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Original research

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

Shamanthi Jayasooriya ,[1] Francesca Dimambro-Denson,[2] Claire Beecroft,[3] Julie Balen,[3] Babatunde Awokola,[4] Caroline Mitchell,[1] Beate Kampmann ,[4,5] Fiona Campbell,[3] Pete Dodd,[3] Kevin Mortimer [6,7,8]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2021-217663).

For numbered affiliations see end of article.

Correspondence to
Dr Shamanthi Jayasooriya, Academic Unit of Primary Medical Care, The University of Sheffield, Sheffield, UK; s.jayasooriya@sheffield.ac.uk

PD and KM are joint senior authors.

Received 21 May 2021
Accepted 7 December 2021

To cite: Jayasooriya S, Dimambro-Denson F, Beecroft C, *et al*. *Thorax* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/thoraxjnl-2021-217663

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 14 527 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.

PROSPERO registration number CRD42018100004.

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.[1] Diagnostic tests are often not affordable or designed for application in LMICs and can, therefore, represent a barrier to high-quality healthcare access.[1] 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.[2]

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.[3] 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.[4] The WHO describes the use of both passive and active case-finding strategies to detect TB cases.[2] 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.[5] More recent observational data from The Gambia[6] 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.[7 8] The rapid rise of non-communicable disease—including chronic respiratory diseases[1]—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.[9] 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 “diagnos*”, “sensitivity” and “specificity”), TB and used filters for North,[10] East,[11] South,[12] West[13] and Central Africa.[14] 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. Multisite 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.[15]

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.[16] 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[6] that used Xpert MTB/RIF.

All data analyses were done using R (V.4.0.2) and the metafor package V.2.4–0 (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

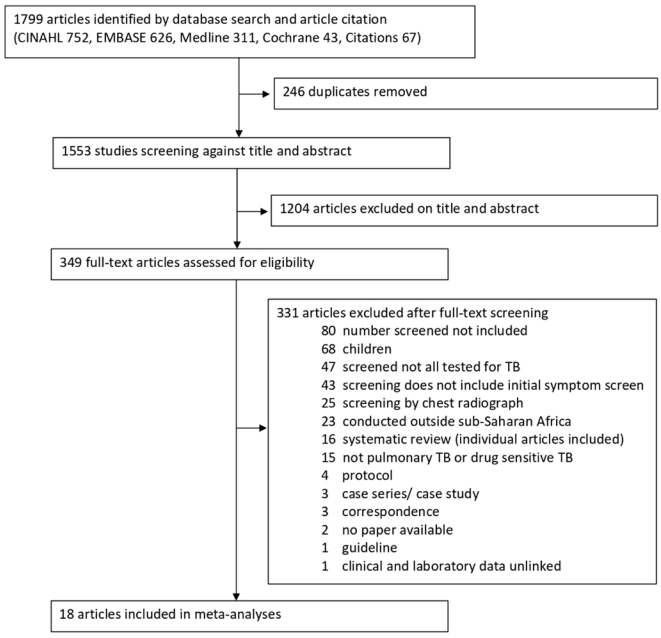

Figure 1 Study selection. TB, tuberculosis.

articles that did not meet the eligibility criteria. Therefore, 18 articles with 14 527 participants from 10 African countries were included in this systematic review and meta-analysis.

No studies were excluded following a risk of bias assessment (online supplemental data). All studies included reported 70% minimum study population coverage for TB diagnostic testing. Theron *et al*[17] and Ling *et al*[18] reported consecutive presumptive TB patient recruitment of 480 over 4 years and 398 over 5 years, respectively. It was unclear how sampling was performed (breaks during sampling or sampled on certain days) and clinic sizes were not stated that could account for the long study periods with relatively low recruitment numbers.

Passive case-finding studies

There were seven studies including (table 1)[6 17 19–23] and five studies not including (table 2)[18 24–27] 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*[25] did not document whether a clinical assessment was performed. Ling *et al*,[18] Lawson *et al*,[27] Hanrahan *et al*[26] and Cuevas *et al*[24] 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 ($I^2>95\%$ for all estimates). Meta-regressions with HIV prevalence, TB incidence, calendar year and country group did not find significant associations with our outcome (see statistical analyses online supplemental data 3).

Active case-finding studies

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.[28–31] No clinical assessments were reported by Sekandi *et al* in Uganda.[31]

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).

Smear negative studies

A further two articles included patients with presumed TB that were already smear negative on microscopy (table 4). Affolabi *et al*[32] did not include and Huerga *et al*[33] included clinically diagnosed TB cases, with 89% and 61% of patients with presumed TB subsequently found not to have TB, respectively.

Alternative diagnoses

Five studies reported diagnoses other than active TB (table 5).[6 20 21 26 33] 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.[20 26 33] Jayasooriya *et al*[6] and Munyati *et al*[21] 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*[32] and Huerga *et al*[33] 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.[6 20 21 26 33] Of these studies, only two reported a range of alternative diagnoses.[6 21] In both of these studies, clinical judgement, rather than a standardised approach, was used to decide on investigations performed, and no spirometry was conducted.[6 21] Just over half of included studies captured prior histories of TB and none indicated how many times patients 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 inversely associated with the fraction of clinically diagnosed TB cases. While this could imply overdiagnosis of active TB through reliance on clinical judgement, it is important to note that many LMICs have high rates of active TB.[4] This does highlight a need for improved point of care diagnostics for both TB and other respiratory

Table 1 Tuberculosis studies meeting inclusion criteria using passive case finding including clinically diagnosed tuberculosis cases

								Diagnosed with tuberculosis				Not tuberculosis	
	Study title	Study type	Country	Age (median, IQR)	Male (%)	Setting	Presumptive TB (included/ eligible)	Laboratory (bacteriological)	Clinical	Total (%)	HIV	Total (%)	HIV
Boehme *et al* (2011)[19]	Feasibility, diagnostic accuracy and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study	Cross-sectional Study	South Africa	36, 29–46	51	Health centre	1968/1968	473	824	1297 (66)	NR	671 (34)	NR
			Uganda	32 26–38	54	General hospital	307/307	146	17	163 (53)	NR	144 (47)	NR
Bruchfeld *et al* (2002)[20]	Evaluation of outpatients with suspected pulmonary tuberculosis in a high HIV prevalence setting in Ethiopia: Clinical, Diagnostic and epidemiological characteristics	Cross-sectional study	Ethiopia	33†	56.3†	General hospital	493/509	168	113	281 (57)	148/281	212 (43)	73 /212
Jayasooriya *et al* (2019)[6]	The burden of non-TB lung disease presenting to TB clinics in the Gambia: Preliminary data in the Xpert MTB/ rif era	Cross-sectional Study	The Gambia	40† 28–47	50†	Research clinic	233/239	114	17	131 (56)	17/131	102 (44)	12 /102
Munyati *et al* (2005)[21]	Chronic cough in primary healthcare attendees, Hasrare, Zimbabwe: diagnosis and impact of HIV infection	Cross-sectional Study	Zimbabwe	33	48	Health centre	544/550	184	50	234 (43)	207/234	310 (57)	247 /310
Nliwasa *et al* (2016)[22]	The Sensitivity and Specificity of Loop-Mediated Isothermal Amplification (LAMP) Assay for Tuberculosis Diagnosis in Adults with Chronic Cough in Malawi	Cross-sectional Study	Malawi	32 25–41	48	Health centre	233/273	53	3	56 (24)	24/56	177 (76)	97 /177
Reither *et al* (2010)[23]	Evaluation of diagnos TB AG, a flow-through immunoassay for rapid detection of pulmonary tuberculosis	Cross-sectional Study	Tanzania	36	47.4	Research clinic	171/202	45	33	78 (46)	51/78	93 (54)	50 /93
Theron *et al* (2011)[17]	Evaluation of the Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis in a high prevalence setting	Cross-sectional Study	South Africa	36 18–83*	68	Health centre	480/496	141	182	323 (67)	46/323	157 (33)	84 /157

*(Range).
†Not TB patients.
NR, not recorded; TB, tuberculosis.

Table 2 Tuberculosis (TB) studies meeting inclusion criteria using passive case finding not including clinically diagnosed TB cases

	Study title	Study type	Country	Age (median, IQR)	Male (%)	Setting	Presumptive TB (included/ eligible)	Diagnosed with TB				Not TB	
								Laboratory (bacteriological)	Clinical	Total (%)	HIV	Total (%)	HIV
Cuevas *et al* (2011)[24]	A multicountry non-inferiority cluster randomised trials of frontloaded smear microscopy for the diagnosis of pulmonary tuberculosis	Cluster randomised trial	Ethiopia	33.7* (±14.1)	52.8	Health centre	1770/1909	586	0	586 (33)	0/586	1184 (67)	NR
			Nigeria	34.4* (±10.7)	51.9	Health centre	1196/1238	233	0	233 (19)	0/233	963 (81)	NR
Dorman *et al* (2018)[25]	Xpert MTB/RIF Ultra for detection of Mycobacterium tuberculosis and rifampicin resistance: a prospective multicentre diagnostic accuracy study	Cross-sectional study	South Africa (Cape Town)	41, 34–49	41	District hospital	152/152	27	NR	27 (18)	NR	125 (82)	NR
			South Africa (Johannesburg)	34, 30–43	63	District hospital	234/234	74	NR	74 (32)	NR	160 (68)	NR
			Kenya	33, 26–44	51	District hospital	135/135	28	NR	28 (21)	NR	107 (79)	NR
			Uganda	30, 26–39	64	District hospital	181/181	67	NR	67 (37)	NR	114 (63)	NR
Hanrahan *et al* (2014)[26]	Xpert MTB/RIF as a measure of sputum bacillary burden. Variation by HIV status and immunosuppression	Cross-sectional study	South Africa	37, 29–46	38	Health centre	2091/2406	406	0	406 (19)	NR	1685 (81)	NR
Lawson *et al* (2008)[27]	Clinical presentation of adults with pulmonary tuberculosis with and without HIV infection in Nigeria	Cross-sectional study	Nigeria	33* (±10)	61	District hospital	1186/1321	731	0	731 (62)	329† /625	455 (38)	217† /377
Ling *et al* (2011)[18]	Are interferon-gamma release assays useful for diagnosing active tuberculosis in a high-burden setting?	Cross-sectional study	South Africa	40* (±12)	66	Health centre	395/500	138	0	138 (35)	43 /138	257 (65)	65 /257

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

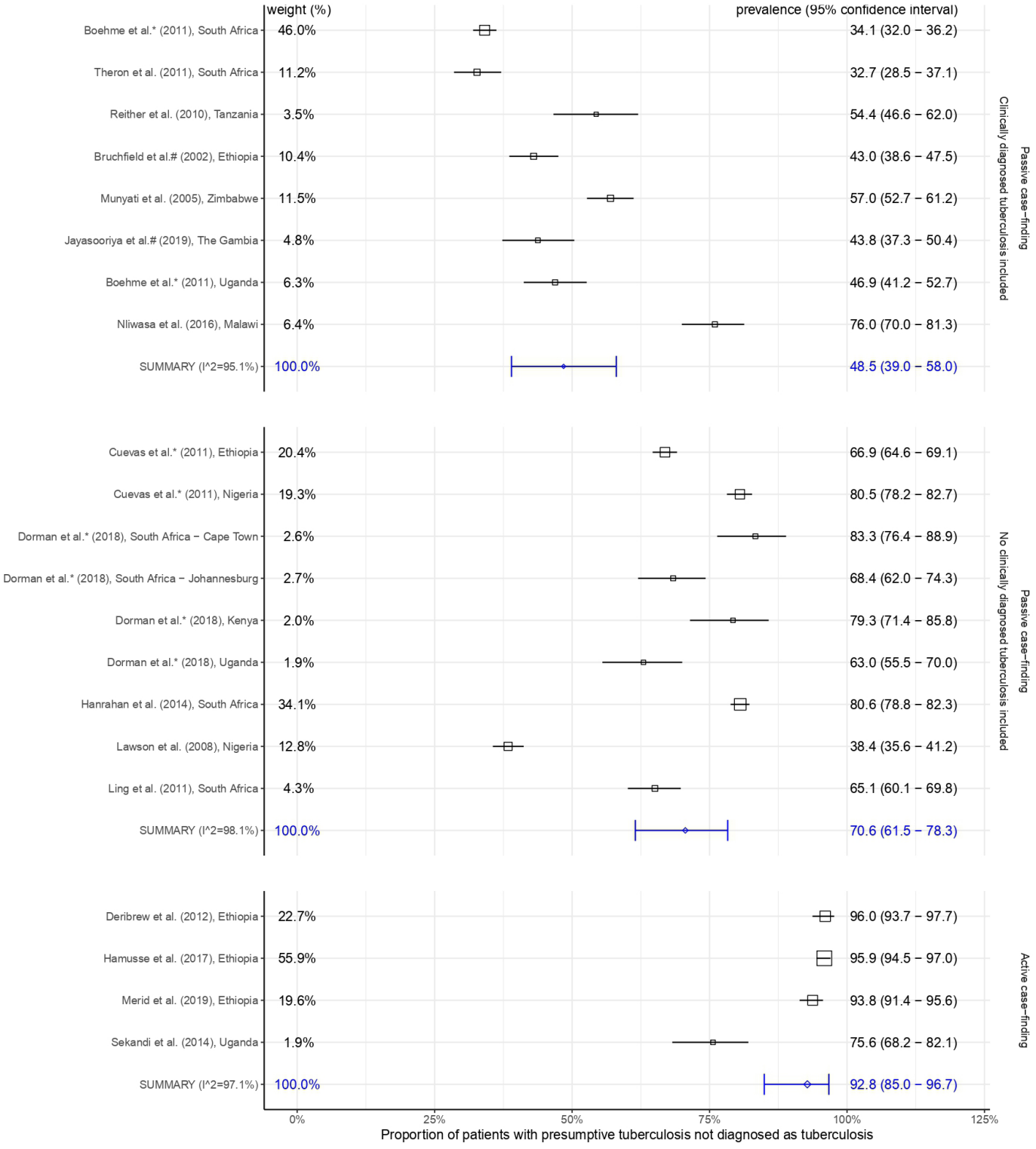

Figure 2 Random effects meta-analyses of the proportion of patients with presumptive tuberculosis not diagnosed as tuberculosis. The weight, listed on the left-hand side is the percentage of the total inverse variance associated with a study in each analysis. Prevalence (95% CI) of patients not diagnosed 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.[34] 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.[6 21] 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

								Diagnosed with TB				Not TB	
	Study title	Study type	Country	Age (median, IQR)	Male (%)	Setting	Presumptive TB (included/ eligible)	Laboratory (bacteriological)	Clinical	Total (%)	HIV	Total (%)	HIV
Deribew *et al* (2012)[28]	Prevalence of pulmonary TB and spoligotype pattern of *Mycobaterium tuberculosis* among TB suspects in a rural community in Southwest Ethiopia	Cross-sectional study	Ethiopia	41* (±16.2)	39.3	Community	428/482	17	0	17 (4)	NR	411 (96)	NR
Hamusse *et al* (2017)[29]	Prevalence and Incidence of Smear-Positive Pulmonary Tuberculosis in the Hetosa District of Arsi Zone, Oromia Regional State of Central Ethiopia	Cross-sectional study	Ethiopia	33.3*† (±16)	51†	Community	1041/1041	43	0	43 (4)	0/43	998 (96)	NR
Merid *et al* (2019)[30]	Population-based screening of pulmonary tuberculosis utilising community health workers in Ethiopia	Cross-sectional study	Ethiopia	36 29–48	35	Health Centre	544/544	34	0	34 (6)	0/31†‡	510 (94)	NR
Sekandi *et al* (2014)[31]	Yield of undetected tuberculosis and HIV coinfection from active case finding in urban Uganda	Cross-sectional study	Uganda	24 20–30	37.2	Community	160/199	39	NR	39 (24)	13/39	121 (76)	32

*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

								Diagnosed with TB				Not TB	
	Study title	Study type	Country	Age (median, IQR)	Male (%)	Setting	Presumptive TB (included/ eligible)	Laboratory (bacteriological)	Clinical	Total (%)	HIV	Total (%)	HIV
Affolabi *et al* (2011)[32]	Smear-negative, culture-positive pulmonary tuberculosis among patients with chronic cough in Cotonou, Benin	Cross-sectional Study	Benin	NR	NR	General Hospital	207/251	22	0	22 (11)	10/22	185 (89)	81/185
Huerga *et al* (2012)[33]	Performance of the 2007 WHO Alorithm to Diagnose Smear-Negative Pulmonary Tuberculosis in a HIV Prevalent Setting	Cross-sectional Study	Kenya	34 (26-48)	37.1	District Hospital	380/380	61	89	150 (39)		230 (61)	

NR, not reported.

Table 5 Tuberculosis studies handling and reporting of patients with presumed tuberculosis found not to have tuberculosis

						WHO estimated incidence (year of study)	
	Country	Diagnoses	Management	History of tuberculosis	Previous tuberculosis testing	Tuberculosis (per 100 000)	HIV (per 1000)
Affolabi *et al* (2011)[32]	Benin	NR	15 days erythromycin	NR	NR	71	0.69
Boehme *et al* (2011)[19]	South Africa	NR	NR	NR	NR	1260	10.29
	Uganda	NR	NR	NR	NR	213	3.55
Bruchfeld *et al* (2002)[20]	Ethiopia	8 pneumocystis pneumonia	NR	66*	NR	NR	1.79
Cuevas *et al* (2011)[24]	Ethiopia	NR	NR	NR	NR	296	0.44
	Nigeria	NR	NR	NR	NR	219	0.79
Deribew *et al* (2012)[28]	Ethiopia	NR	NR	NR	NR	282	0.41
Dorman *et al* (2018)[25]	South Africa (Cape Town)	NR	NR	59	NR	805	5.45
	South Africa (Johanesburg)	NR	NR	55	NR	805	5.45
	Kenya	NR	NR	20	NR	348	1.17
	Uganda	NR	NR	15	NR	201	1.89
Hamusse *et al* (2017)[29]	Ethiopia	NR	NR	NR	NR	224	0.25
Hanrahan *et al* (2014)[26]	South Africa	9 non-tuberculous mycobacteria	NR	NR	NR	1200	8.67
Huerga *et al* (2012)[33]	Kenya	11 non-tuberculous mycobacteria	5 days amoxicillin	92	NR	566	2.22
Jayasooriya *et al* (2019)[6]	The Gambia	2 malignancy: 2 lung 1 haematological	Clinically indicated	16*	NR	162	1.07
		32 other respiratory tract infections					
		8 pneumonia					
		4 asthma					
		2 pleural effusions					
		1 lung abscess					
		10 heart failure					
		2 structural heart disease					
		1 ischaemic heart disease					
		2 chronic renal failure					
		43 unknown					
Lawson *et al* (2008)[27]	Nigeria	NR	NR	NR	NR	219	0.91
Ling *et al* (2011)[18]	South Africa	NR	NR	NR	NR	1200	8.67
Merid *et al* (2019)[30]	Ethiopia	NR	NR	151*	NR	177	0.2
Munyati *et al* (2005)†[21]	Zimbabwe	178 other respiratory tract infections	Clinically indicated	97	NR	607	8.67
		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					

Continued

Table 5 Continued

	Country	Diagnoses	Management	History of tuberculosis	Previous tuberculosis testing	WHO estimated incidence (year of study)	
						Tuberculosis (per 100 000)	HIV (per 1000)
Nliwasa *et al* (2016)[22]	Malawi	NR	NR	NR	NR	261	3.2
Reither *et al* (2010)[23]	Tanzania	NR	NR	NR	NR	492	2.75
Sekandi *et al* (2014)[31]	Uganda	NR	NR	NR	NR	217	3.7
Theron *et al* (2011)[17]	South Africa	NR	NR	158	NR	1270	11.82

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

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.[35] 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.[36] 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.[35] 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.[37] 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[38] and post-TB lung disease,[39] 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,[40] of which a disproportionately high burden is seen in LMICs.[1] 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

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.

Author affiliations
[1]Academic Unit of Primary Medical Care, The University of Sheffield, Sheffield, UK
[2]The Medical School, The University of Sheffield, Sheffield, UK
[3]School of Health and Related Research (ScHARR), The University of Sheffield, Sheffield, UK
[4]Vaccines and Immunity Theme, Medical Research Council The Gambia, Banjul, Gambia
[5]Paediatric Infection & Immunity, London School of Hygiene and Tropical Medicine Faculty of Infectious and Tropical Diseases, London, UK
[6]Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK
[7]Deparment of Respiratory Medicine, Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK
[8]Department of Medicine, University of Cambridge, Cambridge, UK

Twitter Shamanthi Jayasooriya @de_shami, Claire Beecroft @mscihta and Babatunde Awokola @BAwokola

Acknowledgements We thank the NIHR Global Health Research Unit on Lung Health and tuberculosis in Africa at LSTM - 'IMPALA' for helping to make this work possible. In relation to IMPALA (grant number 16/136/35) specifically: This research was funded by the National Institute for Health Research (NIHR) (IMPALA, grant reference 16/136/35) using UK aid from the UK Government to support global health research.

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

Funding KM is the director of the NIHR Global Health Research Unit on Lung Health and tuberculosis in Africa at LSTM (16/136/35). PD was supported by a fellowship from the UK Medical Research Council (MR/P022081/1); this UK-funded award is part of the EDCTP2 programme supported by the European Union. SJ was supported by an NIHR Clinical Lectureship Award.

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.

ORCID iDs
Shamanthi Jayasooriya http://orcid.org/0000-0002-1147-5744
Beate Kampmann http://orcid.org/0000-0002-6546-4709
Kevin Mortimer http://orcid.org/0000-0002-8118-8871

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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 Chefchaoouen 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 Tamanrasette 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 Khartoum or Nyala or Kassala or Ubayyid or Kosti or Wad Madani or Qadari f or Al - Fashir or Daein or Damazin or Geneina or Merowe or (north* adj2 africa*)).ti,ab. (67388)
31 exp Africa, Eastern/ or (((east* 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 Iles Crozet or Scattered Islands or Iles Eparses or Mwanza or Zanzibar or Eldoret or Morogoro or Hargeysa or Berbera 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 Dese 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 Dodomoa or Bujumbura or Nakuru or Anananarivo or Kisumu or Maputo or Asmara or Lusaka or Harare 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 lodwar 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 Kambioos or Kayaka II or Kobe or Kyangwali Nakivale or Nyarugusu or Wad Sherife or Bokolmanyo or Melkadida or Rwamanja)) adj5 (camp or refug*)).ti,ab. (54617)
32 exp africa, western/ or ((africa*adj2 west* or benin* or burkina fas* or cape verd* or cabo verd* or ivory coast or cote d'ivoire* or gambia* or ghana* or guinea* or bissau or liberia* or (mali not fowl) or malian or mauritania* 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 Kumasi or Monrovia or Ibadan or Kano or Port harcourt or Benin City or Porto Novo or Niamey or Yamoussoukro or Banjul or Timbuktu or Djenne or Abomeyu 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 Sikasso or Kalabankoro or Nouakchott or Dakhlet Nouadhibou or Benin City or Port Harcourt or Ilorin or Kaduna or Enugu or Ikorodu or Onitsha or Bauchi or Akure or Abeokuta or Sokoto or Bouake or Makeni or Kaduan or Sosgbo or Osogbo or Gombe or Ilesa or Badagry or makurdi or Sagamu or Iseyin or obbomosho or Awka or Ado Ekiti or Nsukka or Ikeja 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 Ziguinch 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 Nganoundere or Maroua or Kouosseri 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 Coquilhatville or Matadi or Butembo or Kabinda or Mwene Ditu or Isiro or Paulis 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 Johannesburg 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 Nampula or Chimoio or Nacala or Quelimane or Lusaka 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

	Was sample frame appropriate to address the target population?	Were study participants sampled in an appropriate way?	Was the sample size adequate?	Were the study subjects and the setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for identification of the condition?	Was the condition measured in a standard, reliable way for all participants?	Was there appropriate statistical analysis?	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Overall appraisal
Affolabi et al. 2011*	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	INCLUDE
Boehme et al. 2011	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Uganda borderline sample size Sampled set days INCLUDE
Bruchfeld et al. 2002	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Convenience sampling Sampled set days INCLUDE
Cuevas et al. 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	INCLUDE
Deribew et al. 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11% not included INCLUDE
Dorman et al. 2018	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	INCLUDE
Hamusse et al. 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	INCLUDE
Hanrahan et al. 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	INCLUDE
Huerga et al. 2012*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	INCLUDE
Jayasooriya et al. 2019	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	INCLUDE
Lawson et al. 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11% not included

										INCLUDE
Ling et al. 2011	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Sampled over 3years 21% not included INCLUDE
Merid et al. 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	INCLUDE
Munyati et al. 2005	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Convenience sampling INCLUDE
Nliwasa et al. 2016	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Borderline sample size INCLUDE
Reither et al.	Yes	Unclear	No	No	Yes	Yes	Yes	Yes	Yes	Limited setting detail INCLUDE
Sekandi et al. 2014	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Small sample size INCLUDE
Theron et al. 2011	No	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Sampled over 3years INCLUDE

* 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

This document is generated from an R script in literate programming fashion. All R code is quoted in this document, together with output (preceeded 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')` 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
```


Jayasooriya S, *et al. Thorax* 2022;0:1–11. doi: 10.1136/thoraxjnl-2021-217663

```
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$platform,                 #platofm
        sI$running,                  #OS
        sI$otherPkgs$metafor$Version #metafor version
    )
)
knitr::kable(dI)
```

item	version
R version	R version 4.1.0 (2021-05-18)
platform	x86_64-pc-linux-gnu (64-bit)
OS	Pop!_OS 21.04
metafor version	3.0-2

Main analyses

Approach

We use a generalized linear mixed effects (GLMM) approach to meta-analysis assuming a binomial response and logit link[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.[2]

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

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

Create exact binomial confidence intervals:

[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.

[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

```
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:

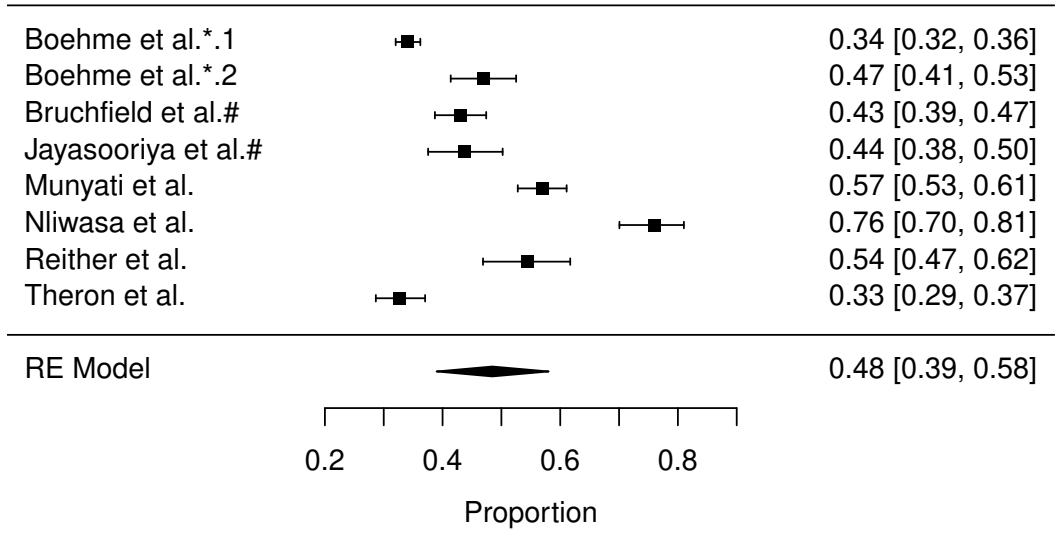
```
maPU <- rma.glmm(measure = "PLO", #  binomial w/ logit link
            xi = NnotTB,     # numerator
            ni = N,          # denominator
            data = DD[mode=='Passive' &
                      clinical=='(Unconfirmed TB included)'],
            slab = Author)      # what to use as labels 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
```

```
forest(maPU,transf = transf.ilogit,refline=NA)
```

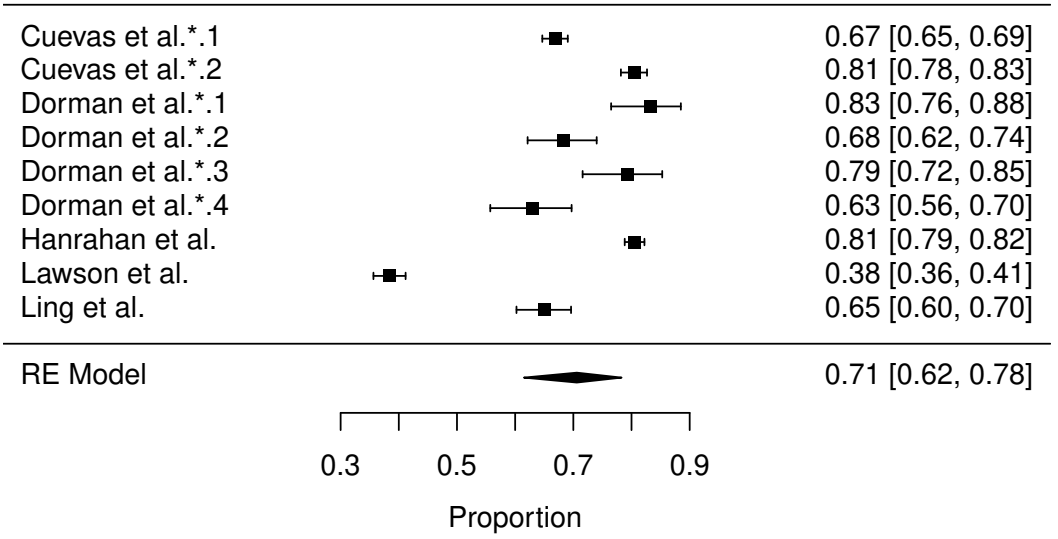


Meta-analysis for passively found TB patients with bacteriologically unconfirmed TB excluded:

```
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
summary(maPN)
```

```
##
## Random-Effects Model (k = 9; tau^2 estimator: ML)
##
##   logLik  deviance       AIC       BIC      AICc
## -28.8910    0.2865   61.7821   62.1765   63.7821
##
## 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:
## Wld(df = 8) = 679.9414, p-val < .0001
## LRT(df = 8) = 727.2051, p-val < .0001
##
## Model Results:
##
## estimate      se    zval    pval   ci.lb   ci.ub
##   0.8757  0.2078  4.2139  <.0001  0.4684  1.2830  ***
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
forest(maPN,transf = transf.ilogit,refline=NA)
```

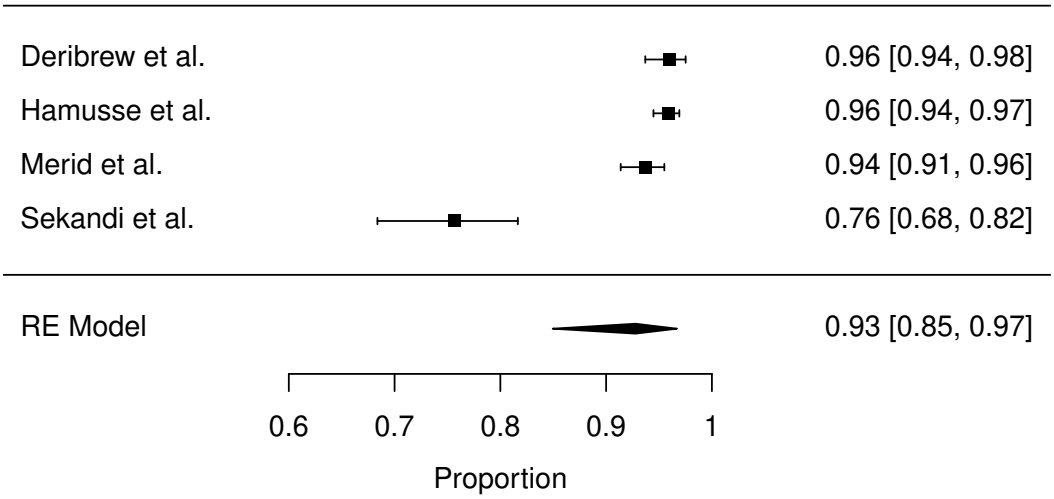


Meta-analysis for actively found TB patients:

```
maA <- rma.glmm(measure = "PLO", #  binomial w/ logit link
            xi = 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:

```
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:

```
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,map$pred),
                    lo = c(mup$ci.lb,mnp$ci.lb,map$ci.lb),
                    hi = c(mup$ci.ub,mnp$ci.ub,map$ci.ub),
                    lab=paste0('SUMMARY (',expression(I^2),'=',
                               f1(c(maA$I2,maPN$I2,maPU$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:

```
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]
```

```
DD[,wt:=paste0(f1(wt),'%')]
DD[,w:=0]
```

Combined plot data:

```
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:='Clinically diagnosed tuberculosis included']
B[clinical=='(No unconfirmed TB)',
  clinical.g:='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:

```
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))+
```

```
    ggpubr::grids()

ggsave(SA,file=here('output/ForestPlot.pdf'),h=13,w=12)
ggsave(SA,file=here('output/ForestPlot.eps'),h=13,w=12)
```

Meta-regressions

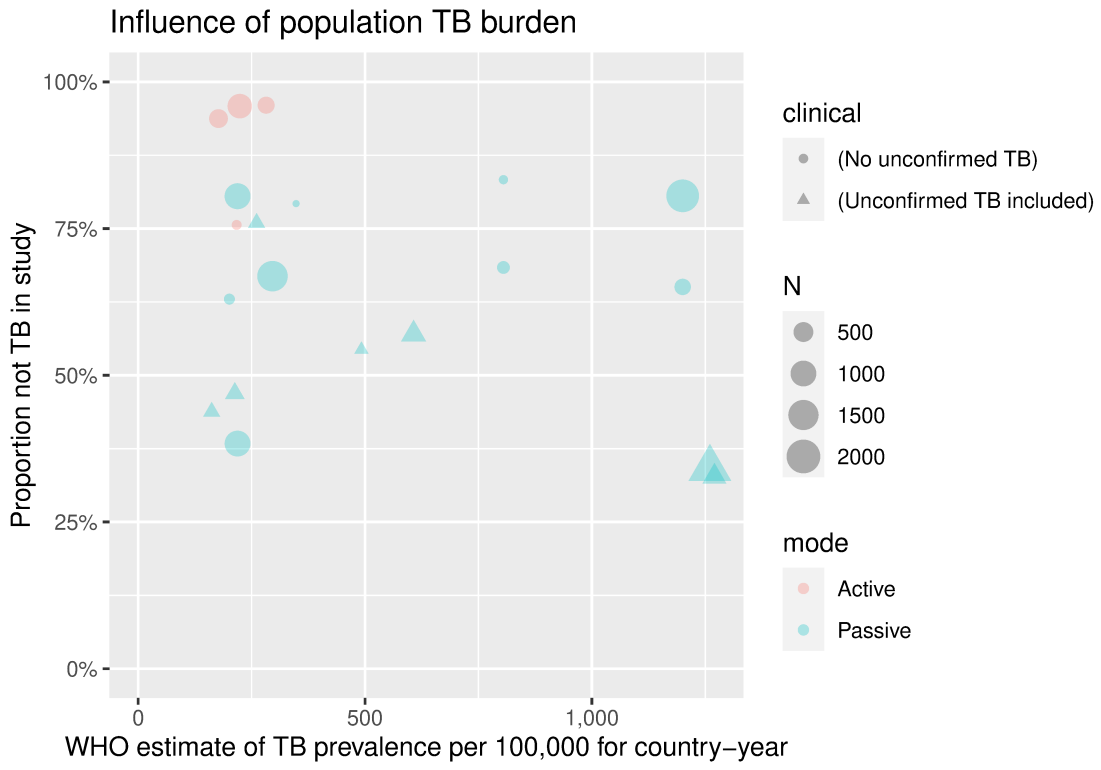
In this section we consider various potential sources of heterogeneity through scatter plots and meta-regression.

TB prevalence

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

```
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).
```



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

```
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.
```

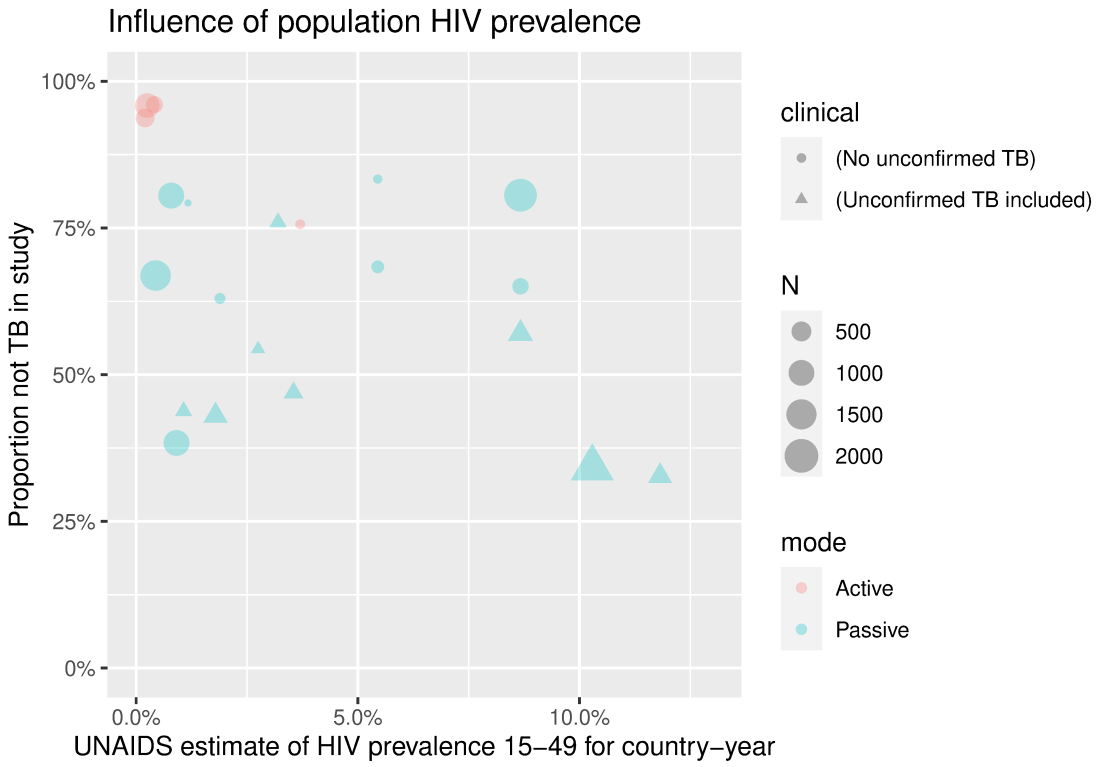
```
summary(tbmr)
```

```
##
## 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:
##
##                                    estimate      se     zval    pval    ci.lb
## intrcpt                              2.5877  0.3453   7.4931  <.0001   1.9109
## modePassive                         -1.6174  0.4233  -3.8210  0.0001  -2.4471
## clinical(Unconfirmed TB included)   -0.8999  0.3286  -2.7386  0.0062  -1.5439
## tb                                  -0.0002  0.0004  -0.4084  0.6830  -0.0009
##                                     ci.ub
## intrcpt                            3.2646  ***
## modePassive                       -0.7878  ***
## clinical(Unconfirmed TB included) -0.2559   **
## tb                                 0.0006
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

HIV prevalence

Population HIV prevalence may plausibly influence the proportion of presumptives not diagnosed with TB both by inluencing 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/1e2,`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))+
    geom_point(alpha=a)+
    xlab('UNAIDS estimate of HIV prevalence 15-49 for country-year')+
    ylab('Proportion not TB in study')+
    ggtitle('Influence of population HIV prevalence')
```



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

```
hivmr <-  rma.glmm(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)
```

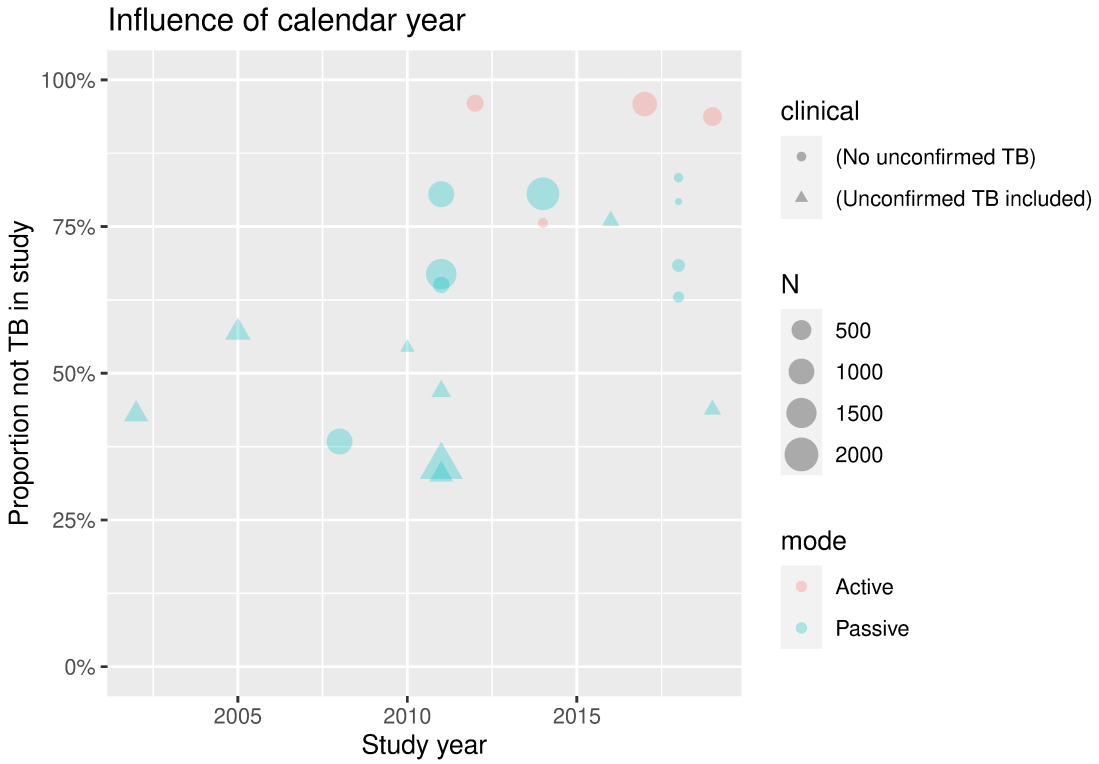
```
##
## Mixed-Effects Model (k = 21; tau^2 estimator: ML)
##
##   logLik  deviance       AIC       BIC      AICc
## -65.1479    1.0280  140.2958  145.5184  144.2958
##
## tau^2 (estimated amount of residual heterogeneity):     0.3839
```

```
## 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
##
## Tests for Residual Heterogeneity:
## Wld(df = 17) =  973.1809, p-val < .0001
## LRT(df = 17) = 1025.3297, p-val < .0001
##
## Test of Moderators (coefficients 2:4):
## QM(df = 3) = 44.7803, p-val < .0001
##
## Model Results:
##
##                                   estimate      se     zval    pval    ci.lb
## intrcpt                             2.5888  0.3279   7.8949  <.0001   1.9461
## modePassive                        -1.5920  0.4019  -3.9609  <.0001  -2.3798
## clinical(Unconfirmed TB included)  -0.8801  0.3153  -2.7914  0.0052  -1.4981
## hiv                                -0.0325  0.0420  -0.7730  0.4395  -0.1149
##                                    ci.ub
## intrcpt                           3.2315  ***
## modePassive                      -0.8042  ***
## clinical(Unconfirmed TB included) -0.2622   **
## hiv                               0.0499
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Calendar time

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

```
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')
```



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

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

```
## Warning: Redundant predictors dropped from the model.
```

```
summary(yearmr)
```

```
##
## 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):     0.3586
## tau (square root of estimated tau^2 value):             0.5989
## 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:
##
##                                   estimate       se     zval    pval
## intrcpt                          -88.8442  64.9689  -1.3675  0.1715
## modePassive                       -1.6045   0.3784  -4.2400  <.0001
## clinical(Unconfirmed TB included)  -0.7813   0.3167  -2.4673  0.0136
## Year                               0.0453   0.0322   1.4068  0.1595
##                                      ci.lb    ci.ub
## intrcpt                          -216.1809  38.4926
## modePassive                        -2.3462  -0.8628  ***
## clinical(Unconfirmed TB included)  -1.4019  -0.1606    *
## Year                               -0.0178   0.1085
##
## ---
## 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:

```
tmp <- DD[mode=='Passive' & clinical=='(No unconfirmed TB)']
tmp[,Country.Simple:=gsub(" \\-.+$","",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
```

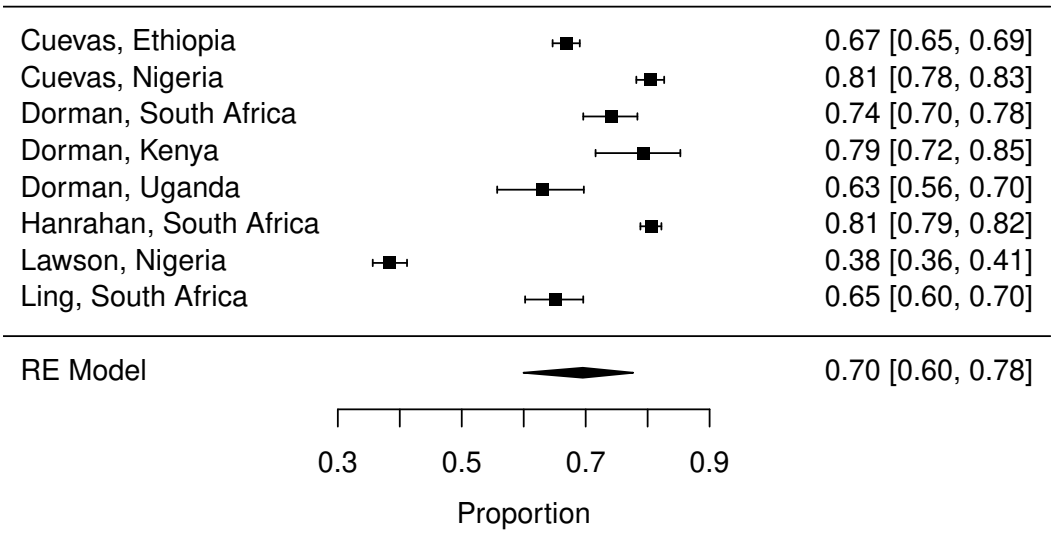
authorcountry	NnotTB	N
Cuevas, Ethiopia	1184	1770
Cuevas, Nigeria	963	1196
Dorman, South Africa	285	384
Dorman, Kenya	107	135
Dorman, Uganda	114	181
Hanrahan, South Africa	1685	2091
Lawson, Nigeria	455	1186
Ling, South Africa	257	395

Rerun this meta-analysis with the new data:

```
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)
##
##   logLik  deviance       AIC       BIC      AICc
## -26.5760    0.1654   57.1519   57.3108   59.5519
##
## 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
##
## Model Results:
##
## estimate      se    zval    pval   ci.lb   ci.ub
##   0.8252  0.2149  3.8406  0.0001  0.4041  1.2463  ***
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
forest(maPNsa,transf = transf.ilogit,refline=NA)
```



This is very similar to the main analysis above.

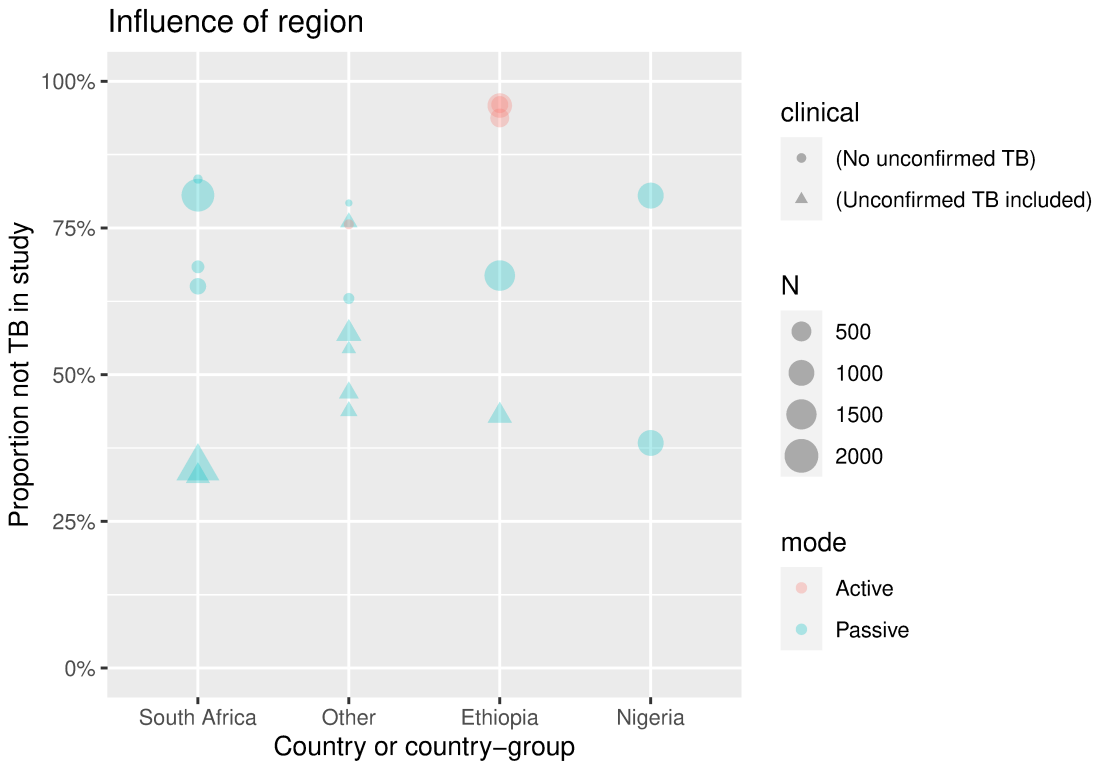
Regional groupings

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.

```
DD[,Country.Group:=gsub(" \\-.+$","",Country)]                    #remove cities
DD[!Country.Group %in% c("South Africa","Ethiopia","Nigeria"),Country.Group:="Other"] #group
DD[,Country.Group:=factor(Country.Group,levels=unique(Country.Group))] #make factor
```

Plot this data:

```
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')+
    ggtitle('Influence of region')
```



Perform meta-regression on country-group:

```
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
```

```
## 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:
##
##                                   estimate      se     zval    pval    ci.lb
## intrcpt                             2.1567  0.5023   4.2940  <.0001   1.1723
## modePassive                        -1.2854  0.4723  -2.7217  0.0065  -2.2110
## clinical(Unconfirmed TB included)  -1.1151  0.3371  -3.3082  0.0009  -1.7757
## Country.GroupOther                  0.2021  0.3565   0.5669  0.5708  -0.4966
## Country.GroupEthiopia               0.4592  0.4521   1.0158  0.3097  -0.4269
## Country.GroupNigeria               -0.4006  0.5052  -0.7931  0.4277  -1.3908
##                                    ci.ub
## intrcpt                           3.1412  ***
## modePassive                      -0.3597   **
## clinical(Unconfirmed TB included) -0.4544  ***
## Country.GroupOther                0.9008
## Country.GroupEthiopia             1.3453
## Country.GroupNigeria              0.5895
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```