Subclinical tuberculosis disease - a review and analysis of prevalence surveys to inform definitions, burden, associations and screening methodology

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SUMMARY

Our analysis of TB prevalence surveys showed that a median of 50.4% of prevalent bacteriologically-confirmed TB was subclinical, i.e. negative on symptom screening. Chest X-ray detected 89% of cases. This could potentially suggest a change in TB case-finding policies.
ABSTRACT

While it is known that a substantial proportion of individuals with tuberculosis disease (TB) present subclinically, usually defined as bacteriologically-confirmed but negative on symptom screening, considerable knowledge gaps remain. Our aim was to review data from TB prevalence population surveys and generate a consistent definition and framework for subclinical TB, thus enabling an estimate of the proportion of TB that is subclinical, explore associations with overall burden and programme indicators, and performance of screening strategies. We extracted data from all publicly available prevalence surveys conducted since 1990. Between 36.1–79.7% (median 50.4%) of prevalent bacteriologically-confirmed TB was subclinical. No association was found between prevalence of subclinical and all bacteriologically confirmed TB, patient diagnostic rate or country-level HIV prevalence (p-values, 0.32, 0.4, 0.34, respectively). Chest X-ray detected 89% (range 73–98%) of bacteriologically-confirmed TB disease, highlighting the potential of optimizing current TB case-finding policies.

KEY WORDS

Subclinical TB; TB screening; TB prevalence surveys; Symptom screening; Chest X-ray screening.
MEETINGS WHEREIN THE INFORMATION HAS PREVIOUSLY BEEN PRESENTED

An early version of this analysis was presented at the 50th Union World Conference on Lung Health in Hyderabad, India, October 30th – November 2nd 2019.
BACKGROUND

Tuberculosis disease (TB) remains the leading cause of death from an infectious disease in the world [1]. Not all individuals with bacteriologically-confirmed TB will present with, or be aware of (clinical) symptoms [2]. When presenting to TB services, this asymptomatic yet infectious group is usually missed, as access to care mostly relies on positive symptom screening to start the TB diagnostic pathway [3]. Individuals with so-called subclinical TB could therefore continue to contribute to transmission [4], hindering global TB care and prevention efforts [1].

While the importance of the subclinical TB subpopulation is recognized, a clear definition has not been agreed upon. Both “asymptomatic” and “bacteriologically-confirmed” are inherently ambiguous. The extent and duration of symptoms used for screening will change the proportion of cases that have a positive symptom screening [5]. Similarly, the extent of bacteriological examination, e.g. the number of samples or technique used, will change the proportion that will be bacteriologically confirmed [6][7].

To enable progress, we propose to define asymptomatic and bacteriologically-confirmed TB as defined by TB prevalence surveys, which are population-based surveys that investigate representative samples of the population to estimate the national prevalence of bacteriologically-confirmed adult pulmonary TB. Through X-ray and symptom screening, individuals become eligible for sputum investigation with Xpert and/or culture (Table 1) [8]. While some variation remains, prevalence surveys can provide comparable measurements for the majority of high-burden countries [9], both between and within countries over time for the proportion of TB that is subclinical, i.e. asymptomatic (usually defined as negative on screening for cough of a certain
duration) and bacteriologically-confirmed (usually defined as positive on at least one culture or PCR-based test). Through this definition, subclinical TB can be placed in a comprehensive framework that reflects the relevant stages and flows in the spectrum of TB infection and disease.

Our aim was to review data from TB prevalence population surveys and generate a consistent definition and framework for subclinical TB, thereby enabling us to estimate of the proportion of TB that is subclinical as well as explore associations with overall burden and programme indicators. Finally, we considered the potential performance of chest X-ray based screening strategies to replace the current symptom-focused TB care and prevention policies.

METHODS

We considered for inclusion population-based TB prevalence surveys completed from 1990, with reports or papers publicly available by August 2019. A literature search for the period from January 1990 to August 2019, restricted to the English language, was conducted by one author (I.L.) in PubMed (August 2019) using the following search terms: “tuberculosis” and “prevalence” in the title and “survey” as text words. Reference lists of identified studies were also examined. Studies that were about a subset of TB cases (e.g. drug-resistant TB, women only, health care workers), TB infection rather than TB disease and risk factors for TB (e.g. diabetes), and review articles were excluded. Grey literature, such as unpublished survey reports produced by national TB programmes, abstracts and presentations from international meetings, and routine progress updates collated by the WHO Global Task Force on TB Impact Measurement on the status of surveys since 2008, was also systematically reviewed.
Subnational TB prevalence surveys were included from the review by Horton et al [10]. Surveys were included if both symptom screening interview and X-ray were performed on all eligible participants, and surveys reported the proportion of bacteriologically-confirmed cases by screening modality as well as the proportion of bacteriologically-confirmed cases that were negative on symptom screening.

We extracted data on the burden of TB (prevalence of bacteriologically-confirmed TB), screening and bacteriological confirmation methods, outcomes of screening of the study population, and outcomes of screening of bacteriologically-confirmed cases. To explore the impact of programme performance, we generated the patient diagnostic rate (PDR), as the case notification rate (number of individuals diagnosed with TB disease and reported to the National TB Programme, per 100,000 population), divided by the prevalence of bacteriologically-confirmed TB [10] (inverse of the prevalence to notification ratio).

We defined subclinical TB cases as all participants who were negative on symptom screening, following the criteria established in each survey, but confirmed on bacteriological testing. A framework for the natural history of TB was then developed to place subclinical disease in the spectrum of Mycobacterium tuberculosis infection and TB disease.

Bacteriological confirmation generally included at least one positive culture or PCR-based test [8]. Participants not eligible for X-ray screening (e.g. because of pregnancy) were considered negative at X-ray screening.
In settings where TB prevalence surveys were repeated in the same geographical area using similar methodology, we examined longitudinal trends in subclinical TB.

We performed a meta-regression (metareg in STATA v15) analysis for the effect of covariates on the proportion of subclinical TB. To avoid interdependency, one survey per country or area was included. We explored the association with TB prevalence in country, continent, country-level HIV prevalence, definition of symptom screen, the PDR as a metric of programme performance, and proportion of cases that was male. We also performed a random-effects meta-analysis, using the metaprop command in STATA v15 [11], to quantify between study heterogeneity.

To examine the relative contribution of symptoms compared to X-ray as a screening tool, we analyzed the proportion of bacteriologically-confirmed cases identified through each method. We also analyzed the proportion of participants that screened positive via symptoms interview, on X-ray, or on both methods, and were considered eligible for bacteriological examination.

RESULTS

We included 23 national surveys and 5 subnational surveys, conducted in 23 countries across Africa and Asia, representing 36% of the global TB burden in 2018[1], and 57.5% (23/40) of all national level surveys completed since 1990 (Data available in Tables 1-3, List of references for included surveys available in Supplementary Material as Appendix 1). The reasons for exclusion of the remaining prevalence surveys are available in Figure 1.
The 2013 Malawi survey was excluded because of reported issues in the quality of X-ray in many clusters [12]. Surveys from China were excluded because results were only reported for smear-positive or ‘active pulmonary cases’, the latter including an unknown proportion of bacteriologically negative, clinically diagnosed cases, which did not match our criteria [13]. Data from these surveys are included in Tables 1-3.

Across included surveys, the median percentage of subclinical TB cases was 50.4% (Interquartile range (IQR) 39.8–62.3%, range 36.1–79.7%), which was 49.4% (IQR 38.8–52.4%) in African countries, while in the Asian countries the median was 56.4% (IQR 42.8–68.5%), with no discernable trend by TB prevalence (Figure 2) in either continent.

Data on repeated surveys were available from Cambodia and Tamil Nadu state in India, although no clear trend is present, they seemed to suggest that the proportion of subclinical TB increased as TB prevalence declined (Tables 2-3). An indication for this trend was also seen among smear-positive TB in surveys repeated in China from 2000 and 2010 (Table 3).

As Figure 3 shows, X-ray screening identified the vast majority of bacteriologically-confirmed cases in all countries (median=89%, range 73–98%). In contrast, the percentage of bacteriologically-confirmed TB cases that were negative on X-ray but positive on symptom was below 25% (median 7%, range 0.7–22%) in all surveys, with between 0.01 and 15% of bacteriologically-confirmed cases diagnosed through direct bacteriological examination (see Figure 3 or Table 1).
In the sampled population, surveys found that 8.8% of individuals screened positive on X-ray (range 4.8-26%), whereas 6.3% (range 3–21%) were positive on symptoms (Figure 3).

We frame subclinical pulmonary TB in the wider context of TB natural history in Figure 5. Here, subclinical TB is a distinct intermediary disease state, which follows after a minimal disease state with initial pathological changes (e.g. visible on imaging), but not bacteriologically confirmed (at least within the limits of sampling undertaken) and unlikely to be contributing to transmission. Crucially, individuals can progress and regress from each stage, although how fast or frequent individuals move between stage will vary widely [14][15].

Table 4 shows the results from the meta-regression, which provided evidence that in our sample, the proportion of subclinical TB cases was higher in surveys from Asia compared to those from Africa (15.2%, 95% CI (5.6 – 24.8)). There was no evidence for an association with any of the other variables, including country-level TB or HIV prevalence, symptom-screen algorithm or PDR. Results from the meta-analysis showed very high heterogeneity (I² = 96%, p-value<0.001). The forest plot is shown in Appendix 2 of Supplementary Material.

**DISCUSSION**

Where measured, around half of the prevalent infectious TB disease burden is subclinical, making it likely that ignoring this burden will diminish the impact of TB care and prevention efforts.

Our results show that cough, the cornerstone of symptom-based screening policies, was only self-reported by around half of bacteriologically-confirmed cases in populations across Asia and Africa. Expecting extensive population-level impact on transmission from such policies seems misplaced.
Similar to historical observations that a large bacillary load is not required for transmission [16][17], cough is unlikely to be required for transmission[18],

We found that nine out of ten individuals with bacteriologically-confirmed TB, including those with subclinical disease, were positive on X-ray-based screening, which is based on a single posterior anterior image. We would therefore argue that X-ray as a clinical screening tool needs a re-evaluation as part of the End TB Strategy. Aside from its ability to detect the majority of infectious TB, rapid advancements in digitalization, portability of X-ray screening and computer aided X-ray reading now enable clear and consistent choices, which can be adjusted to fit the context of each country to further enhance performance [19]. It is now possible to strike a reproducible balance between the need to increase the proportion of all infectious TB disease found (sensitivity) and the proportion of screened individuals that are referred for bacteriological testing (positivity rate) [19], the latter of which varied between 7.1% to 24% in surveys included in our analysis. As such, the X-ray screening can be optimized depending on the population screened, whether these are clinic attendees or community-based.

Prevalence surveys do not capture individuals with symptom-negative, X-ray negative, bacteriologically-confirmed TB. While the data is limited, it suggests that another 0-5% of all bacteriologically-confirmed TB would be classified as subclinical [20], which means our estimates for subclinical TB would be conservative. In addition, pediatric and extrapulmonary TB are not measured in prevalence surveys.

Our results are limited to 36% of the global TB burden, and therefore key gaps remain, including China (where surveys have not reported details for bacteriologically-confirmed TB cases), India and
South Africa (surveys underway). We strongly argue that surveys should report results separately by screening and bacteriological confirmation, and data could be enriched, for example with further subdivisions by gender, urban or rural strata, and HIV status to help inform strategies to address this burden. In addition. Our data reflect the proportion that is subclinical amongst the prevalent burden of the infectious disease, not incident disease. In addition, our study does not include data from low TB incidence settings.

In particular, increased trends over time in the size and composition of the subclinical TB population as the overall TB prevalence changes would improve our understanding of population dynamics. Maximizing the number of repeat data points within countries would enable a within-country analysis of the impact of programme performance, including their (limited) ability to address subclinical TB. Our ecological analysis found no association between programme performance and subclinical TB, likely due to unmeasured confounding factors specific to each setting. Improved reporting would also provide more data points, which may increase power for more subtle analyses, such as the proportion of subclinical TB by duration of cough, sex, or differences between continents.

We would caution for overinterpretation of the evidence for a difference by continent from meta-regression (Table 4) and meta-analysis (Appendix 2), especially given that only a subset of countries for each continent is included in our study. Unmeasured confounding factors include differences in the host genetics and bacillary strains which could affect the natural history of the disease[21]. In addition, not all surveys followed exactly same protocol, not all of which was captured in our analysis. Other possible factors are related to cultural differences regarding awareness of symptoms.
and bacteriological confirmation criteria and techniques. Further studies are necessary to explore the causes and consequences of this result.

Despite the limitations described above, prevalence surveys offer clear advantages as a framework for analysis. Firstly they represent the most consistent, valid and extensive effort for TB burden estimation of the past three decades [1] and aim to reflect in-country clinical practice and case definitions. As a consequence, we could address the persistent ambiguity of the definitions for subclinical TB, in particular the precise interpretation of ‘asymptomatic’ and ‘bacteriologically-confirmed’.

Our framework places subclinical TB as a distinct intermediary disease state, which precedes clinical (i.e. symptomatic) disease and follows after a minimal disease state. Moreover, incipient disease is not a stage, but, as indicated in the name, represents the flow from minimal to subclinical disease. It must be noted that the prevalence of the minimal disease state might be influenced by the limitations of X-ray, and more sensitive imaging techniques, such as CT scan, would be more sensitive for initial pathological changes. Progression and regression across the TB natural history spectrum has been postulated, and is supported by historical and recent data. [22]. The term ‘incipient TB’ has been widely used to refer to a group of individuals who will soon progress to subclinical disease. While this makes it an attractive diagnostic target for predictive tests [23][24], the word and concept of ‘incipient’ implies both a transition and direction, which is a flow, not be a disease state.
Our analysis and conceptual framework should enable scientific discourse and policy progress on the unaddressed burden of subclinical TB. A key consideration is how subclinical TB contributes to transmission, given that individuals do not report (prolonged) cough. However, people may not recognize cough as a symptom, and cough not be required for effective transmission[4]. A comparison of health seeking behavior between individuals with subclinical (asymptomatic) and clinical (symptomatic) disease could shed more light on the impact of recognizing symptoms on accessing care, but unfortunately prevalence surveys did not report the required stratified data. Another advantage is that these disease stages could help distinguish a sub-population of patients for whom shorter treatment is both beneficial and safe. [25]

A significant proportion of the global TB burden is asymptomatic and not detectable by current symptom-based screening efforts, and fueling the TB epidemic through continued Mycobacterium tuberculosis transmission [4]. Detecting subclinical TB provides an opportunity to provide care early in the disease history, which should benefit individuals by preventing extensive lung damage and the risk of post-TB sequelae[26], and benefit society by interrupting transmission. There are both historical and recent precedents to support this thesis, showing that symptom-agnostic screening through X-ray[27] or Xpert[28] has near immediate impact disease burden in high incidence settings. The TB community needs to recognize both the challenge and opportunities of subclinical TB and develop strategies to address it. If we do so, we should have a much better chance of ending TB in our lifetime.
DECLARATION OF FUNDING

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CONFLICT OF INTEREST

None declared
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Table 1. Prevalence of TB and characteristics of screening

| Survey | Crude Prevalence of TB (95% CI) n/100 000 population | Estimated incidence (95% CI) n/100 000 population | Symptom screening criteria | X-ray screening device | X-ray screening criteria | Bacteriological confirmation test | Criteria for eligibility for bacteriological examination | Total number of individuals screened | Proportion of individuals screened that is S-X- (%) | Proportion of individuals screened that is S+X- (%) | Proportion of individuals screened that is S+X+ (%) | Proportion of individuals screened that is S-X+ (%) | Other (%) |
|--------|-----------------------------------------------------|---------------------------------------------------|---------------------------|-------------------------|-------------------------|---------------------------------|---------------------------------|---------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|---|
| Bangladesh 2015 | 287 (244-330) | 221 (160-290) | Symptom screening score ≥ 3 | Digital mobile X-ray | Any lung abnormality consistent with TB | Culture positive and/or Xpert positive | S+ and/or X+ or XNA and symptom score ≥1 | 98710 | 79.4 | 4.2 | 3.1 | 13.8 | S+XNA 0.04 |
| Country  | Year | Patients (95% CI) | Disposition | Cough Duration | Radiological Examination | Smear Test | S+ and/or X+ or XNA | S- and/or XNA | S+XNA | “Other” | Total | S-XNA | S+XNA | “Other” |
|---------|------|------------------|-------------|----------------|--------------------------|------------|---------------------|--------------|--------|--------|-------|-------|-------|--------|
| Cambodia | 2002 | 1208 (992-1463)  | 600         | Cough ≥ 3 weeks and/or hemoptysis in the previous month | Portable X-ray machine | Smear positive and/or culture positive | not reported | 4.6 | 2.6 | 8.2 | include XNA |
| Cambodia | 2011 | 831 (707-977)   | Not reported | Cough ≥ 2 weeks and/or hemoptysis | Portable X-ray machine | Any abnormal shadow in the lung field or mediastinum other than a single small calcification nodule with a size less than 10 mm or pleural adhesion at costophrenic angle | Smear positive and/or culture positive | 37417 | 87.22 | 3.1 | 1.9 | 7.2 | S-XNA 0.4 |

*S+ and/or X+ or XNA* refer to positive results of smear and/or culture for Mycobacterium tuberculosis.
| Country   | Year | ID  | Method                  | Tests                                      | Findings                                                                 | Value 1 | Value 2 | Value 3 | Value 4 | Value 5 | Value 6 |
|-----------|------|-----|-------------------------|--------------------------------------------|---------------------------------------------------------------------------|---------|---------|---------|---------|---------|---------|
| China     | 2000 | 466 | Not reported            | Chest fluoroscopy to all subjects, then X-ray if they showed abnormal results | Abnormal findings except hilar calcification, a few fibrotic indurated lesions, small area of pleural thickening     | S+ and/or X+ and all known TB cases | Not    | Not     | Not     | Not     | Not    | applicable |
| China     | 2010 | 459 | Not reported            | Not reported                               | Smear microscopy and culture                                              | S+ and/or X+ and all known TB cases | 252940  | Not     | Not     | Not     | Not    | applicable |
| DPR Korea | 2016 | 567 | Not reported            | Portable X-ray machine                     | Abnormal chest radiograph in the lung field or mediastinum other than a single small calcification nodule with a size less than 10 mm or pleural adhesion at costophrenic angle(s) | Culture positive S+ and/or X+ | 60683   | Not     | Not     | 1.7     | 3.1    | S-X- or S-XNA 92 |
| Indonesia |      | 759 | Not reported            | Digital                                   | Any lung or pleura                                                          | Smear S+ and/or X+               | 67944   | 77.3    | 5.7     | 6.6     | 9.9    | S+XNA |

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| Year | Region   | Total (with range) | Reported | Cough ≥ 2 weeks and/or hemoptysis | Mobile X-ray abnormality | Mobile X-ray abnormality depiction | Smear positive and/or culture positive and/or Xpert positive | S+ and/or X+ with any symptom of TB | S+X- or S+XNA | S+XNA | SNA X+ | SNA XNA | S+XNA 2.1 |
|------|----------|--------------------|----------|-----------------------------------|--------------------------|-----------------------------------|----------------------------------------------------------------|----------------------------------|----------------|--------|--------|--------|---------|------------|
| 2014 | Lao PDR 2011 | 595 (457-733) | Not reported | Cough ≥ 2 weeks and/or hemoptysis in the previous month | Full size conventional CXR | Any abnormal lung field shadow | Culture positive | S+ and/or X+ | 39212 | 83.8 | Not reported | 3.3 | 7.9 | S+X- or S+XNA 4.9 |
| 2015 | Mongolia | 559.6 (454.5-664.7) | 428 (220-703) | Cough ≥ 2 weeks | Digital mobile X-ray | Any abnormal shadow in lung field and mediastinum or pleural effusion | Smear positive and/or culture positive | S+ and/or X+ or XNA | 50309 | 79.3 | 3.4 | 1.6 | 14 | S+XNA 0.08 | S+XNA 0.06 | S+XNA XNA 1.5 |
| 2009 | Myanmar 2009 | 612.8 (502.2-747.6) | 526 (307-802) | Any symptom | Portable X-ray machine | Any abnormality in the lung field or mediastinum greater than a single small calcification | Smear positive and/or culture positive | S+ and/or X+ or XNA | 51367 | 76.2 | 0.8 | 2.5 | 18.3 | S+XNA 2.1 | S+XNA 0.1 | Suspected false negative |
| Country   | Year | Number (Range) | Cough ≥ 2 weeks and/or hemoptysis | Mass miniature radiography | Any abnormality suggestive of TB | Culture positive and/or Xpert positive | Smear positive and/or culture positive | Smear positive and/or culture positive | S+ and/or X+ or TB current treatment or history of treatment within 2 years | CXR |  |
|-----------|------|----------------|----------------------------------|-----------------------------|--------------------------------|---------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------------------------------------------------|-----|---|
| Philippines | 2016 | 1159 (1016-1301) | Cough ≥ 2 weeks and/or hemoptysis in the previous month | Mass miniature radiography | Any abnormality suggestive of TB | Culture positive and/or Xpert positive | Smear positive and/or culture positive | Not obtainable | S+ and/or X+ or XNA | 46689 | 60.2 | 2.8 | 2.9 | 22.9 | S+XNA | 0.3 |
| Thailand | 2012 | 142 (166.3-287.8) | Not obtainable | Not obtainable | Not obtainable | Not obtainable | Not obtainable | Not obtainable | Not obtainable | 62536 | 90.3 | 2.8 | 0.8 | 6 | includes XNA |
| Vietnam | 2007 | 286 | 171 | Cough ≥ 2 weeks | Either mass miniature radiography or digital mobile X-ray | Any abnormality suggestive of TB | Smear positive and/or culture positive | S+ and/or X+ or TB current treatment or history of treatment within 2 years | 94179 | 92.2 | 0.01 | 0.6 | Not reported | S+XNA | 0.4 |
| Ethiopia | 2011 | 277 (208-347) | 258 (191-335) | Cough ≥ 2 weeks | Portable X-ray machine | Any abnormality in lung field or mediastinum, | Culture positive | S+ and/or X+ | 46697 | Not reported | Not reported | 1.7 | 6.4 | S-X- or S-XNA 87.1 | 0.4 | S+X- or
| Country | Sample Size | Upper Limit | Lower Limit |
|---------|-------------|-------------|-------------|
| Gambia 2012 | 179 (149-231) | 175 (132-215) | 0.13 (0.13-0.13) |

- Cough ≥ 2 weeks, or cough ≤ 2 weeks plus ≥ 2 symptoms suggestive of TB, or no cough but ≥3 symptoms suggestive of TB
- Digital mobile X-ray
- Any abnormality in lung field or mediastinum, including cavities, infiltrates, pleural effusion, hilar or mediastinal lymphadenopathy, pulmonary nodules, interstitial abnormalities suggestive or TB
- Culture positive
- S+ and/or X+
- 43100
- Not reported
- 5.5
- 2.4
- 5.5
- S+XNA 4.7
- S-XNA or S-X 86.2
| Country | Year | Total (Range) | Not reported | Cough ≥ 2 weeks | Digital mobile X-ray | Any abnormalities in lung, pleura, mediastinum | Culture positive and/or Xpert positive with X+ | $S+ \ and/or \ X+$ or XNA | $S-$ | $S+\ XNA$ | $S-XNA$ |
|---------|------|--------------|--------------|----------------|---------------------|-----------------------------------------------|-----------------------------------------------|-----------------|------|-------------|----------|
| Ghana   | 2013 | 327 (282-347) | Not reported | Cough ≥ 2 weeks | Digital mobile X-ray | Any abnormalities in lung, pleura, mediastinum | Culture positive and/or Xpert positive with X+ | $S+ \ and/or \ X+$ or XNA | $S-$ | $S+\ XNA$ | $S-XNA$ |
| Kenya   | 2015 | 558 (455-662) | Not reported | Cough ≥ 2 weeks | Digital mobile X-ray | Any finding suggestive of TB | Culture positive and/or Xpert positive | $S+ \ and/or \ X+$ or XNA | $S-$ | $S+\ XNA$ | $S-XNA$ |
| Malawi  | 2013 | 452 (312-593) | Not reported | ≥ 1 week of cough or sputum or blood in sputum or chest pain or weight loss or night sweat or fatigue or fever or shortness of breath | Conventional radiography (film system), portable X-ray generator | Any lung abnormality (opacities, cavitation, fibrosis, calcification) | Culture positive and/or Xpert positive | $S+ \ and/or \ X+$ or XNA | $S-$ | $S+\ XNA$ | $S-XNA$ |
| Country  | Year | Cases (CI) | Cough or weight loss or fever or night sweats | Portable X-ray machine | Any abnormality suggestive of TB, read by automatic software and radiologist | Culture positive and/or Xpert positive | S+ and/or X+ or XNA | Sensitivity (%) | Specificity (%) | Positive Predictive Value (%) |
|---------|------|------------|-----------------------------------------------|------------------------|-----------------------------------------------------------------|----------------------------------------|----------------------------|-----------------|-----------------|-------------------------------|
| Namibia | 2017 | 431 (361.4-514.3) | Not reported | Portable X-ray machine | Any abnormality suggestive of TB, read by automatic software and radiologist | Culture positive and/or Xpert positive | S+ and/or X+ or XNA | 29495 | 63.2 | 14 | 5.8 | 11.3 | S+XNA 1.5 | S-XNA 4.3 |
| Nigeria | 2012 | 524 (378-670) | 108 (50-186) | cough ≥ 2 weeks | Mass miniature radiography | Any abnormality suggestive of TB | Smear positive and/or culture positive | S+ and/or X+ or XNA | 44186 | Not reported | Not reported | 1.7 | 5 | S-X- or S-XNA 89.4 | S+X- or S+XNA 3.9 |
| Rwanda  | 2012 | 119.3 (78.8-159.9) | Not reported | cough any duration | Not reported | Any abnormality suggestive of TB | Culture positive | S+ and/or X+ or XNA | 43128 | 88.8 | 4.8 | 1.3 | 4.9 | S+ XNA 0.02 | S- XNA 0.1 | SNA X- 0.02 |
| Sudan   | 2014 | 183.4 (129.6-237.2) | Not reported | cough ≥ 2 weeks | Digital mobile X-ray | Any lung abnormality, including pleura | Culture positive and/or NAAT positive | S+ and/or X+ or XNA or TB current treatment | 83202 | 78.2 | Not reported | 2.2 | Not reported | S-X- or SNA XNA 0.7 | SNA XNA 0.13 | S+XNA or S+X- 0.8 | S-X+ or |
| Country   | Year | Cases (Range) | Symptoms Reported | Diagnostic Methods | (S+) X+ or XNA | (S-) X+ or XNA | (S+) XNA | (S-) XNA |
|-----------|------|---------------|-------------------|--------------------|---------------|---------------|----------|----------|
| Tanzania  | 2012 | 307 (261-360) | Not reported      | Digital mobile X-ray | Any abnormalities in the lung field or mediastinum | Culture positive | S+ and/or X+ or XNA | 50447 | 87.5 | 6.4 | 1.7 | 3.7 |
| Uganda    | 2014 | 401 (291-509) | Not reported      | Digital mobile X-ray | Any abnormalities in lung | Culture positive and/or Xpert positive | S+ and/or X+ or XNA | 41154 | 87.5 | 5.2 | 1.3 | 5.6 |
| Zambia    | 2014 | 638 (505-774) | Not reported      | Digital mobile X-ray | Any lung abnormality excluding heart and bone abnormality | Culture positive and/or Xpert positive | S+ and/or X+ or XNA | 46099 | 84.2 | 6.3 | 3.6 | 4.9 |
| Zimbabwe  | 2014 | 317.1 (250.5-360) | Not reported | Digital mobile X-ray | Any abnormalities in lung | Culture positive | S+ and/or X+ or XNA | 33736 | 82.7 | 3.4 | 1.9 | 8.3 |

For Tanzania, Uganda, Zambia, and Zimbabwe, the table shows the number of cases, symptoms reported, diagnostic methods, and results. The table includes columns for the percentage of cases with specific symptoms and diagnostic test results.
| 383.8 |     |     | and/or Xpert positive | S+XNA |
|-------|-----|-----|-----------------------|-------|
| 0.1   |     |     |                       | "other" |
| 0.03  |     |     |                       |        |

NA= not applicable, used when results for symptom (SNA) or X-ray screening (XNA) were not available; S= symptoms; X= X-ray

A list of references for included prevalence surveys is available in Supplementary Material as Appendix 1.

\(^a\)Surveys from China were excluded from the analysis because results active pulmonary cases, of which the proportion of bacteriologically negative clinically diagnosed cases is unknown

\(^b\)Malawi 2013: Results were excluded from the analysis because the quality of images observed in some clusters was sub-standard, and could not be compared with results from other countries[12]

\(^c\)Some data was not obtainable from Thailand 2012, because the only version of the survey report available was in Thai
Table 2. Subnational surveys in India

| Survey               | Prevalence of TB (95%CI) /100 000 population | Bacteriological confirmation test               | Criteria for eligibility for bacteriological examination | S-X+ cases (%) | S- cases (%) |
|----------------------|---------------------------------------------|------------------------------------------------|--------------------------------------------------------|----------------|-------------|
| Tamil Nadu (India) 1999 | 605                                         | One culture positive sample                    | S+ and/or X+                                           | 46.3           | 46.3        |
| Tamil Nadu (India) 2001 | 454                                         | Culture positive                               | S+ and/or X+ and all known TB cases                    | 33.7           | 36          |
| Tamil Nadu (India) 2004 | 309                                         | Culture positive                               | S+ and/or X+ and all known TB cases                    | 36.4           | 39.1        |
| Region               | Year | Sample Size | Study Type | Positive S+ and/or X+ and all known TB cases | Prevalence S+ | Prevalence X+ |
|----------------------|------|-------------|------------|---------------------------------------------|--------------|--------------|
| Tamil Nadu (India)   | 2006 | 388         | Culture    | S+ and/or X+ and all known TB cases         | 34.9         | 39.2         |
| Tamil Nadu (India)   | 2010 | 259         | Culture    | S+ and/or X+ and all known TB cases         | 32.9         | 55           |

A list of references for included prevalence surveys is available in Supplementary Material as Appendix 1.

S= symptoms; X= X-ray
Table 3. Characteristics of bacteriologically confirmed cases

| Survey | S-X+ cases (%) | S- cases (%) | S+ cases (%) | X+ cases (%) | S+X- cases (%) | S+X+ cases (%) | Proportion negative on ANY symptom among cases (%) | Proportion of males among all bacteriologically confirmed cases (%) | HIV prevalence among all bacteriologically confirmed cases (%) | Percentage of cases found already in TB care (%) | Bacteriologically confirmed notification rate (n/100,000) | Prevalence to notification ratio |
|--------|----------------|--------------|--------------|--------------|----------------|----------------|-----------------------------------------------|-------------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------|
| Bangladesh 2015 | 61.9 | 61.9 | 38.1 | 90.3 | 9.7 | 36 | Not reported | 72.3 | Not measured | 1.8 | 101.7 | 2.8 |
| Cambodia 2002 | 60.9 | 60.9 | 39.1 | 95.6 | 4.4 | 34.7 | 15.9 | 60 | Not measured | 4.2 | 222.9 | 2.0 |
| Country      | Year | Incidence | PCR | NTM | FTB | ISQ | PPD | HIV | CD4 | BCG | M. Tuberculosis Vaccine | M. Tuberculosis Vaccine | Not measured | 2   | 161.4 | 1.7 |
|--------------|------|-----------|-----|-----|-----|-----|-----|-----|-----|-----|----------------------------|----------------------------|--------------|-----|--------|-----|
| Cambodia    | 2011 | 69.4      | 70.4| 29.1| 95.6| 3.5 | 25.6| 10.2| 59.9| Not measured | 2   | 161.4 | 1.7 |
| China       | 2000 | Not reported | 12.1| 87.9| 49.5| Not reported | Not reported | Not reported | 70.4| Not reported | Not reported | Not reported | Not available |
| China       | 2010 | Not reported | 43.1| 56.9| Not reported | Not reported | Not reported | Not reported | 69.9| Not reported | Not reported | Not reported | 38.7 | 1.7 |
| DPR Korea   | 2016 | 42.9      | 42.9| 57  | 97.9| 0.7 | 55  | Not reported | 69.7| Not measured | 31.2 | 482.1 | 1.2 |
| Indonesia   | 2014 | 42.5      | 42.5| 57.5| 94.1| 4.9 | 51.6| Not reported | 65.5| Not measured | 4.5  | 113.3 | 2.3 |
| Lao PDR     | 2011 | 50.2      | 50.2| 49.8| 97  | 2.9 | 46.8| Not reported | 66.2| Not measured | 2.5  | 80.4  | 3.5 |
| Mongolia    | 2015 | 77.8      | 79.4| 20.6| 96  | 2.5 | 18.1| 42.7| 64.5| Not measured | 4.4  | 83.2  | 2.5 |
| Myanmar     | 2009 | Not reported | 78.8| 19.7| 95.2| Not reported | Not reported | 38.2| 66.2| Not measured | 3.5  | 114.4 | 2.1 |
| Philippines | 2016 | 63.9      | 67.8| 32.2| 92.2| 1.7 | 28.3| 26  | 69  | Not measured | 6.4  | 142.2 | 3.1 |
| Thailand    | 2012 | 66.2      | 66.2| 33.8| 95.8| 4.2 | 29.6| Not obtainable | Not obtainable | Not obtainable | 56.4 | 1.8 |
| Vietnam     | 2007 | 67.3      | 73.6| 26.4| 85.1| 8.5 | 17.8| Not reported | 78.8| Not measured | 0.07 | 85.2  | 2.3 |
| Ethiopia    | 2011 | 48.2      | 48.2| 51.8| 89  | 10.9| 40.9| Not reported | 55.3| 8.00  | 2.7  | 91.0  | 1.2 |
| Country   | Year | Value | Value2 | Value3 | Value4 | Value5 | Value6 | Value7 | Value8 | Value9 |
|-----------|------|-------|--------|--------|--------|--------|--------|--------|--------|--------|
| Gambia    | 2012 | 36.6  | 38.    | 62     | 81.7   | 15.5   | 45     | Not reported | 62     | Not measured | 5     | 145.3  | 0.6  |
| Ghana     | 2013 | Not reported | 59 | 41 | 75.2 | not reported | Not reported | Not reported | 50 | Not reported | 5 | 45.2 | 2.5 |
| Kenya     | 2015 | 50.5  | 51.8   | 40.2   | 88.2   | 10.5   | 38     | Not reported | 62 | 13.4 | 4.9 | 158.2 | 3.5 |
| Malawi    | 2013 | 30.3  | 30.3   | 69.7   | 49.2   | 50.76  | 18.9   | Not reported | 47.7 | 16.7 | 4.5 | 86.8  | 2.5 |
| Namibia   | 2017 | Not reported | 51.3 | 48.7 | 95 | not reported | not reported | Not reported | 60 | 15.1 | 4.2 | 551.9 | 0.8 |
| Nigeria   | 2012 | Not reported | 36.1 | 63.9 | 89 | not reported | not reported | Not reported | 22.9 | 67.7 | Not measured | 0.2 | 55 | 5.8 |
| Rwanda    | 2012 | 50    | 50     | 50     | 79.6   | 20.4   | 27.8   | Not reported | 73.7 | 3.7 | 5.3 | 56.1 | 1.3 |
| Sudan     | 2014 | 40    | 40     | 45.1   | 78     | 7.1    | 38     | Not reported | Not reported | Not measured | 7.1 | 25 | 3.5 |
| Tanzania  | 2012 | not reported | 36.7 | 63.2 | 73.5 | not reported | not reported | Not reported | 60 | 5.9 | Not measured | 92.8 | 3 |
| Uganda    | 2014 | 50.6  | 50.6   | 49.4   | 88.7   | 10     | 38.1   | Not reported | 75 | 26.9 | 10 | 141.8 | 2.8 |
| Zambia    | 2014 | 39    | 39     | 61     | 83     | 17     | 44     | Not reported | 66.7 | 13.2 | 2.6 | 159.2 | 2.0 |
| Zimbabwe  | 2014 | Not reported | 63.55 | 36 | 86 | not reported | not reported | Not reported | 54.2 | Not reported | Not reported | 137.9 | 2.5 |
A list of references for included prevalence surveys is available in Supplementary Material as Appendix 1.

S= symptoms, X= X-ray

\(^a\) Surveys from China were excluded from the analysis because results active pulmonary cases, of which the proportion of bacteriologically negative clinically diagnosed cases is unknown

\(^b\) Malawi 2013: Results were excluded from our study because the quality of images observed in some clusters was sub-standard, and could not be compared with results from other countries\(^{[12]}\)

\(^c\) Some data was not obtainable from Thailand 2012, because the only version of the survey report available was in Thai
Table 4. Survey level associations with the proportion of prevalent TB that is subclinical

| Variable                                | Change in proportion of subclinical TB (95% CI) | p-value |
|-----------------------------------------|-----------------------------------------------|---------|
| **Continent (24)**                      |                                               |         |
| Africa                                  | Reference                                     |         |
| Asia                                    | 15.2% (5.6 – 24.8)                            | 0.003   |
| **HIV prevalence in country (24)**      |                                               |         |
| Continuous variable                     | -0.7% (-2.0 – 0.7)                            | 0.34    |
| **HIV prevalence in country (24)**      |                                               |         |
| Below 1%                                | Reference                                     |         |
| 1-2%                                    | -5.4% (-18.9 – 8.1)                           | 0.41    |
| ≥2%                                     | -10.9% (-24.4 – 2.7)                          | 0.11    |
| **Symptom screening (24)**              |                                               |         |
| Any symptom                             | Reference                                     |         |
| Cough ≥ 2 weeks                         | -5.0% (-22.1 – 12.1)                          | 0.55    |
| Cough ≥ 2 weeks and/or other symptoms   | -10.1% (-26.8 – 6.5)                          | 0.22    |
|                           | Range          | p-value |
|--------------------------|----------------|---------|
| TB Prevalence (23)       | 0.01% (-0.001 – 0.003) | 0.32    |
| Patient Diagnostic Rate, | -8.7% (-29.8 – 12.4) | 0.4     |
| average in the previous 5 years (22) |                |         |
| Proportion of male among the cases (21) | 0.1% (-0.8 – 1.0) | 0.79    |

Results from univariate meta-regression.
FIGURES

**Figure 1: TB prevalence surveys selection flowchart**

**Figure 2: Proportion of subclinical disease in prevalence surveys**

Figure 2 shows the proportion of all prevalent cases that was subclinical (bars – left side Y-axis) by the adult crude prevalence of bacteriologically-confirmed TB found in that survey (crosses – right side Y-axis). The first three bars show the median (bar) and interquartile range (error bars) for values found in surveys in Africa, Asia and overall.

Sub= subnational surveys

**Figure 3: Screening modality for bacteriologically-confirmed cases**

Figure 3 shows the proportion of bacteriologically-confirmed cases in prevalence surveys that screened positive on X-ray (Y-axis), or on symptom-screen only (X-axis). Raw data is available in Table 3.

Note: The Vietnam 2007 and Sudan 2014 surveys did not report symptom screening and X-ray results for TB cases who were under treatment or had history of treatment within 2 years, but did receive bacteriological examination; In the Philippines 2016 survey, 5% of bacteriologically-confirmed cases were exempted from X-ray (see Table 1).
Figure 4: Population screening results

Figure 4 shows the proportion of population included in prevalence surveys that screened positive on X-ray (S-X+), symptom screen (S+X-), both (S+X+) or neither (S-X-).

Figure 5: Model representation of the natural history of *Mycobacterium tuberculosis* infection and tuberculosis disease

Figure 5 shows different states of M.tb infection (green) and TB disease (purple) and that infected individuals can progress and regress across the spectrum.

Naive = never been infected; Infected = viable M.tb infection, with potential to progress to disease;
Self-cleared = individual has cleared the M.tb infection, and cannot progress to disease without re-infection (dashed arrows); Minimal disease = pathological changes caused by M.tb, but bacteriologically negative; Incipient disease= transition from minimal to subclinical disease;
Subclinical disease = bacteriologically-confirmed, negative at symptom screening; Clinical disease = bacteriologically confirmed and symptomatic;
Incipient disease (gray circle) = transition from minimal to subclinical disease;
