High HIV and active tuberculosis prevalence and increased mortality risk in adults with symptoms of TB: a systematic review and meta-analyses

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Abstract
Introduction: HIV and tuberculosis (TB) remain leading causes of preventable death in low- and middle-income countries (LMICs). The World Health Organization (WHO) recommends HIV testing for all individuals with TB symptoms, but implementation has been suboptimal. We conducted a systematic literature review and meta-analyses to estimate HIV and TB prevalence, and short-term (two to six months) mortality, among adults with TB symptoms at community- and facility level.

Methods: We searched Embase, Global Health and MEDLINE databases, and reviewed conference abstracts for studies reporting simultaneous HIV and TB screening of adults in LMICs published between January 2003 and December 2017. Meta-analyses were performed to estimate prevalence of HIV, undiagnosed TB and mortality risk at different health system levels.

Results: Sixty-two studies including 260,792 symptomatic adults were identified, mostly from Africa and Asia. Median HIV prevalence was 19.2% (IQR: 8.3% to 40.4%) at community level, 55.7% (IQR: 20.9% to 71.2%) at primary care level and 80.7% (IQR: 73.8% to 84.6%) at hospital level. Median TB prevalence was 6.9% (IQR: 3.3% to 8.4%) at community, 20.5% (IQR: 11.7% to 46.4%) at primary care and 36.4% (IQR: 22.9% to 40.9%) at hospital level. Median short-term mortality was 22.6% (IQR: 15.6% to 27.7%) among inpatients, 3.1% (IQR: 1.2% to 4.2%) at primary care and 1.6% (95% CI: 0.45 to 4.13, n = 1 study) at community level.

Conclusions: Adults with TB symptoms have extremely high prevalence of HIV infection, even when identified through community surveys. TB prevalence and mortality increased substantially at primary care and inpatient level respectively. Strategies to expand symptom-based TB screening combined with HIV and TB testing for all symptomatic individuals should be of the highest priority for both disease programmes in LMICs with generalized HIV epidemics. Interventions to reduce short-term mortality are urgently needed.

Keywords: Tuberculosis; HIV; screening; mortality; policy; health systems

Additional supporting information may be found online in the Supporting Information section at the end of the article

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1 INTRODUCTION

Tuberculosis (TB) and human immunodeficiency virus (HIV) are the two leading causes of adult infectious disease deaths worldwide. In 2016, there were 1.7 million deaths due to TB globally, including 0.4 million deaths among HIV-positive individuals [1]. Reducing the high mortality from HIV-related TB has become an increasingly high priority of The Joint United Nations Programme on HIV/AIDS (UNAIDS) and The United States President’s Emergency Plan for AIDS Relief (PEPFAR) programmes, and the recently ratified End TB Strategy includes a 35% reduction in TB deaths by 2025 among other targets [2].

Early diagnosis and treatment are key components of both HIV and TB programmes [3]. HIV testing is being scaled-up as countries work towards the UNAIDS “90-90-90” HIV diagnosis and care targets for 2020 [4]. Similarly, the End TB Strategy places increased emphasis on systematic screening for TB, including facility attendees and high risk communities, as part of early TB diagnosis [4]. Guidelines for TB/HIV collaborative activities released by the World Health Organization (WHO) in 2004 were updated in 2012 [5]. The 2004 guidelines...
focused on HIV testing and care for diagnosed TB patients and TB screening and prevention as part of HIV care, with annual reporting requirements. The 2012 guidelines recommend HIV testing among patients with suspected TB, noting high HIV prevalence and suboptimal service integration for this group, but without good quality of evidence, additional data reporting recommendations, or consideration of HIV testing in the context of TB screening programmes [5].

TB patients undergoing treatment in national TB programmes are at high risk of death, especially if HIV positive [6,7]. A 2011 meta-analysis estimated that 18.8% (95% confidence interval [CI]: 14.8% to 22.8%) of HIV-positive and 3.5% (95% CI: 2.0% to 4.9%) of HIV-negative TB patients die during TB treatment [7,8]. Adults with symptoms such as cough with or without confirmed TB disease in high HIV prevalence settings also face a high risk of early mortality, with HIV infection a risk factor for worse outcomes [9]. Despite the 2012 recommendation and suggestions of similar HIV prevalence and short-term mortality risks as notified TB patients, routine management of adults with TB symptoms in health services remains suboptimal with missed opportunities for HIV testing and referral for ART [9]. In addition, monitoring for HIV testing and linkage to ART is still not well established among patients with TB symptoms, with neither HIV nor TB programmes reporting coverage or outcomes. Accurate estimates of HIV and TB burden and risk of death among adults with symptoms of TB may help policymakers, researchers and implementers to prioritize appropriate collaborative interventions at the different levels of the healthcare system. We, therefore, set out to systematically summarize HIV prevalence, active TB prevalence and mortality risk among people with symptoms of TB (with or without confirmed TB disease) identified at community level (the general population) and in health facilities in low- and middle-income countries (LMICs) with different underlying burden of HIV and TB.

2 | METHODS

2.1 | Search strategy

In accordance with our published protocol (PROSPERO ID: CRD42015021944), we searched MEDLINE, Embase and Global Health electronic databases using a predefined search strategy (Table S1) for studies reporting outcomes of HIV and TB screening among adults identified in the community or during health facility attendance in LMICs that were published between 1 January 2003 and 31 December 2017. The start of the literature search was set in 2003 because it is the year the ART scale-up commenced in many LMICs. We additionally hand-searched abstracts from the Union World Conferences on Lung Health and International AIDS Society (IAS) Conferences from January 2014 to December 2017.

2.2 | Eligibility criteria

Studies were eligible for inclusion if they offered participants systematic screening for HIV at the time of TB screening. Acceptable TB screening algorithms comprising either symptom screening followed by microbiological confirmatory testing for active TB, or universal microbiological testing for TB, as well as HIV testing. We included randomized controlled trials (RCTs), cohort studies, cross-sectional studies, TB prevalence surveys, studies of evaluation of new TB diagnostic tests and published reports of programmatic activities, but excluded commentaries, editorials, case reports, case series, economic analyses and qualitative studies.

Studies conducted in countries defined to be low- or middle income by the World Bank lending groups in 2016 were included. We included studies that recruited only adults (≥16 years), or where both children and adults were included and age-disaggregated data were reported. We excluded studies that reported only a preselected, unrepresentative group of participants, including diagnosed TB or HIV-positive patients only, sputum smear-negative patients, TB household contacts, participants with suspected multidrug-resistant TB, miners and pregnant women.

Studies were imported into an EndNote X7 database and duplicates were removed. MN screened the titles and abstracts of all studies against inclusion and exclusion criteria, and the full text of potentially eligible studies were reviewed in duplicate by MN and AGW against inclusion and exclusion criteria using a predesigned electronic assessment form. Discrepancies were resolved by discussion between the reviewers, with arbitration by a third reviewer (PM) in case of disagreement.

2.3 | Data extraction

MN and AGW extracted data from selected studies using a previously piloted electronic data extraction form; inconsistencies were resolved by discussion. For each study, we extracted the author name, year, country and setting, and we described details of the TB and HIV screening algorithms used. The following data were extracted for each outcome: total number of participants, number screened for TB symptoms and number screening positive for TB symptoms. For adults with TB symptoms, we then extracted the numbers screened and diagnosed with HIV and TB and the number of deaths.

2.4 | Assessment of study quality

For assessment of methodological quality, RCTs were distinguished from non-randomized studies (see Supplementary material). For RCTs, the Cochrane Collaboration’s Tool for Assessing Risk of Bias was used. For non-randomized studies, a modified version of the Newcastle-Ottawa Scale was used to assess selection of participants and methods of assessment of each of the three outcomes (Table S2). For the HIV prevalence outcome, we assessed uptake of HIV testing and the quality of the diagnostic algorithm used; studies relying only on participants’ verbal report were classified as having high risk of bias. Similarly, for the TB prevalence outcome, we assessed uptake of testing and if TB disease was bacteriologically confirmed (i.e. based on sputum smear microscopy, Xpert® MTB/RIF or culture testing) or clinically diagnosed (when classified as TB patient without bacteriological confirmation). For mortality risk, we assessed methods of ascertainment of deaths (i.e. hospital/study record, verbal autopsy or vital registration) and the completeness of follow-up of the cohorts. For each study, the overall risk of bias for each outcome was categorized as low-, high- or unclear depending on the assessment of the domains above.
2.5 | Definitions

We classified participants symptomatic of TB as either having chronic cough (defined as ≥2 weeks as commonly used in community surveys) or as having ≥1 symptom in the WHO-recommended four-symptom screening tool (current cough of any duration, fever, night sweats, or weight loss).

We defined four levels of healthcare. The community level encompassed the general population that is studies recruiting adults from households or temporary mobile service in residential areas (excluding those in schools, prisons or other institutions). The primary care level included general practitioner services and health centres. The hospital-level category included studies on inpatients admitted to a ward and stayed at least one night in hospital. An additional category of mixed setting was used to define studies that included participants from more than one level that is both primary care clinics and hospitals (without disaggregated data), or for participants recruited at specialist outpatient clinics.

For each study, we defined national adult (aged 15 to 49 years old) HIV prevalence by year and country using UNAIDS estimates. For studies spanning more than one year, estimates were based on the middle year, if study covered an even number of years the average national prevalence of the two middle years was used. National incidence of TB was estimated from data reported in the WHO global TB reports for each year, and categorized as: low (<30 per 100,000), moderate (30 to 100 per 100,000), medium (100 to 300 per 100,000) and high (>300 per 100,000) [10]. Geographical distribution of studies was categorized based on WHO regions [11]. For mortality outcome, short-term or early mortality was defined as deaths occurring in the first six months of follow-up among those with TB symptoms.

A case of TB disease diagnosed after recruitment was defined as report by a study of a bacteriologically confirmed case (at least one positive sputum smear microscopy sample, positive culture for Mycobacterium tuberculosis (MTB), or a positive Xpert® MTB/RIF result) or a clinically diagnosed case (when TB treatment was initiated without bacteriological confirmation).

2.6 | Statistical analyses

The primary outcomes of the study were: HIV prevalence (the number of participants with confirmed HIV infection divided by the total number with TB symptoms), prevalence of active TB (the number with active TB divided by the number with TB symptoms) and mortality risk (the number of participants confirmed to have died by six months divided by the number with TB symptoms). We stratified analyses by level of healthcare (community, primary care, mixed and hospital inpatients). For HIV and TB prevalence outcomes, we undertook subgroup analyses by geographical region, type of TB symptoms, national HIV prevalence and TB incidence. For HIV, we also determined the number needed to screen (NNS) to detect a newly diagnosed HIV-positive individual. The NNS for TB was not conducted because it was discussed in detail in a 2013 systematic literature review by Shapiro et al. [12].

We assessed heterogeneity between studies using the I² statistic. Meta-analyses were conducted using random effects models to estimate weighted summary outcome measures and 95% CI for each of the three outcomes, stratified by level of healthcare. Arcsine transformation of proportions was implemented in the calculation of pooled prevalence to handle zero or unitary values. When it was not appropriate to conduct meta-analyses (i.e. if substantial heterogeneity with an I² ≥ 50%) [13], prevalence estimates were summarized as medians and interquartile ranges (IQR).

Meta-regression analyses were performed to examine associations between HIV and TB prevalence and geographical region, group of TB symptoms, country-level HIV prevalence and country-level TB incidence. Characteristics showing strong association with respective outcomes on univariate meta-regression were included in the multivariate meta-regression. The variable TB symptom type (chronic cough only or ≥1 symptom from the WHO tool) was included in the model a priori. Due to the small number of studies reporting mortality, meta-regression analyses were not conducted for this outcome. Analyses were conducted using R version 3.2.3 (The R Foundation for Statistical Computing, Vienna, 2016).

2.7 | Ethics statement

This review used published data and ethical review was not required.

3 | RESULTS

3.1 | Characteristics of included studies

The search strategy identified 20,863 records, from which we selected 289 eligible manuscripts (Figure 1). We included 59 manuscripts in the qualitative synthesis; 58 manuscripts reported single-site studies and one manuscript reported on a multisite study (four eligible sites were treated as individual studies). The final number of studies included in the analysis was 62; all 62 for HIV prevalence outcome, 59 for TB prevalence and 28 for mortality (Figure 1). Common reasons for exclusion included studies in preselected, unrepresentative populations (68.7%, 158/230) and not presenting outcome data stratified by presence of TB symptoms (20.9%, 48/230) (Table S3).

In keeping with our requirement for systematic HIV testing in parallel with TB investigations, most studies were from the African region (51/62, 82.3%), with the largest number from South Africa (37/62, 60.0%) (Table 1). In total, studies included 260,792 adults with TB symptoms, with one study from India (14) contributing 115,308 participants.

Twelve (12/62, 19.4%) studies were conducted at community level, 26/62 (41.9%) at primary care level, 9/62 (14.5%) at hospital level (inpatients) and 15/62 (24.2%) were conducted in mixed settings (Table 1). Studies at community level were cross-sectional [15-19] and cohort in design (Table 2) [20-22]. Studies at primary care level were either diagnostic evaluations [23-30], programme evaluations [31-33] or other cross-sectional designs [34-37]. Studies among hospital inpatients were predominantly diagnostic evaluations [38-41].

3.2 | Quality of included studies

For HIV prevalence outcome, 47/62 (75.8%) of the studies had low risk of bias while 15/62 (24.2%) had high or unclear risk of bias (Supplementary material). Studies were...
3.3 Prevalence of HIV by level of health care

Of the total 260,792 adults with symptoms of TB reported in 62 included studies, 184,601 (70.8%) were successfully screened for HIV. There was substantial variability in estimated HIV prevalence (range: 0.5% to 100%) (Table 2 and Figure S1). By level of care, the median HIV prevalence among adults with TB symptoms was 19.2% (IQR: 8.3% to 40.4%, n = 12 studies) at community level, 55.7% (IQR: 20.9% to 71.2%, n = 26 studies) at primary care level, 28.6% (IQR: 21.4% to 52.0%, n = 15 studies) in mixed settings, and was 80.7% (IQR: 73.8% to 84.6%, n = 9 studies) among hospital inpatients (Table 3).

In univariate and multivariate meta-regression, HIV prevalence among adults with TB symptoms was significantly higher in the following studies: among hospital inpatients, from the African region, with high national HIV prevalence, and those reporting chronic cough only (Table 3). Compared to adults with TB symptoms in the community, those at higher levels of care had higher HIV prevalence; adjusted prevalence ratio (aPR) 1.32 (95% CI: 1.15 to 1.50) at primary care, aPR 1.29 (95% CI: 1.12 to 1.50) in mixed settings, and aPR 1.66 (95% CI: 1.40 to 1.97) among hospital inpatients. Adults with TB symptoms from countries with higher HIV prevalence also had higher HIV prevalence, aPR 1.45 (95% CI: 1.30 to 1.62).

Seven studies reported on the number of participants newly diagnosed with HIV following screening (Table S6). At community level, the number of adults with TB symptoms needed to screen to detect one new HIV-positive individual was 11 in Malawi [48], 4 in South Africa [19] and 121 in Rwanda [49].
In primary care clinics the NNS was 2 in Malawi [29] and Zimbabwe [50], 4 in Zambia [51] and 30 in India (Table S6) [32].

### 3.4 Prevalence of TB disease by level of healthcare

There were 59 studies (155,167 adults with TB symptoms) that reported on results of TB screening. In these studies, estimated TB prevalence ranged from 0.8% to 71.9% (Table 2). By level of healthcare, the median TB prevalence was lowest at community level (6.9% [IQR: 3.3% to 8.4%, n = 12 studies]), followed by primary care level (20.5% [IQR: 11.5% to 46.8%, n = 23 studies]), mixed settings (36.4% [IQR: 22.9% to 41.0%, n = 15 studies]) and hospital inpatients (44.8% [IQR:26.5% to 40.7%, n = 9 studies]) (Table 4).

On univariate analysis, neither high national HIV prevalence (PR 1.05 [95% CI: 0.93 to 1.19]) nor high national TB incidence (PR 1.08 [95% CI: 0.94 to 1.26]) was associated with higher TB prevalence among adults with TB symptoms (Table 4), although statistical power was limited by the small number of studies from low HIV prevalence settings. In addition, there was no association with geographical region or group of symptoms used (Table 4).

On univariate and multivariate analysis, TB prevalence was higher in symptomatic adults identified in all of primary care setting (aPR 1.27 [95% CI: 1.11 to 1.46]), mixed settings (aPR 1.44 [95% CI: 1.21 to 1.72]) and among hospital inpatients (aPR 1.42 [95% CI: 1.21 to 1.64]) than those in the community (Table 4). However, the 95% CI for TB prevalence ratios overlapped at levels higher than community, therefore differences were not statistically significant (also see Figure 2).

### 3.5 Mortality in adults with symptoms of tuberculosis

Eleven studies were included for analysis of cumulative incidence (risk) of mortality reported between two and six months of follow-up; all were from Africa (Figure S2). Given the small number of studies we did not attempt to differentiate mortality by follow-up duration, instead considering all as short-term mortality (i.e., up to six months). Short-term mortality risk was highest among hospital inpatients, with a median risk of death of 22.6% (IQR: 15.6% to 27.7%, n = 3 studies). Median risk of short-term death was substantially lower among participants identified at primary care level (3.1% [IQR: 1.2% to 4.2%, n = 6 studies]) and community (1.6% [95% CI: 0.45 to 4.13], n = 1 study).

### 3.6 Influence of study quality on estimates

There was no significant difference in the estimate of HIV prevalence between low-quality studies (median 34.0% [IQR: 19.2% to 68.1%]) and high-quality studies (median 46.2% [IQR: 20.3% to 69.7%]), prevalence ratio 0.98 (95% CI: 0.81 to 1.19) (Table S7). Similarly, there was also no difference in estimate of TB prevalence between low-quality studies (median 15.4% [IQR: 8.9% to 28.9%]) and high-quality studies 22.1% (IQR: 11.1% to 39.8%), PR 0.89 (95% CI: 0.74 to 1.08) (Table S7). Notably, estimates of mortality risk were mostly based on low-quality studies 54.5% (6/11), representing the need for better quality studies for this outcome.

## 4 DISCUSSION

The main findings of this study, largely restricted to settings with generalized HIV epidemics by our selection criteria of studies reporting systematic HIV testing during investigation of TB symptoms, demonstrate extremely high HIV prevalence even for patients identified in the community during TB prevalence surveys (median 19.2% HIV prevalence). HIV prevalence was higher than TB prevalence in patients with TB symptoms at every level in the health system. The prevalence

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**Table 1. Characteristics of included studies**

| Region               | Countries | Studies | Community | Primary care | Hospital inpatients | Mixed | Number with TB symptoms |
|----------------------|-----------|---------|-----------|--------------|---------------------|-------|------------------------|
| African region       |           |         |           |              |                     |       |                        |
| Southern Africa³     | 5         | 27      | 4         | 15           | 6                   | 2     | 37,285                 |
| East Africa³         | 5         | 17      | 5         | 5            | 2                   | 5     | 27,019                 |
| West Africa³         | 3         | 6       | 1         | 1            | 1                   | 3     | 4,775                  |
| Central Africa³      | 1         | 1       | 0         | 1            | 0                   | 0     | 49,832                 |
| SE Asia region³      | 2         | 8       | 0         | 4            | 0                   | 4     | 122,237                |
| W Pacific region     | 1         | 1       | 1         | 0            | 0                   | 0     | 12,201                 |
| Americas             | 2         | 2       | 1         | 0            | 0                   | 0     | 7,443                  |
| Total                | 19        | 62      | 12        | 26           | 9                   | 15    | 260,792                |

³Countries are South Africa (studies=13), Botswana (2), Malawi (5), Zambia (4) and Zimbabwe (3).

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| Country, author, year<sup>a</sup> | Study design | Study description | Participant Eligibility criteria | TB diagnosis algorithm | Participants with symptoms n | HIV prev. n (%) | TB prev. n (%) |
|---------------------------------|--------------|-------------------|---------------------------------|-----------------------|-----------------------------|----------------|---------------|
| Cambodia, Lorent (2012) [18]    | Cross-sectional study | Active TB case finding (door to door strategy) | Any TB symptoms | Microscopy (fluorescence), Xpert MTB/RIF, culture (LJ) + species ID and DST | 12,201 | 319 (2.6) | 774 (6.3) |
| Ethiopia, Deribew (2012) [17]   | Cross-sectional study | Regional TB prevalence survey | Cough ≥2 weeks | Microscopy (fluorescence, ZN), culture (LJ) + species ID | 482 | 5 (0.9) | 17 (2.9) |
| Guinea Bissau, Bjerregaard-Andersen (2009) [22] | Cross-sectional study | Regional TB prevalence survey | Cough or any two other TB symptoms | ZN microscopy, CXR | 116 | 24 (20.7) | 8 (6.9) |
| Malawi, Nliwasa (2016) [20]    | Cohort study (individuals with chronic cough vs no cough) | Assessing TB yield and mortality risk | Cough ≥2 weeks | Microscopy (fluorescence), Xpert MTB/RIF, culture (MGIT) + species ID | 178 | 56 (31.5) | 6 (3.4) |
| Haiti, Rivera (2017) [65]      | Cross-sectional study | Active TB case finding (door to door strategy) | Cough ≥2 weeks | CXR, Microscopy, Xpert MTB/RIF | 5598 | 528 (9.4) | 1,000 (17.9) |
| Rwanda, 2014 [49]              | Cross-sectional study | National TB prevalence survey | Cough (any duration) or abnormal CXR | Microscopy (fluorescence), culture (MGIT) + species ID | 4747 | 218 (4.6) | 54 (1.1) |
| South Africa, Kranzer (2012) [19] | Cross-sectional study | Mobile multi-disease screening service | Any TB symptoms, or if HIV positive or diabetic | Microscopy (fluorescence), culture (MGIT) + species ID | 1385 | 758 (54.7) | 103 (7.4) |
| Tanzania, 2013 [42]            | Cross-sectional study | National TB prevalence survey | Cough ≥2 weeks or abnormal CXR | Microscopy (fluorescence), culture (MGIT) + species ID | 6271 | 782 (12.5) | 149 (2.4) |
| Uganda, Sekandi (2014) [21]    | Cross-sectional study | Active TB case finding (door to door strategy) | Cough ≥2 weeks | ZN microscopy and culture (LJ) | 199 | 82 (41.2) | 39 (19.6) |
| Uganda, 2017 [66]              | Cross-sectional study | National TB prevalence survey | Cough ≥2 weeks or abnormal CXR | ZN microscopy, Xpert MTB/RIF and culture (LJ) | 4386 | 417 (9.5) | 160 (3.6) |
| Zambia, Ayles (2009) [15]      | Cross-sectional study | TB prevalence survey – selected area | All adults in rural and urban communities | ZN microscopy. culture (MGIT & LJ) + species ID | 578 | 230 (39.8) | 34 (5.9) |
| Zimbabwe, Corbett (2010) [16]  | Cross-sectional study | TB prevalence survey – selected area | All adults from randomly selected households | Microscopy (fluorescence), culture (LJ) + species ID | 333 | 153 (45.9) | 37 (11.1) |

Primary care
| Country, author, year | Study design | Study description | Participant Eligibility criteria | TB diagnosis algorithm | Participants with symptoms n | HIV prev. n (%) | TB prev. n (%) |
|-----------------------|--------------|-------------------|----------------------------------|------------------------|-----------------------------|----------------|---------------|
| DR Congo, Yotebieng (2013) [67] | Cross-sectional study | Evaluation of HIV PITC in patients with TB symptoms | Cough any duration or other symptoms | Not described | 28,568 | 3,029 (10.6) | - |
| Ethiopia, Deribew (2010) [34] | Cross-sectional study | Evaluation of HIV PITC in patients with TB symptoms | Chronic cough or other symptoms | Not described | 506 | 81 (16.0) | 233 (46.0) |
| Ethiopia, Sahle (2017) [68] | Cross-sectional study | LAM evaluation study | Any TB symptom | Urinary LAM, LJ culture | 122 | 21 (17.2) | 35 (28.7) |
| Guinea-Bissau, Rudolf (2017) [69] | Prospective observational study | Assessing biomarkers for predicting mortality | Cough any duration or other symptoms | Not described | 1011 | 161 (15.9) | 101 (10.0) |
| India, Boehme (2011) [23] | Cross-sectional study | Evaluation of HIV PITC in patients with TB symptoms | Chronic cough or suspected MDR TB | Xpert MTB/RIF, culture (LJ, MGIT, Ogawa) + species ID and DST | 902 | 40 (4.4) | 108 (12.0) |
| India, Achanta (2012) [32] | Cross-sectional study | Evaluation of HIV PITC in patients with TB symptoms | Cough ≥2 weeks or other symptoms | Smear microscopy | 2,918 | 246 (8.4) | 407 (13.9) |
| India, Naik (2012) [33] | Cross-sectional study | Evaluation of HIV PITC in patients with TB symptoms | Clinician identified | Not described | 1539 | 108 (7.0) | 100 (6.5) |
| India, Kumar (2016) [14] | Cross-sectional study | Evaluation of HIV PITC in patients with TB symptoms | Patients submitting sputum samples | Not described | 115,308 | 7,559 (6.5) | - |
| Kenya, Kiviha-Ndugga (2003) [70] | Cross-sectional study | Assessing TB diagnostic algorithms | Clinician identified | Microscopy (ZN, fluorescence) and culture (LJ) smear microscopy | 993 | 128 (12.9) | 554 (55.8) |
| Kenya, Odhiambo, (2008) [35] | Cross-sectional study | Evaluation of HIV PITC in patients with TB symptoms | Any TB symptom | Smear microscopy | 5457 | 2,988 (54.8) | 2,595 (47.6) |
| Malawi, Munthali (2006) [71] | Cross-sectional study | Assessing HIV prevalence in patients with TB symptoms | Chronic cough | Not described | 145 | 79 (54.5) | 31 (21.4) |
| Malawi, Nliwasa (2016) [29] | Cross-sectional study | TB-LAMP diagnostic evaluation study | Cough ≥2 weeks | Microscopy (fluorescence, ZN), LAMP, Xpert MTB/RIF, culture (MGIT) + species ID | 273 | 121 (44.3) | 56 (20.5) |
| South Africa, Mwansa-Kambafwile (2011) | Cross-sectional study | Xpert MTB/RIF evaluation study | Clinician identified | Microscopy, Xpert MTB/RIF | 1981 | 1442 (72.8) | 271 (18.8) |
| Country, author, year | Study design | Study description | Participant Eligibility criteria | TB diagnosis algorithm | Participants with symptoms n | HIV prev. n (%) | TB prev. n (%) |
|-----------------------|--------------|-------------------|---------------------------------|------------------------|-------------------------------|----------------|---------------|
| South Africa, Brunet (2011) [72] | Cross-sectional study | Assessing HIV and smoking prevalence in patients with TB symptoms Xpert MTB/RIF evaluation study | Clinician identified | Microscopy and culture | 424 | 119 (28.1) | 286 (67.5) |
| South Africa, Scott (2011) [30] | Cross-sectional study | Xpert MTB/RIF evaluation study | Clinician identified | MTBDRplus and the LCTB assays, Xpert MTB/RIF | 319 | 220 (69.0) | 175 (54.9) |
| South Africa, Theron (2011) [73] | Cross-sectional study | Xpert MTB/RIF evaluation study | Definition: clinician identified | Microscopy (fluorescence), Xpert MTB/RIF, culture (MGIT) and DST | 480 | 130 (27.1) | 232 (48.3) |
| South Africa, Hanrahan (2013) [27] | Prospective observational study | Xpert MTB/RIF evaluation study | Cough any duration or other symptoms | Smear microscopy, culture and Xpert MTB/RIF | 641 | 443 (69.1) | 116 (18.1) |
| South Africa, Cox (2014) [25] | Pragmatic Randomized Trial | Xpert MTB/RIF evaluation study | Cough any duration or other symptoms | Xpert MTB/RIF, smear microscopy, culture, DST | 1985 | 965 (48.6) | 424 (21.4) |
| South Africa, Geldenhuys (2014) [74] | Cross-sectional study | Assessing sputum collection methods | Chronic cough or other symptoms | Culture used (MGIT) + species ID and DST | 555 | 118 (21.3) | 105 (18.9) |
| South Africa, Van Rie (2014) [37] | Cross-sectional study | Assessing uptake of TB screening | Prolonged cough and weight loss | Xpert MTB/RIF | 1505 | 933 (62.0) | 90 (6.0) |
| South Africa, Churchyard (2015) [24] | Cluster-randomized trial | Xpert MTB/RIF evaluation study | Clinician identified | Microscopy and Xpert MTB/RIF | 4656 | 2,206 (47.4) | 385 (8.3) |
| South Africa, Hanrahan (2015) [26] | Prospective observational study | Xpert MTB/RIF evaluation study | Cough any duration or other symptoms | Smear microscopy, culture and Xpert MTB/RIF | 1861 | 1,336 (71.8) | 204 (11.0) |
| Uganda, Srikantiah (2007) [36] | Cross-sectional study | Assessing HIV prevalence in patients with TB symptoms Xpert MTB/RIF evaluation study | Clinician identified | ZN microscopy plus CXR | 565 | 238 (42.1) | 378 (66.9) |
| Zambia, Muyoyeta (2015) [28] | Cross-sectional study | Xpert MTB/RIF evaluation study | Cough any duration | Xpert MTB/RIF, chest X-ray, fluorescence microscopy | 13,926 | 7,190 (52.6) | 2,861 (20.5) |
| Zimbabwe, Dlodlo (2015) [50] | Cross-sectional study | Evaluation of HIV PITC in patients with TB symptoms Xpert MTB/RIF evaluation study | Cough ≥ 2 weeks | Microscopy, Xpert MTB/RIF, if HIV positive | 422 | 297 (70.4) | - |
| Zimbabwe, Munyati (2004) [75] | Cross-sectional study | Assess causes of chronic cough | Chronic cough | Microscopy (ZN) and culture (LJ) + species ID | 544 | 454 (83.5) | 184 (33.8) |

Mixed settings
| Country, author, year | Study design | Study description | Participant Eligibility criteria | TB diagnosis algorithm | Participants with symptoms n | HIV prev. n (%) | TB prev. n (%) |
|-----------------------|--------------|-------------------|---------------------------------|------------------------|-----------------------------|----------------|----------------|
| Ethiopia, Legesse (2010) [76] | Cross-sectional study | Diagnostic evaluation study | Clinician identified Microscopy (ZN) and culture (LJ) | 140 | 27 (19.3) | 37 (26.4) |
| Ethiopia, Belay (2015) [77] | Cross-sectional study | Assessing HIV prevalence in patients with TB symptoms | Chloroquine Microscopy (ZN) and culture (LJ) | 325 | 82 (34.9) | 110 (33.8) |
| Ghana, Adjei (2006) [78] | Cross-sectional study | Assessing HIV prevalence in patients with TB symptoms | Clinician identified Microscopy (ZN) | 277 | 128 (46.2) | 108 (39.0) |
| India, Kaur (2011) [79] | Cross-sectional study | Chronic cough Microscopy (ZN) | 3 (0.5) | 243 (39.3) |
| Malawi, Van Lettow (2015) [44] | Prospective observational study | Assessing 6 m outcomes for inpatients | Definition: adults in chronic cough register. Tests: microscopy and chest X-ray | Routine care HIV testing | 348 | 191 (54.9) | 53 (15.2) |
| Peru, Boehme (2011) [23] | Cross-sectional study | Xpert MTB/RIF evaluation study | Chronic cough or suspected MDR TB | 1845 | 5 (0.3) | 209 (11.3) |
| Nigeria, Aliyu (2013) [80] | Cross-sectional study | Assessing prevalence of NTM | Any TB symptom Culture (MGIT, LJ) and species ID | 1603 | 378 (23.6) | 444 (27.7) |
| Nigeria, Chuks (2013) [81] | Cross-sectional study | Assessing HIV prevalence in patients with TB symptoms | Patients submitting sputum microscopy (ZN) | 1544 | 184 (11.9) | 237 (15.3) |
| South Africa, Boehme (2011) [23] | Cross-sectional study | Xpert MTB/RIF evaluation study | Chronic cough or suspected MDR TB | 2522 | 947 (37.5) | 493 (19.5) |
| Tanzania, Rachow (2011) [82] | Cross-sectional study | Diagnostic evaluation study of Xpert | Patients with suspected TB Microscopy (ZN), Xpert MTB/RIF and culture/DST | 292 | 172 (58.9) | 146 (50.0) |
| Tanzania, Mulder (2017) [45] | Cross-sectional study | Assessing use of rats in TB diagnosis | Patients with suspected TB Xpert MTB/RIF and Culture | 771 | 264 (34.2) | 345 (44.7) |
| Thailand, Kawkatinarong (2017) [83] | Cross-sectional study | Diagnostic evaluation study of Xpert | Patients with suspected TB Microscopy, Xpert MTB/RIF and culture | 494 | 128 (25.9) | 355 (71.9) |
| Thailand, Nanta (2011) [84] | Cross-sectional study | Diagnostic evaluation study of Xpert | No description ICT-TB tests | 401 | 206 (51.4) | 146 (36.4) |
| Thailand, Pinyopornpanish (2015) [85] | Cross-sectional study | Diagnostic evaluation study of Xpert | Patients with suspected TB Microscopy, Xpert MTB/RIF culture | 57 | 15 (26.3) | 27 (47.4) |
## Table 2. (Continued)

| Country, author, year | Study design | Study description | Participant Eligibility criteria | TB diagnosis algorithm | Participants with symptoms n | HIV prev. n (%) | TB prev. n (%) |
|-----------------------|--------------|-------------------|----------------------------------|------------------------|-----------------------------|----------------|----------------|
| Uganda, Boehme (2011) [23] | Cross-sectional study | Xpert MTB/RIF evaluation study | Chronic cough or suspected MDR TB | Xpert MTB/RIF, culture/DST | 372 | 254 (68.3) | 147 (39.5) |
| Hospital inpatients Botswana, Talbot (2004) [86] | Cross-sectional study | Assessing HIV prevalence in patients with TB symptoms | Cough ≥2 weeks | Microscopy (ZN), culture (LJ, MGIT, blood) + 4 serological TB tests | 465 | 384 (82.6) | 175 (37.6) |
| Botswana, Morse (2008) [47] | Cross-sectional study | Assessing PTB diagnosis from different samples | Clinician identified | fluorescence microscopy and culture (LJ, MGIT) | 140 | 113 (80.7) | 57 (40.7) |
| Malawi, Gawa (2011) [43] | Cross-sectional study | TB programme evaluation study | Clinician identified | Smear microscopy and chest X-ray | 141 | 50 (35.5) | 11 (7.8) |
| Nigeria, Hirao (2007) [87] | Cross-sectional study | Assessing number of samples for TB diagnosis | Cough ≥3 weeks | Smear microscopy and culture | 224 | 106 (47.3) | 78 (34.8) |
| South Africa, Shah (2009) [88] | Cross-sectional study | LAM diagnostic evaluation study | Patients with suspected TB | Fluorescent microscopy, LAM, culture (MGIT, MycoF Lytic) + species ID | 499 | 422 (84.6) | 282 (56.5) |
| Uganda, Yoon (2012) [41] | Prospective observational study | Evaluation study of Xpert MTB/RIF | Cough for ≥2 weeks | Fluorescence microscopy, Xpert MTB/RIF, culture (LJ, MGIT) + species ID | 477 | 362 (75.9) | 262 (54.9) |
| Uganda, Jones-Lopez (2014) [89] | Cross-sectional study | Assessing small membrane filtration for TB diagnosis | Cough ≥2 weeks or other | Fluorescence microscopy, Xpert MTB/RIF, culture (MGIT, LJ) + species ID | 212 | 173 (81.6) | 70 (33.0) |
| Zambia, O’Grady (2012) [39] | Cross-sectional study | Evaluation study of Xpert MTB/RIF | Patients submitting sputum | fluorescent smear microscopy, Xpert MTB/RIF, culture (MGIT) + species ID | 881 | 595 (67.5) | 202 (22.9) |
| Zambia, Bates (2013) [38] | Cross-sectional study | Evaluation study of Xpert MTB/RIF | Productive cough | Microscopy (fluorescence), culture (MGIT) and DST | 98 | 62 (63.3) | 26 (26.5) |

*Sorted by country alphabetical order, for each level of healthcare.*

TB, tuberculosis; LJ, Lowenstein-Jensen media; ID, Identification; ZN, Ziehl-Neelsen stain; MGIT, mycobacteria growth indicator tube; DST, drug susceptibility testing; ICT, immunochromatographic tests; PITC, provider-initiated testing and counselling; NTM, non-tuberculous mycobacteria.
of previously undiagnosed TB was also substantial, increasing from 6.9% of adults with TB symptoms identified in the community to 20.5% and 34.8% in primary care facilities and inpatient units respectively. Patients admitted to hospital with TB symptoms had a very high risk of short-term mortality (median 22.6%). These findings emphasize the critical need for adults identified with TB symptoms in HIV prevalent settings to be prioritized for HIV testing and ART services, including adults identified during community outreach or prevalence surveys. There is also urgent need to better understand and intervene to reduce short-term mortality in this patient group, most pressingly so for inpatients, although mortality at

| Level of care          | Studies | Participants screened | Median HIV prevalence % (IQR) | Univariate meta-regression Prevalence ratio (95% CI) P | Multivariate meta-regression Prevalence ratio (95% CI) P |
|------------------------|---------|-----------------------|-------------------------------|-------------------------------------------------------|-------------------------------------------------------|
| Community              | 12      | 32,472                | 19.2 (8.3 to 40.4)            | 1                                                     | 1                                                     |
| Primary care           | 26      | 139,933               | 55.7 (20.9 to 71.2)           | 1.34 (1.11 to 1.61) 0.002 1.32 (1.15 to 1.50) <0.001 |
| Mixed                  | 15      | 9230                  | 28.6 (21.4 to 52.0)           | 1.14 (0.93 to 1.40) 0.216 1.29 (1.12 to 1.50) <0.001 |
| Hospital inpatients    | 9       | 2966                  | 80.7 (73.8 to 84.6)           | 1.90 (1.50 to 2.40) <0.001 1.66 (1.40 to 1.97) <0.001 |
| National HIV prevalence|         |                       |                               |                                                       |                                                       |
| Low (0% to 5%)         | 25      | 134,965               | 17.2 (9.4 to 26.3)            | 1                                                     | 1                                                     |
| High (>5%)             | 37      | 49,636                | 62.3 (45.9 to 73.8)           | 1.56 (1.37 to 1.76) <0.001 1.45 (1.30 to 1.62) <0.001 |
| Group of symptoms      |         |                       |                               |                                                       |                                                       |
| Any TB symptom         | 41      | 170,885               | 32.8 (17.2 to 59.4)           | 1                                                     | 1                                                     |
| Chronic cough          | 21      | 13,716                | 68.3 (42.1 to 80.1)           | 1.24 (1.05 to 1.46) 0.011 1.14 (1.03 to 1.27) 0.013 |
| WHO regiona            |         |                       |                               |                                                       |                                                       |
| Non-Africa region      | 11      | 84,658                | 9.9 (5.1 to 26.1)             | 1                                                     | 1                                                     |
| Africa region          | 51      | 99,943                | 54.5 (26.1 to 70.9)           | 1.42 (1.16 to 1.72) <0.001                               |

*There was collinearity between geographical region and country-level HIV prevalence, geographical region was not included in the multivariate analysis.

| Level of care          | Studies | Participants screened | Median TB prevalence % (IQR) | Univariate meta-regression Prevalence ratio (95% CI) P | Multivariate meta-regression Prevalence ratio (95% CI) P |
|------------------------|---------|-----------------------|-------------------------------|-------------------------------------------------------|-------------------------------------------------------|
| Community              | 12      | 35,187                | 6.9 (3.3 to 8.4)              | 1                                                     | 1                                                     |
| Primary care           | 23      | 105,234               | 20.5 (11.5 to 46.8)           | 1.29 (1.13 to 1.49) 0.001 1.27 (1.11 to 1.46) <0.001 |
| Mixed                  | 15      | 11,609                | 36.4 (22.9 to 41.0)           | 1.42 (1.22 to 1.66) 0.001 1.42 (1.22 to 1.65) <0.001 |
| Hospital inpatients    | 9       | 3,137                 | 34.8 (26.5 to 40.7)           | 1.43 (1.21 to 1.71) <0.001 1.45 (1.22 to 1.72) <0.001 |
| National HIV prevalence|         |                       |                               |                                                       |                                                       |
| Low (0% to 5%)         | 24      | 99,334                | 23.1 (9.3 to 37.1)            | 1                                                     | 1                                                     |
| High (>5%)             | 35      | 55,833                | 24.1 (11.0 to 44.1)           | 1.05 (0.93 to 1.19) 0.414                               |
| National TB incidence  |         |                       |                               |                                                       |                                                       |
| Moderate/medium incidence | 28    | 99,014                | 20.3 (9.1 to 39.1)            | 1                                                     | 1                                                     |
| High incidence         | 15      | 36,819                | 26.5 (17.9 to 41.2)           | 1.08 (0.94 to 1.26) 0.270                              |
| Very high incidence    | 16      | 19,334                | 18.8 (10.3 to 42.6)           | 1.04 (0.90 to 1.21) 0.562                              |
| Symptom group          |         |                       |                               |                                                       |                                                       |
| Any TB symptom         | 39      | 138,490               | 26.4 (9.1 to 46.7)            | 1                                                     | 1                                                     |
| Chronic cough          | 20      | 16,677                | 19.9 (11.3 to 33.8)           | 0.94 (0.83 to 1.07) 0.355 0.94 (0.84 to 1.03) 0.289 |
| WHO regiona            |         |                       |                               |                                                       |                                                       |
| Non-Africa region      | 11      | 67,647                | 13.9 (9.4 to 37.9)            | 1                                                     | 1                                                     |
| Africa region          | 48      | 87,520                | 22.2 (10.7 to 39.8)           | 1.05 (0.90 to 1.23) 0.524                              |
focus on established target groups such as young and pregnant women, missing the opportunity to combine forces with TB programmes to provide an essential service for this high HIV prevalence patient group.

This is the first systematic literature review to estimate the prevalence of HIV among adults with TB symptoms. However, other reviews have addressed related subjects. A previous systematic literature review assessed the diagnostic utility of symptoms for TB among people with HIV [3]. This review reported that the best performing rule was the presence of any one of: current cough (any duration), fever, night sweats or weight loss with sensitivity of 78.9% (95% CI 58.3% to 90.9%) and specificity of 49.6% (95% CI 29.2% to 70.1%) [3]. Another systematic literature review highlighted the importance of respiratory symptoms among HIV-positive individuals [53], with a pooled odds ratio for the prevalence of cough of 3.05 (95% CI 2.24 to 4.16) among HIV-positive compared to HIV-negative individuals [53]. HIV-positive people remain at higher risk of respiratory symptoms even when started on ART, and are at increased risk of chronic lung disease from a variety of causes [54]. Ideally, advice on smoking cessation and links to specialist services providing diagnosis and management of infectious and non-infectious causes of lung disease should be included as part of routine HIV care, along with regular screening for TB [53].

As discussed above, our TB prevalence and mortality findings are not representative of low HIV prevalence settings. Within this limitation, however, we show the level of healthcare at which adults with TB symptoms present to be an important determinant of expected yield of TB on further screening. The median prevalence of undiagnosed TB was 6.9% for symptomatic adults identified at community level, 20.5% at primary care level and 34.8% for inpatients (Figure 2). At community as well as facility level, TB screening using symptoms and chest radiography combined with HIV testing for all with suspected TB, could then make an important contribution to early TB diagnosis as well as simultaneously providing HIV programmes with high yields of previously undiagnosed HIV. Oral kits packaged for HIV self-testing provide safe, accurate and highly acceptable access to HIV diagnosis that can more easily be integrated into high-throughput TB screening programmes than standard HIV testing services [55]. Community-based TB screening can lead to rapid reduction in undiagnosed infectious TB by reaching people who may otherwise remain undiagnosed for prolonged periods, potentially averting deaths and post-tuberculous disability [56,57].

The risk of early mortality among adults with TB symptoms also increased substantially with level of care at presentation, but with the major step-up for this outcome at inpatient level. Death within two to six months of follow-up was reported for 1.6% with TB symptoms at community level, 3.1% at primary care and 22.6% among hospital inpatients (Figure 2). All studies contributing to these estimates were from high HIV prevalence settings. The largest contributing study, conducted in outpatient facilities in South Africa, reported a threefold increase in the risk of death at six months for HIV-positive compared to HIV-patients are prompt HIV testing and linkage to cotrimoxazole and ART [58,59] plus rapid diagnosis of TB disease, including use of urine lipoarabinomannan assay for HIV-positive inpatients, followed by prompt TB treatment.
With mortality at such unacceptably high levels for such a common clinical presentation, intensified research and programmatic efforts aimed at reducing this risk should be of the highest priority, including intensified TB screening approaches, prophylactic broad-spectrum antibiotics and host-directed therapies (Table 5) [60,61].

**Table 5. Recommendations and future directions**

| Identified problem | Research directions | Programme priorities | References |
|-------------------|---------------------|----------------------|------------|
| Community level   |                     |                      |            |
| High HIV prevalence among adults with cough | Cluster randomized controlled trials to increase access to HIV testing in the community | Implement initiatives to achieve UNAIDS 90-90-90 targets: Community strategies, e.g. home-based or mobile HIV testing and HIV self-testing (HIVST) | [55, 90.91] |
| High prevalence of undiagnosed TB and delayed access to care in community | Randomized controlled trials (RCT) to investigate effective TB diagnostic algorithms, e.g. use of digital chest X-ray screening | Implement active TB case finding in communities including community-led initiatives | [92-94] |
| Few studies investigating risk of death associated with respiratory symptoms at community | Prospective studies investigating risk of death and risk factors and RCTs to modify risk of death | Improve death registration by setting-up vital registration systems | [95] |
| Primary care      |                     |                      |            |
| High HIV prevalence among adults with cough | Operational research to achieve high coverage of accurate provider-initiated testing and counselling | HIV testing for all health facility attendees | [5,96] |
| High TB prevalence among adults with cough | RCTs to investigate algorithms for TB screening, e.g. those that include Xpert MTB/RIF and digital chest radiography | TB screening for all health facility attendees for infection control and to improve care of patients Systematic TB screening using of digital chest X-ray screening and Xpert MTB/RIF | [5] |
| High risk of death among adults with cough | RCTs to investigate impact of new TB diagnostic tests to reduce risk of early death, potentially Xpert MTB/RIF Ultra | Operational recommendations are early HIV diagnosis, immediate ART and cotrimoxazole prophylaxis, and isoniazid preventive therapy if HIV positive | [96,97] |
| Hospital           |                     |                      |            |
| Very high HIV prevalence among adults with cough | Operational research to achieve high coverage of accurate PITC | HIV testing for all health facility attendees | [5,96] |
| Very high TB prevalence among adults with cough | RCTs to investigate algorithms for TB screening in hospitals that include Xpert MTB/RIF and digital chest radiography | TB screening for all health facility attendees for infection control and to improve care of patients Isolation to reduce nosocomial spread | [5] |
| Very high risk of early death | RCTs to investigate impact of new TB diagnostic tests to reduce risk of early death, potentially Xpert MTB/RIF Ultra | Operational recommendations are early HIV diagnosis, immediate ART and cotrimoxazole prophylaxis, and isoniazid preventive therapy if HIV positive Use of urinary LAM to screen all HIV-positive individuals for disseminated TB | [60, 96,97] |
|                   | RCTs to investigate effect of antibiotics, nutrition and host-directed therapies |                      |            |

TB, tuberculosis; DHS, demographic and health survey; ART, antiretroviral therapy; LAM, lipoarabinomannan; HIVST, HIV self-testing.

Limitations to this study include those that relate to selection of studies and those relating to approaches of analysis. There was the pronounced under-representation of studies from low HIV as well as low TB prevalence settings. The included studies, mostly from high HIV prevalence settings, also potentially had different coverage of ART, and ART is...
likely to reduce prevalence of TB and also prevalence of TB symptoms. Due to our inclusion criteria, estimates of TB prevalence were limited to studies that also conducted HIV testing, thereby excluding most TB prevalence surveys. We only included studies published in English language; this may bias our estimates. There was considerable heterogeneity that was found in meta-analyses for all three outcomes that could not be explained by differences in type of participants, geographical region or background burden of HIV and TB. Therefore, summary estimates from meta-analyses were not presented. This may also be partly because statistical tests for heterogeneity do not work well with pooled proportions [64].

In conclusion, the findings from this systematic literature review illustrate the urgent need to improve the management of patients with TB symptoms in high HIV prevalence settings. HIV prevalence among adults with TB symptoms was high at all levels of healthcare, including in general population surveys, while TB prevalence and mortality risk increased substantially at primary care and hospital level respectively. The high yield of undiagnosed HIV should make both community- and facility-based TB screening interventions of high interest to HIV programmes trying to reach UNAIDS 90-90-90 targets for HIV service coverage. TB programmes need to develop the necessary partnerships and expertise to ensure that HIV testing is provided alongside all TB screening interventions. More usable and effective high-throughput TB screening algorithms are needed at all levels of the health system. The high risk of early death, most notable for inpatients, but also at primary care is an issue in urgent need of more research and intervention. Annual reporting to WHO of the coverage of HIV testing, yield of HIV, linkage to ART and treatment outcomes among people investigated for TB would increase the international visibility of this important patient group, encourage national programmes to implement existing international recommendations, and enable progress to be tracked over time.

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COMPETING INTERESTS

There are no conflicts of interest to declare.

AUTHORS’ CONTRIBUTIONS

MN, PM and ELC conceived and designed the experiments. MN, MM, JO, AGW, PM and ELC performed the experiments. MN, CF and KH analysed the data. MN, AGW, KH and ELC wrote the first draft of the manuscript. MN, MM, CF, AGW, JO, PM and ELC contributed to the writing of the manuscript. MN, AGW, KH, PM, JO, MM and ELC agreed with the manuscript’s results and conclusions. MN, AGW, CF, PM and ELC assisted with design of analyses and interpretation of result

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Search strategy
Table S2. Modified Newcastle Ottawa scale for non-randomized studies
Table S3. Reasons for exclusion of studies with full-text review (n = 230)
Table S4. Methodological quality assessment of included RCTs
Table S5. Methodological quality assessment of non-randomized studies
Table S6. Influence of study quality on HIV and TB estimates
Figure S1. Forest plot of HIV and TB prevalence in adults with symptoms of TB stratified by level of healthcare.
Figure S2. Forest plot of mortality risk in adults with symptoms of TB stratified by level of care.