Subclinical tuberculosis: a meta-analysis of prevalence and scoping review of definitions, prevalence and clinical characteristics

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Shareable abstract (@ERSpublications)
This scoping review highlights the need for standardised subclinical TB definitions. Variability in definitions affects prevalence estimates. Subclinical TB was more common in high-burden areas, community settings and among immunocompetent individuals. https://bit.ly/3SIcexO

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Abstract

Background: This scoping review aimed to characterise definitions used to describe subclinical tuberculosis (TB), estimate the prevalence in different populations and describe the clinical characteristics and treatment outcomes in the scientific literature.

Methods: A systematic literature search was conducted using PubMed. We included studies published in English between January 1990 and August 2022 that defined "subclinical" or "asymptomatic" pulmonary TB disease, regardless of age, HIV status and comorbidities. We estimated the weighted pooled proportions of subclinical TB using a random-effects model by World Health Organization reported TB incidence, populations and settings. We also pooled the proportion of subclinical TB according to definitions described in published prevalence surveys.

Results: We identified 29 prevalence surveys and 71 other studies. Prevalence survey data (2002–2022) using "absence of cough of any duration" criteria reported higher subclinical TB prevalence than those using the stricter "completely asymptomatic" threshold. Prevalence estimates overlap in studies using other symptoms and cough duration. Subclinical TB in studies was commonly defined as asymptomatic TB disease. Higher prevalence was reported in high TB burden areas, community settings and immunocompetent populations. People with subclinical TB showed less extensive radiographic abnormalities, higher treatment success rates and lower mortality, although studies were few.

Conclusion: A substantial proportion of TB is subclinical. However, prevalence estimates were highly heterogeneous between settings. Most published studies incompletely characterised the phenotype of people with subclinical TB. Standardised definitions and diagnostic criteria are needed to characterise this phenotype. Further research is required to enhance case finding, screening, diagnostics and treatment options for subclinical TB.

Introduction

In recent years, the concept of the tuberculosis (TB) disease spectrum has emerged, recognising that TB exists along a continuum ranging from latent infection through incipient and subclinical disease to active TB disease [1, 2]. Depending on immune status, genetic factors and the presence of comorbidities, individuals can progress or regress along this spectrum [3, 4]. After exposure to *Mycobacterium tuberculosis*, some individuals may present with TB infection in a quiescent state that is asymptomatic and noncontagious and can be detected using tuberculin skin tests or interferon-gamma release assays (IGRAs). Preventive treatment can be given to eliminate the bacteria and prevent the progression to active TB disease. At the other end of the spectrum, TB disease is characterised by symptoms such as cough, fever, weight loss and night sweats. TB disease diagnosis can usually be confirmed using sputum smear

microscopy, mycobacterial culture or molecular tests. Untreated TB disease can be lethal and is a leading cause of morbidity and mortality worldwide.

Subclinical TB is a disease state that lacks typical clinical symptoms but is detectable *via* radiologic abnormalities or microbiologic testing [2]. Data from representative TB prevalence surveys suggest that 50.4% of the prevalent bacteriologically confirmed TB in the general community was subclinical [5]. While only around half of the people with subclinical TB will progress to clinical TB [6], their potential ability to transmit the disease has serious implications for public health and the global efforts to end TB by 2035 [7–9]. Pathological changes occur while affected individuals remain at the subclinical stage [1], making it critical to identify and treat those at this disease phase. Early detection is likely to improve prognosis, reduce post-TB sequelae and prevent catastrophic healthcare costs. Contrary to this more nuanced understanding, the dichotomised understanding of TB infection and disease underpins most standard TB control strategies.

In many settings, symptom evaluation comprises the initial step in TB screening algorithms, despite its poor sensitivity and specificity [10]. The use of diagnostic tests at the first stage of evaluation, such as chest radiography, is frequently rejected on the basis of inadequate access and a shortage of trained personnel, particularly in resource-limited settings [11]. In these instances, people with subclinical TB are likely missed and a diagnosis only made if symptoms subsequently become apparent.

Most published reviews of subclinical TB have focused on the findings of TB prevalence surveys [5, 12]. Its prevalence in specific key populations has not been well characterised. Key questions remain regarding definitions of subclinical TB, its epidemiology and testing and treatment options [2]. This scoping review aimed to describe how subclinical TB is defined in the scientific literature, to estimate the proportion of people in different populations with prevalent subclinical TB and to characterise the clinical characteristics of people with subclinical TB and their treatment outcomes.

Methods

Search strategy and selection criteria

This review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR) guidelines [13].

Literature search strategy and study selection

We searched PubMed using a combination of medical subject heading terms, index terms and keywords centred around three domains (TB, the presence of symptoms and the subclinical status of the disease) for articles published between January 1990 and August 2022. Boolean logic operators (AND and OR) were used to search for the relevant articles (supplementary material). Additional studies were sought from the key review and opinion article reference lists. We also reviewed the Global Tuberculosis Report 2021 [14] and other sources [5] to obtain a list of national TB prevalence surveys. Prevalence survey reports and relevant journal publications were then assessed.

Citations were managed using EndNote X9 (Clarivate Analytics, Philadelphia, USA). Duplicate citations were removed and the remainder was exported to Microsoft Excel (Microsoft Corporation, Washington, USA) for further assessment. A.K.J. Teo screened the titles, abstracts and full-text articles based on the inclusion and exclusion criteria. Independent verification of abstracts was completed for a random 10% of the entries by one reviewer (E.L-H. MacLean). All the full-text articles were reviewed by two reviewers. Discrepancies were resolved by consensus.

Inclusion and exclusion criteria

This review sought to identify publications reporting individuals with subclinical TB according to the definition provided by Drain *et al.* [2]: TB disease due to *M. tuberculosis* that does not give rise to typical clinical symptoms but instead leads to other detectable abnormalities using radiologic or microbiologic testing. We included studies that defined subclinical or asymptomatic pulmonary TB disease, either bacteriologically confirmed (diagnoses made based on positive culture, nucleic acid amplification test (NAAT), acid-fast bacilli or reported bacteriological confirmation) and/or clinician-diagnosed (TB disease ascertained by a medical practitioner without bacteriological confirmation), regardless of age, HIV status and other comorbidities. Studies that did not define subclinical TB but reported people with asymptomatic TB disease were included in the ancillary analyses (supplementary material). Articles only comprising people with extrapulmonary TB or reported TB infection were excluded.

We included observational and intervention studies published in English. Excluded manuscripts included reviews and meta-analyses, publications in the form of letters, editorials, commentaries, case reports and studies lacking or with unclear reporting of key outcomes (including modelling studies). We also excluded studies that reported the results from national TB prevalence surveys.

Data extraction

Data were extracted by A.K.J. Teo and entered into Microsoft Excel (Microsoft Corporation, Washington, USA). All data were reviewed by E.L-H. MacLean independently. The agreement on extraction was excellent. We recorded the study details, participant characteristics and screening outcomes in a standardised manner. Reported data included the following: 1) publication year, country and settings, study design, data collection period, and the populations; 2) the proportions of people with subclinical or asymptomatic TB disease; 3) the definitions of TB disease and subclinical TB, including the diagnostic modalities used; 4) characteristics (radiological, microbiological, clinical and laboratory markers), if any, of people with subclinical/asymptomatic TB and clinical symptomatic TB disease; 5) disease progression (time from subclinical TB to symptoms onset and clinical features of disease progression); and 6) treatment outcomes (success, failure and death) among people with subclinical/asymptomatic and clinical/symptomatic TB disease. We also extracted the number of people with subclinical/asymptomatic TB disease and the definitions of symptom screen positive reported by various national TB prevalence surveys. Both reviewers also independently assessed the risks of bias for included studies using the JBI critical appraisal tools [15]. We did not find articles with a high risk of bias pertaining to the review objective. Therefore, all studies that met the inclusion criteria were reviewed.

Data synthesis and analyses

Studies were included in the narrative synthesis if they met the inclusion criteria. Only studies that defined subclinical TB (*e.g.* provided a study-specific definition in the main body of text) and presented the proportions of affected individuals were included in the meta-analysis. We described the studies by the populations, countries, settings, study designs, the total number of people with TB disease and the number of people with asymptomatic/subclinical TB. We tabled the definitions of subclinical TB and the modalities used to diagnose TB disease. Disease progression and treatment outcomes of people with subclinical/asymptomatic TB were summarised wherever relevant information was available.

Meta-analyses were performed to estimate the weighted pooled proportions of people with subclinical/asymptomatic TB and its 95% confidence interval using the "Metaprop" package [16] on Stata 14.1 (StataCorp, College Station, TX, USA). We applied a random-effects model and stratified the analyses by World Health Organization (WHO) TB burden classifications [17], populations and settings (community/outpatient/inpatient). Between-study heterogeneity was quantified using I^2 statistics. Furthermore, we built on the work by Frascella *et al.* [5] by including recent data in the meta-analysis to present a comprehensive summary of the proportions of people with subclinical/asymptomatic TB disease identified in published prevalence surveys conducted to date by definitions. We did not attempt a meta-analysis on other outcomes due to few studies and inconsistent definitions and measurements.

Results

Study search and selection

The initial search yielded a total of 4931 records after deduplication. Of these, 4751 were excluded based on title and abstract screening. After a full-text assessment of the remaining articles, 71 studies were included in this review. The 27 studies that explicitly defined subclinical TB were classified by population, country, settings, screening and diagnostic modalities, and subclinical TB definitions. Most studies were conducted among people living with HIV (PLHIV) and the general population (table 1). The remaining 44 that did not define subclinical TB disease but reported the number of people with asymptomatic TB disease and other outcomes such as characteristics, disease progression and/or treatment outcomes of subclinical TB disease are described in the supplementary material. The study selection process is summarised in a PRISMA flow diagram (figure 1).

Definitions of subclinical TB disease

Overall, the definitions of subclinical TB typically describe a manifestation of TB disease without clinical symptoms (table 1). One study used the absence of cough as a threshold in distinguishing subclinical TB from TB disease [40]. We further explored the definitions of "symptom screen negative" using information reported by other prevalence surveys conducted up to August 2022. Studies that used "absence of any symptoms" as a threshold between clinical TB disease and subclinical TB disease had the lowest proportion of individuals with subclinical TB in the general community (45%, 95% CI 35–56%) (figure 2). Contrarily, studies that utilised the less stringent symptom screen negative threshold of "absence of cough

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TABLE 1 Tuberculosis (TB) disease screening and diagnosis and the definitions of subclinical TB

First author [ref.], year	Title	Country	Setting	Screening and diagnostic modalities used to diagnose TB						Subclinical/asymptomatic TB definitions
				CXR	Symptoms	AFB smear	NAAT	Culture[§]	Others[f]	
Children ⩽15 years old (unless indicated otherwise)										
Huang [18], 2022	The contribution of chest radiography to the clinical management of children exposed to tuberculosis	Peru	Community	•	•	•		•		Asymptomatic and smear/culture positive for TB
Fritschi [19], 2022	Subclinical tuberculosis in children: diagnostic strategies for identification reported in a 6-year national prospective surveillance study	Switzerland	Healthcare facilities (outpatient)	•	•		•	•		Persons with TB but asymptomatic and/or reported none of the following: cough, wheezing, fever >38°C, failure to thrive or weight loss
Ziemele [20], 2017	Pediatric and adolescent tuberculosis in Latvia, 2011–2014: case detection, diagnosis and treatment[#]	Latvia	Healthcare facilities[##]	•	•	•	•	•	•	Bacteriologically confirmed or clinically diagnosed TB and abnormalities visualised only on CT
Loveday [21], 2016	Dilemma of managing asymptomatic children referred with "culture-confirmed" drug-resistant tuberculosis	South Africa	Healthcare facilities (outpatient)		•		•	•	•	No signs or symptoms suggestive of active disease
PLHIV										
Mendelsohn [22], 2022	Clinical predictors of pulmonary tuberculosis among South African adults with HIV	South Africa	Community				•	•		Asymptomatic individuals with sputum microbiology positive for TB
Naidoo [23], 2022	Recurrent subclinical tuberculosis among ART accessing participants: incidence, clinical course, and outcomes	South Africa	Community	•	•	•		•		Negative TB symptoms screen with the identification of TB by sputum smear or culture
Auld [24], 2021	Derivation and external validation of a risk score for predicting HIV-associated tuberculosis to support case finding and preventive therapy scale-up: a cohort study	Botswana	Healthcare facilities (outpatient)		•	•	•			Asymptomatic TB disease, detectable by microbiologic tests or radiography
Capocci [25], 2020	Cost effectiveness of testing HIV infected individuals for TB in a low TB/HIV setting	UK	Healthcare facilities (outpatient)	•	•		•	•		Positive culture with or without radiographic changes and in the absence of symptoms
Rickman [26], 2020	Subclinical tuberculosis and adverse infant outcomes in pregnant women with HIV[¶]	South Africa	Healthcare facilities (outpatient)		•	•		•		Persons not suspected (asymptomatic) of TB disease according to clinical records but had a positive culture
Darboe [27], 2019	Detection of tuberculosis recurrence, diagnosis and treatment response by a blood transcriptomic risk signature in HIV-infected persons on antiretroviral therapy	South Africa	Healthcare facilities (outpatient)		•			•		Asymptomatic at microbiological diagnosis of TB

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TABLE 1 Continued

First author [ref.], year	Title	Country	Setting	Screening and diagnostic modalities used to diagnose TB						Subclinical/asymptomatic TB definitions
				CXR	Symptoms	AFB smear	NAAT	Culture[§]	Others[ƒ]	
Bajema [28], 2019	Subclinical tuberculosis among adults with HIV: clinical features and outcomes in a South African cohort	South Africa	Healthcare facilities (outpatient)		•			•		Presence of *Mtb* in either solid or liquid media but no TB-related symptoms
Lawn [29], 2011	Progression of subclinical culture-positive tuberculosis to symptomatic disease in HIV-infected individuals	South Africa	Healthcare facilities (outpatient)	•	•			•		Sputum culture positive but asymptomatic at screening
Oni [30], 2011	High prevalence of subclinical tuberculosis in HIV-1-infected persons without advanced immunodeficiency: implications for TB screening	South Africa	Healthcare facilities (outpatient)	•	•	•		•		At least one culture-positive sputum specimen in the absence of symptoms (cough of any duration, fever, unintentional weight loss, loss of appetite and night sweats)[¶¶]
Agizew [31], 2010	Tuberculosis in asymptomatic HIV-infected adults with abnormal chest radiographs screened for tuberculosis prevention	Botswana	Healthcare facilities (outpatient)	•	•	•		•	•	Abnormal CXR and asymptomatic but culture positive, AFB smear positive, or reported clinical response to anti-TB treatment[¶¶]
Bakari [32], 2008	Basis for treatment of tuberculosis among HIV-infected patients in Tanzania: the role of chest X-ray and sputum culture	Tanzania	Healthcare facilities (outpatient)	•	•	•		•		No symptoms and negative CXR
Mtei [33], 2005	High rates of clinical and subclinical tuberculosis among HIV-infected ambulatory subjects in Tanzania	Tanzania	Healthcare facilities (outpatient)	•	•	•		•		Clinical features were absent but sputum cultures were positive for *Mtb*
General population										
Tang [34], 2021	Prevalence and risk factors of subclinical tuberculosis in a low-incidence setting in China	China	Healthcare facilities[##]	•	•	•	•	•		No TB-associated clinical symptoms but presenting abnormalities detectable by radiologic and/or microbiologic assays
Kendall [35], 2021	The spectrum of tuberculosis disease in an urban Ugandan community and its health facilities	Uganda	Mixed (community and healthcare facilities)				•	•		Bacteriologically positive asymptomatic TB disease
Mok [36], 2021	Role of digital tomosynthesis in the context of tuberculosis contact investigation: comparisons with digital radiography	South Korea	Community		•			•	•	Subclinical: positive IGRA, culture positive, evidence of TB disease on CT but do not have clinical symptoms Minimal: positive IGRA, culture negative, evidence of TB disease on CT
Min [37], 2020	Clinical profiles of subclinical disease among pulmonary tuberculosis patients: a prospective cohort study in South Korea	Republic of Korea	Healthcare facilities[##]	•	•	•	•	•		Presence of radiographic or microbiologic test results consistent with TB without clinical symptoms

Continued

TABLE 1 Continued

First author [ref.], year	Title	Country	Setting	Screening and diagnostic modalities used to diagnose TB						Subclinical/asymptomatic TB definitions
				CXR	Symptoms	AFB smear	NAAT	Culture[§]	Others[f]	
Gunasekera [38], 2020	Smoking and HIV associated with subclinical tuberculosis: analysis of a population-based prevalence survey	South Africa	Community		•			•		Positive culture but without TB symptoms specified by the WHO (cough, 1 month of fever, weight loss and night sweats)
Bekken [39], 2020	Identification of subclinical tuberculosis in household contacts using exposure scores and contact investigations	India	Community	•	•			•		Positive culture in sputum or gastric aspirate (children <5 years) but asymptomatic
Dorjee *et al.* [40], 2019	High prevalence of active and latent tuberculosis in children and adolescents in Tibetan schools in India: the Zero TB Kids Initiative in Tibetan refugee children[+]	India	Community (school)	•	•		•	•		Active TB without cough[¶¶]
Yu [41], 2019	Correlation between 18F-FDG PET CT SUV and symptomatic or asymptomatic pulmonary tuberculosis	China	Healthcare facilities[##]						•	Asymptomatic pulmonary TB
Bahammam [42], 1999	Utility of gastric aspirates in screening for pulmonary tuberculosis in high risk subjects: the Manitoba experience	Canada	Community	•	•			•		Asymptomatic defined as having no fever, night sweats, cough, haemoptysis, chest pain or weight loss
People with diabetes										
Berkowitz [43], 2018	The prevalence and determinants of active tuberculosis among diabetes patients in Cape Town, South Africa, a high HIV/TB burden setting	South Africa	Healthcare facilities (outpatient)		•	•	•	•		Active TB but with an absence of any clinical symptoms
Nair [44], 2016	Prevalence of pulmonary tuberculosis in young adult patients with type 1 diabetes mellitus in India	India	Healthcare facilities (outpatient)	•	•	•		•		No clinical symptoms and normal CXR but positive sputum culture

[#]: Children ⩽18 years. [¶]: Among pregnant women. [+]: School goers between ages <5 and 24 years. [§]: Liquid and/or solid culture media. [f]: Other clinical assessments, histology, response to anti-TB treatment or the initiation of treatment without an alternative diagnosis. [##]: Data extracted from health facilities records. Did not specify outpatient or inpatient. [¶¶]: Not included in the meta-analyses due to the inclusion of people who were asymptomatic (subclinical) only (Oni *et al.* [30] and Agizew *et al.* [31]) and defined subclinical TB as absence of cough (Dorjee *et al.* [40]). AFB: acid-fast bacilli; CT: computed tomography; CXR: chest radiography; FDG: fluorodeoxyglucose; IGRA: interferon-γ release assay; *Mtb*: *Mycobacterium tuberculosis*; NAAT: nucleic acid amplification test; PET: positron emission tomography; PLHIV: people living with HIV; SUV: standardised uptake value; WHO: World Health Organization.

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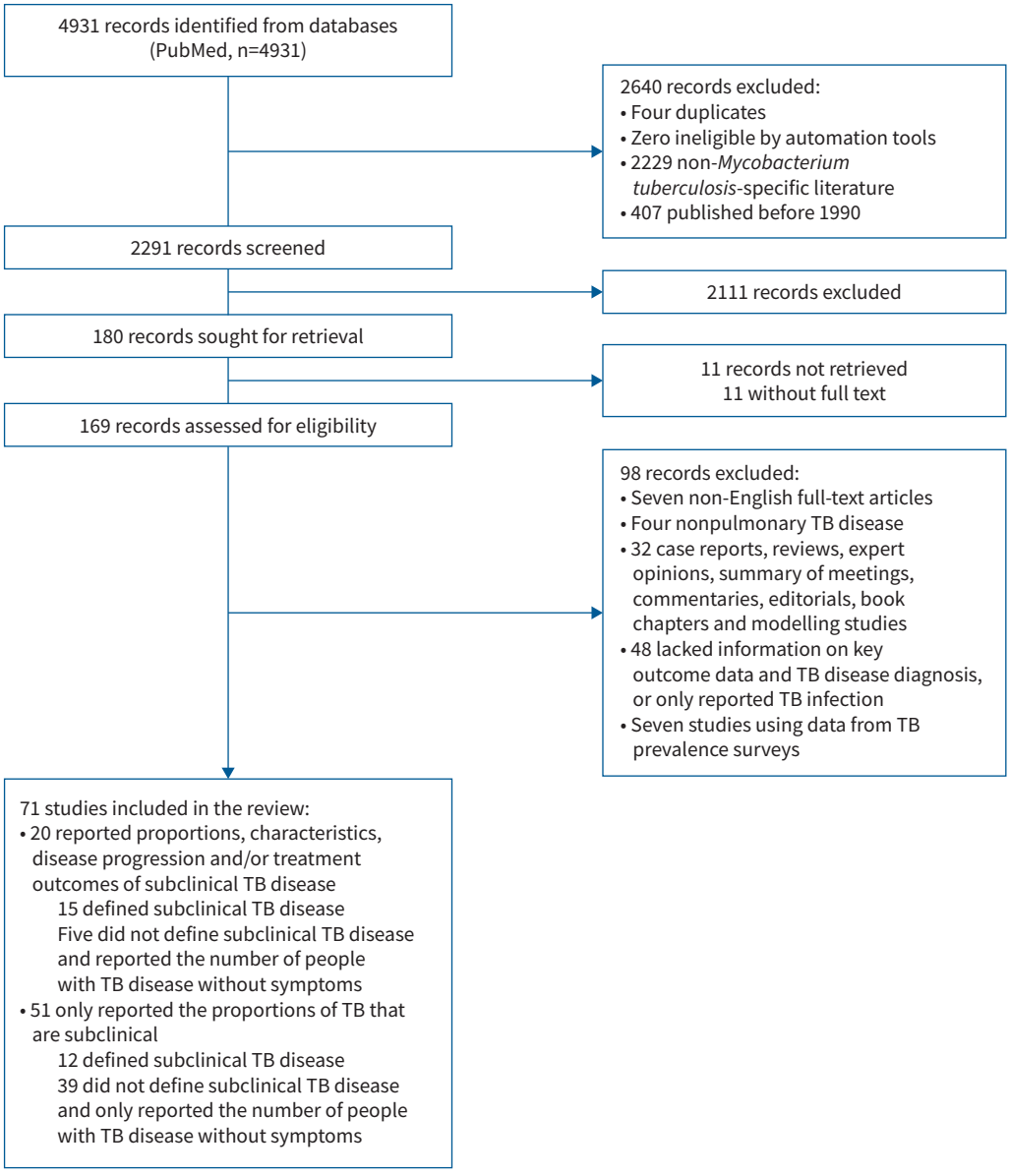

FIGURE 1 Study selection. TB: tuberculosis.

of any duration" resulted in a higher estimated proportion of prevalent TB that was subclinical (60%, 95% CI 55–65%) (figure 2). Nevertheless, there is an overlap in the confidence intervals of subclinical TB in prevalence surveys using other symptoms and cough duration (figure 2).

Proportions of people with subclinical TB

The confidence intervals of prevalent TB that was subclinical overlapped among children (42%, 95% CI 23–61%), people with diabetes (41%, 95% CI 21–61%) and the general population (41%, 95% CI 27–55%) (figure 3). For studies conducted among PLHIV, we further segregated the analysis by cluster of differentiation 4 (CD4) count. The pooled estimated proportion of people with TB that was subclinical was higher among PLHIV with a higher median CD4 count (49%, 95% CI 31–67%) relative to studies conducted among PLHIV with a lower median CD4 count (22%, 95% CI 12–31%).

In the subgroup analysis by settings (figure 3), we observed higher estimates of subclinical TB among community participants (48%, 95% CI 32–63%) compared to those recruited from outpatient/inpatient facilities (34%, 95% CI 19–49%) and outpatient facilities only (25%, 95% CI 18–33%), with overlapping confidence intervals.

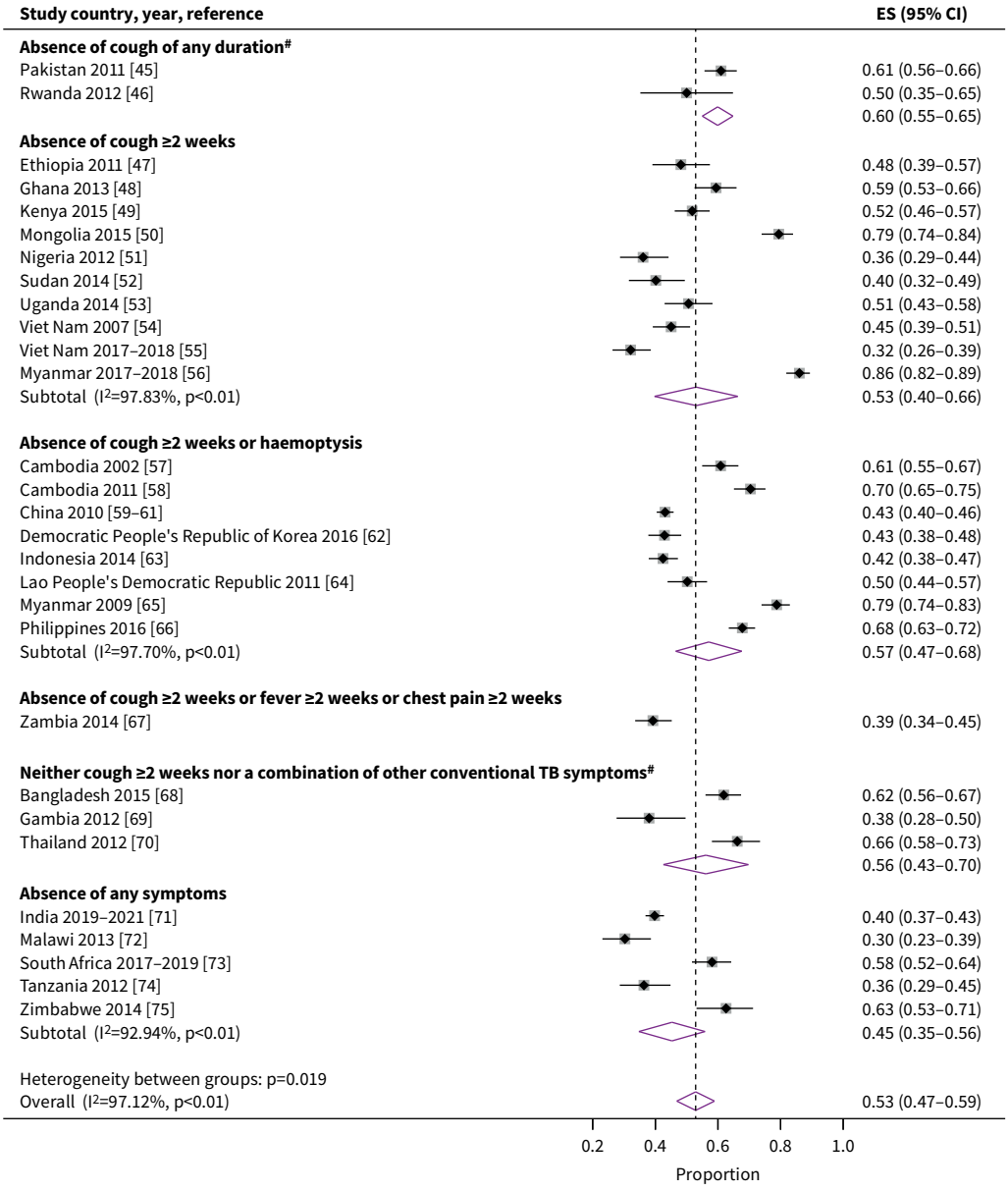

FIGURE 2 Proportions of people with tuberculosis (TB) that were subclinical reported in national TB prevalence surveys by definitions of being symptom positive. Symptom definitions for countries that were grouped under "neither cough ⩾2 weeks nor a combination of other conventional TB symptoms" were as follows. Bangladesh 2015 [68] and Thailand 2012 [70]: presence of cough ⩾2 weeks, haemoptysis, any three symptoms (weight loss, cough <2 weeks, fever ⩾1 week, night sweats) or any one or two symptoms with chest radiography exempted; Gambia 2012 [69]: presence of cough ⩾2 weeks, cough <2 weeks with ⩾2 other symptoms or no cough with ⩾3 other TB symptoms (haemoptysis, weight loss, fever ⩾1 week, night sweats). Symptom definitions for countries that were grouped under "absence of any symptoms" were as follows. India 2019–2021 [71]: any of the following – persistent cough for ⩾2 weeks, fever for ⩾2 weeks, significant weight loss (loss of ⩾4.5 kg of the usual body weight over the past 6 months), presence of blood in sputum at any time during the last 6 months, chest pain in the previous month and history of TB treatment (past/current); Malawi 2013 [72]: any symptoms ⩾1 week (cough, sputum production, haemoptysis, chest pain, weight loss, night sweats, fatigue, fever, shortness of breath); South Africa 2017–2019 [73]: at least one of the symptoms – cough (persistent of any duration), drenching night sweats, unexplained weight loss and unexplained fever for at least 2 weeks; Tanzania 2012 [74]: cough ⩾2 weeks or haemoptysis or fever ⩾2 weeks or weight loss or excessive night sweats; and Zimbabwe 2014 [75]: cough of any duration, current night sweats, haemoptysis at any time in the past 12 months prior to study. ES: effect size. #: I^2 statistics and p-values were not available because of the small number of studies in the subgroup analysis (n⩽3).

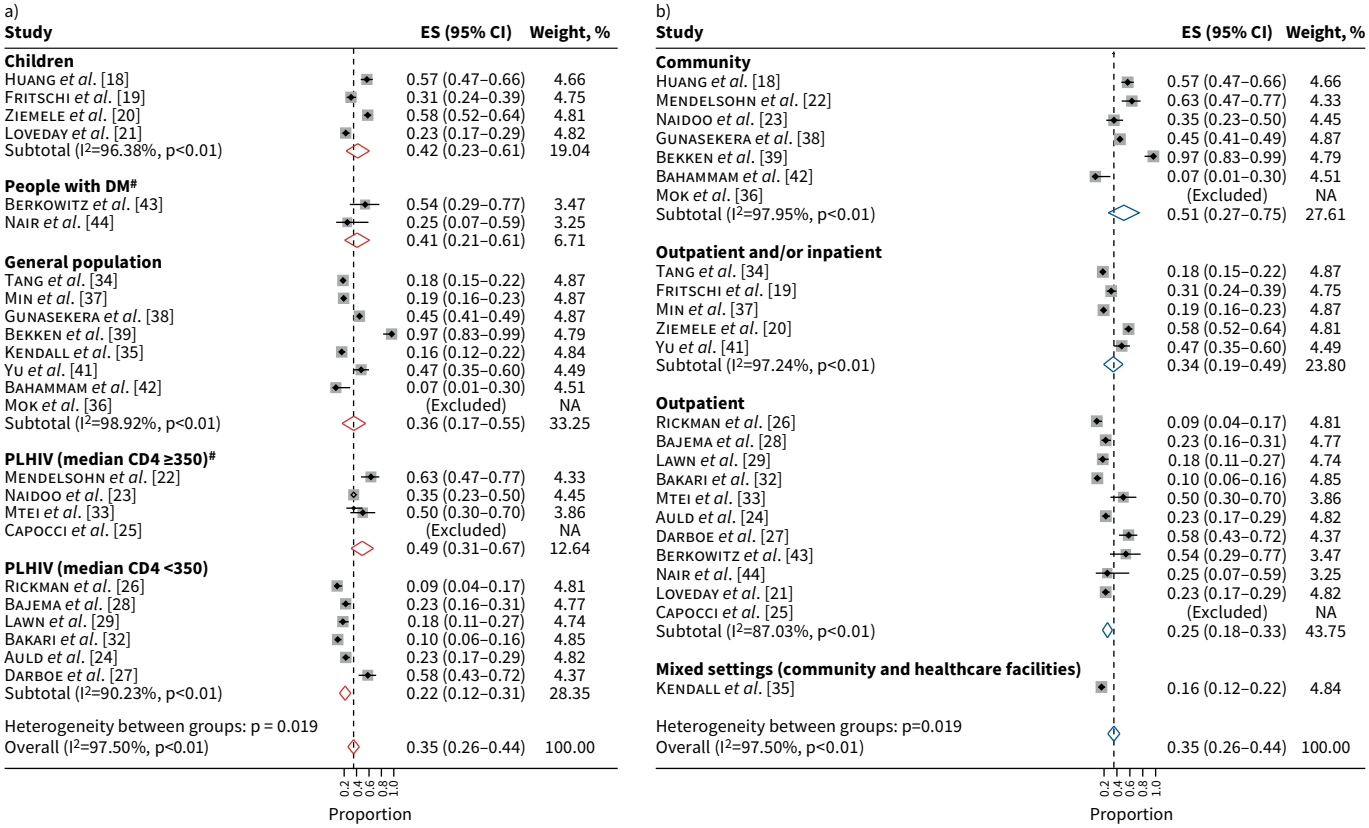

FIGURE 3 Proportions of people with tuberculosis (TB) that were subclinical by a) population groups and b) settings. We classified PLHIV by median CD4 count. If the overall CD4 count was not provided, a weighted average of the CD4 count by disease status (subclinical/clinical) was used. Outpatient and/or inpatient refers to data extracted from medical records, and we were not able to differentiate study participants by health service settings. Excluded estimates were omitted due to a small eligible sample size of fewer than five. *Post hoc* analysis that included these estimates are presented in the supplementary material. DM: diabetes mellitus; ES: effect size; PLHIV: people living with HIV; CD4: cluster of differentiation 4. #: I^2 statistics and p-values were not available because of the small number of studies in the subgroup analysis (n⩽3).

In the subgroup analysis by WHO TB burden classifications (supplementary material), the point estimate proportion of people with TB that was subclinical was higher among studies conducted in high-burden countries (40%, 95% CI 29–50%) compared to countries that were not in the high burden list (29%, 95% CI 8–50%) (although confidence intervals overlapped).

Among studies that did not define subclinical TB, the pooled estimates by TB burden, population and settings followed the same trajectory as those included in the main analyses (supplementary material). The variations in country, settings, subclinical TB definitions and screening and diagnostic modalities used are illustrated in table 2 and supplementary table 1.

Screening and diagnostic modalities used to diagnose TB disease

Symptom screening was the most frequently used initial step in TB screening algorithms (table 1). Chest radiography was utilised less frequently than symptom screening at the first stage. Among studies that compared the screening and diagnostic test outcomes between people with subclinical TB and clinical TB disease (table 2), those with clinical disease were more likely to test positive on NAAT or culture. Five studies reported a higher proportion of positive radiologic tests among those with clinical TB disease, of which two were statistically significantly different [18, 23, 37, 41, 76]. However, this review also identified two studies that described a higher proportion of chest radiographs suggestive of TB disease among people with subclinical TB relative to those with clinical disease [19, 75].

Specific chest radiography findings included a higher proportion of multilobar infiltrates among those with clinical TB disease [23, 76]. Two studies that examined the radiographic findings of chest computed tomography (CT) found higher proportions of multi-lobar involvement [37, 41], consolidation [37], and

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TABLE 2 Screening and diagnostic test outcomes among people with subclinical tuberculosis (TB) and clinical TB disease

First author [ref.], year	Country	Denominator (total number of people with)	Subclinical TB disease				Clinical/symptomatic active TB disease			
			Radiography+ (CXR unless indicated), n (%)	AFB smear+, n (%)	NAAT+, n (%)	Culture+, n (%)[#]	Radiography+ (CXR unless indicated), n (%)	AFB smear+, n (%)	NAAT+, n (%)	Culture+, n (%)[#]
Children ⩽15 years old (unless indicated otherwise)										
Huang [18], 2022	Peru	Symptom screen− and CXR+ (n=46), symptom screen+ and CXR+ (n=25)	Baseline: 17 (37)	NA	NA	NA	Baseline: 19 (76)	NA	NA	NA
Fritschi [19], 2022	Switzerland	Subclinical TB (n=43) and clinical TB (n=95)	41 (95.3)	NA	5 (11.6)[##] Culture or NAAT: 15 (34.9)[##] Culture and NAAT: 3 (7)[##]	13 (30.2)[##]	83 (89.2)	NA	44 (46.3)[##] Culture or NAAT: 65 (69.1)[##] Culture and NAAT: 39 (41.1)[##]	60 (63.8)[##]
People living with HIV										
Bajema [28], 2019	South Africa	Subclinical TB (n=28) and clinical TB (n=96)	NA	8 (29)	NA	NA	NA	13 (14)	NA	NA
Naidoo [23], 2022	South Africa	Subclinical (n=17) and clinical TB (n=31)	Lung infiltrates (one or bilateral): 3 (17.6)	NA	NA	NA	Lung infiltrates (one or bilateral): 12 (38.7)	NA	NA	NA
		Subclinical TB on treatment (n=11)	2 (18.2)	NA	NA	NA	Characteristics among those treated for TB were not described			
General population										
Min [37], 2020	Republic of Korea	Subclinical TB (n=81) and clinical TB (n=339)	CT multilobar involvement: 24 (95% CI 20.8– 40.3%)[¶,§]	11 (95% CI 7.5–15.2%)[¶,§]	36 (95% CI 35.5–57.1%)[§]	44 (95% CI 43.5–64.7%)[¶,§]	CT multilobar involvement: 144 (95% CI 38.3– 48.9%)[¶,§]	105 (95% CI 26.3–36.1%)[¶,§]	228 (95% CI 65.0–74.9%)[§]	245 (95% CI 67.3–76.8%)[¶,§]
Sengai [75], 2019	Zimbabwe	Subclinical TB (n=153) and clinical TB (n=510)	144 (94)	NA	NA	NA	473 (92.7)	NA	NA	NA
Yu [41], 2019	China	Subclinical TB (n=27) and clinical TB (n=30)	PET/CT[f] SUVmax >2: 19 (70.3)	NA	NA	NA	PET/CT[f] SUVmax >2: 30 (100.0)	NA	NA	NA
Detainees and incarcerated persons										
Boardman [76], 2021	USA	Subclinical TB (n=259) and clinical TB (n=68)	Cavitary lesions: 18 (6.9)[##] Multilobar: 73 (28.2)[§§]	33 (12.7)[##]	60 (29.7)[¶¶]	123 (48.6)	Cavitary lesions: 17 (25)[##] Multilobar: 33 (48.5)[§§]	31 (45.6)[##]	26 (48.1)[¶¶]	41 (62.1)

[#]: Liquid and/or solid culture media. [¶]: Reported as significantly different. [§]: Article presented numbers with the corresponding 95% confidence intervals of their proportion. [f]: The criterion for positive positron emission tomography (PET) was defined as maximum standardised uptake value (SUVmax) above 2. [##]: p<0.001. [¶¶]: p=0.01. [§§]: p=0.002. AFB: acid-fast bacilli; CT: computed tomography; CXR: chest radiography; NA: not available; NAAT: nucleic acid amplification test.

fibrotic scar [37] among those with the clinical disease compared to subclinical TB. The presence of cavitary lesions was significantly associated with clinical TB disease [76]. However, one study did not observe a difference in lung cavity occurrence between individuals with subclinical and clinical diseases [23].

One study reported that a significantly higher proportion of children with subclinical TB responded to heparin-binding hemagglutinin antigen-based IGRA than children with clinical disease [77]. This distinction, however, was not observed using QuantiFERON TB-Gold In-tube assay [77]. The prevalence of antibodies to 81 [88]-kDa malate synthase and MPT51 protein among people with TB-HIV co-infection was shown to be high regardless of clinical status [78].

Disease progression

Four studies on PLHIV (supplementary material) described that the time between subclinical TB diagnosis and symptoms onset could take up to 9 months [23, 29, 30, 31, 33]. One study reported that weight loss was the most common clinical feature of progression to clinical disease; [23] one-fifth of the cohort remained asymptomatic throughout the follow-up period, while 10% reported mild dry cough [23].

Treatment outcomes

People diagnosed with TB were treated using standard TB treatment regimens as recommended by global bodies in all studies. The proportion of people who achieved treatment success was comparable between people with subclinical TB and clinical TB disease (table 3). One study illustrated a significantly higher proportion of treatment success without recurrence among people with subclinical TB [37]. The death rate was higher among individuals with clinical TB as opposed to those with subclinical manifestations.

Discussion

This scoping review identified a range of definitions for subclinical TB, ranging from individuals with TB who were completely asymptomatic to those whose clinical symptoms were below a threshold. Scientific literature definitions of subclinical TB frequently imply the absence of any clinical symptoms. However, different symptom thresholds could influence the proportions of individuals with subclinical TB in keeping with published study [81]. In this review, data from prevalence surveys showed a range of thresholds for subclinical TB, ranging from the absence of cough, irrespective of other symptoms, absence of cough for $\geqslant$2 weeks with or without other symptoms, to the absence of any symptoms which resulted in varying prevalence of subclinical TB. The narrower definition of "asymptomatic" in research studies could explain the lower estimated proportion of subclinical TB found in this review compared to data from prevalence surveys conducted up to August 2019 (53% 95% CI 47–58%) [5] and August 2022 (53% 95% CI 47–59%). Nevertheless, there were other key contributing factors to the discrepancies, such as variability in study methodologies, symptom reporting and the screening and diagnostic tests used, which are discussed in the limitations section.

Symptoms screening, particularly the requirement for cough of at least 2 weeks, is widely used in the clinical assessment of people with presumptive TB [10]. However, symptoms are often self-reported and may introduce information bias as people with TB might not have recognised or reported them [81]. We found that in the published literature the requirement for the "presence of cough" as a criterion for further testing would have missed >50% of people with TB disease. This would lead to further transmission and adverse consequences of delayed diagnosis. Reducing the reliance on symptom-based screening for case-finding strategies should also be considered. To date, there is no universally accepted definition of subclinical TB [2, 5, 81]. Considering that the clinical symptoms of TB disease, if present, may vary, future work could focus on characterising this population to inform the definition of subclinical TB. How symptoms are perceived and reported by affected individuals should be systematically investigated. Symptom screening tools could be refined by integrating other variables, such as TB risk factors and quantifiable metrics, for example symptom severity score, into the screening algorithms. The possibility of leveraging digital technologies and artificial intelligence could be explored to improve efficiency and accuracy.

In the subgroup analyses by TB burden, the confidence intervals of subclinical TB overlapped between high- and low-burden countries. Groups investigated in studies from low-burden settings primarily originated from high-risk nations [19, 20, 25, 36, 37, 42], implying that screening algorithms for immigrants should be able to detect subclinical TB. Across the groups included in this review, the confidence interval range of subclinical TB was lower among severely immunocompromised populations (characterised by low CD4) than for those who were immunocompetent. Those with advanced HIV may manifest symptoms typical of TB and have a greater likelihood of being symptomatic (clinical TB disease) compared to people with HIV who have a high CD4 cell count [82]. It could also be difficult to discern if the symptoms that are present were attributable to TB or other infections related to immunosuppression.

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TABLE 3 Treatment outcomes

First author [ref.], year	Title	Country	Bacteriologically confirmed TB, clinician diagnosed, or both (TB disease)	Subclinical/asymptomatic TB disease				Clinical/symptomatic TB disease			
				People who initiated treatment/ evaluated, n	Treatment success[#], n (%)	Treatment failure/not evaluated, n (%)	Death, n (%)	People who initiated treatment/ evaluated, n	Treatment success[#], n (%)	Treatment failure/not evaluated, n (%)	Death, n (%)
People living with HIV											
Naidoo [23], 2022	Recurrent subclinical tuberculosis among ART accessing participants: incidence, clinical course, and outcomes	South Africa	Recurrent TB (bacteriologically confirmed)	11	8 (72.7)	3 (27.3)	0 (0)	29	18 (62.1)	8 (27.6)	3 (10.3)
Huerga [79], 2020	Systematic, point-of-care urine lipoarabinomannan (Alere TB-LAM) assay for diagnosing tuberculosis in severely immunocompromised HIV-positive ambulatory patients	Mozambique	Both	10	NA	NA	0 (0)	30	NA	NA	4 (13.3)
Bajema [28], 2019	Subclinical tuberculosis among adults with HIV: clinical features and outcomes in a South African cohort	South Africa	Bacteriologically confirmed	27	NA	NA	3 (11)	96	NA	NA	25 (26)
Worodria [80], 2011	Antiretroviral treatment-associated tuberculosis in a prospective cohort of HIV-infected patients starting ART	Uganda	Baseline (both) ART-associated TB (both)	2 3	2 (100) 1 (33.3)	0 (0) 2 (66.7)	0 (0) 0 (0)	4 5	2 (50) 4 (80)	1 (25) 0 (0)	1 (25) 1 (20)
Agizew [31], 2010	Tuberculosis in asymptomatic HIV-infected adults with abnormal chest radiographs screened for tuberculosis prevention	Botswana	Both	43	35 (81.4)	1 (2.3)	5 (11.6)	All participants were asymptomatic and only those with abnormal chest radiographs were included in the study			
General population											
Min [37], 2020	Clinical profiles of subclinical disease among pulmonary tuberculosis patients: a prospective cohort study in South Korea	Republic of Korea	Both Both (drug-sensitive TB) Both (drug-sensitive TB)	81 75 75	71 (87.7)[#] 67 (89.3)[#] 67 (89.3)[¶]	NA NA NA	1 (1.2) 1 (1.3)* NA	339 308 308	278 (82)[#] 252 (81.8)[#] 246 (79.9)[¶]	NA NA NA	26 (8.3) 26 (8.4)[+] NA
Sengai [75], 2019	Mobile targeted screening for tuberculosis in Zimbabwe: diagnosis, linkage to care and treatment outcomes	Zimbabwe	Both	153	100 (65)	5 (3)	7 (5)	510	297 (59)	21 (4)	16 (3)

[#]: Sum of cured and treatment completed. [¶]: Treatment success and no tuberculosis (TB) recurrence. [+]: p=0.031. ART: antiretroviral treatment; NA: not available..

So, to facilitate early TB diagnosis among people with HIV, the use of additional WHO-recommended tools [10] such as C-reactive protein, chest radiography and molecular-based sputum tests should be considered in tandem with the four-symptom screen. Additionally, the effectiveness of these tools should be further evaluated in the context of subclinical TB.

This review also highlighted the considerable variation in the prevalence estimates and their confidence limits of subclinical TB between settings. Similar to what was observed in prevalence surveys, community participants had higher estimated proportions with slightly overlapping confidence intervals of subclinical TB than those recruited from healthcare facilities. This is expected since the latter group would likely be presenting at the later stages of the disease [1]. Data from prevalence and tuberculin surveys in Vietnam and mathematical models have further underscored the potential contribution of people with bacteriologically confirmed subclinical TB to *M. tuberculosis* transmission [9, 83, 84]. Considering the potential infectiousness of this population, relying on passive case finding [7, 84] upon presentation at the health facilities or symptoms-based screening approaches could lead to further diagnostic delays, poorer prognosis and more severe post-TB sequelae. Community-wide screening [85], regardless of symptoms and other nonselective strategies based on TB symptoms, has demonstrated a significant reduction in TB transmission among children residing in the same household and, correspondingly, resulted in a reduction in TB incidence [85, 86]. This could be due to the proactive identification of prevalent cases, including the early detection of subclinical TB in the community and, therefore, could be further considered as an effective means to improve TB case detection.

This study has important policy implications. The WHO recommends systematic screening for TB disease using symptom-based tools, chest radiography or NAAT, alone or in combination [10]. Despite the lower sensitivity and specificity of symptom screening, it is often performed prior to employing more sensitive tests for TB case-finding due to the ease of implementation. However, gatekeeping the screening and testing algorithm based on symptoms will likely result in missing cases. Case detection among individuals with high bacterial load (characterised by positive smear, NAAT or culture), irrespective of symptoms, could avert between 62% and 78% of transmission [84].

Chest radiography has an important role in the detection of subclinical TB. It is the recommended tool for TB disease screening among the general population [10] and its incorporation could potentially optimise TB case-finding strategies. In general, chest radiography has been shown to detect 89% of bacteriologically confirmed cases [5], albeit the sensitivity may be lower in key populations, such as people living with HIV [87], those with a history of TB [88] and older adults [89, 90]. Nevertheless, chest radiographs can also be valuable for detecting other pulmonary and thoracic conditions besides TB. Furthermore, other chest radiologic abnormalities such as fibrotic lesions, commonly seen in people with previous TB, have been associated with an increased risk of TB disease development [91].

Although some studies have reported a higher proportion of chest radiographs suggestive of TB disease among subclinical TB cases compared to those with clinical disease, the radiological features varied among individuals with subclinical TB. Cavitary lesions, seen frequently in people with clinical TB, may not typically be observed among people with subclinical TB disease [20]. Characterising the radiographic features of people with subclinical TB disease could further optimise the use of these imaging tools for case-finding. The role of biomarkers in detecting subclinical TB was inconclusive, and more research is needed.

Studies included in the qualitative synthesis did not report differences in treatment outcomes between clinical and subclinical TB. In general, study participants reportedly received the same treatment regimens because treatments are not tailored to clinical status. Shorter treatment options have been shown to be a viable option for people with drug-sensitive pulmonary TB disease [92, 93]. A secondary analysis of patient-level pooled data found fluoroquinolone-based short regimens were noninferior to standard 6-month treatment [94–96] for people with lower bacterial load and noncavitary TB disease [97]. These are typical features of people with subclinical TB [23, 34], thereby suggesting that shortened treatment options could be beneficial for this population. Research to evaluate the effectiveness of shorter treatment regimens for subclinical TB is also warranted to reduce the burden for people with minimal early TB disease. Regarding the use of biomarkers to guide TB treatment, the assessments of radiographic, microbiological and other immunological biomarkers in identifying populations suitable for shorter treatment duration are underway (PredictTB) [98, 99]. Extension to and inclusion of people with subclinical TB in future studies should be considered in improving treatment options.

This review has significant limitations. Most importantly, significant heterogeneity was observed between the included studies. This finding may be explained by differences in the true prevalence of TB between

populations, differing diagnostic algorithms and variable definitions of subclinical TB and symptoms. To assess the risk of bias contributing to this heterogeneity, we evaluated study quality for all included studies. The decision to pool the results across studies was based on our assessment that the characteristics of included populations were sufficiently similar to allow pooling. On account of the observed heterogeneity, our summary estimates need to be interpreted with caution. Identified studies that only presented the number of asymptomatic cases (*i.e.* without providing a definition of subclinical TB) may only represent a small fraction of the breadth and scope of TB literature where the occurrence of TB symptoms is commonly reported. Applying a requirement for a stated definition of subclinical TB ensured that the outcome classification in pooled studies was accurate. Therefore, we decided to exclude studies without a stated definition from the primary analyses and presented them in the supplementary material for reference.

Few studies provided a clear definition of subclinical TB, possibly due to a limited comprehension of this disease state and a lack of consensus on its definition. This ambiguity is also apparent in some literature, where the subclinical state has been treated more as an infection rather than an active disease. The reporting of symptoms can be influenced by various factors, including the person reporting, the location of reporting and the timing of the inquiry. Misclassification may arise based on differences in perception, interpretation or willingness to disclose symptoms, leading to potential inaccuracies in the data.

Variability in definitions across prevalence surveys and published studies could contribute to discrepancies in the classification of subclinical TB cases, as shown in this review. The pooled prevalence estimates included in this review solely reflect subclinical TB disease when it is defined as asymptomatic; they are not reflective of subclinical TB defined by using other symptom thresholds (*e.g.* absence of cough only).

The variability in screening and diagnostic algorithms used in the studies may have missed TB cases, particularly early TB disease with low bacillary load, resulting in a potential under-detection of those with a subclinical phenotype of the disease [100]. Other possible factors affecting the sensitivity of NAAT or smear microscopy used to ascertain TB diagnoses in the studies, such as sputum volume and quality, sample collection methods, and other quality assurance measures, were not reported [101, 102]. There is a small number of studies comparing clinical and subclinical TB. Hence, diagnostic test performance and outcome measures may not be representative of the full range of observed measures.

Conclusion

This scoping review found that the definitions of subclinical TB based on symptoms influence its prevalence. The proportion of people with subclinical TB varies considerably among different population groups and settings. Most studies have not comprehensively described the phenotype and bacteriological status of individuals with subclinical TB. This is mainly due to a lack of clear and consistent diagnostic criteria, as well as differences in the methods used to identify and measure the condition, resulting in highly variable prevalence between different settings. A standardised approach to characterise this phenotype and apply it prospectively in future epidemiological studies is needed. Furthermore, research to optimise case finding, screening and diagnostic modalities, and treatment options for subclinical TB is also warranted for timely diagnosis and treatment.

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