Original research

Patients with presumed tuberculosis in sub-Saharan Africa that are not diagnosed with tuberculosis: a systematic review and meta-analysis

Shamanthi Jayasooriya, Francesca Dimambro-Denson, Claire Beecroft, Julie Balen, Babatunde Awokola, Caroline Mitchell, Beate Kampmann, Fiona Campbell, Pete Dodd, Kevin Mortimer

ABSTRACT

Background Many patients in sub-Saharan Africa whom a diagnosis of tuberculosis is considered are subsequently not diagnosed with tuberculosis. The proportion of patients this represents, and their alternative diagnoses, have not previously been systematically reviewed.

Methods We searched four databases from inception to 27 April 2020, without language restrictions. We included all adult pulmonary tuberculosis diagnostic studies from sub-Saharan Africa, excluding case series and inpatient studies. We extracted the proportion of patients with presumed tuberculosis subsequently not diagnosed with tuberculosis and any alternative diagnoses received. We conducted a random effects meta-analysis to obtain pooled estimates stratified by passive and active case finding.

Results Our search identified 1799 studies, of which 18 studies (2002–2019) with 14527 participants from 10 African countries were included. The proportion of patients with presumed tuberculosis subsequently not diagnosed with tuberculosis was 48.5% (95% CI 39.0 to 58.0) in passive and 92.8% (95% CI 85.0 to 96.7) in active case-finding studies. This proportion increased with declining numbers of clinically diagnosed tuberculosis cases. A history of tuberculosis was documented in 55% of studies, with just five out of 18 reporting any alternative diagnoses.

Discussion Nearly half of all patients with presumed tuberculosis in sub-Saharan Africa do not have a final diagnosis of active tuberculosis. This proportion may be higher when active case-finding strategies are used. Little is known about the healthcare needs of these patients. Research is required to better characterise these patient populations and plan health system solutions that meet their needs.

Key messages

What is the key question?

► What are the numbers and nature of alternative final diagnoses among patients with presumed tuberculosis in sub-Saharan Africa?

What is the bottom line?

► Nearly half of all patients with presumed tuberculosis in sub-Saharan Africa are subsequently found not to have tuberculosis, with few receiving any alternative diagnoses.

Why read on?

► Patients with symptoms suggestive of tuberculosis who may eventually receive an alternative diagnosis represent a major unmet need in sub-Saharan Africa; requiring better characterisation through research to develop health system solutions to meet their needs.

INTRODUCTION

The differential access to high-quality diagnostics experienced in most low-income middle-income countries (LMICs) illustrate important and growing global health disparities. Diagnostic tests are often not affordable or designed for application in LMICs and can, therefore, represent a barrier to high-quality healthcare access. Access to accurate diagnostics for a range of diseases is a cornerstone of high-quality patient care, enabling appropriate timely management, inclusive of transmission control in the case of communicable disease. Pulmonary tuberculosis (TB) is a highly prevalent poverty-related communicable disease that lays bare many of the diagnostic challenges faced in LMICs, not least because of non-specific symptoms at presentation.

Patients with presumed TB are adults or children evaluated for active TB with suggestive signs and symptoms, such as cough, fever, night sweats, weight loss, haemoptysis and fatigue. While sputum culture remains the bacteriological reference standard for TB diagnostics, it is a costly, lengthy process and in LMICs is usually only available in central reference laboratories. At local clinics, a reliance on smear microscopy is being replaced by molecular diagnostics such as Xpert MTB/RIF and Xpert MTB/RIF Ultra nucleic acid amplification tests. Despite these advances, only 57% of global TB cases are bacteriologically confirmed, the rest are clinically diagnosed with negative or no bacteriological testing and notified to WHO as such. Whereas in high-income settings, 80% of TB cases are confirmed bacteriologically. The WHO describes the use of both passive and active case-finding strategies to detect TB cases. Passive case
finding relies on symptomatic patients seeking medical care by presenting to health services, whereas active case finding involves community-based screening of patients who would not otherwise seek healthcare.

A proportion of patients with presumed TB are found not to have tuberculosis, following both bacteriological and clinical investigation. This proportion is likely to depend on tuberculosis prevalence, case-finding strategies (passive or active) and other context-specific factors such as access to alternative diagnostics. A community study in Malawi demonstrated that only 10%–20% of patients presenting to primary care with a persistent cough had TB. More recent observational data from The Gambia showed that nearly half of all patients with presumed TB did receive a final diagnosis of TB. A range of alternative diagnoses—predominantly respiratory—were described, but importantly, non-respiratory diagnoses such as heart failure, malignancy and renal failure were also noted. Furthermore, in 36% of patients not diagnosed with TB, no alternative diagnosis was made. Minimal healthcare was afforded to these patients beyond screening for TB and HIV.

The burden of ill health in patients with presumed TB subsequently found not to have TB and their ongoing engagement with health systems has been largely overlooked. While national guidelines exist for patients that receive a negative sputum smear microscopy result, these focus on further elucidating active TB cases rather than exploring alternative diagnoses. The rapid rise of non-communicable disease—including chronic respiratory diseases—in TB endemic areas, means patients presenting with presumed TB may increasingly have alternative health issues that require investigation and management, once TB is ruled out.

The aim of this study was to undertake a systematic review and meta-analysis of the evidence describing the number and nature of alternative final diagnoses among patients with presumed TB in sub-Saharan Africa (sSA).

METHODS
Search strategy and selection criteria
We performed a systematic review and meta-analysis of the evidence in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidance. We searched Ovid Medline, Embase, Cumulative Index of Nursing and Allied Health Literature (CINAHL) and the Cochrane library. The search strategy involved Medical Subject Heading and free text terms relating to the concepts of WHO tuberculosis symptoms (such as “chronic cough”, “fever” and “weight loss”), diagnostics (such as “diagnostic”, “sensitivity” and “specificity”), TB and used filters for North, East, South, West and Central Africa. The full Medline search strategy is provided in online supplemental data 1 search strategy and was modified for other databases. Human studies that met the inclusion criteria from inception to 27 April 2020 were included. No language restrictions were applied.

We included all studies (Diagnostic, Cohort and Observational) conducted in sSA enrolling adult (≥15 years old) patients with presumed TB presenting with symptoms (cough>2 weeks or any one of cough, fever, weight loss, night sweats or haemoptysis). Duplicate articles, research on non-human subjects, in-patient settings, articles reporting exclusively paediatric, extrapulmonary, pregnant, prison or diabetic populations, and any studies irrelevant to TB and diagnostics not set in sSA were excluded. Narrative reviews, case reports, case series and studies reporting only smear microscopy diagnostics or screening with chest radiographs as opposed to symptoms were also excluded.

We screened citations of relevant articles and systematic reviews to identify additional studies. All articles identified by the initial search underwent title and abstract screening. Full-text review of potentially relevant articles was conducted. This was performed by two independent reviewers (SJ, FD-D), where a third reviewer (CM) was called on if a consensus could not be reached. If multiple studies used the same dataset or populations, we included the most comprehensive study with the largest number of participants and excluded the others. Multi-site studies were included where data from sSA sites were individually extractable from the total number of participants.

Data analysis
Data extraction was performed by two independent reviewers (SJ and FD-D) and compared, disagreements were resolved in the first instance by discussion and a third reviewer (CM) called on if consensus could not be reached. A piloted standardised data extraction form was used to collect information from all eligible studies. All non-English language studies were translated using an online document translator.

For each eligible study, we extracted the year of publication, first authors name, mean or median age, proportion of male participants, study country, study setting (general or district hospital, local health centre or community), total number of participants eligible and included, diagnostic test used (culture or GeneXpert), number of patients with and without a diagnosis of TB disease (Bacteriologically confirmed or clinical) and their HIV rates, where available. Specific details of alternative diagnoses made, and their management were extracted. WHO Global Health Observatory data provided TB and HIV incidence estimates in-country during the years studies were undertaken and if they spanned more than a year the higher annual value used.

Included studies risk of bias was evaluated using a tool specifically for prevalence studies developed by the Joanna Briggs Institute. ” Each study was independently assessed according to ten items of methodological quality (online supplemental data 2 JBI Risk of Bias Table).

We used WHO case definitions for TB case reporting. These are bacteriologically confirmed TB cases and clinically diagnosed TB cases. All study participants included were tested for tuberculosis therefore clinically diagnosed tuberculosis cases in this review include patients with negative bacteriological results only and not patients that have not undergone testing. Bacteriologically confirmed TB refers to sputum culture positivity in all but one study that used Xpert MTB/RIF.

All data analyses were done using R (V.4.0.2) and the metafor package V2.4–0 (online supplemental data 3 Statistical Analysis). We stratified random effects meta-analyses of the proportion of patients with presumed TB found not to have TB by passive or active case finding, and whether cases found passively included clinically diagnosed cases. Meta-regression was used to assess the association between the proportion of patients with presumed TB subsequently found not to have TB and the proportion of clinically diagnosed TB cases, as well as with matched country-year estimates of per capita TB incidence and HIV prevalence.

RESULTS
Our search yielded 1799 articles (64 identified from systematic review references and three through citation). A total of 246 duplicate articles were removed (figure 1). After screening abstracts and titles, we excluded 1204 articles that were not relevant. After screening full texts, we excluded an additional 331...
There were seven studies including (table 1) and five studies not including (table 2) clinically diagnosed TB cases that used passive case-finding strategies. Of the five studies (table 2) not including clinically diagnosed TB cases, only Dorman et al. did not document whether a clinical assessment was performed. Ling et al., Lawson et al., Hanrahan et al. and Cuevas et al. did perform a clinical assessment but reported no cases of clinically diagnosed TB. The proportion of patients with presumed TB subsequently found not to have TB increased with declining numbers of clinically diagnosed TB cases (p<0.0001).

Figure 2 shows included studies and summary estimates grouped by passive and active case-finding. Passive-case-finding studies including clinically diagnosed TB cases (table 1) are shown in the top section of figure 2 with estimates ordered by this proportion. The summary proportion of patients with presumed TB subsequently found not to have TB was lower in passive-case-finding studies that included clinically diagnosed TB cases (table 1) compared with those that did not (table 2), 48.5% (95% CI 39.0% to 58.0%) vs 70.6% (95% CI 61.5% to 78.3%) (figure 2). Heterogeneity was high (I²>95% for all estimates).

In the passive case-finding studies that included clinically diagnosed patients, the proportion of patients with presumed TB subsequently found not to have TB was inversely associated with the fraction of clinically diagnosed TB cases. While this proportion varied according to study, it was not predicted by country incidence of TB or HIV. The few included studies that used active case-finding strategies had much lower proportions of patients with presumed TB with a final diagnosis of TB than those that used passive case finding. Only five of the identified studies attempted to characterise patients with presumed TB who were subsequently found not to have TB by reporting alternative diagnoses. In both of these studies, clinical judgement, rather than a standardised approach, was used to decide on investigations performed, and no spirometry was conducted. Just over half of included studies captured prior histories of TB and none indicated how many times individuals had undergone previous TB testing.

Our findings demonstrate that almost half of patients with presumed TB in SSA were not given a final diagnosis of active TB. While this proportion varied according to study, it was not predicted by country incidence of TB or HIV. The few included studies that used active case-finding strategies had much lower proportions of patients with presumed TB with a final diagnosis of TB than those that used passive case finding. Only five of the identified studies attempted to characterise patients with presumed TB who were subsequently found not to have TB by reporting alternative diagnoses. In both of these studies, clinical judgement, rather than a standardised approach, was used to decide on investigations performed, and no spirometry was conducted. Just over half of included studies captured prior histories of TB and none indicated how many times individuals had been previously tested for TB.

There were four active case-finding studies without any clinically diagnosed TB cases (table 3). Three studies were conducted in Ethiopia reporting clinical assessments, but no clinically diagnosed TB cases found. Clinical assessments were reported by Sekandi et al in Uganda.

Figure 2 illustrates that active case-finding studies had high proportions of patients with presumed TB subsequently found not to have TB, 92.8% (95% CI 85.0% to 96.7%) (table 3, figure 2).

A further two articles included patients with presumed TB that were already smear negative on microscopy (table 4). Affolabi et al. did not include and Huerga et al. included clinically diagnosed TB cases, with 89% and 61% of patients with presumed TB subsequently found not to have TB, respectively.

Five studies reported diagnoses other than active TB (table 5). There were insufficient data available to analyse aetiology and prevalence as stated in the protocol. Two studies described non-TB mycobacteria and one Pneumocystis jirovecii pneumonia as the only alternative diagnoses. Jayasooriya and Munyati et al. described a range of diagnoses which were predominantly respiratory, but importantly non-respiratory diagnoses such as heart failure, malignancy and renal failure were noted. Neither study performed spirometry. Four out of the five studies reported management of patients with presumed TB subsequently found not to have TB, two stating as clinically indicated. Notably, Affolabi et al. and Huerga et al. reported giving empirical antibiotics to all patients subsequently found not to have active TB amounting to mass administration of antibiotics to 207 and 380 patients respectively. Out of 18, 10 (55%) studies recorded historical TB episodes, and none recorded the number of times individuals had undergone previous TB testing.

DISCUSSION

Our findings demonstrate that almost half of patients with presumed TB in SSA were not given a final diagnosis of active TB. While this proportion varied according to study, it was not predicted by country incidence of TB or HIV. The few included studies that used active case-finding strategies had much lower proportions of patients with presumed TB with a final diagnosis of TB than those that used passive case finding. Only five of the identified studies attempted to characterise patients with presumed TB who were subsequently found not to have TB by reporting alternative diagnoses. In both of these studies, clinical judgement, rather than a standardised approach, was used to decide on investigations performed, and no spirometry was conducted. Just over half of included studies captured prior histories of TB and none indicated how many times individuals had been previously tested for TB.

In the passive case-finding studies that included clinically diagnosed patients, the proportion of patients with presumed TB subsequently found not to have TB was lower than the fraction of clinically diagnosed TB cases. While this proportion varied according to study, it was not predicted by country incidence of TB or HIV. The few included studies that used active case-finding strategies had much lower proportions of patients with presumed TB with a final diagnosis of TB than those that used passive case finding. Only five of the identified studies attempted to characterise patients with presumed TB who were subsequently found not to have TB by reporting alternative diagnoses. In both of these studies, clinical judgement, rather than a standardised approach, was used to decide on investigations performed, and no spirometry was conducted. Just over half of included studies captured prior histories of TB and none indicated how many times individuals had been previously tested for TB.

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<table>
<thead>
<tr>
<th>Study title</th>
<th>Study type</th>
<th>Country</th>
<th>Age (median, IQR)</th>
<th>Male (%)</th>
<th>Setting</th>
<th>Presumptive TB (included/eligible)</th>
<th>Diagnosed with tuberculosis</th>
<th>Not tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Uganda</td>
<td>32, 26–38</td>
<td>54</td>
<td>General hospital</td>
<td>307/307</td>
<td>146</td>
<td>17</td>
</tr>
<tr>
<td>Bruchfeld et al (2002)</td>
<td>Cross-sectional study</td>
<td>Ethiopia</td>
<td>33†, 28–47</td>
<td>56.3†</td>
<td>General hospital</td>
<td>493/509</td>
<td>168</td>
<td>113</td>
</tr>
<tr>
<td>Reither et al (2010)</td>
<td>Cross-sectional Study</td>
<td>Tanzania</td>
<td>36</td>
<td>47.4</td>
<td>Research clinic</td>
<td>171/202</td>
<td>45</td>
<td>33</td>
</tr>
</tbody>
</table>

* Range.
† Not TB patients.
NR, not recorded; TB, tuberculosis.
<table>
<thead>
<tr>
<th>Study title</th>
<th>Study type</th>
<th>Country</th>
<th>Age (median, IQR)</th>
<th>Male (%)</th>
<th>Setting</th>
<th>Presumptive TB (included/eligible)</th>
<th>Diagnosed with TB</th>
<th>Not TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cuevas et al (2011)</td>
<td>Cluster randomised trial</td>
<td>Ethiopia</td>
<td>33.7* (±14.1)</td>
<td>52.8</td>
<td>Health centre</td>
<td>1770/1909</td>
<td>586 0</td>
<td>586 (33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nigeria</td>
<td>34.4* (±10.7)</td>
<td>51.9</td>
<td>Health centre</td>
<td>1196/1238</td>
<td>233 0</td>
<td>233 (19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>South Africa (Johannesburg)</td>
<td>34, 30–43</td>
<td>63</td>
<td>District hospital</td>
<td>234/234</td>
<td>74 NR</td>
<td>74 (32)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kenya</td>
<td>33, 26–44</td>
<td>51</td>
<td>District hospital</td>
<td>135/135</td>
<td>28 NR</td>
<td>28 (21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uganda</td>
<td>30, 26–39</td>
<td>64</td>
<td>District hospital</td>
<td>181/181</td>
<td>67 NR</td>
<td>67 (37)</td>
</tr>
</tbody>
</table>

*Age, mean (±SD).†Not all tested, denominator.NR, not recorded.
Respiratory epidemiology

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Weight (%)</th>
<th>Prevalence (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boehme et al. (2011), South Africa</td>
<td>46.0%</td>
<td>34.1 (32.0 – 36.2)</td>
<td></td>
</tr>
<tr>
<td>Tharon et al. (2011), South Africa</td>
<td>11.2%</td>
<td>32.7 (28.5 – 37.1)</td>
<td></td>
</tr>
<tr>
<td>Reithar et al. (2010), Tanzania</td>
<td>3.5%</td>
<td>54.4 (46.6 – 62.0)</td>
<td></td>
</tr>
<tr>
<td>Bruchfeld et al. (2002), Ethiopia</td>
<td>10.4%</td>
<td>43.0 (38.6 – 47.5)</td>
<td></td>
</tr>
<tr>
<td>Muyesi et al. (2005), Zambia</td>
<td>11.5%</td>
<td>57.9 (52.8 – 61.2)</td>
<td></td>
</tr>
<tr>
<td>Jayasooriya et al. (2019), The Gambia</td>
<td>4.8%</td>
<td>43.8 (37.3 – 50.4)</td>
<td></td>
</tr>
<tr>
<td>Bohari et al. (2011), Malawi</td>
<td>6.3%</td>
<td>46.9 (41.2 – 52.7)</td>
<td></td>
</tr>
<tr>
<td>Nwase et al. (2016), Malawi</td>
<td>6.4%</td>
<td>76.0 (70.0 – 81.3)</td>
<td></td>
</tr>
<tr>
<td>SUMMARY (I²=96.1%)</td>
<td></td>
<td>48.9 (39.0 – 58.0)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2 Random effects meta-analyses of the proportion of patients with presumptive tuberculosis not diagnosed as tuberculosis. The weight, listed on the left-hand side is the percentage of the total inverse variance associated with a study in each analysis. Prevalence (95% CI) of patients not diagnosed as tuberculosis is listed on the right-hand side. Studies are stratified by passive or active case finding. Passive case-finding studies including clinically diagnosed tuberculosis are shown with estimates ordered by this proportion.

pathogens. The lack of access to high-quality health systems and diagnostics in SSA means there is likely to be a high burden of unrecognised diseases of all causes and unmet clinical need in the general population. Therefore, patients with presumed TB—symptomatic by definition—risk having the true causes of their symptoms neglected if they are not due to active TB. The implications for missing active TB are clear, yet those of incorrectly labelling people as having active TB and/or missing other health conditions also need to be taken into consideration. For example, patients with non-communicable chronic respiratory diseases such as chronic obstructive airway disease, asthma and bronchiectasis are also likely to present to the health system.
### Table 3  Tuberculosis (TB) studies meeting inclusion criteria using active finding not including clinically diagnosed TB case

<table>
<thead>
<tr>
<th>Study title</th>
<th>Study type</th>
<th>Country</th>
<th>Age (median, IQR)</th>
<th>Male (%)</th>
<th>Setting</th>
<th>Presumptive TB (included/ eligible)</th>
<th>Diagnosed with TB</th>
<th>Not TB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory (bacteriological) Clinical</strong></td>
<td><strong>Total (%)</strong></td>
<td><strong>HIV</strong></td>
<td><strong>Total (%)</strong></td>
<td><strong>HIV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deribew et al (2012)[9]</td>
<td>Prevalence of pulmonary TB and spoligotype pattern of Mycobacterium tuberculosis among TB suspects in a rural community in Southwest Ethiopia</td>
<td>Cross-sectional study</td>
<td>Ethiopia</td>
<td>41* (±16.2)</td>
<td>39.3</td>
<td>Community</td>
<td>42/8482</td>
<td>17</td>
</tr>
<tr>
<td>Hamusse et al (2017)[13]</td>
<td>Prevalence and Incidence of Smear-Positive Pulmonary Tuberculosis in the Hetosa District of Arsi Zone, Oromia Regional State of Central Ethiopia</td>
<td>Cross-sectional study</td>
<td>Ethiopia</td>
<td>33.3 * † (±16)</td>
<td>51†</td>
<td>Community</td>
<td>1041/1041</td>
<td>43</td>
</tr>
<tr>
<td>Sekandi et al (2014)[18]</td>
<td>Yield of undetected tuberculosis and HIV coinfection from active case finding in urban Uganda</td>
<td>Cross-sectional study</td>
<td>Uganda</td>
<td>24 (20–30)</td>
<td>37.2</td>
<td>Community</td>
<td>160199</td>
<td>39</td>
</tr>
</tbody>
</table>

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*Age, mean (±SD).
†Age and Male (%) of community screened.
‡Not all tested.
NR, not reported.

### Table 4  Tuberculosis (TB) studies of smear negative participants meeting inclusion criteria

<table>
<thead>
<tr>
<th>Study title</th>
<th>Study type</th>
<th>Country</th>
<th>Age (median, IQR)</th>
<th>Male (%)</th>
<th>Setting</th>
<th>Presumptive TB (included/ eligible)</th>
<th>Diagnosed with TB</th>
<th>Not TB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory (bacteriological) Clinical</strong></td>
<td><strong>Total (%)</strong></td>
<td><strong>HIV</strong></td>
<td><strong>Total (%)</strong></td>
<td><strong>HIV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affolabi et al (2011)[9]</td>
<td>Smear-negative, culture-positive pulmonary tuberculosis among patients with chronic cough in Cotonou, Benin</td>
<td>Cross-sectional Study</td>
<td>Benin</td>
<td>NR</td>
<td>NR</td>
<td>General Hospital</td>
<td>207/251</td>
<td>22</td>
</tr>
</tbody>
</table>
## Table 5  Tuberculosis studies handling and reporting of patients with presumed tuberculosis found not to have tuberculosis

<table>
<thead>
<tr>
<th>Country</th>
<th>Diagnoses</th>
<th>Management</th>
<th>History of tuberculosis</th>
<th>Previous tuberculosis testing</th>
<th>WHO estimated incidence (year of study)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tuberculosis (per 100 000) HIV (per 1000)</td>
</tr>
<tr>
<td>Affolabi et al (2011)</td>
<td>Benin</td>
<td>NR</td>
<td>15 days erythromycin</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Boehme et al (2011)</td>
<td>South Africa</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Uganda</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Cuevas et al (2011)</td>
<td>Ethiopia</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Nigeria</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Deribew et al (2012)</td>
<td>Ethiopia</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Dorman et al (2018)</td>
<td>South Africa (Cape Town)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>South Africa (Johanesburg)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>Kenya</td>
<td>NR</td>
<td>NR</td>
<td>20</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Uganda</td>
<td>NR</td>
<td>NR</td>
<td>15</td>
<td>NR</td>
</tr>
<tr>
<td>Hamusse et al (2017)</td>
<td>Ethiopia</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Huerga et al (2012)</td>
<td>Kenya</td>
<td>11 non-tuberculous mycobacteria</td>
<td>5 days amoxicillin</td>
<td>92</td>
<td>NR</td>
</tr>
<tr>
<td>Lawson et al (2008)</td>
<td>Nigeria</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Ling et al (2011)</td>
<td>South Africa</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Merid et al (2019)</td>
<td>Ethiopia</td>
<td>NR</td>
<td>NR</td>
<td>151*</td>
<td>NR</td>
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<tr>
<td>Munyati et al (2005)</td>
<td>Zimbabwe</td>
<td>178 other respiratory tract infections 87 bacterial pneumonia 34 fibrotic lung disease: 28 post-tuberculous disease 2 idiopathic diffuse fibrosis 26 asthma 8 pneumocystis pneumonia 5 cryptococcosis 15 heart failure 5 malignancy: 3 Kaposi sarcoma 1 primary bronchus 1 metastatic breast 16 unknown</td>
<td>Clinically indicated</td>
<td>97</td>
<td>NR</td>
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</tbody>
</table>

Continued

8

Jayasooriya S, et al. Thorax 2022;0:1–11. doi:10.1136/thoraxjnl-2021-217663
with a chronic cough, requiring ongoing management. This is not only a missed opportunity for clinical engagement; patients who receive an incorrect diagnosis or are discharged without any follow-up may become reluctant to seek care in the future.

The higher proportions of patients found not to have TB in active case-finding studies is likely to be due to the difference in study population from those identified in passive case-finding studies. In addition, most active case-finding studies reported only bacteriologically confirmed TB cases. A WHO-commissioned systematic review reported general population community-based active case-finding studies set in SSA. These studies only used bacteriological (often smear) diagnoses of TB cases, and none reported any clinical diagnoses of TB. When we compared active with passive case-finding studies that also reported only bacteriologically confirmed TB cases, the former still had a higher proportion of patients with presumed TB subsequently found not to have TB. These findings imply that active case-finding strategies encounter more community members with unidentified health issues that have non-specific symptoms similar to those of active TB. A retrospective review of radiological findings from a Kenyan TB prevalence survey identified a wide variety of abnormalities unrelated to active TB in those that were not classified as having TB. Systematic active screening of high-risk groups is a central component of the WHO End Tuberculosis Strategy and the aforementioned systematic review suggests that community-based active case finding might be effective at detecting active TB early. However, the emphasis on active case-finding strategies in SSA should take into consideration patients with presumed TB subsequently found not to have TB, as they are likely to represent a large proportion of those with positive initial symptom screens. Improving the ability of local health systems to manage patients without TB, alongside making appropriate diagnoses of TB disease is imperative.

A history of TB is important for assessing the risk of active TB in patients with presumed TB. Recording and reporting TB history in future research is essential as it is necessary to fully interpret results, particularly with increasing use of Xpert MTB/RIF and Xpert MTB/RIF Ultra. Patients with presumed TB subsequently found not to have TB will include some of the estimated 155 million patients globally alive today post-TB. Recognition of history of TB could also help identify them allowing for the provision of ongoing care. Long-term effects, such as increased all-cause mortality post disease and post-TB lung disease, could start to be addressed.

Two included studies used mass administration of empirical antibiotics to several hundreds of patients with presumed TB subsequently not diagnosed with TB. With increasing antimicrobial resistance recognised as one of the biggest public health challenges of our time, nuanced strategies to mitigate against administering unnecessary antibiotics are vital. The lack of adequate point of care diagnostics, for both respiratory pathogens and TB alongside unavailable alternative management strategies can drive indiscriminate use of antimicrobials. Strategies such as the Practical Approach to Lung Health (PAL) have demonstrated that better integrated respiratory care can reduce antimicrobial usage in LMICs.

Our findings are also of importance when considering paediatric TB. The nature of limited diagnostics and well recognised high proportions of empirical TB treatment in paediatrics add further complexity. Distinguishing TB from other respiratory infections in children is an important area of ongoing research, and the development of easily applicable paediatric TB diagnostic tests able to do just that remains critical.

This work raises ethical issues around the inclusion of patients in research studies conducted in settings where limited primary care is available. Non-communicable chronic respiratory diseases caused an estimated 3.9 million deaths in 2017, of which a disproportionately high burden is seen in LMICs. Furthermore, the prevalence of TB has declined over time in many settings. It is critical that the care afforded as a minimum to symptomatic patients screening out of TB studies in settings with limited healthcare should be taken into consideration during research planning, offering, for example, in this case follow-up for patients subsequently found not to have TB until an alternative diagnosis is found. This will require improved collaboration between researchers and health system actors as well as greater consideration of the study participant’s health needs.

There are limitations to our review. We acknowledge that the meta-analytical portion was limited by substantial heterogeneity observed across studies. While summary values should, therefore, be treated with caution their general size indicates potentially important unmet needs in SSA communities. We found only two studies with a stated objective to describe patients with presumed TB subsequently found not to have TB. Most studies were cross-sectional and designed to capture patients with active TB. Therefore, understandably data on those essentially screening out of the study may not be as comprehensive as for those that were diagnosed with active TB and included as final study participants. In particular, we highlight that where data was not recorded, it does not always equate to not being performed and the cross-sectional nature of the studies meant there was limited follow-up. However, this absence of data further supports our conclusion that there is a critical lack of reported data on patients with presumed TB subsequently found not to have TB.

This systematic review of the literature highlights that at least half of all patients with presumed TB attending services in SSA are not given a diagnosis of active TB; many not receiving any

### Table 5

<table>
<thead>
<tr>
<th>Country</th>
<th>Diagnoses</th>
<th>Management</th>
<th>History of tuberculosis</th>
<th>Previous tuberculosis testing</th>
<th>WHO estimated incidence (year of study)</th>
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<td>158</td>
<td>1270</td>
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</table>

*History of tuberculosis in participants without tuberculosis,
†Participants diagnosed with multiple conditions.
NR, not reported.
Respiratory epidemiology

alternative diagnoses. In sSA, 1.4 million TB cases were notified in 2019, our data suggest that this figure represents only half of all patients with symptoms consistent with presumptive TB. It is critical we address this by characterising the clinical needs among these hitherto neglected patients, in order to plan appropriate health system solutions. Future studies should explore patient experiences to better understand how these influence subsequent care-seeking behaviours and health system engagement. Generating such data would help facilitate integration of services for non-communicable chronic respiratory diseases with TB programmes.

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Contributors SJ (guarantor) formulated the research questions with input from BK and KMSL, CB formulated the search strategy SJ, FDD screened articles and data extracted with input from FC. PID synthesised data with input from SJ. All authors (SJ, FDD, CB, JB, BA, CM, BK, FC, PID & KM) contributed to data interpretation and drafting the manuscript.

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Disclaimer The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR or the UK Department of Health and Social Care.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. Extraction data are available on github. https://github.com/petedodd/NotTB/

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Beate Kampmann http://orcid.org/0000-0002-6546-4709
Kevin Mortimer http://orcid.org/0000-0002-8118-8871

REFERENCES


Appendix 1: MEDLINE Search example

Search strategy concepts:
Line 1-9 Symptoms related to tuberculosis
Line 10-27,29 Diagnostics testing and screening terms
Line 28 Tuberculosis terms
Line 30-35 African country filters
Line 36 Concepts combined

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to April 27, 2020>
Search Strategy:

1  (tubercul* adj3 symptom*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (889)
2  Cough/ (14630)
3  chronic cough.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3608)
4  exp Weight Loss/ or "weight loss".tw. (90993)
5  malaise.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (6568)
6  fever/ (36688)
7  night sweats.mp. (1823)
8  Hemoptysis/ or (hemoptysis or haemoptysis).tw. (11303)
9  1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (160341)
10 exp "Sensitivity and Specificity"/ (533722)
11 sensitivity.tw. (709915)
12 specificity.tw. (416537)
13 ((pre-test or pretest) adj probability).tw. (1941)
14 post-test probability.tw. (502)
15 predictive value$.tw. (95354)
16 likelihood ratio$.tw. (13524)
17 or/10-16 (1332010)
18 diagnos*.mp. (4528348)
19 active case.tw. (1030)
20 passive case.tw. (363)
21 sputum smear.tw. (2273)
22 sputum genexpert.tw. (4)
23 chest xray.tw. (54)
24 radiography, thoracic/ (30051)
25 screen*.tw. (650548)
26 diagnosis, differential/ (429446) 27 or/18-26 (4952361) 28 tuberculosis.mp. or TB.ti,ab. (250467) 29 17 or 27 (5777639) 30 exp africa, northern/ or (sudan* or western sahara* or algeria* or egypt* or libya* or morocc* or tunisia* or cairo or rabat or casablanca or tripoli or algiers or fes or marrakesh or tunis or carthage or (alexandria not (va or virginia)) or tangier or kairouan or essaouira or luxor or bi zerte or "el aaiun" or sousse or oran or annaba or constantine or biskra or chefchaouen or skikda or "sharm el sheikh" or volubilis or "el oued" or meknes or hippo regius or djemila or sfax or tataouine or port said or "ait benhaddou" or benghazi or juba or tamanrassette or merzouga or "el djem" or oujda or matmata or ghat or tabessa or giza or marj or ifrane or "m'hamid el ghizlane" or agadir or tetouan or "shubra el kheima" or tobruk or kartoum or nyala or kassala or ubayyid or kosti or wad madani or qadari f or al - fashir or dain or damazin or geneina or merowe or (north* adj2 africa*).ti,ab. (67388) 31 exp africa, eastern/ or ((least* adj2 africa*) or british indian ocean territory or burundi* or comoros or djibouti* or eritrea* or ethiopia* or kenya* or madagascar or malawi or mauritius or mayotte or mozambique or reunion or rwanda* or seychelles or somalia* or sudan* or tanzania* or uganda* or zambia or zimbabwe or crozet islands or illes crozet or scattered islands or illes eparses or mwanza or zanzibar or elderset or morogoro or hargeysa or berbela or nyeri or mbeya or machakos or marka or tabora or iringa or gondar or meru or geita or musoma or mtwara or songea or kigoma or dsei or mek'ele or bahir dar or jimma or sinyanga or korogwe or nairobi or "dar es salaam" or mombasa or addis ababa or kampala or kigali or mogadishu or dodoma or bujumbura or nakuru or ananarivo or kisumu or maputo or asmara or haraka or port louis or arusha or kitale or lilongwe or malindi or machakos or hargeisa or bulawayo or ruiru or lamu or kire dawa or kikuyu or naivasha or mwanza or tanga or nanyuki or voi or garissa or lidwar of kakamega or maralal or kitui or webuye or axum or nyahururu or jinja or kismayo or namanga or mumias or moshi or moroni or lokichogio or hola or rwenzori mountains or lake victoria or puntland* or (adiharush or ali-addeh or alinjugur or buramino or dadaab or dagahaley or dollo ado or fugnido or hagadera or hilaweyn or ifo or kakuma or kambios or kayaka ii or kobe or kyangwali nakivale or nyarugusu or wad sherife or bokolmnyo or melkadida or rwamanka) adj5 (camp or refug*).ti,ab. (54617) 32 exp africa, western/ or ((africa*adj2 west* or benin* or burkina fas* or cape verde* or cabo verde* or ivory coast or cote d'ivoire* or gambia* or ghana* or guinea* or bissau or liberia* or (mali not fowl) or malian or mauritanian* or nigeria* or senegal* or sierra leon* or togo*).mp. or (lagos or accra or abidjan or dakar or abobo or abuja or freetown or ouagadougou or conakry or lome or bamako or cotonou or umunia or monrovia or ibadan or cano or port harcourt or benin city or porto novo or niamey or yamoussoukro or banjul or timbuktu or djenne or abomey or zaria or tamale or jos or cape coast or maidugul or aba or gao or calabar or warri or maiduguri or bobo dioulasso or parakou or djougou or bohicon or sekondi takoradi or sunyani or obuasi or teshie or tema or sikaar or kalabankor or naoukhott or dakhlet nouadhibou or benin city or port harcourt or ilorin or kaduna or enugu or ilorin or onitsha or bauchi or akure or abeokuta or sokoto or bouake or makeni or kaduan or sosogbo or osogbo or gombe or ilesa or badagry or makurdi or sagamu or iseyin or obmomosh or awka or ado ekiti or nskuka or ileka or katsina or okene or lafia or minna or ondo city or umuahia or calabar or yola or pikine or touba or thies nones or saint louis or kolak or ziquinchi or (san pedro not (spain or mexico or
Argentina or California or United States or Italy)) or Bandama or Daloa or Owerri or Kandi or Ifi or Dakar or Ogbomosho or Divo or Korhogo)).ti,ab. (255692)
33 exp africa, central/ or ((africa adj2 central) or angola or cameroon* or chad.mp. or tchad.mp. or congo* or DRC or equatorial guinea* or gabon* or Sao Tome or Principe or Luanda or lobito or kuito or huambo or Malanje or Douala or Yaounde or Bamenda or Garoua of Bafoussam or Ngououndere or Maroua or Kouossi or Buena or Kumba or N'Djamena or Moundou or Bangui or Bimbo or Brazzaville or Point Noire or Kinshasa or Lubumbashi or Leopoldville or Elizabethville or Mbuji Mayi or Bakwanga or Bukavu or Costermansville or Kananga or Luluabourg or Kisangani or Stanleyville or Tshikapa or Koalwezi or Likasi or Jadotville or Goma or Kikwit or Uvira or Bunia or Mbandaka or Coquihhatville or Matadi or Butembo or Kabinda or Mwene Ditu or Isiro or Pauls or Boma or Kindu or Bata or Malabo or Libreville).ti,ab. (31864)
34 exp africa, southern/ or ((africa* adj2 south*) or angola* or botswana* or lesotho* or malawi* or mozambiq* or namibia* or swaziland or zambia* or zimbabwe or zulu or tsonga or xhosa or swazi or ndebele or tswana or sotho or shona people or balunda or mbundu or ovimbundu or chaga or sukuma or pretoria or cape town or Johannesb or Durban or Port Elizabeth or Bloemfontein or Windhoek or Maseru or Pietermaritz or (kimberley not Australia) or nespruit or soweto or polokwane or limpopo or rustenburg or mahikeng or oudtshroom or stellenbosch or paarl or gaborone or luanda or cabinda or huambo or lubango or kuit or Malanje or lobito or lilongwe or blantyre or mzuzu or maputo or matola or beira or mapula or chimio or nacala or quelimane or lubakaka or kitwe or ndola or kabwe or copperbelt harare or bulawayo or chitungwiza or mutare or masvingo or monashonaland or manicaland).ti,ab. (83002)
35 30 or 31 or 32 or 33 or 34 (470185)
36 9 and 28 and 29 and 35 (505)
**Appendix 2: JBI Risk of Bias Critical Appraisal Assessment Tool**

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample frame appropriate to address the target population?</th>
<th>Study participants sampled in an appropriate way?</th>
<th>Sample size adequate?</th>
<th>Study subjects and the setting described in detail?</th>
<th>Data analysis conducted with sufficient coverage of the identified sample?</th>
<th>Valid methods used for identification of the condition?</th>
<th>Condition measured in a standard, reliable way for all participants?</th>
<th>Response rate adequate, and if not, was the low response rate managed appropriately?</th>
<th>Overall appraisal</th>
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*Smear negative studies
Patients with presumed tuberculosis in sub-Saharan Africa that are not diagnosed with tuberculosis: a systematic review and meta-analysis (statistical appendix)

S Jayasooriya, F Dimambro-Denson, C Beecroft, J Balen, B Awokola, C Mitchell, B Kampmann, F Campbell, PJ Dodd, K Mortimer

August, 2021

Contents

Pre-amble .......................... 1
  Dependencies .......................... 1

Main analyses ....................... 2
  Approach ............................... 2
  Meta-analyses ......................... 3
  Creation of combined forest plot ....... 6

Meta-regressions ..................... 8
  TB prevalence ........................... 8
  HIV prevalence .......................... 9
  Calendar time .......................... 11

Sensitivity analyses ............... 13
  Dorman et al. by country only ....... 13
  Regional groupings .................... 14

Pre-amble

This document is generated from an R script in literate programming fashion. All R code is quoted in this document, together with output (preceded by ‘##’) and figures. The article forest plot is saved to the output folder but not included in the document since it is too cramped. The script and data are publicly available on GitHub at https://github.com/petedodd/NotTB and once the repository is downloaded, it should be possible to generate this document using R with the command rmarkdown::render("NotTBmeta.R", output_dir="./output") within R, or from a unix-like command line with R -q -e "rmarkdown::render("NotTBmeta.R",output_dir="/./output")". Alternatively, the R script can be run in whole or part as a conventional R script.

Dependencies

To compile this document, the rmarkdown & knitr packages must be installed. The other R packages required to run this analysis should be installed if necessary, and loaded, with:

pkgs.needed <- c("ggplot2","scales","cowplot","ggpubr", #graphs
  "data.table","here", #data mgt
  "metafor") #metaanalysis
install.packages(setdiff(pkgs.needed, rownames(installed.packages())))
suppressMessages(
  devnull <- lapply(pkgs.needed, require, character.only = TRUE) #load for use
)

This analysis was run using:
sI <- sessionInfo()
dI <- data.frame(
  item=c('R version','platform','OS','metafor version'),
  version=c(
    sI$R.version$version.string, #R version
    sI$platform, #platform
    sI$running, #OS
    sI$otherPkg$metafor$Version #metafor version
  )
)
knitr::kable(dI)

<table>
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<tr>
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<th>version</th>
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</thead>
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<td>OS</td>
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</tr>
<tr>
<td>metafor version</td>
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</tr>
</tbody>
</table>

Main analyses

Approach

We use a generalized linear mixed effects (GLMM) approach to meta-analysis assuming a binomial response and logit link\textsuperscript{1}. This means we assume

\[ k_i \sim \text{Binomial}(N_i, p_i) \]
\[ \text{logit}(p_i) = \mu + \varepsilon_i \]
\[ \varepsilon_i \sim \mathcal{N}(0, \tau^2) \]

where \( i = 1, \ldots, S \) indexes the numbers of studies.

Use of arcsine or double arcsine transformations has been criticized in this context, with the GLMM approach recommended instead.\textsuperscript{2}

Read in the data and ensure that factors behave as intended:

```r
DD <- fread(file=here('SRMdata.csv'))
DD[,lab:=factor(lab, levels=rev(DD[order(bac)]$lab)),ordered = TRUE]
```

Create exact binomial confidence intervals:

\textsuperscript{1}Stijnen T, Hamza TH, Ozdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data.

\textsuperscript{2}Schwarzer G, Chemaitelly H, Abu-Raddad LJ, Rücker G. Seriously misleading results using inverse of Freeman-Tukey double arcsine transformation in meta-analysis of single proportions
```r

ciz <- function(x,y){
x <- as.integer(x); y <- as.integer(y)
  list(binom.test(x,y)$conf.int[1],binom.test(x,y)$conf.int[2])
}
DD[, "NotTB Proportion" := NnotTB/N]
for(i in 1:nrow(DD)){ DD[i, c('lo', 'hi') := ciz(NnotTB,N)]; }
DD[,SE := (hi-lo)/3.92]

Meta-analyses

Meta-analysis for passively found TB patients with bacteriologically unconfirmed TB included:
maPU <- rma.glmm(measure = "PLO", # binomial w/ logit link
  xi = NnotTB, # numerator
  ni = N, # denominator
  data = DD[mode=='Passive' &
    clinical=='(Unconfirmed TB included)'],
  slab = Author) # what to use as labels on graphs

## Registered S3 methods overwritten by 'lme4':
##  method from
cooks.distance.influence.merMod car
influence.merMod car
dfbeta.influence.merMod car
dfbetas.influence.merMod car

summary(maPU)

## Random-Effects Model (k = 8; tau^2 estimator: ML)
##
##  logLik deviance AIC  BIC AICc
##  -25.7259  0.4121  55.4518 55.6107 57.8518
##
## tau^2 (estimated amount of total heterogeneity): 0.2977
## tau (square root of estimated tau^2 value): 0.5457
## I^2 (total heterogeneity / total variability): 97.0524%
## H^2 (total variability / sampling variability): 33.9255
##
## Tests for Heterogeneity:
##  Wld(df = 7) = 221.8886, p-val < .0001
##  LRT(df = 7) = 243.5648, p-val < .0001
##
## Model Results:
##
##  estimate  se     zval    pval   ci.lb  ci.ub
##  -0.0619  0.1971 -0.3140 0.7535 -0.4482 0.3244
##
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Jayasooriya S, et al. Thorax 2022;0:1–11. doi: 10.1136/thoraxjnl-2021-217663
Meta-analysis for passively found TB patients with bacteriologically unconfirmed TB excluded:

```r
maPN <- rma.glmm(measure = "PLO", # binomial w/ logit link
                  xi = NnotTB,  # numerator
                  ni = N,      # denominator
                  data = DD[mode=="Passive" &
                             clinical=="(No unconfirmed TB)",
                             slab = Author], # what to use as labels on graphs
                  slab = Author)
summary(maPN)
```

## Random-Effects Model (k = 9; tau^2 estimator: ML)

<table>
<thead>
<tr>
<th></th>
<th>logLik</th>
<th>deviance</th>
<th>AIC</th>
<th>BIC</th>
<th>AICc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-28.8910</td>
<td>0.2865</td>
<td>61.7821</td>
<td>62.1765</td>
<td>63.7821</td>
</tr>
</tbody>
</table>

## tau^2 (estimated amount of total heterogeneity): 0.3714

## tau (square root of estimated tau^2 value): 0.6094

## I^2 (total heterogeneity / total variability): 98.1427%

## H^2 (total variability / sampling variability): 53.8403

## Tests for Heterogeneity:

<table>
<thead>
<tr>
<th></th>
<th>Wld(df = 8)</th>
<th>p-val</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>679.9414</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

## Model Results:

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<th>estimate</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.8757</td>
<td>0.2078</td>
<td>4.2139</td>
<td>&lt; .0001</td>
<td>0.4684</td>
</tr>
</tbody>
</table>

## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
forest(maPN, transf = transf.ilogit, refline = NA)

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cuevas et al.*</td>
<td>0.67</td>
<td>[0.65, 0.69]</td>
</tr>
<tr>
<td>Dorman et al.</td>
<td>0.81</td>
<td>[0.78, 0.83]</td>
</tr>
<tr>
<td>Dorman et al.</td>
<td>0.83</td>
<td>[0.76, 0.88]</td>
</tr>
<tr>
<td>Dorman et al.</td>
<td>0.68</td>
<td>[0.62, 0.74]</td>
</tr>
<tr>
<td>Dorman et al.</td>
<td>0.79</td>
<td>[0.72, 0.85]</td>
</tr>
<tr>
<td>Hanrahan et al.</td>
<td>0.81</td>
<td>[0.79, 0.82]</td>
</tr>
<tr>
<td>Lawson et al.</td>
<td>0.38</td>
<td>[0.36, 0.41]</td>
</tr>
<tr>
<td>Ling et al.</td>
<td>0.65</td>
<td>[0.60, 0.70]</td>
</tr>
</tbody>
</table>

RE Model

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>0.3</td>
</tr>
<tr>
<td>0.5</td>
</tr>
<tr>
<td>0.7</td>
</tr>
<tr>
<td>0.9</td>
</tr>
</tbody>
</table>

0.71 [0.62, 0.78]

Meta-analysis for actively found TB patients:

maA <- rma.glmm(measure = "PLO", # binomial w/ logit link
x1 = NnotTB,    # numerator
ni = N,        # denominator
data = DD[mode=='Active'],
slab = Author)  # what to use as labels on graphs

summary(maA)

###
## Random-Effects Model (k = 4; tau^2 estimator: ML)
##
## logLik deviance AIC     BIC     AICc
## -10.4692  0.2060  24.9385 23.7111  36.9385
##
## tau^2 (estimated amount of total heterogeneity): 0.6678
tau (square root of estimated tau^2 value):  0.8172
I^2 (total heterogeneity / total variability):  95.0642%
H^2 (total variability / sampling variability):  20.2600
##
## Tests for Heterogeneity:
##   Wld(df = 3) = 81.2135, p-val < .0001
##   LRT(df = 3) = 67.4266, p-val < .0001
##
## Model Results:
##
## estimate  se  zval  pval  ci.lb  ci.ub
##   2.5537 0.4199  6.0817 <.0001 1.7307  3.3767 ***
##
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

forest(maA, transf = transf.ilogit, refline = NA)
Make predictions for plot data:

```r
map <- predict(maA, transf = transf.ilogit)
mup <- predict(maPU, transf = transf.ilogit)
mnp <- predict(maPN, transf = transf.ilogit)
```

### Creation of combined forest plot

Summary data for combined forest plot:

```r
f1 <- function(x) format(round(x,1), nsmall = 1)
cnz <- c('(Unconfirmed TB included)',
       '(No unconfirmed TB)',
       '(No unconfirmed TB)')
predz <- data.table(mode = c('Passive', 'Passive', 'Active'),
                   clinical = cnz,
                   'NotTB Proportion' = c(mup$pred, mnp$pred, maA$pred),
                   lo = c(mup$ci.lb, mnp$ci.lb, maA$ci.lb),
                   hi = c(mup$ci.ub, mnp$ci.ub, maA$ci.ub),
                   lab = paste0('SUMMARY (', expression(I^2), ' = ',
                                f1(c(maA$I2, mnp$I2, maA$I2)), ')
                                 )
                   )
predz[,SE := (hi-lo)/3.92]
predz[,qty := 'summary']
predz[,bac := 0]
predz[,mid := 'NotTB Proportion']
predz[,CI := paste0(f1(1e2*mid), '(', f1(1e2*lo), '-', f1(1e2*hi), ')')]
predz[,wt := 100*0%]
predz[,w := 1]
```

Appending plot data to inputs:

```r
DD[,qty := 'study']
DD[,mid := 'NotTB Proportion']
DD[,CI := paste0(f1(1e2*mid), '(', f1(1e2*lo), '-', f1(1e2*hi), ')')]
DD[,wt := 1/SE^2]
DD[,wtt := sum(wt), by = .(mode, clinical)]
DD[,wt := 1e2*wt/wtt]
```
Combined plot data:

```r
B <- rbind(
    DD[,.(lab=`NotTB Proportion`, lo, hi, SE, mode, clinical, qty, bac, CI, wt, w)],
    predz[,.(lab=`NotTB Proportion`, lo, hi, SE, mode, clinical, qty, bac, CI, wt, w)])

lbz <- as.character(B[order(bac)$lab)
lbz2 <- c(lbz[1:3],rev(lbz[-c(1:3)]))
B[,lab:=factor(lab,levels=lbz2,ordered = TRUE)]
B[,clinical.g:=factor(clinical.g,levels=c('Clinically diagnosed tuberculosis included','No clinically diagnosed tuberculosis included'))
B[clinical==='(No unconfirmed TB)',
    clinical.g:=c('No clinically diagnosed tuberculosis included']
B[,mode==='Active'],clinical.g:='']
B[,mode:=paste0(mode,' case-finding')]}
B[,mode:=factor(mode,levels=c('Passive case-finding','Active case-finding'),
    ordered = TRUE)]
B[,clinical.g:=factor(clinical.g,levels=unique(clinical.g))]
labdat <- B[1]
labdat[,txt:= 'weight (%)']
labdat2 <- B[1]
labdat2[,txt:= 'prevalence (95% confidence interval)']

Create publication forest plot figure:

```r
SA <- ggplot(B,aes(lab,y=`NotTB Proportion`,
    ymin=lo,
    ymax=hi,
    col=qty)) +
geom_point(aes(size=1/SE^2,shape=qty)) +
geom_errorbar(aes(width=w/2)) +
scale_y_continuous(label=percent,limits = c(0,NA)) +
scale_color_manual(values=c('study'="black","summary"="blue") +
scale_shape_manual(values=c('study']==22,"summary"==23)) +
xlab('')+
ylab('Proportion of patients with presumptive tuberculosis not diagnosed as tuberculosis')+
facet_grid(mode + clinical.g~.,
    scales = 'free',space='free',
    switch='x') +
coord_flip() +
guides(size='none',color='none',shape='none') +
theme_classic() +
theme(panel.spacing = unit(2, "lines"), #or 3
    strip.background = element_blank(),
    strip.placement = "outside") +
geom_text(aes(x=lab,y=1.2,label=CI,hjust='right')) +
geom_text(aes(x=lab,y=0.0,label=wt)) +
geom_text(data=labdat,aes(x=9.5,y=0,label=txt)) +
geom_text(data=labdat2,aes(x=9.5,y=1,label=txt))
```
Meta-regressions

In this section we consider various potential sources of heterogeneity through scatter plots and meta-regression.

TB prevalence

The burden of TB in a population might reasonably be expected to influence the proportion of presumptive TB that is not TB.

```r
DD[, tb:=`WHO TB estimate (per 100 000 year of study)`]
a <- 0.3

ggplot(DD,aes(tb, `NotTB Proportion`), size=N, col=mode, shape=clinical)+
  scale_x_continuous(label=comma, limits=c(0,NA))+
  scale_y_continuous(label=percent, limits=c(0,1))+
  geom_point(alpha=a)+
  xlab(`WHO estimate of TB prevalence per 100,000 for country-year')+
  ylab(`Proportion not TB in study')+
  ggtitle(`Influence of population TB burden')
```

Warning: Removed 1 rows containing missing values (geom_point).

Influence of population TB burden

---

**WHO estimate of TB prevalence per 100,000 for country-year**

---

**Proportion not TB in study**

---

**Clinical**

- (No unconfirmed TB)
- (Unconfirmed TB included)

---

**N**

- 500
- 1000
- 1500
- 2000

---

**Mode**

- Active
- Passive
We can formally investigating the influence of TB burden in explaining heterogeneity with a meta-regression:

```r
tbmr <- rma.glmm(measure = "PLO", #binomial w/ logit link
    xi = NnotTB,  # numerator
    ni = N,       # denominator
    data = DD,    # what data to use
    mods = ~mode*clinical + tb)
```

## Warning: Studies with NAs omitted from model fitting.
## Warning: Some yi/vi values are NA.
## Warning: Redundant predictors dropped from the model.

```
summary(tbmr)
```

```
## Mixed-Effects Model (k = 20; tau^2 estimator: ML)

## logLik deviance AIC BIC AICc
-61.7991 0.9638 133.5982 138.5769 137.8839

## tau^2 (estimated amount of residual heterogeneity): 0.4095
## tau (square root of estimated tau^2 value): 0.6399
## I^2 (residual heterogeneity / unaccounted variability): 97.6536%
## H^2 (unaccounted variability / sampling variability): 42.6180

## Tests for Residual Heterogeneity:
## Wld(df = 16) = 973.5088, p-val < .0001
## LRT(df = 16) = 1028.1407, p-val < .0001

## Test of Moderators (coefficients 2:4):
## QM(df = 3) = 38.8326, p-val < .0001

## Model Results:

<table>
<thead>
<tr>
<th></th>
<th>estimate</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>intercept</td>
<td>2.5877</td>
<td>0.3453</td>
<td>7.4931</td>
<td>&lt;.0001</td>
<td>1.9109</td>
<td>3.2646</td>
</tr>
<tr>
<td>modePassive</td>
<td>-1.6174</td>
<td>0.4233</td>
<td>-3.8210</td>
<td>0.0001</td>
<td>-2.4471</td>
<td></td>
</tr>
<tr>
<td>clinical</td>
<td>-0.8999</td>
<td>0.3286</td>
<td>-2.7386</td>
<td>0.0062</td>
<td>-1.5439</td>
<td></td>
</tr>
<tr>
<td>tb</td>
<td>-0.0002</td>
<td>0.0004</td>
<td>-0.4084</td>
<td>0.6830</td>
<td>-0.0009</td>
<td></td>
</tr>
</tbody>
</table>
```

HIV prevalence

Population HIV prevalence may plausibly influence the proportion of presumptives not diagnosed with TB both by influencing TB burden, but also by changing the typical clinical characteristics of TB and most importantly, the burden of other illness that could be designated presumptive TB.
ggplot(DD,aes(hiv/le2,'NotTB Proportion', 
size=N,col=mode,shape=clinical))+
scale_x_continuous(label=percent,limits=c(0,0.13))+
scale_y_continuous(label=percent,limits=c(0,1))+
gtext_point(alpha=a)+
xlab('UNAIDS estimate of HIV prevalence 15-49 for country-year')+ 
ylab('Proportion not TB in study')+ 
gtitle('Influence of population HIV prevalence')

Influence of population HIV prevalence

We can formally investigating the influence of HIV in explaining heterogeneity with a meta-regression:

hivmr <- rma.glimm(measure = "PLO", #binomial w/ logit link
  xi = NnotTB, # numerator
  ni = N, # denominator
  data = DD, # what data to use
  mods = ~mode*clinical + hiv)

## Warning: Redundant predictors dropped from the model.
summary(hivmr)

##
## Mixed-Effects Model (k = 21; tau^2 estimator: ML)
##
##  logLik deviance AIC BIC AICc
## -65.1479 1.0280 140.2958 145.5184 144.2958
##
## tau^2 (estimated amount of residual heterogeneity): 0.3839
### tau (square root of estimated tau^2 value): 0.6196
### I^2 (residual heterogeneity / unaccounted variability): 97.5586%
### H^2 (unaccounted variability / sampling variability): 40.9604

---

Calendar time

To explore whether there has been any change over time, we consider calendar year

```r
ggplot(DD, aes(Year, 'NotTB Proportion', size=N, col=mode, shape=clinical))+
  scale_y_continuous(label=percent, limits=c(0,1))+
  geom_point(alpha=a)+
  xlab('Study year')+ ylab('Proportion not TB in study')+ ggtitle('Influence of calendar year')
```

---

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We can formally investigating the influence of year in explaining heterogeneity with a meta-regression:

```r
yearmr <- rma.glmm(measure = "PL0",  # binomial u/ logit link
                    xi = NnotTB,    # numerator
                    ni = N,        # denominator
                    data = DD,     # what data to use
                    mods = ~mode*clinical + Year)
```

```r
## Warning: Redundant predictors dropped from the model.
summary(yearmr)
```

```r
## Mixed-Effects Model (k = 21; tau^2 estimator: ML)
##
##    logLik deviance   AIC   BIC  AICc
## -65.2094  1.1510  140.4188 145.6414 144.4188
##
## tau^2 (estimated amount of residual heterogeneity): 0.35867
## tau (square root of estimated tau^2 value): 0.59893
## I^2 (residual heterogeneity / unaccounted variability): 97.5232%
## H^2 (unaccounted variability / sampling variability): 40.3748
##
## Tests for Residual Heterogeneity:
## Wld(df = 17) = 882.4776, p-val < .0001
## LRT(df = 17) = 919.1171, p-val < .0001
##
## Test of Moderators (coefficients 2:4):
```
## QM(df = 3) = 49.0787, p-val < .0001

## Model Results:

<table>
<thead>
<tr>
<th></th>
<th>estimate</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
</tr>
</thead>
<tbody>
<tr>
<td>intercept</td>
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<td>-1.3675</td>
<td>0.1715</td>
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<tr>
<td>modePassive</td>
<td>-1.6045</td>
<td>0.3784</td>
<td>-4.2400</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>clinical(Unconfirmed TB included)</td>
<td>-0.7813</td>
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<td>Year</td>
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<td>0.1595</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
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<td>38.4926</td>
</tr>
<tr>
<td>modePassive</td>
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<td>-0.8628</td>
</tr>
<tr>
<td>clinical(Unconfirmed TB included)</td>
<td>-1.4019</td>
<td>-0.1606 *</td>
</tr>
<tr>
<td>Year</td>
<td>-0.0178</td>
<td>0.1085</td>
</tr>
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</table>

---

## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1  ' ' 1

### Sensitivity analyses

#### Dorman et al. by country only

In the main analysis, we considered the different sites in the 2018 study by Dorman et al to be separate data. This included considering the two sites in South Africa - Cape Town and Johannesburg - as different, which was motivated by the very distinct TB epidemiology in the Western Cape. Here we investigate the impact of aggregating the two South African sites in Dorman et al on the meta-analysis for studies with passive case finding excluding clinically diagnosed TB.

Restrict to relevant data & aggregate over Dorman in South Africa:

```r
tmp <- DD[mode=="Passive" & clinical=="No unconfirmed TB"]
tmp[,Country.Simple:="Country"]
# remove cities

tmp[,authorcountry:=paste(gsub("^[A-Za-z]+.*", "\1",Author),Country.Simple,sep = ", ")] # new label
tmp <- tmp[,.(NnotTB=sum(NnotTB),N=sum(N)),by=authorcountry]
knitr::kable(tmp) # check
```

<table>
<thead>
<tr>
<th>authorcountry</th>
<th>NnotTB</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cuevas, Ethiopia</td>
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<td>1770</td>
</tr>
<tr>
<td>Cuevas, Nigeria</td>
<td>963</td>
<td>1196</td>
</tr>
<tr>
<td>Dorman, South Africa</td>
<td>285</td>
<td>384</td>
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<tr>
<td>Dorman, Kenya</td>
<td>107</td>
<td>135</td>
</tr>
<tr>
<td>Dorman, Uganda</td>
<td>114</td>
<td>181</td>
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<tr>
<td>Hanrahan, South Africa</td>
<td>1685</td>
<td>2091</td>
</tr>
<tr>
<td>Lawson, Nigeria</td>
<td>455</td>
<td>1186</td>
</tr>
<tr>
<td>Ling, South Africa</td>
<td>257</td>
<td>395</td>
</tr>
</tbody>
</table>

Rerun this meta-analysis with the new data:

```r
maPNsa <- rma.glmm(measure = "PLO", # binomial w/ logit link
                    xi = NnotTB, # numerator
                    ni = N,    # denominator
                    data =tmp, # new data
                    slab = authorcountry) # what to use as labels on graphs
summary(maPNsa)
```
Random-Effects Model (k = 8; tau^2 estimator: ML)

###

<table>
<thead>
<tr>
<th>logLik</th>
<th>deviance</th>
<th>AIC</th>
<th>BIC</th>
<th>AICc</th>
</tr>
</thead>
<tbody>
<tr>
<td>-26.5760</td>
<td>0.1654</td>
<td>57.1519</td>
<td>57.3108</td>
<td>59.5519</td>
</tr>
</tbody>
</table>

###

- **tau^2** (estimated amount of total heterogeneity): 0.3563
- **tau** (square root of estimated tau^2 value): 0.5969
- **I^2** (total heterogeneity / total variability): 98.3044%
- **H^2** (total variability / sampling variability): 58.9761

### Tests for Heterogeneity:
- **Wld(df = 7)** = 671.4861, p-val < .0001
- **LRT(df = 7)** = 716.0656, p-val < .0001

### Results:

<table>
<thead>
<tr>
<th>estimate</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.8252</td>
<td>0.2149</td>
<td>3.8406</td>
<td>0.0001</td>
<td>0.4041</td>
<td>1.2463 ***</td>
</tr>
</tbody>
</table>

###

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```r
forest(maPNsa, transf = transf.ilogit, reline=NA)
```

Cuevas, Ethiopia
- 0.67 [0.65, 0.69]
Cuevas, Nigeria
- 0.81 [0.78, 0.83]
Dorman, South Africa
- 0.74 [0.70, 0.78]
Dorman, Kenya
- 0.79 [0.72, 0.85]
Dorman, Uganda
- 0.63 [0.56, 0.70]
Hanrahan, South Africa
- 0.81 [0.79, 0.82]
Lawson, Nigeria
- 0.38 [0.36, 0.41]
Ling, South Africa
- 0.65 [0.60, 0.70]

###

**RE Model**

0.70 [0.60, 0.78]

Proportion

This is very similar to the main analysis above.

### Regional groupings

Here we investigate whether country can explain some heterogeneity. Since when countries have occur only once, it is not possible to identify a country coefficient, we these countries into an “Other” category.

```r
DD[,Country.Group:=gsub(" /\-.*$","",Country)] #remove cities
DD[!Country.Group %in% c("South Africa","Ethiopia","Nigeria"),Country.Group="Other"] #group
```
Plot this data:

```r
ggplot(DD, aes(Country.Group, \'NotTB Proportion\',
               size=N, col=mode, shape=clinical))+
  scale_y_continuous(label=percent, limits=c(0,1))+
  geom_point(alpha=a)+
  xlab('Country or country-group')+  
ylab('Proportion not TB in study')+  
gtitile('Influence of region')
```

Perform meta-regression on country-group:

```r
cgmr <- rma.glmm(measure = "PLO", # binomial w/ logit link
                 xi = NnotTB,     # numerator
                 ni = N,          # denominator
                 data = DD,       # what data to use
                 mods = ~mode*clinical + Country.Group)
```

```
## Warning: Redundant predictors dropped from the model.
summary(cgmr)
```

```
## Mixed-Effects Model (k = 21; tau^2 estimator: ML)
##
## logLik deviance AIC   BIC AICC
## -65.1801 1.0924 144.3602 151.6718 152.9755

## tau^2 (estimated amount of residual heterogeneity): 0.3559
```

15
## tau (square root of estimated tau^2 value): 0.5966
## I^2 (residual heterogeneity / unaccounted variability): 96.9246%
## H^2 (unaccounted variability / sampling variability): 32.5156
##
## Tests for Residual Heterogeneity:
## Wld(df = 15) = 776.0219, p-val < .0001
## LRT(df = 15) = 809.5261, p-val < .0001
##
## Test of Moderators (coefficients 2:6):
## QM(df = 5) = 49.6317, p-val < .0001
##
## Model Results:
##
<table>
<thead>
<tr>
<th>estimate</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>intercept</td>
<td>2.1567</td>
<td>0.5023</td>
<td>4.2940</td>
<td>&lt;.0001</td>
<td>1.1723</td>
</tr>
<tr>
<td>modePassive</td>
<td>-1.2854</td>
<td>0.4723</td>
<td>-2.7217</td>
<td>0.0065</td>
<td>-2.2110</td>
</tr>
<tr>
<td>clinical(Unconfirmed TB included)</td>
<td>-1.1151</td>
<td>0.3371</td>
<td>-3.3082</td>
<td>0.0009</td>
<td>-1.7757</td>
</tr>
<tr>
<td>Country.GroupOther</td>
<td>0.2021</td>
<td>0.3565</td>
<td>0.5669</td>
<td>0.5708</td>
<td>-0.4966</td>
</tr>
<tr>
<td>Country.GroupEthiopia</td>
<td>0.4592</td>
<td>0.4521</td>
<td>1.0158</td>
<td>0.3097</td>
<td>-0.4269</td>
</tr>
<tr>
<td>Country.GroupNigeria</td>
<td>-0.4006</td>
<td>0.5052</td>
<td>-0.7931</td>
<td>0.4277</td>
<td>-1.3908</td>
</tr>
</tbody>
</table>

**Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1