators were blinded to the outcome, and assessment of reporting bias was not possible due to a lack of information. None of the Cluster Randomized Trials assessed baseline imbalances between clusters or took random effects into account in the analysis. Ten NRS were assessed on risk of bias, including eight cohort studies and two case-control studies. Four studies [20,56,63,66] were not included in the meta-analysis and risk of bias assessment; reasons for exclusion are described in Table 3. Only three NRS adjusted for one or more confounders in the analysis [44,48,53]. Five additional studies were not included because of inadequacy of follow-up and/or assessment of outcome measures [44,48,53,62,68]. More information on the risk of bias assesment of the RCTs and NRS can be found in the supportive information S1–S3 Tables. Quality of evidence was assessed for the included RCTs per outcome measure. The quality of evidence for the RCTs was downgraded with one level for risk of bias, two levels on indirectness of studies and one level for limitations in consistency of the results. Hence, the overall quality of evidence of this systematic review is considered to be very low [40,69–74]. The quality of evidence per outcome measure is similar to the overall quality of evidence and retrievable in the summary of findings table (Table 4). No rating up for the overall quality of evidence was possible. Based on the funnel plot for the results of the ten RCTs included in the meta-analysis, it was not possible to determine whether publication bias was present (Fig 2)[28]

Table 3. Studies excluded from quantitative analysis.

Study	Type of study	Population	Dot	intervention	Outcome	Effect	Reason(s) for exclusion
Bock 2001 [20]	Historically controlled study	Non-adherent TB patients	Yes	Indirect economic support	Adherence	≤32 weeks OR 5.73 [CI 2.25–14.84] ≤52 weeks 7.29 [2.45-22-73]	Methodological diversity: outcome different than in other studies.
Davidson 2000 [56]	Case-control study	TB patients	Yes	Indirect economic support	Adherence	The odds that a patients with 100% adherence under incentives program will adhere 2.7 (1.01^{100}) times as great as person receiving the basic incentive package.	Methodological diversity: not possible to calculate absolute numbers from the effects.
Gelmanova 2011 [66]	Case series	TB patients that participated in at least one intervention to improve adherence before referral to the Sputnik program.	Yes	Home visits, other psychological and other social support	Adherence	Increased from 52.2% [CI 47.5–56.9] to 81.4% [CI 76.8–86.0]	Methodological and clinical diversity: high risk of bias on the 'selection' and 'outcome' domain (S2 Table). Study population only includes non-adherent patients, which were their own controls.
Wei 2012 [63]	Controlled before–and–after study	(Poor) Migrant TB patients	Unclear	Direct economic support	Treatment success, loss to follow-up and death.	Significant reduction of default rates (11% vs 1%, P = 0.03) in intervention district compared to the control district	This study was part of a bigger study (Zou et al. 2013 [64]), therefore this study was excluded.

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Meta-analysis

Eleven RCTs, eight cohort studies, and two case-control studies were included in the meta-analysis, including 17 743 patients (9655 patients participating in RCTs and 8088 patients in NRS). Most data originated from Brazil, China, Russia, Senegal and South Africa. No evidence was found concerning the effect of SSI on financial burden. Only one NRS measured the cost-effectiveness ratio of the provided economic support [64]. Studies assessing the effect of SSI on treatment adherence were too heterogeneous to pool. Meta-analysis of different outcome measures are presented separately (Figs 3 and 4).

Treatment outcomes. In total, nine RCTs had treatment success as an outcome measure (Fig 3). The overall effect of these studies showed a significant positive effect (RR 1.17; CI 1.09–1.25), however significant heterogeneity was observed (I^2 of 72.8%, P = <0.001). Stratified analyses were performed for the different types of interventions. Three studies provided PE support [50,52,55] including counseling, psychotherapy and the organization of self-help groups. A significant pooled effect was found for this intervention (RR 1.37; CI 1.08–1.73). The association between SE support and treatment success was examined by four studies [47,49,58,60] providing food supplementation and economic support. A significant pooled effect was found for this intervention (RR 1.08; CI 1.03–1.13). Combined support was provided by three studies [51,52,67]. Also, a significant pooled effect was found for these interventions on successful treatment outcomes (RR 1.17; CI 1.12–1.22). No significant heterogeneity was observed in two of three stratified analyses (SE: I^2 of 14%, P = 0.32; combined: I^2 of 0%, P = 0.42). Studies that provided PE support were substantially heterogenic and the p-value for the Chi^2 test was significant (I^2 of 78%, P = 0.01) (Fig 3). A sensitivity analysis was performed on the effect of PE support on treatment success, comparing high vs. low risk of bias studies. Omitting one high risk of bias study removed heterogeneity (I^2 of 0%, P = 0.53) (data not shown), and did not change effect size (RR 1.20; CI 1.07–1.35) [55]. Sensitivity analysis on MDR-TB patients vs. non-MDR-TB patients did not change the effect size and statistical significance (data not shown).

Table 4. Summary of findings.

Outcomes	Social support intervention (s)	Relative risk (CI)	Number of participants (studies)	Quality of evidence*	Risk of bias	Inconsistency	Imprecision	Indirectness
Treatment success	Social support interventions (overall)	1.17 (1.09–1.25)	6547, 10 studies	Very low	Serious risk of bias	Serious inconsistency, downgraded with one level due to high heterogeneity (I^2 of 72.8%, P = <0.001).	No serious imprecision, adequate sample size (n = 345).	Very serious indirectness
Treatment success	Psycho-emotional support	1.37 (1.08–1.73)	400, 3 studies	Very low	Serious risk of bias, downgraded with one level for high risk of bias on two domains for one study.	Serious inconsistency, downgraded with one level due to high heterogeneity (I^2 of 78%, P = 0.011) and large variation in point estimates.	No serious imprecision, adequate sample size (n = 44)	Very serious indirectness, downgraded with two levels. The studies provided different PE interventions (counseling, psychotherapy and self-help groups). One study provided the intervention to a different population (MDR-TB patients). In addition, mostly indirect comparisons are made.
Treatment success	Socio-economic support	1.08 (1.03–1.13)	4324, 4 studies	Very low	Serious risk of bias, downgraded with one level on high risk of bias on one domain in three studies.	No downgrading for inconsistency	No serious imprecision, adequate sample size (n = 748).	Very serious indirectness, downgraded with two levels. Three included studies provided food supplementation; one study provided indirect economic support. In addition, mostly indirect comparisons are made.
Treatment success	Combined support	1.17 (1.12–1.22)	1823, 3 studies	Very low	Serious risk of bias, downgraded with one level for high risk of bias on two domains in one study.	No downgrading for inconsistency	No serious imprecision, adequate sample size (n = 133).	Very serious indirectness, downgraded with two levels. All studies provided counseling and one or more PE and/or SE interventions. One study provided the intervention to a different population (MDR-TB patients). In addition, mostly indirect comparisons are made.

(*Continued*)

Table 4. (*Continued*)

Outcomes	Social support intervention (s)	Relative risk (CI)	Number of participants (studies)	Quality of evidence*	Risk of bias	Inconsistency	Imprecision	Indirectness
Unsuccessful treatment outcomes	Social support interventions (overall).	0.53 (0.41–0.70)	7301, 10 studies	Very low	Serious risk of bias	Serious inconsistency, downgraded with one level due to high heterogeneity (I^2 of 80.2%, P = <0.001) and large variation in point estimates.	No serious imprecision, adequate sample size (n = 358)	Very serious indirectness
Unsuccessful treatment outcomes	Psycho-emotional support	0.46 (0.22–0.96)	1419, 4 studies	Very low	Very serious risk of bias, downgraded with two levels for high risk of bias in two studies with high risk of bias on two domains.	Serious inconsistency, downgraded with one level due to high heterogeneity (I^2 of 85.5%, P = <0.001) and large variation in point estimates.	No serious imprecision, adequate sample size (n = 267).	Very serious indirectness, downgraded with two levels. The studies provided different PE interventions (counseling, psychotherapy and self-help groups). One study provided the intervention to a different population (MDR-TB patients). In addition, mostly indirect comparisons are made.
Unsuccessful treatment outcomes	Socio-economic support	0.78 (0.69–0.88)	3967, 2 studies	Very low	Serious risk of bias, downgraded by one level for high risk of bias on one domain in 2 studies.	Serious inconsistency, downgraded with one level due to large variation in point estimates (RR = 0.2 and 0.78).	No serious imprecision, adequate sample size (n = 1059).	Very serious indirectness, downgraded with two levels. The studies provided different SE interventions (food supplementation and indirect economic support). In addition, mostly indirect comparisons are made.
Unsuccessful treatment outcomes	Combined support	0.42 (0.23–0.75)	1915, 4 studies	Very low	Serious risk of bias, downgraded by one level for high risk of bias on two domains in one study and one study with high risk of bias on one domain.	Serious inconsistency, downgraded with one level due to high heterogeneity (I^2 of 64.2%, P = 0.039) and large variation in point estimates.	No serious imprecision, adequate sample size (n = 127).	Very serious indirectness, downgraded with two levels. All studies provided counseling and one or more PE and/or SE interventions. One study provided the intervention to a different population (MDR-TB patients). In addition, mostly indirect comparisons are made.

* GRADE Working Group levels of evidence.

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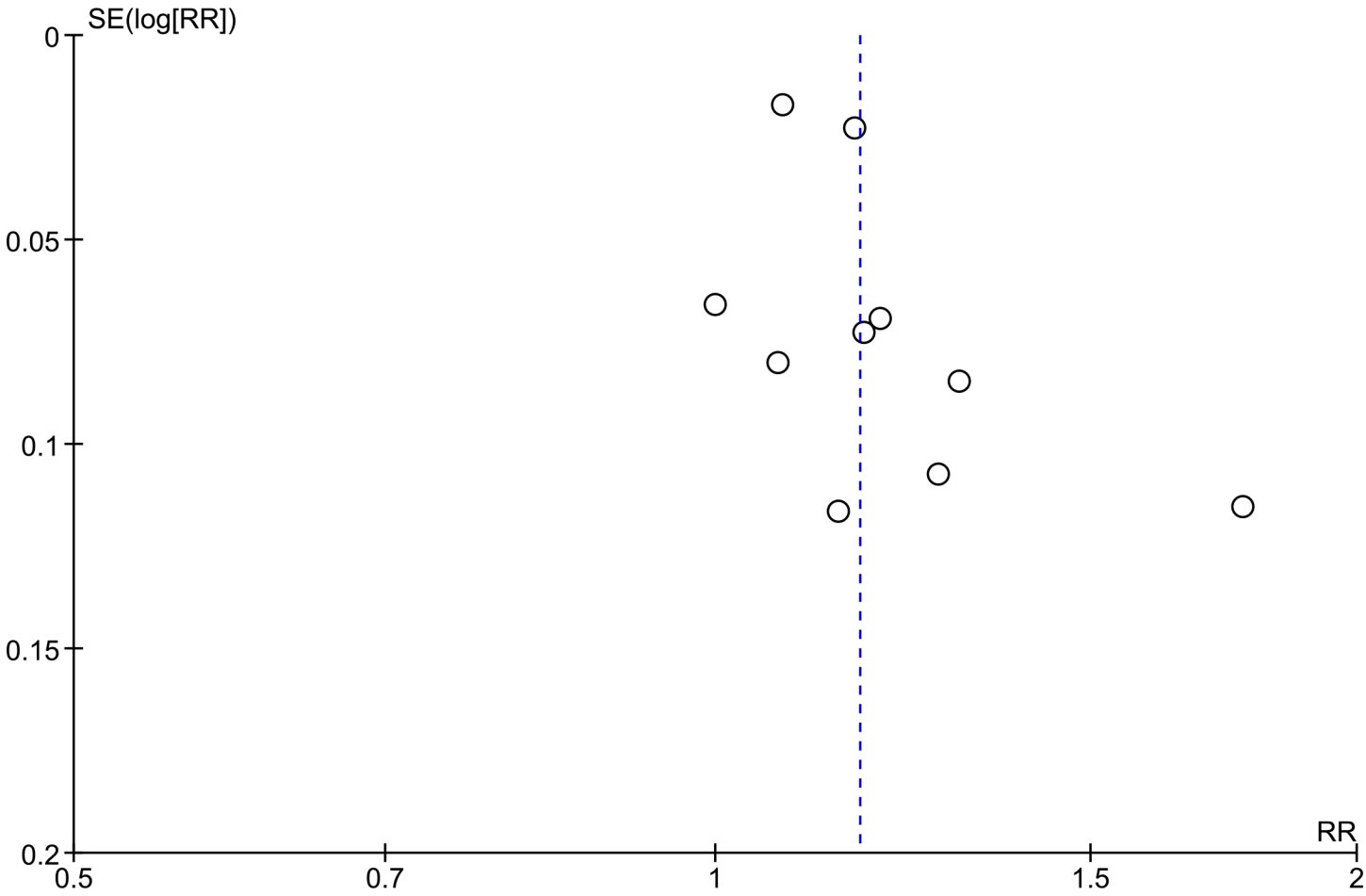

Fig 2. Funnel plot to evaluate publication bias in Randomized Controlled Trials on the effects of social support interventions on treatment outcomes.

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Nine studies had unsuccessful treatment outcomes as an outcome measure including seven also having treatment success as an outcome measure (Fig 4). An overall significant protective effect was found (RR 0.53; CI 0.41–0.70), however, substantial heterogeneity was observed (I^2 of 80.2% and P = <0.001). Stratified analyses were performed on the different interventions provided. Four studies investigated the effect of PE support on unsuccessful treatment outcomes, including counseling, psychotherapy and the organization of self-help groups [46,50,52,55]. Two studies examined the effect of SE support, including food supplementation and economic support [47,58] and four studies assessed the effect of combined support [51,52,61,67]. A significant reduction in unsuccessful treatment outcomes was found for all three stratified analyses: PE support (RR 0.46; CI 0.22–0.96), SE support (RR 0.78; CI 0.69–0.88) and a combination of PE and SE support (RR 0.42; CI 0.23–0.75). Heterogeneity was considered to be very low for the studies that provided SE support interventions (I^2 of 0% and P = 0.37). The studies that provided PE support and combined support were substantially heterogenic (PE: I^2 of 85%, P = <0.001 and combined: I^2 of 64% (P = 0.03) (Fig 4). A sensitivity analysis was performed in the PE stratum on the basis of higher risk of bias compared to the other studies [46,55]. Removal of one high-risk of bias study [46] decreased the I^2 to 0% (P = 0.54) and the effect size changed but remained statistically significant (RR 0.33; CI 0.22–

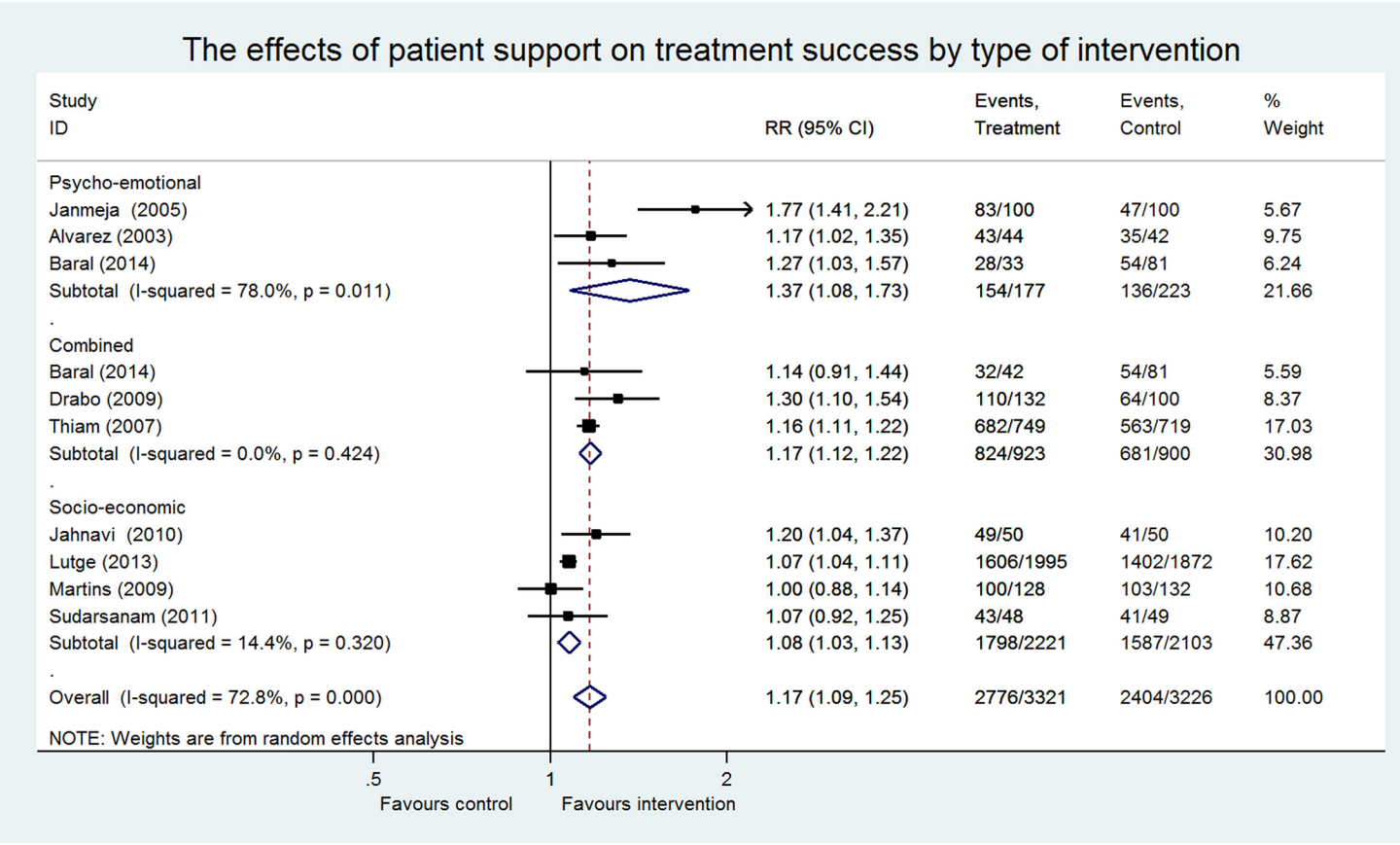

Fig 3. The effects of social support on treatment success by type of intervention in Randomized Controlled Trials.

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0.50). Omitting both biased studies did not change heterogeneity or the effect size. Sensitivity analysis on risk of bias was not possible in the studies providing a combination of PE and SE support, due to the fact that 3 out of 4 studies were classified as biased studies. Sensitivity analyses on MDR-TB patients vs. non-MDR TB patients did not change the effect size or heterogeneity significantly (data not shown).

Treatment adherence. Three RCTs assessed the effect of PE and/or SE on treatment adherence. A PE-intervention study conducted in Mexico showed a significant improvement in treatment adherence (RR 1.20; CI 1.03–1.39). A study from the USA did not show significantly higher levels of adherence in the intervention group compared to the group that received usual care (RR 1.11; CI 0.92–1.33). A third study from Timor-Leste showed no effect for patients that received SE support compared to patients that did not receive this support (RR 1.01; CI .0.85–1.21). Above-described interventions were not pooled as they were too heterogeneous.

Financial burden. None of the RCTs examined the effect of PE or SE support on financial burden for TB patients.

Non-randomized studies. Due to the fact that the studies' characteristics were heterogeneous on several levels and at higher risk of bias than the RCTs, we chose not to pool the effects for these studies (S1 and S3 Figs) [28,75]. Seven NRSs reported an effect of social support on successful treatment outcomes. Effects of interventions on successful treatment outcomes (RR) ranged from 1.03 to 2.51 (CI 0.96–2.99). Five of seven NRSs reported significant effect sizes

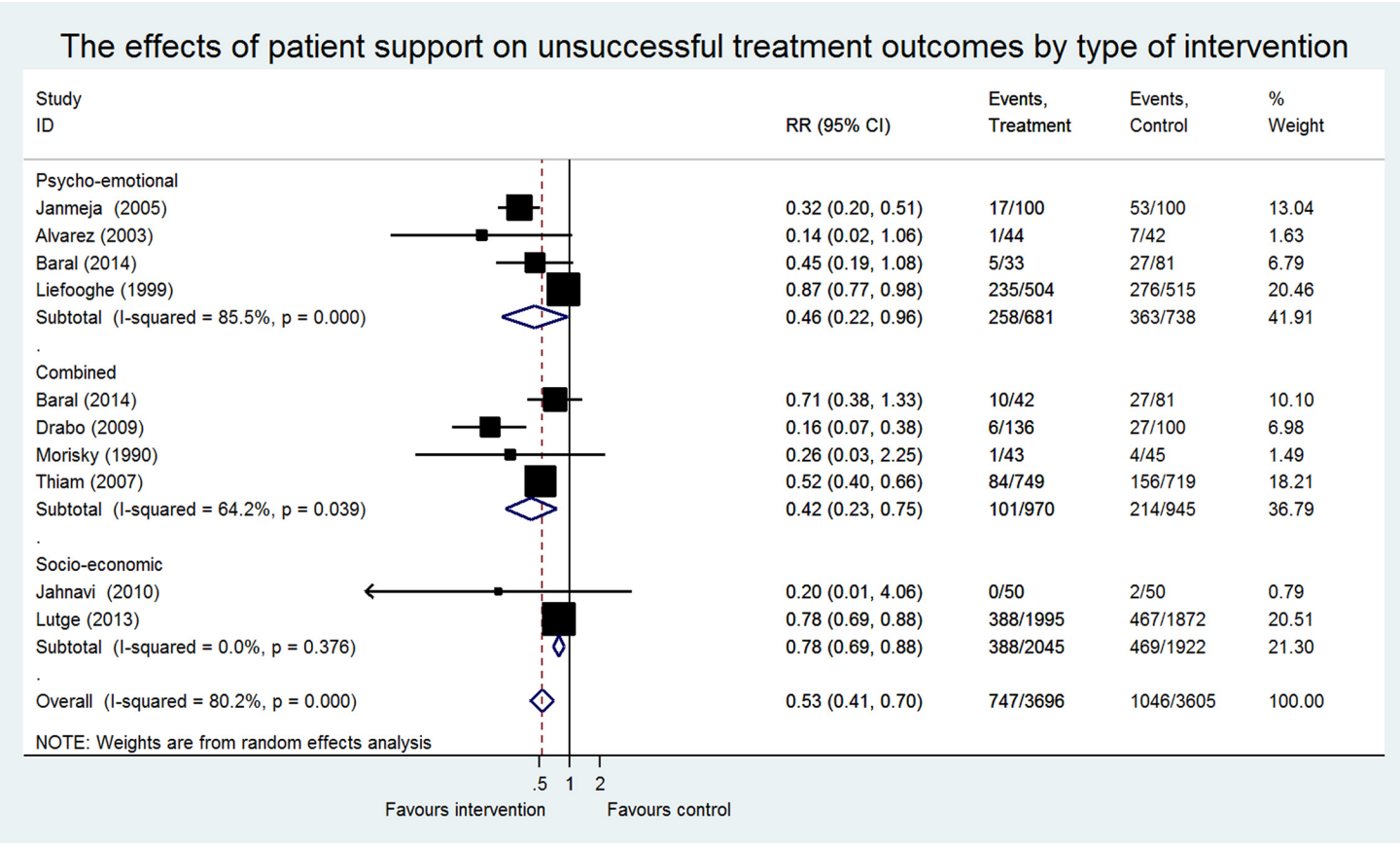

Fig 4. The effects of social support on unsuccessful treatment outcomes by type of intervention in Randomized Controlled Trials.

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[48,54,57,64,68]. Two studies found no significant effects [45,59]. Furthermore, six NRSs examined the effect of social support on unsuccessful treatment outcomes. Effect sizes varied from RR 0.32–0.96 (CI 0.18–3.49). Five out of six NRSs showed significant beneficial effects [45,54,62,64,68]. Only one study reported a non-significant effect [59]. In addition, two case-control studies investigated the effect of social support on unsuccessfull treatment outcomes. Both studies showed significant beneficial effects (RR 0.51 (CI 037–0.70) and RR 0.10 (CI 0.05–0.20)).

Discussion

This review found that PE and SE support did improve treatment outcomes across a variety of settings and patient populations, with a tendency towards better outcomes with PE interventions or a combined approach. However, the quality of evidence was classified as "very low" under the GRADE approach. Food supplementation and counselling were commonly included in the package of support. PE, SE and combined interventions improved treatment outcomes; only for interventions including SE support exclusively there was no significant improvement in treatment success. Overall, support interventions were associated with significantly higher treatment success (overall RR 1.08; CI 1.03–1.13) and reductions in unsuccessful treatment outcomes (overall RR 0.53; CI 0.41–0.70). Hardly any studies assessed the effect of interventions on treatment adherence. However, improved treatment adherence is an intermediate goal with the final aim to improve treatment outcomes, which was shown to improve.

A recent systematic review concluded that the economic burden for patients is considered to be high, loss of income is an important indirect cost factor for TB patients, and transport and nutritional supplementation were important direct cost components [8]. A study in Peru evaluated the expenses for MDR-TB patients that received free treatment and found that having MDR-TB was associated with high costs, which was associated with adverse outcomes (population attributable fraction 18–20%) [76]. In line with our review, these two studies suggest that economic support is of great importance for improving treatment outcomes. Some of the findings of this review however differ from those from other SSI-related reviews. A recent review [77] on RCTs assessing the effect of material incentives on TB treatment adherence and completion of TB treatment identified two trials, both included in our review as well [47,60], and neither demonstrated a clear benefit. However, in one trial the incentive was not well received by the patients and in the other trial fidelity to the intervention was low. A review of Sinclair et al. did not find any evidence that food supplementation had a beneficial impact on treatment outcomes [78]. This may be explained by their focus on micronutrient supplementation alone as reflected in their search strategy. In a systematic review about strategies to reduce loss to follow-up in drug-resistant patients, a comprehensive package of interventions (e.g. financial support and food supplementation) was associated with reduced loss to follow-up [79]. Our review included studies focusing on all TB patients, not only those with MDR-TB [79]. As mentioned in the methods section, we did not consider interventions aimed only at providing improved information or education to TB patients, given the recent systematic review showing a lack of its evidence related to TB treatment [17]. Some of the intervention packages included in our review included an information or education component, but it was not possible to delineate the effects of this specific component in our review. We also did not include interventions focusing only on reminder systems, as these are not considered PE or SE support. However, reminder systems can be integrated into SSI programs to enhance its effects since pre-appointment reminder phone calls and letters or home visits did have a small but potentially relevant effect on treatment completion [30].

There were some limitations to our review. Only a limited number of studies were available on the effect of PE/SE support interventions on TB treatment outcomes and very limited evidence on treatment adherence and financial burden. Within the identified studies, we were not able to stratify results by the type of organization and quality of health service delivery due to insufficient information, although it is known that organization and quality of health service delivery influence treatment adherence [9]. Some NRSs only provided support to subgroups of patients including poor patients [64], patients that already received support before referral to the intervention studied [66] and non-adherent patients [20]. This precludes conclusions on the effects of these interventions when provided to all patients. Such patient selection may have led to overestimations in the observed effect of the PE/SE interventions. On the other hand, selecting patients most in need seems prudent and is in practice applied in resource-limited settings. Although the number of studies included in the meta-analysis was small, the optimal size criterion was sufficient both for the overall meta-analysis and stratified analyses as examined by calculation of the sample size for the overall effect and subgroup analyses [72]. We could not examine for a dose response rate across all included studies, as most studies did not include a comprehensive description of interventions. However, one study did show a positive dose-response within their study regarding provision of indirect economic support: among patients in the intervention group who received the voucher at least once, treatment success rates significantly improved [47]. Furthermore, the more frequent the vouchers were received by patients, the higher their probability of treatment success [47]. Plausible heterogeneity was observed and seven out of

eleven RCTs had a high risk of bias on one or two domains. However, we did not exclude studies on the basis of heterogeneity only, as this may introduce bias [42].

Conclusions

This review provides evidence to endorse implementation of SSI in order to improve treatment outcomes. Firstly, PE and combined PE/SE support have a beneficial impact on treatment success. Secondly, SE support and a combination of PE/SE support are associated with reductions in unsuccessful treatment outcomes. No conclusions can be drawn considering the overall effect of PE and/or SE support on treatment adherence and financial burden due to a lack of evidence. Our findings need to be interpreted with caution, as the quality of the evidence included in the meta-analysis is "very low" based on the GRADE approach. In addition, most support included multifaceted types of interventions, so no conclusions can be drawn on the effect of individual interventions. Simultaneously, this might signify that multifaceted types of interventions are needed to improve treatment outcomes. High quality evidence, from well-designed randomized studies in larger sized populations, would provide more certainty on the effects of different PE and SE interventions. Cluster-randomized studies would provide an opportunity to compare differential packages and delineate the importance of specific components. In addition, more systematic data collection on PE and SE as already used by TB programs to monitor implementation and evaluate its effects and qualitative data collection in both studies and program settings to assess which interventions are most appreciated and most feasible to implement on a wide scale, would be useful. Reports should include information on costs and sustainability to provide information on efficiency and scalability.

Supporting Information

S1 PRISMA Checklist. PRISMA checklist.
(DOC)

S1 Fig. The effects of social support on treatment success in non-randomized cohort studies.
(PNG)

S2 Fig. The effects of social support on unsuccessful treatment outcomes in non-randomized cohort studies.
(PNG)

S3 Fig. The effects of social support on unsuccessful treatment outcomes in Case-control studies.
(PNG)

S1 Table. Risk of bias assessment–Cochrane collaborations tool for randomized controlled trials.
(DOCX)

S2 Table. Risk of bias assessment–New-castle Ottawa scale for non-randomized studies.
(DOCX)

S3 Table. Risk of bias assessment–New-castle Ottawa scale for case-control studies.
(DOCX)

S1 Web Annex. Full text search strategy per database.
(DOCX)

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Author Contributions

Conceived and designed the experiments: SH RH. Performed the experiments: SH RH. Analyzed the data: SH RH. Wrote the paper: SH RH DC EJ AG.

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The tuberculosis profile of the Philippines, 2003–2011: advancing DOTS and beyond

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The Philippines is one of the highest tuberculosis (TB) burden countries in the world with nationwide coverage of directly observed treatment, short-course (DOTS) achieved in 2003. This study reports on the National TB Control Programme (NTP) surveillance data for the period 2003 to 2011. During this period, the number of TB symptomatics examined increased by 82% with 94% completing the required three diagnostic sputum microscopy examinations. Of the 1 379 390 cases diagnosed and given TB treatment, 98.9% were pulmonary TB cases. Of these, 54.9% were new smear-positive cases, 39.3% new smear-negative cases and 4.7% were cases previously treated. From 2008 to 2011, 50 030 TB cases were reported by non-NTP providers. Annual treatment success rates were over 85% with an average of 90%; the annual cure rates had an eight-year average of 82.1%. These surveillance data represent NTP priorities – the large proportion of smear-positive cases reflected the country's priority to treat highly infectious cases to cut the chain of transmission. The performance trend suggests that the Philippines is likely to achieve Millennium Development Goals and Stop TB targets before 2015.

The Philippines is an archipelago of more than 7107 islands with an area of 300 000 km^2 in south-eastern Asia. The country is divided into 17 administrative regions with 81 provinces, 136 cities including 16 highly urbanized centres, 1495 municipalities and 42 008 barangays.[1] The population of the Philippines was 92.3 million in 2010 with 33.4% aged between zero and 14 years, 62.3% in the working age group of 15–64 years, and 4.3% being 65 years and older.[2] Poverty incidence in the population was 26.5% in 2009.[3]

Tuberculosis (TB) is the sixth leading cause of morbidity and mortality in the Philippines; the country is ninth out of the 22 highest TB-burden countries in the world and has one of the highest burdens of multidrug-resistant TB. Directly observed treatment, short-course (DOTS)[4] strategy for TB control commenced in 1997 and nationwide coverage was achieved in 2003.[5] The prevalence of TB in 2007 was 2.0 per 1000 for smear-positive TB and 4.7 per 1000 for culture-positive TB. Compared with 1997, there was a 28% and 38% decline in prevalence for smear-positive and culture-positive TB, respectively.[6]

The National TB Control Programme (NTP) is managed by a central team at the National Center for Disease Prevention and Control of the Department of Health.[4] This team develops policies and plans and provides technical guidance to regional and provincial/city-level NTP management teams, overseeing the implementation of the programme at the municipal and *barangay* levels based on NTP policies and standards.

Under NTP, TB control services are provided mainly through public primary health care facilities (also called DOTS facilities) operated by local government units in a devolved set-up. There are additional DOTS facilities within the NTP's network of service providers that either refer diagnosed TB patients for treatment or directly provide TB treatment services using DOTS strategy. These include private outpatient clinics; public and private primary, secondary and tertiary care hospitals; workplaces; clinics under faith-based organizations and community-based nongovernmental organizations (NGOs); and public institutions such as military facilities, jails and prisons. The NTP has also established public–public and public–private partnerships for TB control consisting of public non-NTP providers such as public hospitals, public medical colleges, prisons/detention centres and military facilities; private DOT providers include private physicians, private hospitals, private clinics, private workplaces and NGOs. Nationwide expansion of TB testing in children has been part of NTP

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since 2004,[7] while the programmatic management of drug-resistant TB was mainstreamed into NTP starting in 2008.[8]

The NTP surveillance system is based on the standardized recording and reporting system used in all DOTS facilities under the NTP network of providers. Reports from rural health units, health centres and other DOTS providers include data for laboratory, case finding and case holding activities. These are reported quarterly and annually to the provincial or city health offices on paper-based, standardized forms. The provincial or city health offices then consolidate these paper-based reports and convert them into an electronic format (in tabular form using Microsoft Excel or Word). These are then forwarded to the respective regional health offices for consolidation and further analysis. The regional electronic-based reports are then forwarded to the central NTP team at the Department of Health.

Modernization of the TB registry was initiated in 2005 with the launching of the electronic TB registry in two regions (National Capital Region and CHD III Central Luzon). However, the initiative was discontinued in 2010 and was replaced by the Integrated TB Information System in 2011. This system is being implemented in phases and is currently used in selected facilities in four of the country's 17 regions including South Luzon, National Capital Region, Central Luzon and Western Visayas.

The objective of this report is to provide a national summary of TB cases reported to the NTP surveillance system from 2003 to 2011.

METHODOLOGY

Data submitted to the central NTP team for the nine-year period 2003 to 2011 were consolidated and summarized. Descriptive statistics were used to analyse the data. Treatment outcome data are for 2003 to 2010 only; 2011 data are not yet complete and not included in the report.

As case finding and treatment outcome data for drug-resistant TB are not fully integrated into the system, they are not included in this report. Data for pulmonary TB (PTB) cases previously treated were disaggregated by case classification starting only in 2008 and are only reported for 2008 to 2011.

RESULTS

TB cases

From 2003 to 2011, a total of 4 638 939 TB symptomatics were examined with sputum smear microscopy (**Figure 1**). On average, 94% of TB symptomatics completed the required three diagnostic sputum microscopy examinations each year. Compared to 2003, the number of TB symptomatics examined increased by 82% in 2011.

From these, a total of 1 379 390 cases of TB all forms were diagnosed and given TB treatment from 2003 to 2011. PTB comprised 98.9% of all TB cases notified; extra-pulmonary TB (EPTB) made up the remaining 1.1%. The nine-year average proportions of PTB cases are disaggregated as follows: new smear-positive, 54.9%; new smear-negative, 39.3%; and cases previously treated, 4.7% (**Figure 2**). Compared to 2003, the number of new smear-positive PTB cases increased by 34% in 2011; new smear-negative PTB cases increased by 70%.

Non-NTP providers

From 2008 to 2011, a total of 50 030 TB cases were reported by non-NTP providers – 7.4% of total cases reported to NTP in this time (**Table 1**). Most of these were from the private sector (38 565, 77.1%); 11 465 were from public partners (22.9% from 2010 to 2011 only).

New smear-positive PTB cases

The case notification rate (CNR) for new smear-positive PTB cases increased from 2003 to 2011 (**Figure 3**). The lowest CNR was in 2003 (86 per 100 000) and the highest was in 2006 (100 per 100 000). During the nine-year period, 63% of new smear-positive cases were aged 25 to 54 years, with 20% in the 25–34 years age group, 22% in the 35–44 years age group and 21% in the 45–54 years age group (**Figure 4**). The average male-to-female ratio for the period was 2.3.

Cases previously treated

The number of PTB cases previously treated increased from 2008 to 2011 (**Table 2**). On average, relatively large proportions of PTB cases previously treated were

Figure 1. **Number of TB symptomatics examined and proportion that had three diagnostic sputum microscopy examinations by year, the Philippines, 2003 to 2011**

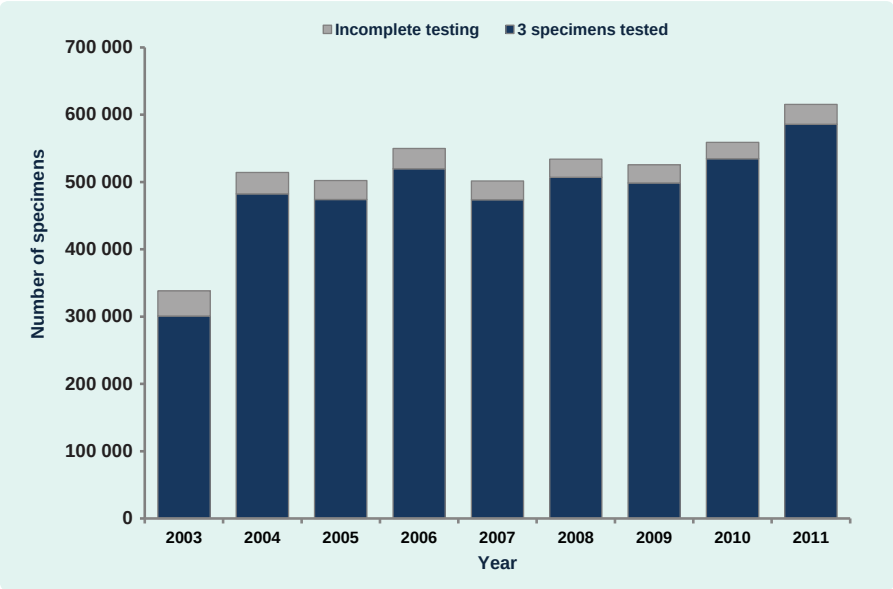
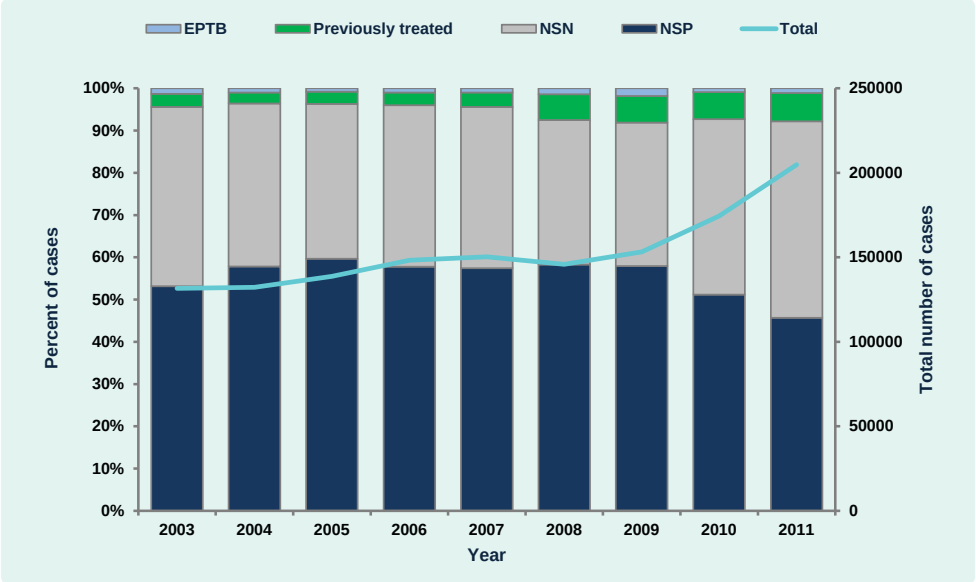


Figure 2. **Total number of TB cases and the proportion by case classification, the Philippines, 2003 to 2011**



EPTB – extrapulmonary TB; NSN – new smear-negative TB; NSP – new smear-positive TB

from relapses (27%) or other smear-negative cases (50%).

Treatment outcomes

Treatment outcomes for successive yearly cohorts of new smear-positive cases from 2003 to 2010 showed treatment success rates of over 85% with an average of 90% (**Table 3**). The average annual cure rate for eight years was 82.1%. The eight-year annual average for the other treatment outcomes were: treatment completed at 7.9%, death at 2.3%, treatment failure at 1%, defaulted from treatment at 4.4%, and transferred out at 2.4%.

DISCUSSION

Changes observed in the TB surveillance data in the Philippines from 2003 to 2011 reflected NTP priorities. The increase in the number of reported TB cases can be attributed to various NTP initiatives to improve access

Figure 3. **Case notification rate of new smear-positive cases by year, the Philippines, 2003 to 2011**

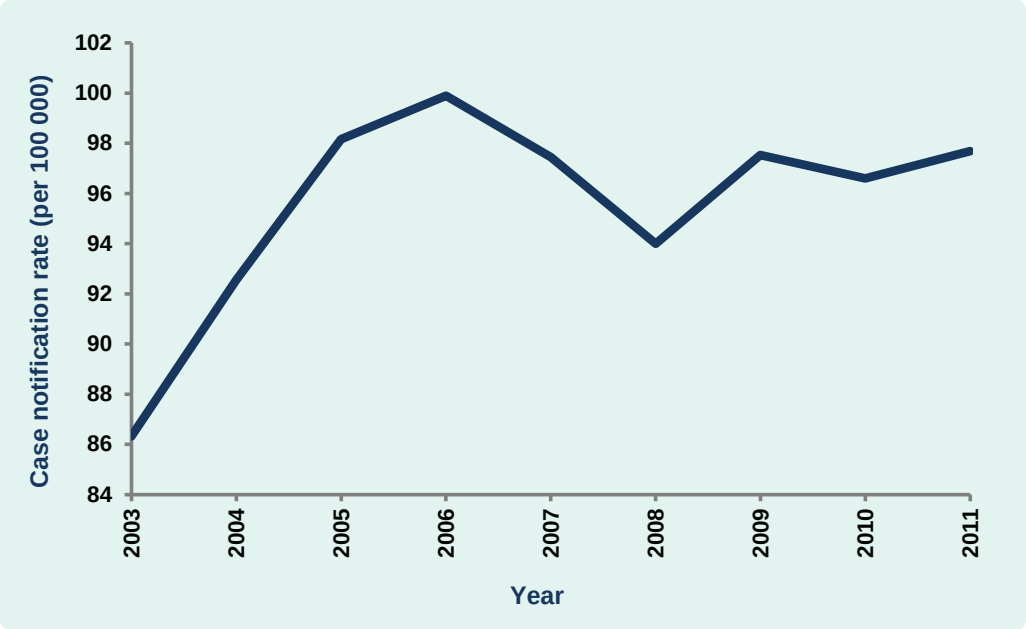


Figure 4. **Proportion of all new smear-positive cases by age group, the Philippines, 2003 to 2011**

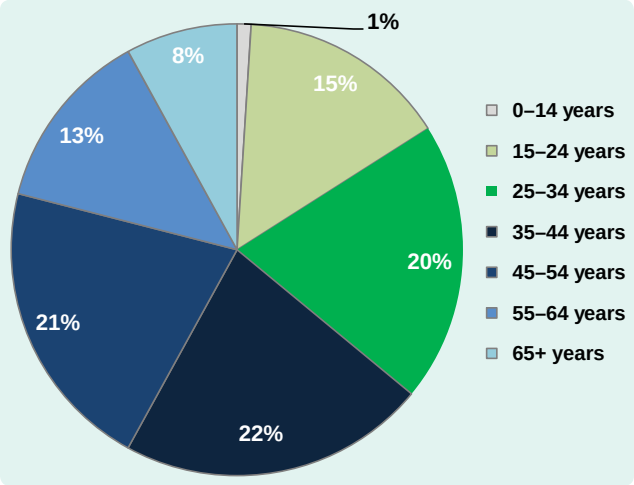


Table 1. **Number of TB cases reported by non-NTP public and private health providers, the Philippines, 2008 to 2011**

Year	Private providers	Non-NTP public providers	Total
2008	6 914	–	6 914
2009	4 866	–	4 866
2010	12 081	2 138	14 219
2011	14 704	9 327	24 031
Total	**38 565**	**11 465**	**50 030**

NTP – National TB Control Programme

to diagnostic and treatment services especially for the vulnerable sectors. Examples of these initiatives include the expansion of laboratory services and establishing partnerships with public and private health providers. The number of cases contributed by the non-NTP public and private partners also increased from 2008 to 2011; in 2011, these partnerships contributed 11.7% of the total number of cases notified.

More than half the cases per year were new smear-positive cases (apart from 2011 at 46%). This reflects NTP's high priority for the detection and treatment of highly infectious TB cases to cut the chain of transmission. The increase in the number of new smear-negative cases in 2010 and 2011 reflects a change in programme priorities to detect all forms of TB following the new WHO recommendations issued at that time.[9] It also explains the decrease in the proportion of new smear-positive cases in 2011. The increasing trend in the number of cases previously treated from 2008 may be due to the heightened efforts to detect drug-resistant TB cases among these cases. Also in 2008 the management of drug-resistant TB cases was mainstreamed into NTP.

The global target for treatment success rate is 85%,[10] this has been exceeded in the Philippines with an

Table 2. **Number and proportion of pulmonary tuberculosis cases previously treated by case classification and year, the Philippines, 2008 to 2011**

Year	Relapses		Returns after default		Treatment failure		Other (smear-positive)		Other (smear-negative)		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
2008	2 577	29	720	8	522	6	864	10	4 183	47	8 866	100
2009	2 973	31	804	8	585	6	947	10	4 266	45	9 575	100
2010	3 075	28	914	8	566	5	1 135	10	5 451	49	11 141	100
2011	3 217	23	900	7	466	3	1 205	9	7 957	58	13 745	100
Total	**11 842**	**27**	**3338**	**8**	**2139**	**5**	**4 151**	**10**	**21 857**	**50**	**43 327**	**100**

Table 3. **Proportion of new smear-positive cases by treatment outcome and year, the Philippines, 2003 to 2010**

Year	Treatment outcome indicators (%)						
	Cure	Treatment completed	Success	Death	Failure	Defaulted	Transferred out
2003	80.5	7.9	88.4	3.0	1.0	5.0	3.0
2004	81.0	7.8	88.8	2.4	1.0	5.0	2.6
2005	82.4	7.4	89.8	2.5	1.0	4.3	2.4
2006	82.2	8.2	90.4	2.4	1.0	3.9	2.4
2007	79.9	9.6	89.5	2.0	1.1	4.4	2.5
2008	82.0	8.4	90.4	2.0	1.1	4.4	2.5
2009	84.1	6.9	91.0	2.0	1.0	4.0	2.0
2010	84.8	6.7	91.5	2.1	0.9	3.8	2.0
Average	**82.1**	**7.9**	**90.0**	**2.3**	**1.0**	**4.4**	**2.4**

eight-year average of 90%. However, the country's target of 85% for annual cure rates[11] was met only in 2010. The low cure rates in previous years were mainly due to the high number of patients who completed treatment without laboratory confirmation of cure (i.e. treatment completed). The average rate of cases defaulting from treatment for the eight-year study period was 4.4%, contributing to the low cure rate and therefore treatment success rates. Moreover, these defaulters may become the future drug-resistant cases.

The death rate of notified TB cases, while low, still contributed to the overall unfavourable treatment outcome as did those cases that transferred out as their outcome is unknown. However, the sustained high treatment success rate reflects ongoing efforts to improve case holding through various NTP strategies such as the administration of DOT in workplaces, homes and other acceptable venues in the community other than the health facility using community volunteers as treatment partners.

In this study, EPTB comprised only 1% of cases, compared to the 15% to 20% reported from other countries.[12,13] The low case detection for EPTB in the Philippines may be due to the limited capability of primary care facilities to diagnose these cases or because EPTB cases are diagnosed in hospitals that are not part of NTP. Only 7% of public and 4% of private hospitals report to NTP. However, the higher number of EPTB cases reported from 2008 onwards may reflect the inclusion of more private and non-NTP public providers to NTP. This limitation to the surveillance system is being addressed by increasing the number of NTP-engaged hospitals and improving capacities to confirm EPTB diagnosis.

The proportion of children aged zero to 14 years notified to NTP was 1% for the whole study period,

and although there was an increase over this time, its proportion relative to other TB cases did not exceed 2% from 2003 to 2011. It has been estimated that the 0–14 age group should comprise around 15% of cases in low-income countries,[14] suggesting that cases in children are either not being diagnosed or if being diagnosed they are not being reported to NTP.

There are some limitations in using NTP surveillance system data to report on TB in the Philippines. Cases diagnosed and treated in health facilities outside the NTP network of providers, including private clinics and hospitals, are not included, therefore the surveillance system is underreporting the total number cases of TB in the Philippines. The submission of case reports are still paper-based, particularly at the peripheral level, which contributes to delays and errors in reporting. Not all regional health units have the capacity to consolidate their data in an electronic format because of gaps in infrastructure and equipment.

CONCLUSION

The Philippines has achieved improvements in case detection and exceeded the target for treatment success despite numerous challenges, particularly in making services accessible in difficult geographic and socioeconomic settings. The country aims to further improve access to diagnostic and treatment services, especially for highly vulnerable groups, while sustaining high cure and treatment success rates particularly among smear-positive PTB cases. Efforts will be directed at improving diagnostic capabilities in DOTS facilities and hospitals, addressing barriers to follow-up examinations for patients under treatment as well as the factors that promote treatment default and improving the referral system to reduce transfer-outs. Factors that contribute to TB mortality such as diagnostic and treatment delay and co-morbidities need to be addressed as well. Finally, the TB information system will be strengthened to improve its usefulness for surveillance, planning and decision-making. With the current trend of NTP performance, it is predicted that the country will achieve Millennium Development Goals and Stop TB partnership targets before 2015.[10]

Conflicts of interest

None declared.

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Implications of the current tuberculosis treatment landscape for future regimen change

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SUMMARY

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

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

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

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

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

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

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

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

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

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

The new regimen that may enter this landscape in

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

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

METHODS

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

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

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

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

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

RESULTS

Public sector regimens

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

Table 1 First-line regimens in the HBCs

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

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

Table 2 Movement of HBC regimens towards a single standard

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

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

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

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

Variants on the standard regimen

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

Table 3 Weight bands used for adult Category I regimens

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

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

Use of fixed-dose combinations

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

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

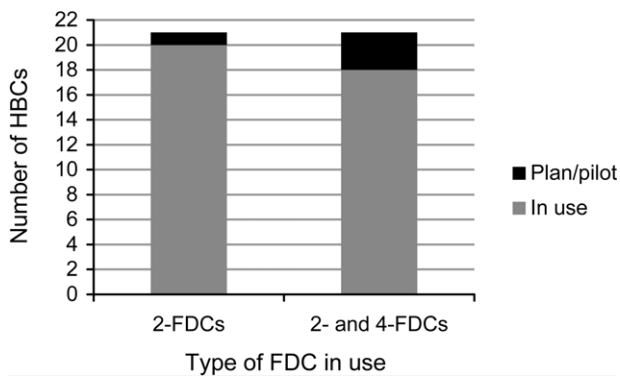

Figure Number of HBCs using 2- and 4-FDCs. HBC = high-burden country; FDC = fixed-dose combination.

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

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

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

Patient kits and drug management

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

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

Extent of drug susceptibility testing

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

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

Extent of directly observed treatment

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

Private sector size and PPM coverage

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

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

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

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

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

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

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

Early adoption by the private sector

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

Table 5 Estimated size of private sector and PPM programs

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

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

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

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

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

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

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

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

DISCUSSION

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

Regimens and their use

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

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

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

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

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

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

The costs and benefits of DOT and adherence

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

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

DST coverage and prospects for its expansion

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

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

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

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

CONCLUSION

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

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RÉSUMÉ

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

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

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

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

RESUMEN

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

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

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

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

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Tuberculosis regimen change in high-burden countries

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SUMMARY

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

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

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

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

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

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

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

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

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

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

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

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

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

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

METHODS

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

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

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

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

Table 1 Country stakeholders interviewed

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

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

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

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

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

RESULTS

Types and lengths of regimen changes

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

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

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

Table 2 Past regimen changes described by stakeholders

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

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

Role of decision-making procedures and bodies at country level

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

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

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

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

Types of evidence used to justify past regimen changes

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

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

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

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

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

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

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

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

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

Table 4 Negative factors during past regimen changes

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

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

Table 5 Evidence required for future regimen change

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

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

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

Evidence needed to support future regimen changes

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

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

Contribution of and requirements for local research

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

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

Table 6 Requirement for local effectiveness studies*

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

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

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

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

Local manufacturing and quality assurance

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

funding for a substantial portion of their TB drug procurement.

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

Procedural delays, difficulties and best practices

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

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

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

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

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

DISCUSSION

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

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

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

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

Planning for regimen change

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

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

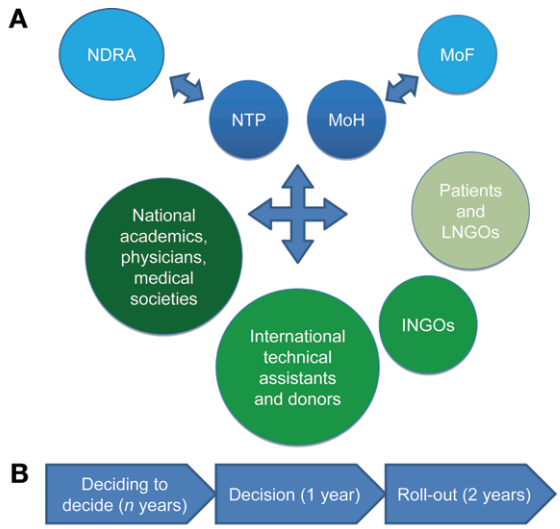

Figure Influence diagram for regimen decision making. **A.** The NTP and MoH are central to decision making, with the NTP providing guidance on priorities to the NDRA, and the MoF requiring a cost justification from the NTP and MoH. In an advisory capacity, national academics, physicians and medical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

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

Costs, risks and benefits

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

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

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

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

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

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

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

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

Local data requirements

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

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

CONCLUSION

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

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RÉSUMÉ

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

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

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

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

RESUMEN

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

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

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

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

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RESEARCH ARTICLE Open Access

Pre-ART retention in care and prevalence of tuberculosis among HIV-infected children at a district hospital in southern Ethiopia

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Abstract

Background: The Ethiopian epidemic is currently on the wane. However, the situation for infected children is in some ways lagging behind due to low treatment coverage and deficient prevention of mother-to-child transmission. Too few studies have examined HIV infected children presenting to care in low-income countries in general. Considering the presence of local variations in the nature of the epidemic a study in Ethiopia could be of special value for the continuing fight against HIV. The aim of this study is to describe the main characteristics of children with HIV presenting to care at a district hospital in a resource-limited area in southern Ethiopia. The aim was also to analyse factors affecting pre-ART loss to follow-up, time to ART-initiation and disease stage upon presentation.

Methods: This was a prospective cohort study. The data analysed were collected in 2009 for the period January 2003 through December 2008 at Arba Minch Hospital and additional data on the ART-need in the region were obtained from official reports.

Results: The pre-ART loss to follow-up rate was 29.7%. Older children (10–14 years) presented in a later stage of their disease than younger children (76.9% vs. 45.0% in 0–4 year olds, chi-square test, $\chi2 = 8.8$, $P = 0.01$). Older girls presented later than boys (100.0% vs. 57.1%, Fisher's exact test, $P = 0.02$). Children aged 0–4 years were more likely to be lost to follow-up (40.0 vs. 21.8%, chi-square test, $\chi2 = 5.4$, $P = 0.02$) and had a longer time to initiate ART (Cox regression analysis, HR: 0.50, 95% CI: 0.25-0.97, $P = 0.04$, controlling for sex, place of residence, enrolment phase and WHO clinical stage upon presentation). Neither sex was overrepresented in the sample. Tuberculosis prevalence upon presentation and previous history of tubercolosis were 14.5% and 8% respectively.

Conclusions: The loss to follow-up is alarmingly high and children present too late. Further research is needed to explore specific causes and possible solutions.

Keywords: HIV, TB, Ethiopia, Children, ART, Arba Minch, Resource-limited, WHO

Background

Recent global reports suggest considerably improved access to antiretroviral therapy (ART) in low and middle-income countries including in Sub-Saharan Africa. According to the 2013 global report, 9.7 million patients were receiving life-saving ART by the end of 2012 [1]. This is a remarkable acheivement as compared to a decade earlier when less than half a million patients were on ART in low and middle-income countries [2]. However, these gains in access are being challenged by emerging set of problems, one of which being retaining patients in care. A recent systematic review revealed problems with patient retention both before and after initiating ART [3]. This challenge and its associated factors are more clearly delineated in adult patient populations than in children.

During 2011, about 24 000 new infections were reported to have occurred and there were around 790 000 people infected with HIV living in Ethiopia, which is 1.5% of the entire population. The latter prevalence is projected to decline as well, along with mortality and incidence [4]. These encouraging results are believed to be the effect of concerted local and global actions including

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free delivery of HIV services at point of care, service decentralization, and task shifting [5,6]. The challenge of poor linkage to and retention in care has been well recognized in the Ethiopian HIV program. Published studies from Arba Minch and Gondar hospitals, for example, suggest high rates of pre-ART patient loss among adult patients living with HIV [6,7]. As elsewhere, there is limited information on the challenges of pre-ART patient retention among children living with HIV in Ethiopia [2].

Despite the success, many challenges still prevail [2,8]. There are problems with low condom use, violence against women and stigma leading to loss of job and income. One in five Ethiopians with HIV experience suicidal feelings. Another major problem is the low coverage of antiretroviral regimens to prevent mother-to-child transmission and rates of infant testing and prophylaxis remain very low [2,9].

Some of the most worrying statistics on HIV in Ethiopia concern the health of children. The deficient prevention of mother-to-child transmission in Ethiopia is central to the problem of HIV among children. Ethiopian studies have shown, similarly to findings from other low-income countries and international reports, that a majority of children with HIV in the country have acquired their infection vertically [9-11]. Apart from this, a big problem is the low ART coverage for children. Although the data are currently under review and may reveal an improvement, reports from 2010 announce that only 14–38% of the ART-need among children is met [9].

For those children who do present to care, further problems ensue. Timely initiation of treatment and retention in care are both crucial for patient outcome [12,13]. Late presentation to care among children have been identified as a problem in both high-income and low-income countries [11,14]. This implies that children in low-income countries are put in a particularly vulrerable situation as late presentation has been shown to be also a general problem in Sub-Saharan Africa [6,15]. A review from 2009 has found the reasons for this to be mainly population-based barriers to access such as lack of information, stigma and perceived high cost of treatment. However, the reviewer stresses that 'there is a paucity of studies on access barriers to ART for HIV-positive children' [16]. Furthermore, not all studies show that children present late. For instance, a study from India showed that children below 14 years of age actually were associated with a lower risk of late presentation [17]. This further underscores the importance of more local research. Extending the knowledge on HIV-infected children presenting to care in Ethiopia is critical for not letting children lag behind in the process to overcome the epidemic.

In this report, we present data from one of the longest-followed cohorts of paediatric HIV patients on TB prevalence and the magnitude and predictors of retention in care. The aim of this study was to describe the main characteristics and to analyze the predictors of pre-ART loss to follow up among children with HIV presenting to care at a district hospital in a resource-limited area in southern Ethiopia.

Methods

Participants

The data were collected at Arba Minch Hospital in southern Ethiopia. The hospital is a general public hospital located in the city of Arba Minch, in the Southern Nations, Nationalities, and People's Region (SNNPR), around 500 kilometres south of Addis Ababa, Ethiopia's capital. Arba Minch Hospital was the first hospital to introduce antiretroviral treatment in SNNPR in 2003—at a time when there were only few such centres in Ethiopia. The hospital serves a population of over 1.5 million in the Gamo Goffa zone of SNNPR. We established the HIV cohort database in 2003 and maintained it through this date. Since this is the longest-followed cohort in Ethiopia and resource constraint did not allow us to establish more of such centres, we opted to continue with analysis and learning from our existing cohort. This study did not entail any active data collection. We used de-identified data from the existing database and restricted our analysis to the paediatric age group as most of our earlier analyses did not involve this age group. All children with HIV presenting to care at Arba Minch Hospital from January 2003 through December 2008 were included in this study. The inclusion criteria were to be under 15 years old and to have an HIV infection. Children with a previous history of ART were excluded.

Procedure of therapy and data collection

The data for this study were collected along with data for adult patients at the same hospital. The findings on those data have been published elsewhere and the method described below is in part described in that study as well [6]. A trained health care worker did the initial evaluation and subsequent follow-up of the patients. During the initial years of the study this evaluation was made using only clinical and total lymphocyte count (TLC) criteria. From mid-2006 and onward CD4 testing was also available. The patients started ART according to the national guidelines issued by the Ethiopian Ministry of Health (MOH), which issued updated versions of the guidelines during the course of this study.

The first Ethiopian ART guidelines were published in 2003 and the paediatric treatment guidelines were included as a chapter in the adult guidelines. The first paediatric ART guidelines were published in 2008 and the recommendations did not change since then. Accordingly, treatment is recommended for all infants with confirmed HIV infection. Treatment is recommended for older children with stage III or IV diseases irrespectively of

CD4 count/percentage. For those with stage I or II disease a table is used as a guide outlining different CD4 count/percentage thresholds for different ages (12–35 months: < 750 cells/mm^3 or < 20%, 36–59 months: < 350 cells/mm^3 or < 20%, 5 years or older - same as adults: < 200 cells/mm^3 or < 15%). These thresholds did slightly change during the course of the study. In the 2003 guidelines the 15% threshold extended down to children of 18 months and the adult thresholds were applied to children 8 years or older. The guidelines also specify how to assess HIV infection and disease stage clinically if proper laboratory tests are unavailable [18-20].

Two data clerks recorded patient information both on paper and electronically. With a data abstraction form as a guide they recorded variables directly into an SPSS file. These variables include date of HIV-testing, date of pre-ART enrolment, WHO clinical stage, total lymphocyte count (TLC), CD4 count, haemoglobin level (HGB), history of TB (as reported by patient or caregiver), current TB (diagnosed within one month before or after presentation), sex, age, place of residence (rural or urban), pre-ART outcome and date of ART-initiation (if initiated).

During most of the time of the study, there was no strict guideline for pre-ART follow-up schedule neither for adults nor for children. Patients at the hospital were told to return after 3–6 months depending on their clinical condition. The 2008 paediatric guidelines formalised the schedule to recommend follow-up every 1–3 months depending on age and clinical condition (or more frequently than monthly if clinically indicated) [20]. However, there was no recording and reporting mechanism for the pre-ART visits and definitions for pre-ART outcomes such as loss to follow-up was not formalized. The Ethiopian Ministry of Health has recently finalized a nation-wide assessment of the status of pre-ART patient care. It is expected to lead to development of a comprehensive national framework for pre-ART care. In the mean time, we continued to use our own operational definition for pre-ART care. The pre-ART outcome was defined as: (a) 'still under pre-ART care' – if the patient was registered with the ART clinic of the hospital, had regular follow-up with the clinic and was not having follow up at another health facility; (b) 'lost to follow-up' – if patient did not have a follow-up visit at least 30 days after the last date of the most recent clinic appointment; (c) 'put on ART' – if patient was started on ART in the hospital clinic; (d) 'died before starting ART' – if patient was known to be dead as reported by treating clinicians or community health agents; and (e) 'transferred out' – if patient moved to another health facility with confirmed written documentation of transfer out.

For those patients that were put on ART, patients were defined as lost to follow-up if they had not attended the hospital within 30 days following the time for their clinical appointment. For patients lost to follow-up an extended follow-up was conducted in 2009 and involved a home visit or phone call using community health agents. Patient status after extended follow-up was defined as (a) 'died' – if a family member, neighbour or community leader reported death of the patient; (b) 'under follow up at another health facility' – if the patient was on treatment at any health facility in the region as reported by family, neighbours or community leaders; (c) 'stopped treatment but alive' – if the patient had not taken antiretroviral drugs (ARVs) for over a month and the patient was alive and did not get ART elsewhere; (d) 'on traditional treatment' – if the patient reported that he or she used traditional medicines or treatment instead of ART and (e) 'left the region' – if patient left the region as reported by family, neighbours or community leaders. If no information was available about the patient, this was defined as (f) 'unknown' ('true loss').

Patient data were updated at each visit. The database was updated on a quarterly basis 2003–2006 and yearly the last two years. In 2009, we undertook a more thorough cohort updating that involved home visits to determine the status of each patient declared to be lost as described above. The recorded data were updated, amended and cross-checked with paper records at the hospital in order to affirm their quality. In addition to the patient data, data on ART-need among girls and boys in SNNPR were obtained from an official report for statistical comparison with data on the participants of the study [4].

Ethics

The prospective cohort follow up system at Arba Minch hospital was established with the approaval of the the National Research Ethics Review Committee in Ethiopia. All patients were given standard care at the hospital, as prescribed in the national guidelines [18,19].

This particular analysis was done based on a separate protocol specifically designed to look into long-term treatment outcomes including pre-ART outcomes for which separate local approval was sought and granted. Since we used de-identified data for this analysis, obtaining patient consent was not feasible but permission was obtained from the hospital administration.

Statistical methods

SPSS was used for the analyses presented in this study. The data was entered into SPSS version 16 and later transferred to SPSS version 21. All data used for describing cohort profile and baseline characteristics were obtained from the SPSS file.

Data were grouped into three cohorts based on date of enrolment to pre-ART care and the chronology of Ethiopia's ART scale-up [5]. The three cohorts were decided to be (i) those enrolled January 2003-August 2006

(Early cohort), (ii) those enrolled September 2006-August 2007 (Rapid scale-up cohort) and (iii) those enrolled between September 2007-December 2008 (Recent cohort). For each cohort the proportion of patients presenting in the different WHO clinical stages of HIV/AIDS was compared. For the sake of clarity, a comparison was also made with the WHO clinical stage dichotomized into less advanced (stages I & II combined) and advanced (stages III and IV). In regard to the small sample size these distributions were only described for each cohort separately and no trend analyses were performed.

Logistic regression including the dichotomized WHO stage variable was used to identify potential risk factors for being in an advanced stage upon presentation. Because of the small sample size only four variables were screened: age, sex, place of residence and cohort. These variables were chosen on bases of biological and social plausibility and on the findings from the adult cohort [6]. A similar logistic regression was used to determine risk factors for being lost to pre-ART follow-up and the same variables were chosen for this analysis. Individual chi-square tests were performed to further analyse factors found to affect pre-ART loss and late presentation. For one analysis where the criteria for performing a chi-square test were not deemed to be met, Fischer's exact test was done instead.

Student's T test was used to determine whether the distribution between boys and girls presenting to care was significantly different from the distribution among HIV-infected children in general. Estimates for these numbers were obtained from official reports on the region, issued by the Ethiopian Ministry of Health [4].

Time to ART-initiation for different age groups was estimated using Cox regression, controlling for sex, place of residence, enrolment phase and WHO clinical stage upon presentation. Statistical significance was defined as $P < 0.05$.

The research adhered to strengthening the reporting of observational studies in epidemiology (STROBE) guidelines [21] (See Additional file 1 for more details).

Results

Cohort profile

Out of the 139 children who initiated pre-ART care from January 2003 through December 2008 all but one were enrolled in the study. The child who was not enrolled had a history of previous ART and thus failed to meet the inclusion criteria. Out of the 138 children included, 79 (57.2%) were put on ART, 15 (10.9%) were still under pre-ART care at the time of follow up, two (1.4%) had been transferred out of the hospital and one child (0.7%) had died. The remaining 41 children (29.7%) were lost to follow-up (Figure 1).

Of the 79 children who were put on ART, a majority was still enrolled in treatment at the time of follow-up, namely 65 children (82.3%). Five children (6.3%) had died, one (1.3%) had been transferred out and one had stopped treatment. The remaining 7 children (8.9%) were lost to follow-up. Three of these children were living in urban addresses and were traced for an extended follow-up. One had died and another was alive, receiving traditional treatment at 'holy water'. The outcome of the last child remains unknown.

The 138 patients enrolled in the study contributed 175.9 person years of observation (PYO). The median time to pre-ART outcome was 1.1 months (IQR: 0.2-6.1) and the median time from ART initiation to ART outcome (for the 79 patients put on ART) was 23.3 months (IQR: 5.1-30.1).

Characteristics of the children

The characteristics of the 138 children upon enrolment to pre-ART care are shown in Table 1. Their median age was 5 years (IQR: 3–8); 60 children (43.5%) were 0–4 years old, 52 children (37.7%) were 5–9 years old and 26 children (18.8%) were 10–14 years old. As for distribution between sexes, there were 79 boys (57.0%) in the entire sample. A vast majority of 121 children (87.7%) were urban residents and the remaining 17 (12.3%) had rural addresses. A previous history of TB was found for 11 children (8.0%) while 20 children (14.5%) had a TB infection upon presentation. CD4 count was recorded for 97 patients and the mean value was 529 cells/mm^3.

Differences between age groups

The distribution of presenting stage for different age groups is shown in Table 2. There were 26 children aged 10–14 years, 6 (23.1%) of these presented in a less advanced stage while the remaining 20 (76.9%) presented in an advanced stage. The higher proportion of children presenting late in the oldest age group was found to be statistically significant when compared to the reference group of 0–4 year olds (Chi-square test, $\chi^2 = 8.8$, $P = 0.01$). No significant difference was found between the middle and the youngest age group.

Pre-ART loss to follow-up proportion within different age groups is shown in Table 3. Among the 78 children who were 5 years or older, 17 (21.8%) were lost to follow-up. The number of children lost to follow-up among the 60 children aged 0–4 years was 24 (40.0%), a significantly higher proportion compared to the older children. (Chi-square test, $\chi^2 = 5.4$, $P = 0.02$).

Risk factors for longer time to ART initiation

The 138 patients enrolled in the study contributed 47.0 person years of observation (PYO) in pre-ART follow-up. The median time to ART initiation for all participants was 18 days (IQR 6–113). When controlling for sex, place of residence, enrolment phase and WHO clinical stage upon

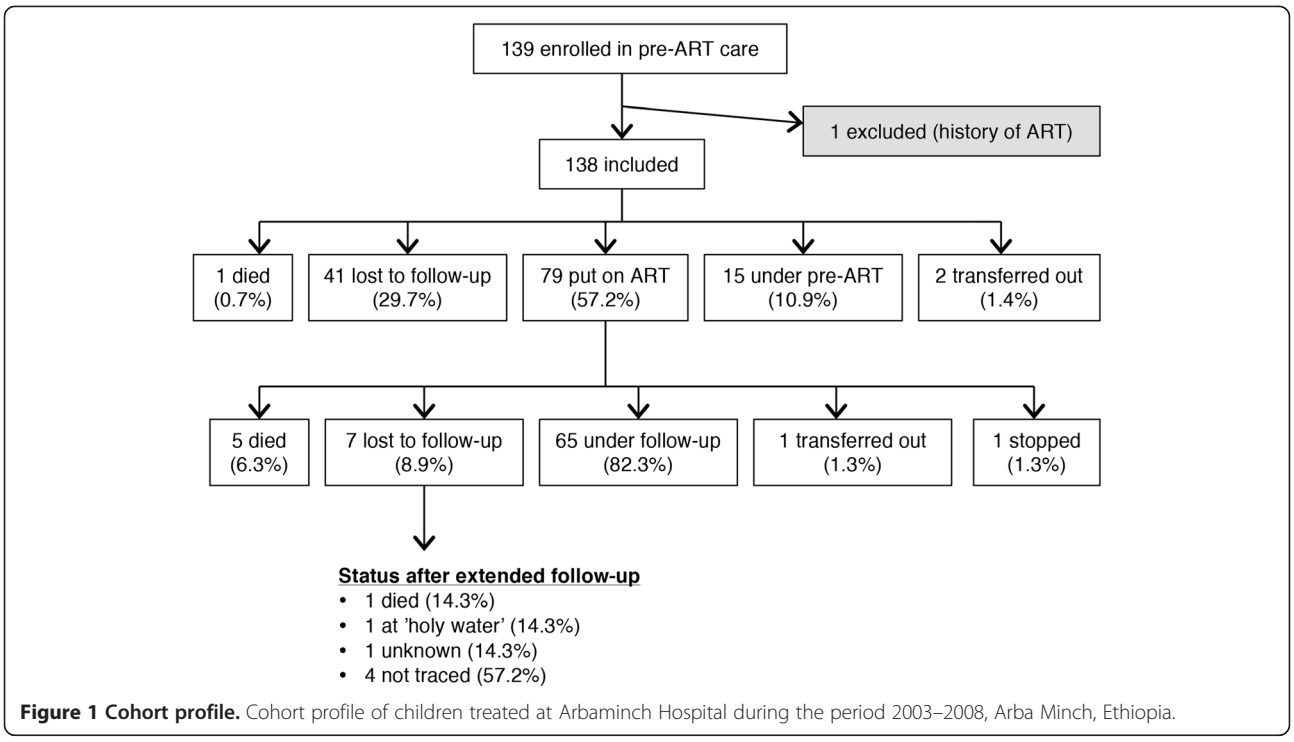

Figure 1 Cohort profile. Cohort profile of children treated at Arbaminch Hospital during the period 2003–2008, Arba Minch, Ethiopia.

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

Characteristic		Number (%)
Age	0-4 years	60 (43.4)
	5-9 years	52 (37.7)
	10-14 years	26 (18.8)
Sex	Female	59 (42.8)
	Male	79 (57.2)
Place of residence	Urban	121 (57.2)
	Rural	17 (12.3)
WHO clinical stage	Stage I	31 (22.5)
	Stage II	37 (26.8)
	Stage III	59 (42.8)
	Stage IV	11 (8.0)
Past history of TB	Yes	11 (8.0)
	No	127 (92.0)
TB upon presentation	Yes	20 (14.5)
	No	118 (85.5)
Characteristic		**Central tendency (variation)**
CD4 count*	Mean	529 cells/mm^3
Hgb**	Mean	10.7 g/dl
Time to ART***	Median (IQR)	18 days (6–113)

*97 cases analysed, 41 missing.
**101 cases analysed, 37 missing.
***For 79 patients put on ART.
Presenting characteristics for 138 children with HIV at Arba Minch Hospital, who initiated pre-ART care during the period 2003–2008.

presentation, it was found that children in the age group 0–4 years waited longer to initiate ART (HR: 0.50, 95% CI: 0.25-0.97, P = 0.04).

A longer time to ART initiation was also found for children presenting in stage I (HR: 0.27, 95% CI: 0.09-0.80, P = 0.02). Table 4 shows the adjusted hazard ratios for all variables mentioned above and Figure 2 shows the survival curves according to Cox regression with separate lines for different age groups.

Differences between sexes

The proportion of patients presenting in an advanced stage (in either stage III or stage IV) for boys and girls respectively is presented in Table 5. Out of the 59 girls in the sample, 35 (59.3%) presented in an advanced stage; for the boys the number was 35 (44.3%) out of 79. The table also shows sex difference in presenting stage stratified by different age groups. For ages 10–14, all 12 (100.0%) of the girls presented late, as compared to 8 (57.1%) out of the 14 boys and this distribution was determined to be statistically significant (Fisher's exact test, P = 0,02). However, the sample size was critically small for further statistical evaluation. The sex differences for the other two age groups were not statistically significant, neither was the difference between sexes for all age groups combined.

Neither boys nor girls were found to be overrepresented at the clinic. According to official reports, the proportion of girls in need of ART in SNNPR was 49.7% in 2011. It was not possible to obtain this proportion for the actual period studied (2003–2008) but the proportion was not

Table 2 Presenting stage of HIV/AIDS for different age groups

	Less advanced (%)	Advanced (%)	Total	χ^2 significance
0-4 years*	33 (55.0)	27 (45.0)	60	-
5-9 years	29 (55.8)	23 (44.2)	52	P > 0.05
10-14 years	6 (23.1)	20 (76.9)	26	P = 0.01

*reference category.
Less advanced = Stage I & II combined.
Advance = Stage III & IV combined.
Presenting stage of HIV/AIDS for different age groups in a cohort of 138 children who initiated pre-ART care during the period 2003–2008.

projected to change for the next five years despite an overall estimated decrease in total numbers [4]. On these grounds it was assumed that the proportion was similar during the period of the study. The proportion of girls in the sample was 43.0% – 6.7 percentage points lower than girls in need of ART in the region – but this difference was not found to be significant for P < 0.05 (two-tailed significance, P = 0.10).

Changes after the scale-up of ART

WHO clinical stage for children presenting to care at Arba Minch Hospital during the three phases of ART scale-up in Ethiopia is shown in Table 6. In the early phase, 17 (41.5%) out of 41 children presented in a less advanced stage, a proportion which in the recent phase rose to 35 (59.3%) out of 59 children. Due to the small size of the sample, an analysis to assess whether this trend was significant was not performed.

Discussion

This study shows that older children present later to care and that among the older children, girls present later than boys. Younger children face other problems, as they are shown to have a longer waiting time to initiate ART and to be more likely to discontinue their pre-ART program. The overall percentage of pre-ART loss to follow-up is alarmingly high and a notable TB prevalence (14,5%) is seen upon presentation. No sex difference was found in presentation to care among the children in need of ART in the region.

Another study was conducted on HIV-infected adults presenting to care at Arba Minch Hospital during the same period as the children participating in this study. In the adult cohort consisting of 2191 patients, 25% were lost to pre-ART follow-up [6]. As was discussed earlier, the ART coverage of children in Ethiopia is lower than that of adults [22]. This fact together with the loss to follow-up reported for adults at the same hospital suggest a worrying pattern where children not only have less access to care but also continue care to a lesser extent than adults. A likely explanation for this is the fact that the children presenting to care in this study were generally healthier (in a less advanced stage of HIV) than the adults but even so the issue ought not be disregarded. It is however worth noting that the new WHO guidance of starting ART for all children under 5 has been endorsed by the Ethiopian Ministry of Health but its cost and associated implications are being studied before its implementation. If implemented, this new guidance may alleviate some of the concerns noted in this study.

It may not be surprising that older children presented later. Studies from around world show that – although figures vary slightly in different settings – a majority of HIV infected children anywhere have acquired their infection vertically. If this is the case also for the area serviced by Arba Minch Hospital, it would mean the disease had had longer time to progress in the children aged 10–14 years. Yet, if perinatal transmission is indeed the dominating mode among these children, it is still troubling that so many cases go undiscovered so long – one in five being over 9 years old and the better part being 5 years or older. This is not unique for Ethiopia. Age distributions such as these have been reported elsewhere in low-income countries; a recent Ugandan study showed roughly similar proportions at two different district hospitals and children's ages were also high in a large Indian cohort [23,24]. The fact that older children present later could also be part of the explanation why younger children are lost to pre-ART follow-up more frequently, as being in a less advanced stage has been shown elsewhere to be a predictor for pre-ART loss to follow-up [6].

As for the older girls presenting later than the older boys, potential explanations are less obvious. Studies on adults have actually reported women in Sub-Saharan Africa to present earlier than men, but additional factors associated with early presentation are pregnancy and

Table 3 Pre-ART loss to follow-up for different age groups

	Not lost to follow-up (%)	Lost to follow-up (%)	Total	χ^2 significance
0-4 years	36 (60.0)	24 (40.0)	60	P = 0.02
5-14 years	61 (78.2)	17 (21.8)	78	

Loss to follow-up for different age groups in a cohort of 138 children who initiated pre-ART care during the period 2003–2008.

Table 4 Factors associated with longer waiting time to ART initiation, Arba Minch Hospital, Ethiopia

Variable		Adjusted HR (95% CI)	P-value
Sex	Male vs Female	0.90 (0.57-1.42)	>0.05
Address	Rural vs Urban	0.98 (0.46-2.05)	>0.05
Phase of enrolment	Early phase	1.36 (0.78-2.37)	>0.05
	Rapid scale-up	1.09 (0.59-2.00)	>0.05
	Recent phase*	1.00	
Age group	0-4 years	0.50 (0.25-0.97)	0.04
	5-9 years	0.40 (0.42-1.41)	>0.05
	10-14 years*	1.00	
WHO clinical stage	Stage I	0.27 (0.09-0.80)	0.02
	Stage II	0.69 (0.27-1.71)	>0.05
	Stage III	0.88 (0.38-2.04)	>0.05
	Stage IV*	1.00	

*reference category.
Hazard ratios for factors associated with having a longer time to ART initiation in a cohort of 138 children who initiated pre-ART care during the period 2003–2008.

having children less than 5 years [6,15]. These factors are naturally less occurrent among younger girls. Younger girls are also much less likely to be married, and being single is associated with presenting late not only in general but especially for women [15]. This kind of extrapolation however is somewhat speculative and probably does not tell the whole story.

On the other hand, previous research may provide a more straightforward explanation for the high loss to follow-up and longer waiting times among the youngest children. One reason that sufficient adherence can be hard to achieve for children is that they have to rely on their caregivers for it, caregivers who are often themselves in poor health due to HIV or difficult social circumstances [25]. The youngest children being most reliant on adults, this could explain their low retention. It could also explain the longer waiting time, since it is not recommended to initiate ART before it has been properly established that the patient is likely to adhere to the treatment [18,19].

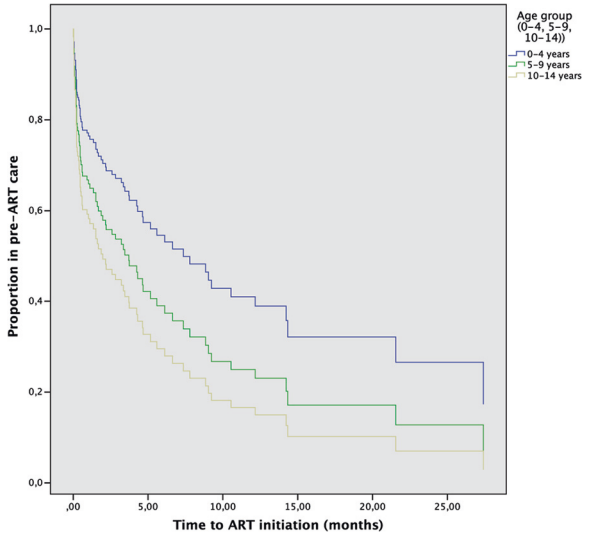

Figure 2 Time to ART for different age groups. Survival curves according to Cox regression analysis showing time to ART initiation for different age groups controlling for sex, place of residence, enrolment phase and WHO clinical stage upon presentation. Survival times for patients not reaching the event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

TB is the leading cause of death for people living with HIV and ART has been shown to substantially reduce the incidence of TB [22,26]. Therefore it is important to note the high rates of previous and current TB infection among the children presenting to care. Sadly, these findings are not that surprising, seeing that high rates have been reported in other child cohorts from low-income countries [11,25,27]. In any event, the findings underline the importance of earlier initiation of ART and generally improving collaborative TB-HIV care.

The main limitation of this study is the small sample size. Due to this fact, changes in presenting stage and mortality after the rapid scale-up of ART could not be analysed properly. This is unfortunate since these and other factors may have improved as a result of the scale-up, as has been shown for the adult cohort. On some instances when analyses were made on sub-groups of the entire cohort the sample size was even smaller. Therefore the finding that older girls present later than boys should be interpreted with caution. The large number of tests performed on this rather small sample also increases the risk of finding false significance and this should be taken into consideration.

Another limitation of this study was that the circumstances of data collection did not allow for a separate

Table 5 Sex difference in presenting stage of HIV/AIDS

		Less advanced (%)	Advanced (%)	Total	Significance
All ages	**Girls**	24 (40.6)	35 (59.3)	59	
	Boys	44 (55.6)	35 (44.3)	79	
0-4 years	**Girls**	11 (47.8)	12 (53.2)	23	$P > 0.05$[a]
	Boys	22 (59.5)	15 (40.5)	37	
5-9 years	**Girls**	13 (54.2)	11 (45.8)	24	$P > 0.05$[a]
	Boys	16 (57.1)	12 (42.9)	28	
10-14 years	**Girls**	0 (0.0)	12 (100.0)	12	$P = 0.02$[b]
	Boys	6 (42.9)	8 (57.1)	14	

[a]Chi-square significance test.
[b]Fisher's exact test.
Less advanced = Stage I & II combined.
Advanced = Stage III & IV combined.
Sex difference in presenting stage of HIV/AIDS stratified by age group in a cohort of 138 children who initiated pre-ART care during the period 2003–2008.

set of variables to be recorded for the child cohort. Information on parents' infections and social status, measures of prevention during pregnancy, mode of delivery and nutritional status of the child would have been valuable supplements for the analyses.

The range of problems seen in the provision of ART and retention in care all point to the same basic conclusion: reducing the rate of mother-to-child transmission is key to improving the paediatric HIV situation in Ethiopia. More research is needed to assess how perinatal care for infected women as well as testing of and prophylaxis for infants can be improved upon.

Nonetheless in addition to this, as long as there are still children infected with HIV, the detection of and care for these children need improvement as well. More research should explore the factors associated with loss to follow-up, late presentation, not presenting to care at all and possible interventions to solve these problems. Although likely candidates have been suggested in this discussion for the most immediate causative factors, there are likely also more general social factors such as poverty that put children at risk for lower access to care, lower adherence and unfavourable disease outcome. For this reason, more social research in addition to purely medical research would be welcome. To determine changes over time in pre-ART and on-ART loss to follow-up, mortality and presenting stage among children, research on larger Ethiopian cohorts of children is of crucial importance in the future.

Table 6 Presenting stage during the different phases of ART scale-up

	Less advanced (%)	Advanced (%)	Total
Early phase	17 (41.5)	24 (58.5)	41
Rapid scale-up phase	16 (42.1)	22 (57.9)	38
Recent phase	35 (59.3)	24 (40.7)	59

Less advanced = Stage I & II combined.
Advanced = Stage III & IV combined.
Presenting stage during the different phases of ART scale-up in a cohort of 138 children who initiated pre-ART care during the period 2003–2008.

Some inequalities between patient groups described in this study may still be prevalent despite the general improvement after the ART scale-up. Thus, even though our data are by now a few years old the results are nonetheless relevant in this respect and hopefully our findings will also serve a purpose for comparison with the contemporary adult cohort, as well as with future studies of this kind.

Conclusions

Although the sample size in this study was too small to make some important analyses on how the situation has developed over time, a number of problems have been identified concerning HIV-infected children presenting to care. The main ones are high pre-ART loss to follow-up rate, high TB prevalence and late presentation. Reasons for the higher loss to follow-up and longer waiting time to initiate treatment among the youngest children need to be further investigated. So do potential reasons for older girls presenting later than older boys and also general social factors that could be associated with several of these problems.

Additional file

Additional file 1: STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies.

Abbreviations

AIDS: Aquired Immunodeficiancy Syndrome; ART: Antiretroviral therapy; ARV: Antiretroviral drug; CI: Confidence interval; HIV: Human immunodeficiancy virus; HR: Hazard ratio; MOH: Ministry of Health (Ethiopia); TLC: Total lymphocyte count; SNNPR: Southern Nations Nationalities and Peoples' Region; SPSS: IBM SPSS statistics software; TB: Tuberculosis; WHO: World Health Organisation.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

DJ and BL established the Arba Minch Hospital HIV treatment cohort and later collaborated with ZM to update the cohort database in 2009. BL and ZM supervised the cohort data updating process. EW analyzed the paediatric cohort data for this manuscript and wrote the first draft of the manuscript. IH commented on the initial and subsequent drafts of the manuscript. DJ assisted with data analysis and commented on the initial and subsequent drafts of the manuscript. All authors have read and approved the final manuscript.

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

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Abstract

Background: The global tuberculosis (TB) estimate in 2011 was 500,000 cases among children under 15 years representing 5.7 % of all cases and 64, 000 deaths among HIV negative children representing 6.5 % of the total deaths. In Uganda, the child TB cases reported in 2012 made up less than 3 % of the total cases while recent modelling estimates it at 15–20 % of adult cases. Mapping of these cases in Kampala district most especially for the children under five years would reflect recent transmission in the various communities in the district. We therefore conducted a retrospective study of reported child TB cases in Kampala district Uganda for 2009–2010 to provide an estimate of child TB incidence and map the cases.

Methods: This was a retrospective cross-sectional study on data collected from the health unit TB registers in the five divisions of Kampala district, Uganda. The data was a starting point in preparation for a TB Vaccine study in children. The extracted data spanned a period from 1st January 2009 to 31st December 2010. The projected population of children below 15 years was 637,922 in 2009 and 744,750 in 2010 for Kampala district. We based our projections on the National Bureau of Statistics most recent census report of 2002 before the study duration while assuming a population growth rate of 3.7 % each year. We captured the data into EPI DATA 3.1 and analysed it using STATA version 12.

Results: We accessed 15,499 records and analysed 1167 records that were of children below 15 years old. The child TB cases represented 7.5 % (7.3 in 2009 & 7.6 % in 2010) of all the registered cases in Kampala district. The females were 47 % and the median age was 4 years (IQR 1, 10). The percent of children less than 5 years old was 54 %. The percent of pulmonary TB cases was 89 % (1041/1167) with 15 % smear positive. The proportion of extra-pulmonary TB cases was 11 % (126/1167). Among those that tested for HIV, 60 % (359/620) had test results available with an HIV co-infection rate of 47 % (168/359). Antiretroviral treatment uptake was 24 % among the co-infected. The incidence of child TB in Kampala was 56 (95 % CI 50–62) per 100,000 in 2009 and 44 (95 % CI 40–49) per 100,000 in 2010. Most of the TB cases (60 % (410/685)) in Kampala live in slum areas.

Conclusion: There was a higher child TB incidence of 56 per 100,000 in 2009 compared with 44 per 100,000 in 2010. The percentage of child TB cases was much higher at 7.5 % of all the reported TB cases than the WHO reported national average. For the review period, the TB cases clustered in particular slums in Kampala district.

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Background

In 2011, the global TB estimate was 8.7 million incident cases with the African region accounting for 26 % and 1.4 million deaths including 430, 000 deaths among HIV-positive people [1]. The 2011 estimates represented for the first time the expanded inclusion of data in children beyond smear positive cases. In the same report, there were an estimated 500, 000 cases among children under 15 years old representing 5.7 % of all cases and 64, 000 deaths in children 6.5 % of the global deaths [1]. Until the global tuberculosis report of 2012, reported PTB cases were the smear positives and therefore included few children. Children mainly have paucibacillary (low TB germ load) disease so are usually smear negative. Consequent to the paucibacillary nature of TB in children, the true burden of TB disease in children remains uncertain.

A recent mathematical modelling estimated about 650,000 incident TB cases in children under 15 years old in 2010 and about 7.5 Million TB infections [2]. There were however no global estimates for the 2010 incident TB cases in children for comparison. The model further estimated that 4–20 % of global TB cases occurs in children while for Uganda it estimated that 15–20 % the cases should be among children [2]. The challenge of childhood TB diagnosis coupled with misdiagnosis of extra-pulmonary TB contributes to uncertain estimates.

Although TB and HIV epidemics link, the drop of 50 % in HIV infection between 2001 and 2012 [3] does not compare with the 2 % decline in TB incidence between 1990 and 2012 [4]. Most of the TB decline is in South-East Asia specifically China. Uganda has registered a remarkable decline in the prevalence of TB and is on track to meet the Millennium Development Goal (MDG) target [5]. We do not know if the decline is in all communities or a few selected population areas. There is a high risk of TB disease in exposed children most especially those with HIV infection and severe malnutrition [6, 7]. The interplay between TB, poverty and overcrowding [8] leads to varying trends in different populations.

In Uganda, the TB cases reported in children in 2012 made up less than 3 % of the total reported TB cases [4]. There is a high likelihood of TB under-reporting in children because most are diagnosed on clinical basis as opposed to bacteriologically confirmed. We also expect the numbers in children to be a reflection of adult numbers since their TB disease is commonly from adults. Tuberculosis in under fives represents recent transmission reflected in mapping of cases in communities [9]. Until 2012, the World TB reports data for Uganda did not provide information on all forms of childhood TB reported. Age broken down data and TB cases location information is important for targeted interventions and may guide the choice of TB research populations.

The specific objective this cross-sectional retrospective study was to provide an estimate of incidence and distribution of childhood TB in Kampala district, Uganda.

Methods

Study design

This was retrospective study on data collected from health unit TB registers as starting data in preparation for a TB vaccine study in children.

Setting

We collected data from the five administrative divisions of Kampala district. Kampala city, the capital city of Uganda is located in Kampala district. It has an estimated population of 1.5 million by night and much higher by day due to large numbers that come to work. Kampala district is surrounded by Wakiso district from where many people travel to work in the capital city. The district has 62 informal settlements referred to as slums. The district had a projected population of children below 15 years of 637,922 in 2009 and 744,750 in 2010. The projection was from the National Bureau of Statistics 2002 population census report (which was the most recent before the study period) assuming a constant annual population growth rate of 3.7 % [10]. During the study period, TB surveillance in most of the health unit was mainly passive. In the passive surveillance patients present to the health unit for TB related symptoms. In active TB surveillance patients presenting to the health unit for any reason are screened for TB. Active TB surveillance or screening was limited to HIV clinics. There are 52 TB diagnostic and treatment units (DTU) in the Kampala district. Each of the DTUs registers TB cases in the Unit TB registers.

Data source

We reviewed all extracted routine NTLP data from 1st January 2009 to 31st December 2010 from the health unit TB registers in Kampala district, Uganda. Following the clinician's diagnosis, unit TB focal person or TB staff record patient data in paper based unit TB registers. We used the national guideline definitions as adapted from WHO TB guidance of 2006 for case classification during the review period [11]. A case of TB was one with bacteriological confirmation (sputum smear positive or culture) or where a clinician decided to treat for TB. Each TB case is reported as pulmonary TB (smear positive or smear negative or smear not done) or extra pulmonary TB. Since not all children had sputum collected, we included PTB smear not done as a category for intervention purposes. All the TB cases are offered an opportunity to test for HIV as part of the routine tests.

Data management and statistical analysis

We captured the data in EPI DATA 3.1 and analysed using the STATA version 12. We described continuous data using medians with inter-quartile ranges while categorical data as proportions. We present the data in tables and graphs. We only included cases of children residing in Kampala district at registration time to calculate incidence rates for Kampala district.

Ethical considerations

The study received ethical approval from Mulago Hospital Research and Ethics committee and consent obtained from the NTLP of the Ministry of Health. We only extracted non-identifying data.

Results

We accessed 15,499 patient TB records and extracted 1167 records of children less than 15 years for analysis.

Descriptive data

Children accounted for 7.5 % (7.3 in 2009 & 7.6 % in 2010) of all the reported TB cases in Kampala. The median age was 4 years (IQR 1, 10) and the majority (54 %) were under 5 years old with 47 % (548/1167) being females. See Table 1 for other demographic characteristics. Most of the children were 0–4 years making up 54 %, those 5–9 years made up 21 % and the 10–14 years were 25 %. The TB cases residing in Kampala were 59 % while those residing outside Kampala district were 41 % (Wakiso –20 %, elsewhere– 21 %).

Table 1 Demographic characteristics of the children with TB notified in Kampala district, Uganda 2009–2010 ($N = 1167$)

Characteristic		Frequency of TB cases	Percentage
Age group in years	0–4	629	54 %
	5–9	246	21 %
	10–14	292	25 %
District	Kampala	685	59 %
	Wakiso	238	20 %
	Others	244	21 %
Division	Kawempe	172	25 %
	Makindye	139	20 %
	Central	38	5.6 %
	Nakawa	120	17 %
	Rubaga	216	31 %
Sex	Female	548	47 %
	Male	619	53 %
TB type	PTB	1041	89 %
	EPTB	126	11 %
Sputum collected	Yes	456	39 %
	No	711	61 %

Seventy five percent (874/1167) had HIV test counselling, 71 % (620/874) were tested and results were available for 60 % (359/620). More children under five had unknown HIV status than other age groups (57 % vs 48 %). Table 2 shows some other characteristics of children with known and unknown HIV status. Of those children with available results, 47 % (168/359) were HIV-positive. Twenty four percent (40/168) of the children with HIV co-infection were on antiretroviral therapy (ART) while 84 % (141/168) were on cotrimoxazole prophylaxis therapy (CPT).

There were 89 % (1041/1167) PTB cases and 10 % (126/1167) EPTB cases. Among the children with pulmonary TB (PTB), 30 % (308/1041) had HIV test results of which 47 % (144/308) were positive. Among extrapulmonary TB (EPTB) cases, 40 % (51/126) had HIV test results of which 47 % (24/51) were positive. The HIV positivity rate by age groups was; 47 % in 0–4, 59 % in 5–9 and 26 % in 10–14 years. The differences were statistically significant (see Table 3).

Of the PTB cases, 15 % (160/1041) were sputum acid-fast bacilli smear positive, 16 % (170/1041) were sputum acid-fast bacilli smear negative and 68 % (711/1041) had no smear done (no sputum collected). Among those with smear not done, most (68 %) were below 5 years old. There was a higher number of PTB cases with smear not done in 2010 (69 %) compared with 53 % in 2009 as shown in Fig. 1. The smear positive and smear

Table 2 Characteristics of children with known and unknown HIV status notified as TB in Kampala district, Uganda 2009–2010 ($N = 1167$)

Characteristic		HIV test result		
		Known *n* (%)	Unknown *n* (%)	*P* value
Age group in years	0–4	172 (48)	457 (57)	0.023
	5–9	84 (23)	162 (20)	
	10–14	103 (29)	189 (23)	
District	Kampala	210 (59)	475 (59))	0.049
	Wakiso	86 (24)	152 (19)	
	Others	63 (18)	181 (22)	
Division of Kampala district	Central	10 (5)	28 (6)	0.044
	Kawempe	43 (20)	129 (27)	
	Rubaga	74 (35)	142 (30)	
	Makindye	36 (17)	103 (22)	
	Nakawa	47 (22)	73 (15)	
Sex	Female	190 (53)	358 (44)	0.006
	Male	169 (47)	450 (56)	
TB type	PTB	307 (86)	733 (91)	0.011
	EPTB	51 (14)	75 (9)	
Sputum collected	Yes	207 (58)	249 (31)	<0.001
	No	151 (42)	560 (69)	

Table 3 General characteristics of HIV positive and negative children with TB notified in Kampala district, Uganda, 2009–2010 ($N = 359$)

Characteristic		HIV test result		
		Positive *n* (%)	Negative *n* (%)	*P* value
Age group in years	0–4	81 (48)	91 (48)	<0.002
	5–9	51 (30)	33 (17)	
	10–14	36 (21)	67 (35)	
District	Kampala	98 (58.33	112 (58.64	0.989
	Wakiso	40 (23.81	46 (24.08	
	Others	30 (17.86	33 (17.28	
Division	Kawempe	15 (15.31	28 (25.00	0.158
	Makindye	19 (19.39	17 (15.18	
	Central	4 (4.08	6 (5.36	
	Nakawa			
	Rubaga	32 (32.65	42 (37.50	
Sex	Female	88 (52.38	102 (53.40	0.846
	Male	80 (47.62	89 (46.60	
TB type	PTB	144 (85.7	163 (85.8)	0.983
	EPTB	24 (14.29)	27 (14.21)	
Sputum collected	Yes	103 (61.3)	104 (54.7	0.208
	No	65 (38.69)	86 (45.26)	

negative PTB cases as well as EPTB cases decreased between 2009 and 2010 (see Fig. 1). Distribution of the smear positive cases by age group was; 73 % (116/160) among 10–14, 15 % (24/160) among 5–9 and 13 % (20/160) among 0–4 years. Distribution of the EPTB cases by age group was: 36 % (45/126) among 10–14, 37 % (46/126) among 0–4 and 28 % (35/126) among 5–9 years old.

Main study results

The proportion of TB cases in the 0–4 years age group was 52 in 2009 and 56 % in 2010. In the 10–14 years age group the percent was 27 in 2009 and 24 % in 2010 while in the 5–9 years age group it was 21 in 2009 and 20 % in 2010.

The overall child TB incidence in Kampala was 56 (95 % CI 50–62) per 100,000 in 2009 and 44 (95 % CI 40–49) per 100,000 in 2010. The child TB incidences by age group and division also decreased over the study period as shown in Fig. 2.

Most of the TB cases, 60 % (410/685), in Kampala lived in slum areas. The Fig. 3 shows distribution of TB cases by area and division.

Discussion

Main findings

Our findings showed a general decrease in TB incidence with most cases of PTB having no smear done and majority of EPTB cases occurring among adolescents. We found a high rate of smear positive cases of up to 15 %. Our study highlights low HIV test uptake, high absence of HIV test results and large percentage TB cases residing in slum areas in the Kampala district.

Relation to literature

Our findings showed that many cases registered in Kampala district live outside the Kampala administrative borders. The incident cases registered in Kampala district may therefore not represent the true picture of TB burden within the various communities in Kampala district.

We noted a decrease in TB incidence over the review period similar to that in the World TB report 2011 [12]. The report shows a declining trend in TB incidence in adults. This trend should reflect in children as we know that TB cases in children especially those below 5 years represents recent transmission in the community [13, 14]. Previous work showed that up to 30 % of the children with TB will have an identifiable household source case

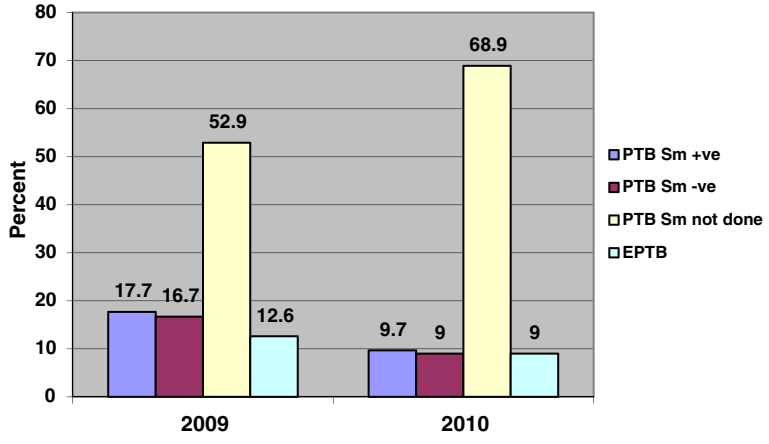

Fig. 1 Distribution of TB types in children in Kampala district, Uganda 2009, 2010 ($N = 1167$)

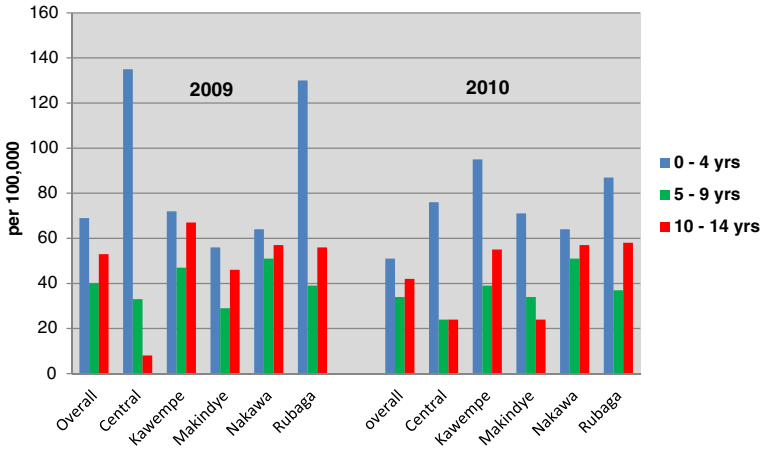

Fig. 2 Childhood TB incidence by age group and division in Kampala district, Uganda 2009, 2010

[15]. Similar to previous reports, our data shows a bimodal distribution with more cases in under five and 10–14 years age groups compared with the 5–9 year olds [16, 17].

Our study found the total number of TB cases had not substantially reduced (the reported TB cases decreased by 8 %) over the review period. The reported decreased incidence may be due to high population growth rate without the proportionate increase in the number of new TB cases. We however report an increased TB incidence in the under fives that we suppose is attributable to improved diagnosis and reporting rather than increasing burden of TB in children. Our report shows that 7.5 % of the TB cases registered in Kampala district were among children. This is much higher than the national average of 1.5 % reported in the world TB report 2013 but less than the estimated expected burden of 15–20 % in the high burden countries [2]. The World TB report 2014 still documented that childhood TB represents 1.5 % of the total cases with no decline in the total number of new cases [18]. We suppose that this discrepancy is due not reporting PTB cases in children with smear negative disease or smear not done. The increased child TB case detection in the under fives is an encouraging finding during this review period. This finding may be a spill over from Tuberculosis control assistance program (TB CAP) activities that included health worker training and provision of tools for TB care [19]. There is evidence that training health workers and provision of the relevant job aids in the diagnosis of children TB increases childhood TB detection rates [20]. Finding more children with no sputum examinations done on the background of several efforts to increase TB detection in children needs innovative ways to cause routine sputum collection from children. The high number of smear not done cases in children is likely due to limited health worker confidence and skills to collect sputum from children. This means most children are diagnosed on

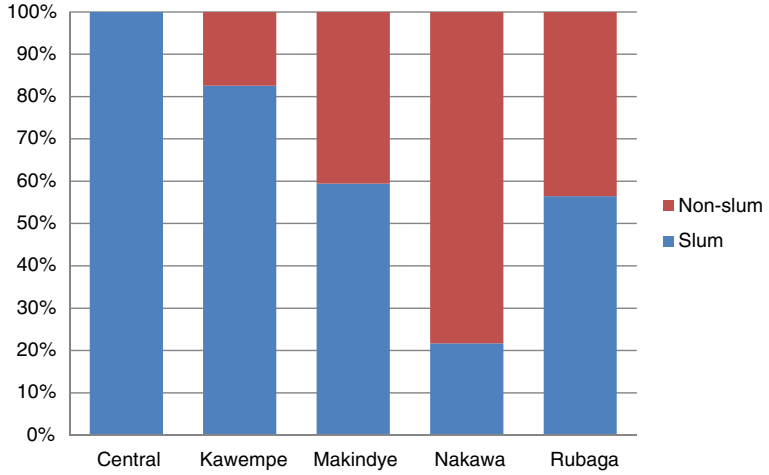

Fig. 3 Distribution of residence of TB cases residing in Kampala District, Uganda 2009–2010 ($N = 685$)

clinical basis with no sputum collection. The reality of multi-drug resistant (MDR) TB makes it even more pressing to build capacity for sputum collection from children.

The lowest TB incidence was in the 5–9 year age group, a safer age group as reported in literature [16]. Most of the childhood TB cases (56 %) were in children below 5 years old. This age group has the highest risk of developing TB disease because of low immunity and other reasons such as malnutrition and HIV [8, 21]. This age group is more likely to get exposure for longer periods to infectious adults within their households [22].

We found most TB cases were pulmonary, a finding reported by other studies [23, 24]. A TB report from Zambia showed that about 72 % of childhood TB cases were pulmonary [25]. Even for the children less than five years old we report more PTB cases than EPTB. Literature reports children are more prone to EPTB most especially if HIV positive [26]. However, we report more cases of PTB than EPTB even when the HIV prevalence was high among the tested patients. We found equal proportions of children with HIV among the PTB and EPTB cases. We expect a higher proportion with EPTB in a population of children with high HIV co-infection and low ART uptake at 24 % on the premise that children are prone to disseminated disease if HIV infected. This finding also reported in other settings [23–25] may be related to training of health workers that mainly focuses on PTB. It is possible the EPTB cases are largely missed. Finding about forty per cent EPTB cases among adolescents is unexpected since at this age there is more TB containment outside the lungs. The available data neither included the sites of EPTB nor provided an explanation for this observation. A study of incident TB cases among adolescents in South Africa found only 3 % had EPTB [27]. The total child TB cases reported in the 2010 and 2011 Global TB reports is 1291 for Uganda while we report 1167 child TB cases for Kampala district alone during the same time period. Our report underpins the reality of child TB under-reporting because of the emphasis on reporting smear positive cases only.

We report an overall smear positivity rate of 15 % among those tested and most of these (72 %) were adolescents 10–14 years. We report a high positive smear rate ranging from 13 % in 0–4 years to 15 % among children 10–14 years. The smear positivity rate among adolescents is similar to the adult smear positivity rate of 20 % reported in Uganda in 2007 [28]. This is not surprising since adolescents get adult type pulmonary disease. We report a smear positivity rate of 13 % among those below 5 years. This suggests that routine use of Xpert® MTB/RIF as recommended in this age group would yield many more bacteriologically confirmed cases in the under fives. The Xpert® MTB/RIF is a hands-free sample real-time PCR analysis system, developed under Cepheid (a molecular diagnostics company), that simultaneously detects mycobacterium tuberculosis (MTB) and resistance to rifampicin (RIF). In our previous study in a research setting, Xpert® MTB/RIF identified twice as many cases as microscopy [29].

The low HIV testing and results availability reported in this paper suggests gaps in integration of TB and HIV services. A similar finding was reported in non-integrated TB and HIV services in South Africa where only 26 % of the TB patients knew their HIV status. In the same report, the number tested for HIV was low at diagnosis compared to at 2 or 6 months while on TB treatment [30].

There were many TB cases residing outside Kampala district but registered and treatment in Kampala. This finding may reflect limited confidence and capacity of health workers outside Kampala district to diagnose TB in children. The likely implication is potential increase in TB transmission by caregivers (who are the likely source of TB) during their travel by public transport to access services in Kampala district. This exposure may vary from as short as 10 min to as long as one hour depending on the traffic flow and distance to the health units in Kampala. We found TB cases clustered in particular areas especially slum areas. Most of TB cases originate from slum areas. This observation may represent ongoing transmission in these areas. A study in high TB incidence urban setting in South Africa found 72 % of the cases were clustered within slum communities [31]. We found similar TB case notifications in the same slum areas over the two years of our report. This suggests the transmission cycle in those particular slum areas is uninterrupted.

Strengths and limitations

This is the first report to document the burden of TB in Kampala from the routine programmatic data. We collected all the data reported in Kampala district during the review period for at least two years. At the minimum this would provide insight on TB epidemiology in children in Kampala district. We conducted this work before availability of Xpert® MTB/RIF in Kampala provides important comparative data in assessing the impact of Xpert® MTB/RIF wide use on TB detection in children.

We acknowledge some limitations to this work. We had two data points (2009 and 2010) which are not enough to show a trend in TB epidemiology constituting a selection bias. There is no comparative published childhood TB data for Kampala district to affirm our the observation as part of a national downward trend of TB incidence in Uganda [18]. We could not confirm the accuracy of the TB diagnoses. We report the bacteriologically confirmed cases based on only sputum smears

which is an under estimate. Work done in South Africa found 22 % of the children with TB were smear negative but culture positive [27]. We used programmatic data that did not capture important aspects of paediatric TB epidemiology such as TB contact history, those on isoniazid preventive therapy and BCG vaccination status. The population projections we used depend on birth rates but for urban settings in Uganda population growth is mainly because in-migrations. Also population projects beyond 10 years become increasingly inaccurate. This is a reasonable explanation for the wide confidence intervals around our incidence estimates. We believe this is the best estimate within our limitations.

Implication for practise, policy and research

This paper highlights the reality of under-reporting of childhood TB where documenting all childhood TB cases would improve the estimates. The sputum collection for TB detection in children was low and there is need to understand the underlying reasons. Assuming limited skills and knowledge of health workers as the explanation for low sputum collection in children may only be part of a larger problem. The finding that many children reside outside Kampala district but are diagnosed and treated in Kampala district requires further study. Contacts of smear positive cases were not captured in the unit TB registers representing missed opportunities for control of TB. The reality of large number of TB cases arising from the same slum areas means that targeted TB control interventions would break this cycle. In this study we noted the TB cases remained clustered in the same slum areas over the review period. The finding that 100 % of TB cases in the central division of Kampala resided in slum areas requires specific TB control interventions at household level. Using private health units in the slum areas to detect and treat TB has proved an effective intervention that is worthy strengthening. The Slum Partnerships to Actively Respond to Tuberculosis in Kampala (SPARK-TB) project showed impact of this approach by being able to identify an extra 1267 smear positive cases [32].

Conclusions

There was a reduction in child TB incidence in Kampala district over the review period. The incidence was 56 per 100,000 in 2009 and 44 per 100,000 in 2010. The number of child TB cases was much higher at 7.5 % of all cases during the review period compared to the national average of 2.5 % in the world TB reports 2010, 2011. There was a high HIV co-infection rate and low antiretroviral uptake over the review period. Pulmonary TB remains the commonest form of TB in children with children below five years bearing the biggest burden. For the review period, the TB cases clustered in particular Kampala district slum areas.

Competing interest

The authors declare that they have no competing interests.

Authors' contributions

EW conceived the research idea, developed the proposal, interpreted the data and wrote the manuscript draft. DL helped to develop the research proposal, collected the data, analysed, interpreted the data and contributed to the manuscript writing. IL helped in developing the research proposal, data interpretation and contributed the manuscript. FM contributed to interpreting and writing of the manuscript. MS contributed to interpreting and writing of the manuscript. PM contributed to interpreting and writing of the manuscript. All the authors read and approved the manuscript.

Authors' information

Not applicable.

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