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SYSTEMATIC REVIEW

Strategies to detect and manage latent tuberculosis infection among household contacts of pulmonary TB patients in high TB burden countries - a systematic review and meta-analysis

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Abstract

Objective: To summarise latent tuberculosis infection (LTBI) management strategies among household contacts of bacteriologically confirmed pulmonary tuberculosis (TB) patients in high-TB burden countries.

Methods: PubMed/MEDLINE (NCBI) and Scopus were searched (January 2006 to December 2021) for studies reporting primary data on LTBI management. Study selection, data management and data synthesis were protocol-driven (PROSPERO-CRD42021208715). Primary outcomes were the proportions of LTBI, initiating and completing tuberculosis preventive treatment (TPT). Reported factors influencing the LTBI care cascade were qualitatively synthesised.

Results: From 3694 unique records retrieved, 58 studies from 23 countries were included. Most identified contacts were screened (median 99%, interquartile range [IQR] 82%–100%; 46 studies). Random-effects meta-analysis yielded pooled proportions for: LTBI 41% (95% confidence interval [CI] 33%–49%; 21,566 tested contacts); TPT initiation 91% (95% CI 79%–97%; 129,573 eligible contacts, 34 studies); TPT completion 65% (95% CI 54%–74%; 108,679 TPT-initiated contacts, 28 studies). Heterogeneity was significant ($I^2 \geq 95\%$–100%) and could not be explained in subgroup analyses. Median proportions (IQR) were: LTBI 44% (28%–59%); TPT initiation 86% (60%–100%); TPT completion 68% (44%–82%). Nine broad themes related to diagnostic testing, health system structure and functions, risk perception, documentation and adherence were considered likely to influence the LTBI care cascade.

Conclusion: The proportions of household contacts screened, detected with LTBI and initiated on TPT, though variable was high, but the proportions completing TPT were lower indicating current strategies used for LTBI management in high TB burden countries are not sufficient.

KEYWORDS
diagnosis, high TB burden settings, household contacts, isoniazid preventive therapy, latent TB infection, screening, TB preventive therapy, treatment, tuberculosis

Sustainable Development Goal: Good Health and Wellbeing.

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INTRODUCTION

Tuberculosis (TB) is a major public health problem and a leading cause of death worldwide. Over 10 million people are estimated to have developed TB in 2020; the majority were from 30 high TB burden, resource-constrained, low- and middle-income countries (LMICs) [1]. In 2014, the World Health Assembly adopted World Health Organisation's (WHO) End TB Strategy which aims to eliminate the global TB epidemic by the year 2035 [2].

Latent tuberculosis infection (LTBI) is a condition of persistent immune response to infection by *Mycobacterium tuberculosis* (M.tb) in people with no evidence of active TB disease [3, 4]. It is estimated that approximately 1.7 billion individuals (nearly a quarter of the global population) were infected with LTBI in 2014, with a 5%–10% lifetime risk of developing active TB; and that over 50% of the household contacts of smear-positive index TB patients in LMICs have LTBI [5, 6]. Hence, WHO recommends that those with LTBI should be treated with tuberculosis preventive therapy (TPT) to realise the goals of the End TB Strategy [7].

Contact investigation is an essential component of the WHO's TB management algorithms to detect those with LTBI among high-risk groups, and to initiate TPT [4, 7, 8]. WHO guidelines recommend home visits as the preferred mode of contact investigation; however, when home visits are not possible, contact investigation at a health facility is recommended. In either case, WHO advocates that trained staff should elicit the required information from the index TB patients [8] and counsel patients and their family members on the importance of LTBI testing, TPT initiation and completion [4, 7, 8]. WHO recommends the tuberculin skin test (TST) or interferon-gamma release assays (IGRA) to detect LTBI [8]. TST is a reasonably low-cost tool; however, its production is limited. IGRA results in fewer false-positive results than with TST, but has higher cost and supply chain issues that challenge its routine induction in national TB programmes in LMICs [8].

The options for TPT currently recommended by WHO for adults and children with LTBI, regardless of human immunodeficiency virus (HIV) status, include: (1) isoniazid monotherapy daily for 6 or 9 months, (2) rifampicin plus isoniazid daily for 3 months, (3) rifapentine plus isoniazid weekly for 3 months, (4) a 1-month daily regimen of rifapentine or isoniazid, or (5) 4 months of daily rifampicin [8]. As per the recommendations, child contacts under 5 years of age can be provided with TPT irrespective of their LTBI status after excluding TB [4, 7, 8].

The first-ever United Nations high-level meeting (UNHLM) declaration in 2018 envisaged the rapid scale-up of access to LTBI testing and provision of TPT, with a special focus on high TB burden countries, so that at least 30 million people receive TPT by 2022 [9]. In many low-burden, high-income countries, systematic LTBI management has contributed to lower rates of active TB. However, in high TB burden LMICs, this is challenging as it requires the diversion of resources from treating people with active TB.

An ideal cascade of care for TPT starts with identifying the eligible population, screening for and excluding active TB, diagnosing LTBI, initiating TPT and ensuring TPT completion. Multiple factors operating at every step of the cascade affect the implementation of TPT. For instance, limited finance and manpower, low rates of contact screening and treatment initiation, inadequate documentation of cascade components and so on are some of the factors that adversely affect TPT implementation in LMICs with a high TB burden [3, 10–13].

Synthesising evidence on implementation strategies and factors that affect TPT in high TB burden settings is imperative to inform attempts to achieve the global targets for managing LTBI. A recent systematic review and meta-analysis found that contact investigation was effective in high-burden settings [14]. Another mixed-methods systematic review discussed the child contact losses that occur through the care cascade, along with the variations in the screening, initiation and completion of isoniazid preventive therapy among child contacts [15]. However, strategies used for child contact management were not described. While these reviews provide information on the prevalence of LTBI and the risk of incident TB, information on effective implementation strategies for the care cascade remains unclear.

This systematic review aimed to summarise the strategies used in high TB burden countries for screening and determining the eligibility for TPT among the household contacts of bacteriologically confirmed pulmonary TB patients, and to evaluate the outcomes of these strategies with respect to TPT initiation and completion. We also sought to ascertain the factors influencing these strategies and outcomes.

METHODS

This review followed the methods described in the Preferred Reporting Items for a Systematic Review and Meta-analysis (PRISMA) 2020 statement [16] and was based on a protocol registered on the International Prospective Register of Systematic Reviews (PROSPERO ID # CRD42021208715).

Search strategy and eligibility criteria

We searched PubMed/MEDLINE (NCBI) and SCOPUS (Elsevier) for primary studies published between 1 January 2006 and 31 December 2021 describing the strategies for implementing TPT among household contacts of pulmonary TB patients in high-burden countries that reported data on aspects of the TPT care cascade. The initial search did not yield studies in child contacts; therefore, to ensure that all age groups were covered, the search strategy was rerun with additional keywords (child contacts) and the new output

was reviewed for inclusion (Table S1). We included studies published in English that reported data on strategies used in screening household contacts of bacteriologically confirmed pulmonary TB patients for LTBI. The operational definitions we used are provided in Table S2. The permitted study designs included randomised/non-randomised controlled trials (RCTs/non-RCTs), prospective and retrospective cohort studies, cross-sectional studies, longitudinal studies, cost-effectiveness studies and studies with mixed designs. Studies without usable numerical data for any component of the TPT care cascade, as well as those conducted primarily in clinically vulnerable and immunocompromised groups, qualitative studies, and studies published in languages other than English, were excluded.

Selection of studies and data management process

The search results were exported to the web-application Rayyan (https://www.rayyan.ai/). Three review authors (KS, KDS and MM) independently screened titles and abstracts for eligibility and selected studies. Full texts were evaluated, or study authors were contacted, for additional information to determine eligibility, and disagreements were resolved through discussion. A fourth author (PT) independently checked the appropriateness of study selection.

We used a data extraction form that had been pretested by two review authors (KS and KSS). Data were extracted independently by three review authors (KS, MM and KSS) and were checked by a fourth author (PT). From each study, we extracted data regarding the target population, sample size, age of household contacts, setting, study design, screening strategies, tests used, and the proportions with positive test results, proportions initiating and completing TPT among those eligible, loss-to-follow-up, adverse events and treatment failures (incident TB while on TPT). We listed the factors that were reported by study authors as influencing the TPT care cascade. We contacted study authors for clarifications and for missing data. Since different study designs that assessed different aspects of the TPT care cascade were used, a formal risk of bias assessment was not possible, but deficiencies in reporting relevant data were recorded.

Data synthesis and statistical analysis

Extracted data regarding the characteristics of the included studies were analysed using descriptive statistics with Microsoft Excel. The primary outcomes of interest were the proportions of household contacts who were screened and tested for LTBI, and who initiated and completed TPT. We conducted meta-analyses using the metafor package for the statistical software environment R (https://www.metafor-project.org/doku.php) and generated forest plots of the pooled estimates with 95% confidence intervals (CIs) for the proportions with LTBI (positive either by TST or IGRA or both as defined by study authors), and for the proportions initiating TPT among those eligible, and completing TPT. We anticipated that studies estimating LTBI positivity conducted in different regions of the world over several decades, and using different screening and diagnostic tests, algorithms and treatment protocols would result in substantial heterogeneity, and used the random-effects model in meta-analyses. We quantified heterogeneity using the I^2 statistic with a value more than 50% to denote significant inconsistency in the estimates. This indicates that more than half of the total heterogeneity stems from between-study variance that could not be explained by sampling error. We also reported Tau^2 (τ^2) with a value more than zero denoting the absolute value of the true variance (heterogeneity); higher values of τ^2 indicate greater heterogeneity.

We explored potential causes for significant heterogeneity in LTBI estimates in the following subgroup analyses: (1) the tests used to diagnose LTBI (TST, IGRA, combination); (2) the place of testing (hospital or health facility, household, both); and (3) the study design used (prospective, cross-sectional or retrospective). We separately analysed the LTBI positivity in studies done in Africa, Asia and South America, sub-grouped by countries within geographical regions within these continents. We also explored LTBI positivity in studies using TST alone sub-grouped by the place of testing, and by the size of the skin induration used to denote a positive TST result (≥5 mm; ≥10 mm). Regarding the proportions initiating and completing TPT, we explored heterogeneity in subgroup analysis of studies including children aged <6 years; <18 years; all age groups. We also reported the range and the median and interquartile range (IQR) of these proportions for the overall pooled results and in the subgroups. Factors reported in the studies that were considered by study authors to have influenced the TPT care cascade outcomes were extracted and grouped under common categories.

RESULTS

Search results

The search yielded 3694 unique records after duplicates were removed. Figure 1 depicts the flow of the search and selection process.

After screening the title and abstracts, 3584 records not relevant to this review were excluded (Figure 1). The full texts of 110 potentially eligible studies were assessed, and 52 studies were excluded because disaggregated data for household and non-household contacts were not available ($n = 29$); or the study designs were inappropriate ($n = 9$); or there were insufficient data regarding components of the TPT cascade ($n = 11$). We included 58 studies that satisfied eligibility criteria in qualitative and quantitative synthesis (meta-analysis).

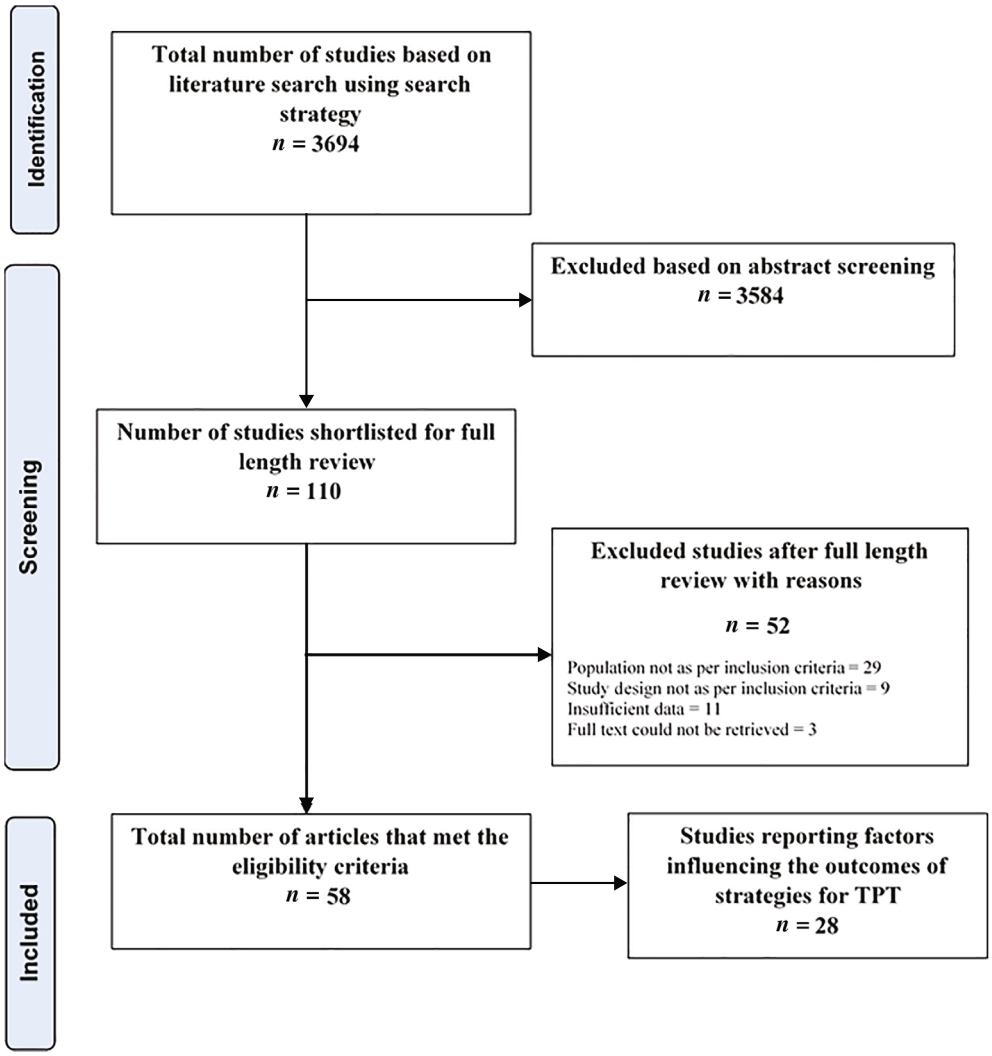

FIGURE 1 Flow diagram for study selection. TPT, tuberculosis preventive treatment

Study characteristics

Table 1 summarises the characteristics of the 58 studies conducted in 23 LMICs that were included in this review. Twenty-eight studies (48%) were conducted in Africa (12 from countries in East Africa, 7 from West Africa and 9 in Southern Africa). Twenty-five studies (43%) were conducted in Asia, of which 17 were conducted in countries in South Asia (with 15 from India); 5 in South East Asia and 3 in East Asia. Three studies were done in South America (all from Brazil). Two were multi-country cost-effectiveness studies (one included countries in Central and West Africa and the other included centres in Asian and African countries). The majority of the studies (45/58, 78%) were published between 2011 and 2020, while six were published before 2010 (2006–2009), and seven were published in 2021. The study designs included prospective cohorts [$n = 28$], prospectively ascertained programme datasets [$n = 6$], RCTs [$n = 2$], cross-sectional studies [$n = 19$], retrospective cohorts [$n = 1$] and mixed designs [$n = 2$].

In 27 (46%) of the studies, the target population was children, with only children <6 years of age included in 25 (43%). Children and adolescents were the target population in 12 (21%), only adult contacts in 1 (2%), only adolescents and adults in 1 (2%) and contacts of all ages in 17 (29%) of the studies. Household screening strategies were used in 19 (33%), and facility-based screening was used in 35 (60%) of the studies. Three studies used both approaches, and the approach was unclear in one.

Thirty-six (62%) of the studies reported data on screening and LTBI diagnosis, of which 14 also reported on TPT initiation/completion. Thirty-four (59%) reported on components of TPT initiation/completion, of which 20 did not report data for LTBI diagnosis. Twenty-eight studies (48%) provided information on the factors that may have affected the outcomes of the TPT cascade.

Components of the TPT care cascade

The implementation of the recommended sequence of steps that formed the strategy used to implement TPT among household contacts varied in the 58 studies from the high TB burden, LMIC countries included in the review.

TABLE 1 Characteristics of the included studies

No.	Study ID	Geographic region	TB incidence/100,000 people[a]	Target population	Household contacts screened among those identified (%)	Place/setting	Study design	Screening	Diagnostic test(s)	TPT initiated/ completed
1.	Bonnet_Uganda_2017 [17]	East Africa	196	Children <5 years	281/339 (82.9)	HC/urban	Prospective cohort	V + CXR	TST	Both
2.	Chandrasekaran_India_2018 [18]	South Asia	188	Adults + children	1048/NR	HC/NR	Prospective cohort	CXR	TST + IGRA	NR
3.	Machado_Brazil_2009 [19]	South America	45	Adults + children	261/301 (86.7)	HC/NR	Prospective cohort	NR	TST	Both
4.	MacPherson_South Africa_2020 [20]	Southern Africa	554	Adults + children	2725/2985 (91.3)	HH/NR	RCT	V + CXR	TST	NR
5.	Odera_Kenya_2020 [21]	East Africa	259	Adults ≥18 years	175/NR	HC/semi-urban	Cross-sectional	NR	IGRA	NR
6.	Praveen_India_2020 [22]	South Asia	188	Adults + children ≥12 years	220/NR	HH/NR	Cross-sectional	V	TST	NR
7.	Ronge South Africa_2021 [23]	Southern Africa	554	Children ≤15 years	669/669 (100)	HH/urban	Cross-sectional	CXR	IGRA	NR
8.	Rutherford_Indonesia_2012 [24]	South East Asia	301	Children 6 months to 9 years	320/320 (100)	HC/urban	Prospective cohort	V	TST + IGRA	NR
9.	Shah_South Africa_2011 [25]	Southern Africa	554	Children 6–16 years	270/270 (100)	HH + HC/NR	Prospective cohort	NR	TST + IGRA	NR
10.	Sharma_India_2017 [26]	South Asia	188	Adults + children 1–65 years	1511/1511 (100)	HH/NR	Prospective cohort	V + CXR	TST + IGRA	NR
11.	Stein_Uganda_2018 [27]	East Africa	196	Adults + children	2585/3102 (83.3)	HH/NR	Prospective cohort	V	TST	NR
12.	Zhang_China_2019 [28]	East Asia	59	Adults + adolescents >14 years	196/196 (100)	HC/NR	Prospective cohort	V + CXR	IGRA	NR
13.	Akhtar_Pakistan_2009 [29]	South Asia	259	Adults + ≥3 months	385/385 (100)	HH/rural	Cross-sectional	V	TST	NR
14.	Hu_China_2013 [30]	East Asia	59	Children + adolescents 9–18 years	1120/1136 (98.6)	School/urban	Cross-sectional	V + CXR	IGRA	NR
15.	Araujo_Brazil_2020 [31]	South America	554	Adults + children	394/NR	HC/urban	Retrospective cohort	V	TST	Both
16.	Maraise_South Africa_2006 [32]	Southern Africa	554	Children <5 years	260/274 (94.9)	HC/urban	Prospective cohort	CXR	TST	Both
17.	Nakaoka_Nigeria_2006 [33]	West Africa	219	Children <15 years	161/161 (100)	HH/urban	Cross-sectional	V	TST + IGRA	NR
18.	Oxlade_Multicentric_2021 [34][b]	South East Asia (Indonesia, Vietnam), West Africa (Ghana)	Indonesia = 301, Viet Nam = 176, Ghana = 143	Children <5 years	1619/1619 (100)	HC/rural + urban	RCT	V + CXR	TST	Initiated

(Continues)

TABLE 1 (Continued)

No.	Study ID	Geographic region	TB incidence/100,000 people[a]	Target population	Household contacts screened among those identified (%)	Place/setting	Study design	Screening	Diagnostic test(s)	TPT initiated/ completed
19.	Sun_China_2021 [35]	East Asia	59	Children + adolescents ≤18 years	95/95 (100)	HC/rural + urban	Prospective cohort	V	TST + IGRA	NR
20.	Triasih_Indonesia_2016 [36]	South East Asia	301	Children ≤15 years	269/413 (65.1)	HC/NR	Prospective cohort	V + CXR	TST	Both
21.	Adjobimey_Benin_2016 [37]	West Africa	55	Children <5 years	497/499 (99.6)	HC/urban	Prospective cohort	V	ND	Both
22.	Amisi_Kenya_2021 [38]	East Africa	259	Children <5 years	553/NR	HC/rural + urban	Programme data	V + CXR	ND	Both
23.	Silva_Brazil_2016 [39]	South America	45	Children ≤15 years	1078/NR	HC/NR	Cross-sectional	CXR	TST	Both
24.	Burmen_Kenya_2014 [40]	East Africa	259	Children <5 years	337/345 (97.7)	NR/rural + urban	Programme data	V	ND	Initiated
25.	Garie_Ethiopia_2011 [41]	East Africa	132	Children <15 years	184/184 (100)	HC/urban	Prospective cohort	V	TST	Both
26.	Ginderdeuren_South Africa_2021 [42]	Southern Africa	554	Children <15 years	77/170 (45.1)	HC/urban	Prospective cohort	V	ND	Both
27.	Krishnamoorthy_India_2021 [43]	South Asia	188	Adults + children	1523/NR	HC/NR	Prospective cohort	V + CXR	TST	NR
28.	Narasimhan_India_2017 [44]	South Asia	188	Adults + children	359/491 (73.1)	HH/NR	Prospective cohort	V	TST + IGRA	NR
29.	Paradkar_India_2020 [45]	South Asia	188	Adults + children ≥1 year	997/1009 (98.8)	HH + HC/NR	Prospective cohort	V	TST + IGRA	NR
30.	Okwara_Kenya_2017 [46]	East Africa	259	Children <5	428/428 (100)	HC/rural	Prospective cohort	V	TST	Both
31.	Paul_Nigeria_2019 [47]	West Africa	219	Children ≤5 years	63/NR	HC/NR	Prospective cohort	V + CXR	TST	Both
32.	Rekha_India_2009 [13]	South Asia	188	Children ≤14 years	31/220 (14.1)	HC/rural + urban	Cross-sectional	V	NR	Both
33.	Rutherford _Indonesia_2012 [48]	South East Asia	301	Children <5 years	150/150 (100)	HC/NR	Prospective cohort	V	TST + IGRA	Both
34.	Sulis_Burkina Faso_2018 [49]	West Africa	46	Children <5 years	956/1166 (82.0)	HH/ rural + urban	Programme data	V	ND	Initiated
35.	Pothukuchi _India_2011 [10]	South Asia	188	Children <6 years	116/172 (67.4)	HH/ rural + urban	Cross-sectional	V	ND	Both
36.	Rekha_India_2013 [50]	South Asia	188	Children <6 years	53/87 (60.9)	HH/ rural + urban	Prospective cohort	U	ND	Both
37.	Shivaramakrishna_India_2014 [51]	South Asia	188	Children <6 years	218/271 (80.4)	HH/rural	Cross-sectional	U	ND	Both

(Continues)

TABLE 1 (Continued)

No.	Study ID	Geographic region	TB incidence/100,000 people[a]	Target population	Household contacts screened among those identified (%)	Place/setting	Study design	Screening	Diagnostic test(s)	TPT initiated/ completed
38.	Seid_Ethiopia_2020 [52]	East Africa	132	Children <5 years	125/129 (96.9)	HC/urban	Mixed methods	U	ND	Both
39.	Singh_India_2017 [12]	South Asia	188	Children <5 years	51/59 (86.4)	HH/rural	Mixed methods	U	ND	Both
40.	Tadesse_Ethiopia_2016 [53]	East Africa	132	Children <5 years	237/282 (84.0)	HC/NR	Programme data	U	ND	Both
41.	Belgaumkar_India_2018 [11]	South Asia	188	Children <6 years	53/178 (29.8)	HC/NR	Cross-sectional	U	ND	Both
42.	Birungi_Rwanda _2019 [54]	East Africa	58	Children <5 years	94/94 (100)	HC/NR	Prospective cohort	V + CXR	ND	Both
43.	Black_South Africa_2018 [55]	Southern Africa	554	Children <5 years	184/261 (70.5)	HC/NR	Cross-sectional	V + CXR	TST	Both
44.	Chauhan_India_2013 [56]	South Asia	188	Children <5 years	253/NR	HC/NR	Prospective cohort	V + CXR	TST	NR
45.	Datiko_Ethiopia_2017 [57]	East Africa	132	Adults + Children	24,267/24,267 (100)	HC/rural	Prospective cohort	V + CXR	ND	Both
46.	Egere_Gambia_2016 [58]	West Africa	157	Children <5 years	404/404 (100)	HH/ rural + urban	Prospective cohort	V	TST	Both
47.	Wysocki_Brazil_2016 [59]	South America	554	Adults + children	267/326 (81.9)	HC/urban	Cross-sectional	V	TST	Both
48.	Fentahun_Ethiopia_2020 [60]	East Africa	132	Children <5 years	149/230 (64.8)	HC/urban	Cross-sectional	V	ND	Initiated
49.	Faksri_Thailand_2015 [61]	South East Asia	150	Adults + children	100/100 (100)	HC/NR	Cross-sectional	V	TST + IGRA	NR
50.	Sayedi_Afghanistan_2020 [62]	South Asia	193	Adults + Children	586,292/856,782 (68.4)	HH/urban	Programme data	V	ND	Both
51.	Schwoebel_Multicentric_2020 [63]	Central Africa (Bangui, Cameroon), West Africa (Benin, Burkina Faso)	815	Children <5 years	1965/1965 (100)	HH/urban	Prospective cohort	V + CXR	TST	Both
52.	Sharma_India_2021 [64]	South Asia	188	Children <5 years	86/NR	HH/urban	Prospective cohort	V	ND	Both
53.	Soelen_South Africa_2012 [65]	Southern Africa	554	Children <5 years	39/NR	HC/urban	Programme data	NR	ND	Initiated
54.	Gomes_Guinea-Bissau_2011 [66]	West Africa	361	Children <15 years	1895/1904 (99.5)	HH/urban	Prospective cohort	V	TST	Both

(Continues)

TABLE 1 (Continued)

No.	Study ID	Geographic region	TB incidence/100,000 people[a]	Target population	Household contacts screened among those identified (%)	Place/setting	Study design	Screening	Diagnostic test(s)	TPT initiated/ completed
55.	Hector_Malawi_2017 [67]	Southern Africa	141	Children <15 years	56/56 (100)	HC/urban	Cross-sectional	V	TST	NR
56.	Mensah_Ghana_2017 [68]	West Africa	143	Adults + children ≥6 months	112/112 (100)	HC/urban	Cross-sectional	NR	IGRA	NR
57.	Nguyen_Laos_2009 [69]	South East Asia	149	Adults + children	148/148 (100)	HH/urban	Cross-sectional	NR	TST	NR
58.	Mzembe_South Africa_2020 [70]	Southern Africa	554	Children + adolescents 10–19 years	1809/NR	HH + HC/rural	Cross-sectional	NR	IGRA	NR

Abbreviations: CXR, only chest x-ray; HC, health centre; HH, house-to-house; IGRA, interferon-gamma release assay; ND, not done; NR, not reported; RCT, randomised controlled trial; TB, tuberculosis; TST, tuberculin skin test; U, unclear; V, only verbal screening; V + CXR, verbal screening + chest x-ray.

[a]TB Incidence: The World Bank Data, 2020, https://data.worldbank.org/indicator/SH.TBS.INCD?locations=BJ.

[b]Data only for children <5 years from the low- and middle-income countries evaluated.

Screening strategies

Twelve (21%) of the 58 included studies did not report the proportion of household contacts screened among those identified as contacts. In the 46 (79%) studies that provided these data, the proportion of household contacts screened among those identified ranged from 14% to 100% (Table 1). Thirty-six studies (78%) screened >80% of identified contacts, 27 (59%) screened ≥95% and 20 (44%) screened 100% of the identified contacts. Only three studies (7%) reported screening <50% of the identified contacts. The median proportion of eligible contacts screened across the studies was 99% (IQR 82%–100%). Of the 45 studies that reported on the method used to screen out active TB, only verbal screening for symptoms was used in 26 (58%) studies and chest x-rays were used in 19 (42%) of the studies (Table 1).

Diagnosis of LTBI

Of the 58 studies, 22 (38%) did not test for TB; most of them included children under 5–6 years of age where LTBI testing was not required to initiate TPT (Table 2). Of the 36 studies that tested for LTBI, 21 (58%) used only TST, with 17 requiring a skin induration size of ≥10 mm to denote a positive TST result, while an induration size of ≥5 mm was used in the remainder. Four studies (11%) used only IGRA, while 11 (31%) used both TST and IGRA to aid diagnosis. In the studies where both tests were used, we reported the proportions diagnosed as having LTBI based on the study authors' definitions. If this was not reported, we used the IGRA results to denote LTBI positivity (Table 2).

Estimates of LTBI positivity among household contacts

Estimates of the proportions with LTBI among the 21,566 household contacts from 36 studies are presented in the forest plot in Figure 2, sub-grouped by studies that used TST alone or IGRA alone or a combination of the two to diagnose LTBI.

The pooled random-effects estimate for LTBI positivity in the 36 studies was 41% (95% CI 33%–49%); however, there was significant heterogeneity in these estimates that far exceeded what could be accounted for by chance ($I^2 = 99\%$; $\tau^2 = 1.0$; $p = 0$). The proportions diagnosed with LTBI varied considerably among the studies and ranged from 5% to 81%. In 15/36 studies (42%; TST 9, IGRA 1, both 5), the upper and lower bounds of the 95% CI for the LTBI positivity estimates did not overlap with the 95% CI of the pooled estimates for the proportions with LTBI in the sample (Figure 1). The median LTBI positivity estimate across the studies was 44%, with an IQR of 28%–59% (Table 3).

TABLE 2 Diagnosis of LTBI among household contacts

No.	Study_ID	Eligible household contacts	Number tested (%)	Test used (TST/IGRA)	TST positive, *n* (%)	IGRA positive, *n* (%)	TST + IGRA positive, *n* (%)	LTBI diagnosed (%, 95% CI)	Testing personnel
1.	Bonnet_Uganda_2017 [17]	281	278 (98.9)	TST	144 (51.8)[a]	NA	NA	111 (39.9, 34.4–45.8)	Doctor
2.	Chandrasekaran_India_2018 [18]	869	869 (100)	Both	478 (55)[a]	468(53.9)	300 (34.5)	646[b] (74.3, 71.3–77.1)	Trained lab staff
3.	Machado_Brazil_2009 [19]	301	261 (86.4)	TST	145 (55.6)[c]	NA	NA	145 (49.5–61.5)	Trained nursing and lab staff
4.	MacPherson_South Africa_2020 [20]	2725	2725 (100)	TST	458 (16.8)[a]	ND	ND	458 (16.8, 15.5–18.3)	Nurse
5.	Odera_Kenya_2020 [21]	175	174 (99.4)	IGRA	NA	97 (55.6)	NA	97 (55.6, 48.3–62.9)	NR
6.	Praveen_India_2020 [22]	220	220 (100)	TST	96 (43.6)[c]	NA	NA	96 (43.6, 37.3–50.2)	Trained staff
7.	Ronge_South Africa_2021 [23]	669	669 (100)	Both	302 (45.1)[c]	500 (74.7)	NA	500 (74.7, 71.3–77.9)	Nurse
8.	Rutherford_Indonesia_2012 [24]	304	302 (99.3)	Both	145 (48)[c]	152 (50.8)	180 (59.2)	180 (59.2, 54.6–64.6)	Project staff
9.	Shah_South Africa_2011 [25]	270	270 (IGRA) (100) 263 (TST) (97.4)	Both	71/254 (28)[a]	79 (29) QFT	NR	71/254 (28.0, 23.0–34.0) QFT 79/270 (29.3, 24.0–35.0)	Project staff
10.	Sharma_India_2017 [26]	1511	1511 (100)	Both	732 (48.4)[c]	917 (60.7)	540 (35.7)	917 (60.7, 58.2–63.1)	Trained staff
11.	Stein_Uganda_2018 [27]	2585	2562 (99.1)	TST	1683 (65.7)[c]	NA	NA	1683 (65.7, 63.8–67.5)	NR
12.	Zhang_China_2019 [28]	159	159 (100)	Both	72 (45.3)[c]	75 (47.2)	NR	75 (47.2, 39.6–55.0)	Trained staff
13.	Akhtar_Pakistan_2009 [29]	385	359 (93.3)	TST	179 (49.9)[c]	NA	NA	179 (49.9, 44.7–55.0)	Project staff
14.	Hu_China_2013 [30]	1120	1106 (98.8)	IGRA	NA	52 (4.7)	NA	52 (4.7, 3.6–6.1)	Trained staff
15.	Araujo_Brazil_2020 [31]	475	435 (91.6)	TST	351 (80.7)[a]	NA	NA	351 (80.7, 76.7–84.1)	NR
16.	Maraise_South Africa_2006 [32]	260	243 (93.5)	TST	122 (50.2)[c]	NA	NA	122 (50.2, 44.0–56.4)	NR
17.	Nakaoka_Nigeria_2006 [33]	161	TST 161 (100) IGRA 145 (90.1)	Both	51 (31.9)[c]	61 (42.1)	NA	61 (42.1, 34.3–50.2)	Trained staff
18.	Sun_China_2021 [35]	95	95 (100)	Both	17 (17.9)[c]	5 (5.3)	4 (4.2)	5 (5.3, 2.3–11.7)	NR
19.	Triasih_Indonesia_2016 [36]	413	269 (65.1)	TST	119 (44.2)[c]	NA	NA	102 (37.9, 32.3–43.8)	NR
20.	Silva_Brazil_2016 [39]	1078	981[d] (91)	TST	322 (32.8)[c]	NA	NA	321 (32.7, 29.9–35.7)	NR
21.	Garie_Ethiopia_2011 [41]	184	184 (100)	TST	106 (57.6)[c]	NA	NA	106 (57.6, 50.4–64.5)	NR
22.	Krishnamoorthy_India_2021 [43]	1523	1523 (100)	TST	801 (52.6)[a]	NA	NA	801 (52.6, 50.1–55.1)	NR
23.	Narasimhan_India_2017 [44]	359	TST 357 (99.4) IGRA 324 (90.1) Both 323 (90)	Both	193 (54.1)[c]	143 (44.1)	NR	143 (44.1, 38.8–49.6)	Trained lab staff
24.	Paradkar_India_2020 [45]	997	997 (100)	Both	524 (52.6)[a]	485 (48.5)	301 (30.2)	707 (70.9, 68.0–73.7)[b]	Trained lab staff

(Continues)

TABLE 2 (Continued)

No.	Study_ID	Eligible household contacts	Number tested (%)	Test used (TST/IGRA)	TST positive, *n* (%)	IGRA positive, *n* (%)	TST + IGRA positive, *n* (%)	LTBI diagnosed (%, 95% CI)	Testing personnel
25.	Okwara_Kenya_2017 [46]	428	428 (100)	TST	96 (22.4)[c]	NA	NA	96 (22.4, 18.7–26.6)	NR
26.	Paul_Nigeria_2019 [47]	63	62 (98.4)	TST	6 (9.7)[c]	NA	NA	6 (9.7, 4.5–19.6)	NR
27.	Chauhan_India_2013 [56]	240	200 (83.3)	TST	78 (39)[c]	NA	NA	78 (39.0, 32.5–45.9)	Project staff
28.	Egere_Gambia_2016 [58]	404	328 (81.2)	TST	63 (19.2)[c]	NA	NA	63 (19.2, 15.3–23.8)	NR
29.	Wysocki_Brazil_2016 [59]	336	267 (79.5)	TST	106/221 (48.0)[a]	NA	NA	106 (48.0, 41.5–54.5)	NR
30.	Faksri_Thailand_2015 [61]	70	70 (100)	Both	NR	NR	15 (21.4)[c]	15 (21.4, 13.4–32.4)	Trained nurse
31.	Schwoebel_Multicentric_2020 [63]	1965	1866 (95.0)	TST	520 (27.9)[c]	NA	NA	520 (27.9, 25.9–30.0)	Nurse
32.	Gomes_Guinea-Bissau_2011 [66]	1159	1159 (100)	TST	253 (21.8)[c]	NA	NA	253 (21.8, 19.6–24.3)	NR
33.	Hector_Malawi_2017 [67]	56	56 (100)	TST	37 (66.1)[c]	NA	NA	37 (66.1, 53.0–77.1)	NR
34.	Mensah_Ghana_2017 [68]	112	100 (89.3)	IGRA	NA	65 (65)	NA	65 (65.0, 55.1–73.6)	NR
35.	Nguyen_Laos_2009 [69]	148	148 (100)	TST	46 (31.1)[c]	NA	NA	46 (31.1, 24.2–39.0)	Project staff
36.	Mzembe_South Africa_2020 [70]	1809	266 (14.7)	IGRA	NA	78 (29.3)	NA	78 (29.3, 24.2–35.1)	NR

Abbreviations: IGRA, interferon-gamma release assay; LTBI, latent tuberculosis infection; NA, not applicable; ND, not done; NR, not reported; TST, tuberculin skin test.

[a]TST positive = induration ≥5 mm.

[b]LTBI diagnosed if either TST or IGRA or both were positive (as defined by study authors); in other studies where both tests were done and authors had not defined LTBI diagnosis, IGRA positives were diagnosed to have LTBI.

[c]TST positive = induration ≥10 mm.

[d]Ninety-seven children did not return for TST reading.

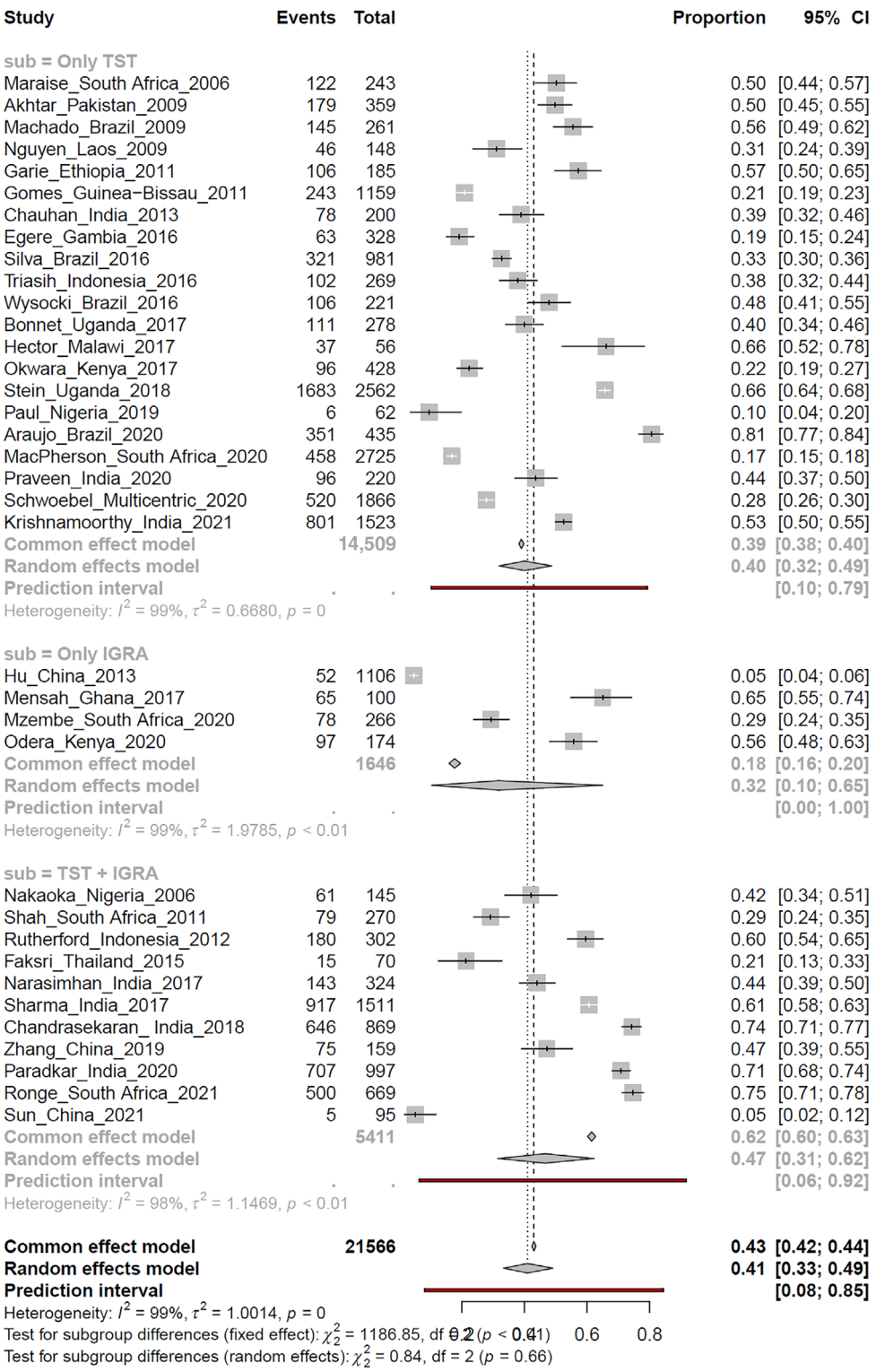

FIGURE 2 Forest plot of the latent tuberculosis infection positivity estimates in studies using tuberculin skin test or interferon-gamma release assay or a combination of tests

Exploration of heterogeneity in the estimates of LTBI

Table 3 summarises the results of subgroup analyses exploring heterogeneity in the LTBI positivity estimates. The pooled estimates for the proportions with LTBI in the subgroup of studies using TST alone, IGRA alone or a combination of tests were similar to the pooled overall estimates, with no significant differences between the subgroups, as evident from the overlapping 95% CIs, and formal tests for

TABLE 3 Summary of LTBI positivity using TST, IGRA or both and exploration of heterogeneity based on the tests used, the place of testing, the study design and geographical location of the studies

	Studies	Household contacts	LTBI positive	Proportion with LTBI (%)		Pooled LTBI positivity (random effects)		Forest plot
				Range	Median (IQR)	% (95% CI)	I^2, τ^2; p	
LTBI diagnosis: all (TST/IGRA/both)	36	21,566	9290	4.7–80.7	43.9 (28.3–58.8)	41.0 (33.0–49.0)	99%, 1.0; <0.01	Figure 2, Figures S1 and S2
Subgroups analysis 1: diagnostic tests used								
TST alone	21	14,509	5670	9.7–80.7	39.9 (25.2–51.4)	40.0 (32.0–49.0)	99%, 0.67; <0.01	Figure 2, subgroup 1
IGRA alone	4	1646	292	4.7–65.0	42.5 (10.9–62.7)	32.0 (10.0–65.0)	99%, 1.98; <0.01	Figure 2, subgroup 2
Both	11	5411	3328	5.3–74.7	47.2 (29.3–70.9)	47.0 (37.0–62.0)	98%, 1.2; <0.01	Figure 2, subgroup 3
Subgroup analysis 2: place of testing								
Health facility	22	8236	4235	9.7–80.7	49.5 (35.3–62.1)	44.0 (35.0–55.0)	98%, 0.96; <0.01	Figure S1, subgroup 1
Household	11	11.688	4846	16.8–74.7	43.6 (27.9–60.7)	43.0 (32.0–54.0)	99%, 0.65; <0.01	Figure S1, subgroup 2
Both/school	3	1642	209	4.7–29.3	29.3 (4.7–29.3)	17.0 (6.0–39.0)	99%, 0.99; <0.01	Figure S1, subgroup 3
Subgroup analysis 3: study design								
Prospective	22	16,616	7286	9.7–74.3	44.1 (25.2–58.4)	39.0 (30.0–49.0)	99%, 0.89; <0.01	Figure S2, subgroup 1
Not prospective	14	4950	2004	4.7–80.7	45.8 (30.7–65.3)	44.0 (31.0–58.0)	99%, 1.14; <0.01	Figure S2, subgroup 2
LTBI diagnosis (TST/IGRA/both): geographical regions								
Africa	17	11,516	4325	9.7–74.7	39.9 (22.1–61.3)	39.0 (29.0–50.0)	99%, 0.81; <0.01	Figure S3
Subgroup analysis: regions								
West and Central Africa	6	3660	958	9.7–65.0	24.9 (16.8–47.8)	28.0 (16.0–44.0)	96%, 0.72; <0.01	Figure S3, subgroup 1
East Africa	5	3627	2093	22.4–65.7	55.6 (31.2–61.7)	48.0 (34.0–62.0)	96%, 0.44; <0.01	Figure S3, subgroup 2
Southern Africa	6	4229	1274	16.8–74.7	39.8 (26.2–68.3)	43.0 (26.0–62.0)	99%, 0.88; <0.01	Figure S3, subgroup 3
Asia	15	8152	4042	4.7–74.3	44.1 (21.4–51.2)	40.0 (27.0–54.0)	99%, 1.24; <0.01	Figure S4
Subgroup analysis: regions								
South Asia	8	6003	3567	39.0–74.3	51.3 (43.7–58.4)	55.0 (46.0–64.0)	97%, 0.26; <0.01	Figure S4, subgroup 1
East Asia	3	1360	132	4.7–47.2	5.3 (4.7 to –)	12.0 (3.0–39.0)	99%, 1.82; <0.01	Figure S4, subgroup 2
South East Asia	4	789	343	5.3–59.2	29.7 (9.3–53.9)	37.0 (25.0–52.0)	95%, 0.34; <0.01	Figure S4, subgroup 3
South America Brazil	4	1898	923	32.7–80.7	48.8 (36.5–72.9)	55.0 (36.0–73.0)	99%, 0.60: <0.01	Figure S5

Abbreviations: CI, confidence interval; IGRA, interferon-gamma release assay; IQR, interquartile range; LTBI, latent tuberculosis infection; TST, tuberculin skin test.

subgroup differences (Table 3; Figure 2). Significant heterogeneity was also present within the subgroups, indicating that the inconsistency in LTBI estimates was not explained by the tests used. Similarly, neither the place of testing (Table 3; Figure S1), nor the study designs (Table 3; Figure S2) explained the heterogeneity in LTBI estimates. LTBI estimates did not also appear to be influenced by the year of publication of the studies (Figure 2). The median and IQR for the proportions with LTBI in these subgroups also overlapped (Table 3).

Geographical variations in screening and testing protocols and in resources were also explored as potential causes of heterogeneity in subgroup analyses. LTBI estimates from studies among household contacts in Africa were

TABLE 4 Summary of LTBI positivity using TST only and exploration of heterogeneity based on place of testing and the size of skin induration

	Studies	Household contacts	LTBI positive	Proportion with LTBI (%)		Pooled LTBI positivity (random effects)		Forest plot
				Range	Median (IQR)	% (95% CI)	I^2, τ^2; p	
LTBI diagnosis: TST only	22	14,811	5850	5.3–80.7	39.9 (25.2–51.4)	41.0 (33.0–49.0)	99%, 0.66; <0.01	Figures S6 and S7
Subgroup analysis 1: place of testing								
Health facility	15	5772	2625	9.7–80.7	48.0 (32.7–57.6)	44.0 (34.0–54.0)	97%, 0.68; <0.01	Figure S6, subgroup 1
Household	7	9039	3225	5.3–65.7	27.9 (16.8–49.9)	36.0 (24.0–48.0)	100%, 0.53; <0.01	Figure S6, subgroup 2
Subgroup analysis 2: size of induration								
Induration ≥5 mm	5	5182	1827	16.8–80.7	39.9 (28.4–66.7)	47.0 (28.0–68.0)	100%, 0.94; <0.01	Figure S7, subgroup 1
Induration ≥10 mm	17	9629	4023	5.3–66.1	39.0 (22.1–53.9)	39.0 (31.0–48.0)	99%, 0.55; <0.01	Figure S7, subgroup 2

Abbreviations: CI, confidence interval; IQR, interquartile range; LTBI, latent tuberculosis infection; TST, tuberculin skin test.

separately analysed, sub-grouped by countries in West and Central Africa, East Africa and Southern Africa (Table 3; Figure S3). Studies from Asia were sub-grouped by studies from countries in South Asia, East Asia and South East Asia (Table 3; Figure S4). Pooled estimates from studies from South America were represented by three studies from Brazil (Table 3; Figure S5). None of these sub-group analyses adequately explained the heterogeneity in LTBI estimates.

Additionally, we explored heterogeneity in LTBI estimates in studies using TST alone sub-grouped by the place of testing (Table 4; Figure S6) and the size of skin induration (Table 4; Figure S7). These sub-group analyses also did not explain the heterogeneity in LTBI estimates.

Tuberculosis preventive treatment

Table 5 provides summary estimates of the proportion of household contacts in whom TPT was initiated and the proportion completing TPT in the studies that reported these outcomes. Of the 58 included studies, 34 (59%) reported data regarding treatment initiation among the 129,573 household contacts considered eligible for TPT. Twenty-six of these studies initiated TPT in children ≤6 years of age, four studies included children and adolescents and four included contacts of all ages (Table 5). Eighteen studies were conducted in Africa. Ten studies were conducted in Asia (seven in India). Four studies were from Brazil, and two were multi-country studies (Table 5). Twenty-two studies used a prospective design, while nine studies were cross-sectional, one was a retrospective cohort study, and two used mixed methods.

Of the 34 studies reporting on TPT initiation, 28 (82%) also reported the proportions completing TPT. Six of the 26 studies that initiated TPT in children ≤6 years of age did not report treatment completion rates, with three reporting that they had referred household contacts with LTBI elsewhere after treatment initiation. The methods used to facilitate treatment adherence were reported in only 13/34 studies (38%) and the proportions actually adherent was infrequently reported. Adverse event monitoring and management were also poorly reported. Various TPT regimens were used, though daily isoniazid for 6 months was the most commonly used regimen.

In the 28 studies reporting treatment initiation and completion, 108,679 contacts were initiated on TPT. The numbers considered to be TPT treatment failures (incident TB developed while on TPT) were reported in 12 (43%) of these studies. Treatment failures were rare, affecting 25 of 74,991 (0.03%) contacts completing treatment in the 28 studies (Tables 5 and 6).

As with the estimates of LTBI, the proportions that initiated and completed TPT varied considerably in the studies reporting these estimates. The proportions initiated on TPT in the 34 studies ranged from 15% to 100%; and in the 28 studies that also reported treatment completion, the proportions ranged from 5% to 94% (Tables 5 and 6).

Figure 3 displays the forest plot of the proportions initiating TPT, and Figure 4 displays the forest plot of the proportions completing TPT; sub-grouped by the age of the household contacts included. Table 6 summarises the pooled estimates for the proportions initiating and completing treatment and the results of subgroup analyses exploring heterogeneity, as well as the median proportions (with the IQR) for treatment initiation and completion.

Figure 3 displays the estimates for treatment initiation rates among 129,573 household contacts who were eligible for treatment in the 34 studies. The pooled estimate for the proportions initiating TPT was 91% (95% CI 79%–97%). There was significant heterogeneity in the estimates ($I^2 = 99\%$; $\tau^2 = 7.79$; $p < 0.01$), that was not explained by subgroup analysis. The median proportion that was initiated on TPT was 86% (IQR 60%–100%) (Table 6).

TABLE 5 Tuberculosis preventive therapy (TPT) initiation and completion among household contacts

No.	Study_ID	Age (years)	Eligible for treatment (*n*)	Treatment initiated, *n* (%, 95% CI)	Adherence monitoring	Treatment completion, *n* (%, 95% CI)	Treatment regimen used	Treatment failure[a]
1.	Bonnet_Uganda_2017 [17]	<5	234	234 (100, 98.0–100)	NR	188 (80.3, 74.8–84.9)	6HZ	1
2.	Machado_Brazil_2009 [19]	All	101	101 (100. 96.0–100)	NR	54 (53.5, 43.8–62.9)	6H	NR
3.	Araujo_Brazil_2020 [31]	All	320	281 (87.8, 83.8–91.0)	NR	233 (82.9, 78.1–86.9)	6HZ	1
4.	Maraise_South Africa_2006 [32]	<5	236	180 (76.3, 74.5–81.2)	Yes	36 (20.0, 14.8 to 26.4)	6H	4
5.	Oxlade_Multicentric_2021 [34][b]	<5	347	250 (72.1, 67.1–76.5)	Yes	NR	6H	NR
6.	Triasih_Indonesia_2016 [36]	≤5	99	86 (86.9, 78.8–92.2)	NR	50 (58.1, 47.6–68.0)	6H	None
7.	Adjobimey_Benin_2016 [37]	<5	497	496 (99.8, 98.9–99.99)	Yes	427 (86.1, 82.8–88.9)	9H	3
8.	Amisi_Kenya_2021 [38]	<5	472	427 (90.5, 87.5–92.8)	NR	205 (48.0, 43.3–52.7)	6H	6
9.	Silva_Brazil_2016 [39]	≤15	322	109 (33.9, 28.9–39.2)	Yes	73 (67.0, 57.7–75.1)	9H, 6H	1
10.	Burmen_Kenya_2014 [40]	<5	337	51 (15.1, 11.7–19.4)	NR	NR	6H	NR
11.	Garie_Ethiopia_2011 [41]	<15	82	82 (100, 95.5–100)	Yes	10 (12.2, 6.8–21.0)	6H	1
12.	Ginderdeuren_South Africa_2021 [42]	<15	56	56 (100, 93.5–100)	NR	24 (42.9, 30.8–52.9)	6H	1
13.	Paul_Nigeria_2019 [47]	≤5	55	55 (100, 93.5–100)	Yes	24 (43.6, 31.4–56.7)	6H	NR
14.	Rekha_India_2009 [13]	≤6	84	16 (19.1, 12.1–28.7)	NR	NR	6H	NR
15.	Rutherford _Indonesia_2012 [48]	<5	82	82 (100, 95.5–100)	Yes	21 (25.6, 17.4–36.0)	6H	NR
16.	Sulis_Burkina Faso_2018 [49]	<5	941	852 (90.5, 88.5–92.6)	NR	NR	6H	NR
17.	Pothukuchi _India_2011 [10]	<6	116	97 (83.6, 75.8–85.3)	NR	83 (85.6, 77.2–91.2)	6H	NR
18.	Rekha_India_2013 [50]	<6	53	53 (100, 93.2–100)	NR	39 (73.6, 60.4–83.6)	6H	NR
19.	Shivaramakrishna_India_2014 [51]	<6	209	70 (33.5, 27.4–40.1)	NR	16 (22.9, 14.6–40.0)	6H	NR
20.	Seid_Ethiopia_2018 [52]	<5	125	94 (75.2, 67.0–81.9)	NR	74 (78.7, 69.4–85.8)	6H	NR
21.	Singh_India_2017 [12]	<5	50	11 (22.0 1.8–35.2)	NR	10 (90.9, 62.3–98.4)	6H	NR
22.	Tadesse_Ethiopia_2016 [53]	<5	221	142 (64.3, 57.7–70.3)	NR	114 (80.3, 73.0–84.0)	6H	None
23.	Belgaumkar_India_2018 [11]	<6	33	28 (84.9, 69.1–93.1)	NR	21 (75.0, 56.6–87.3)	6H	NR
24.	Birungi_Rwanda_2019 [54]	<5	94	84 (89.4, 81.5–94.1)	Yes	74 (88.1, 79.5–93.4)	6H	1
25.	Black_South Africa_2018 [55]	<5	182	74 (40.7, 33.8–48.0	NR	4 (5.4, 2.1–13.1)	6H	NR
26.	Datiko_Ethiopia_2017 [57]	All	3027	1761 (58.2, 56.4–60.0)	Yes	1574 (89.4, 87.9–90.7)	6H	3
27.	Egere_Gambia_2016 [58]	<5	368	328 (89.1, 85.5–91.9)	Yes	255 (77.7, 72.9–81.9)	6H	NR
28.	Wysocki_Brazil_2016 [59]	All	106	64 (60.4, 50.9–69.2)	NR	36 (56.3, 44.1–67.7)	6H	NR
29.	Fentahun_Ethiopia_2020 [60]	<5	138	44 (31.9, 24.7–40.1)	NR	NR	6H	NR
30.	Sayedi_Afghanistan_2020 [62]	<5	117,593	101,084 (86.0, 85.8–86.2)	NR	69,273 (68.5, 68.2–68.8)	6H	NR

(Continues)

TABLE 5 (Continued)

No.	Study_ID	Age (years)	Eligible for treatment (*n*)	Treatment initiated, *n* (%, 95% CI)	Adherence monitoring	Treatment completion, *n* (%, 95% CI)	Treatment regimen used	Treatment failure[a]
31.	Schwoebel_Multicentric_2020 [63]	<5	1909	1746 (91.5, 90.1–92.6)	Yes	1642 (94.0, 92.8–95.1)	3RH, 6H	1
32	Sharma_India_2021 [64]	<5	86	62 (72.1, 61.8–80.5)	Yes	42 (67.7, 55.4–78.1)	6H	NR
33.	Soelen_South Africa_2012 [65]	<5	54	54 (100, 93.4–100)	NR	20 (37.0, 25.4–50.4)	6H	NR
34.	Gomes_Guinea-Bissau_2011 [66]	<15	989	820 (82.9, 80.4–85.1)	Yes	378 (46.1, 42.71–49.5)	9H	2

Abbreviations: CI, confidence interval; H, isoniazid; NR, not reported; R, rifampicin; TPT, tuberculosis preventive treatment; Z, pyrazinamide; the numbers before the drug names denote the number of months of treatment.
[a]Treatment failure: incident tuberculosis disease during the course of treatment.
[b]Data only for children <5 years from the low- and middle-income countries evaluated.

Compared to the more than 90% pooled estimates for TPT initiation, the pooled estimate for the proportions completing TPT (Figure 4) was considerably lower (65%, 95% CI 54%–74%), with significant heterogeneity in the estimates ($I^2 = 98\%$, $\tau^2 = 1.48$, $p < 0.01$). The pooled treatment completion proportions did not significantly differ between the subgroups based on age; and did not explain the heterogeneity in the estimates of the proportions completing treatment. The true estimates of treatment completion with TPT are uncertain, but the median estimate for proportions completing treatment was 68% (IQR 44%–82%) (Table 6).

Factors affecting the TPT care cascade

The factors reported in 28 studies which the authors considered to have affected one or more components of the TPT care cascade are summarised in Table 7.

For the diagnosis of LTBI, short duration of the follow-up, and the type of tests used were reported as potentially important (Table 7). The time of testing was reported as another factor that might have affected the results since contacts incubating the infection might test negative if tested early, thus leading to an underestimation of the infection prevalence. In studies where data were collected retrospectively, inadequate documentation of the care cascade components was reported to have likely impacted the study outcomes. In many settings, the information on the household contacts (especially for child contacts) was retrieved from the index patient's card, thus inadequate documentation could have led to selection bias for household contacts. Furthermore, in studies that collected information from the participants, recall bias, and the general tendency to provide socially desirable responses were reported as factors that could have resulted in over/underestimation of the findings of the studies.

For preventive treatment, factors such as higher cost of transportation, medication palatability, treatment duration, social support and the knowledge and beliefs of healthcare workers were thought to have influenced the reported treatment outcomes. Where described, treatment adherence was defined based on pill count or the monthly prescription of the medicines collected from the subjects. This might have led to an overestimation of treatment adherence. Another factor that might have impacted the results was the risk perception of the participants; parents' or caregivers' own experience concerning TB disease and its health consequences that could have motivated them to initiate treatment among their close contacts; whereas, in studies where adherence was poor, absence of signs and symptoms among contacts could have adversely impacted the treatment-related decisions. In some studies, participants' characteristics in terms of their immune status were reported to have likely impacted the findings. Health worker-related factors such as high patient to health worker ratio and their working hours could compromise the quality of care. The timing of household visits by the

TABLE 6 Summary of the proportions initiating and completing TPT for LTBI and exploration of heterogeneity based on age of household contacts

	Studies	Eligible household contacts	On TPT	Proportion on TPT (%)		Pooled proportion on TPT (random effects)		Forest plot
				Range	Median (IQR)	% (95% CI)	I^2, τ^2; p	
TPT initiation	34	129,573	109,974	15.1–100.0	85.5 (59.9–100)	91.0 (79.0–97.0)	99%, 7.79; 0.00	Figure 3
Subgroup analysis: age								
<6 years	26	124,570	106,700	15.1–100.0	85.5 (58.4–98.9)	90.0 (75.0–97.0)	99%, 7.54; <0.01	Figure 3, subgroup 1
<18 years	4	1449	1067	33.9–100.0	91.5 (46.2–100.0)	98.0 (32.0–100.0)	99%, 14.88; <0.01	Figure 3, subgroup 2
All ages	4	3554	2207	58.2–100.0	74.1 (58.8–97.0)	89.0 (45.0–99.0)	97%, 4.63; <0.01	Figure 3, subgroup 3
TPT completion	28	108,679	74,991	5.4–94.0	68.1 (44.2–82.3)	65.0 (54.0–74.0)	98%, 1.48; <0.01	Figure 4
Subgroup analysis: age								
<6 years	20	105,159	72,364	5.4–94.0	71.1 (38.7–84.3)	64.0 (49.0–76.0)	98%, 1.95; <0.01	Figure 4, subgroup 2
<18 years	4	1313	730	42.9–77.7	56.6 (43.7–75.2)	60.0 (44.0–73.0)	97%, 0.38; <0.01	Figure 4, subgroup 2
All ages	4	2207	1897	53.5–89.4	69.6 (54.2–87.8)	74.0 (55.0–87.0)	98%, 0.71; <0.01	Figure 4, subgroup 2

Abbreviations: CI, confidence interval; IQR, interquartile range; LTBI, latent tuberculosis infection; TPT, tuberculosis preventive treatment.

workers could lead to under-representation of certain age groups (especially school-going children) as many might not be available at that time (Table 7).

As reported in the studies, factors operating at multiple levels can facilitate or hinder the execution of each component of the care cascade. Therefore, for a successful realisation of the care cascade, it is imperative to address these factors in contextually appropriate ways.

DISCUSSION

This systematic review aimed to describe the strategies used in studies from high TB burden countries for detecting LTBI in household contacts of people with bacteriologically confirmed pulmonary TB who were not immunocompromised, and to ascertain the proportions initiated on and completing TPT. The 58 included studies provide updated estimates to supplement estimates from existing systematic reviews in this area [3, 6, 14, 15]. The pooled estimates for LTBI positivity of 41% (95% CI 33%–49%), using a combination of TST or IGRA or both, in 21,566 household contacts of people with bacteriologically confirmed pulmonary TB in the 36 studies provide a timely reminder of the hidden burden of TB infection. Even though there was significant heterogeneity in these estimates, the median LTBI positivity estimates (44%, IQR 28%–59%) indicate that between a third to over half of the household contacts of people with bacteriologically proven TB are likely to have LTBI.

Over half of these studies used TST alone to detect LTBI. Since most studies also used only verbal screening of symptoms to rule out active TB, concerns exist about the potential for false negative results with the use of TST alone. The number of studies that used IGRA (alone or in combination with TST) to diagnose LTBI was fewer. The relatively higher LTBI yield in these studies (albeit with wide 95% CI that overlapped with the TST-diagnosed LTBI estimates), coupled with the likelihood of fewer false-positive results, suggest that increasing the use of imaging modalities and molecular tests could augment the utility of contact tracing for LTBI management. However, this would need to be balanced against available resources and other programmatic considerations.

WHO recommends that contact investigation be conducted through home visits but the data in this review did not find the LTBI diagnostic yield to differ significantly with health facility-based versus home-based contact investigations.

The other notable finding in this review was the higher proportions of contacts with LTBI initiating TPT compared to the lower proportions completing treatment. The pooled estimates for treatment initiation in 129,573 eligible household contacts in the 34 studies was an impressive 91% (95% CI 79%–97%), compared to the pooled estimates of the proportions completing treatment (65%, 95% CI 54%–74%) among 108,679 contacts who commenced TPT in 28 of these studies. In spite of the significant heterogeneity in these estimates, the nearly 20% difference in the median proportion completing compared to initiating treatment, reveals a flaw in the TPT care cascade that can adversely impact the effectiveness of LTBI management among household contacts.

The qualitative synthesis of the factors reported by study investigators provide complementary insights about the factors related to the various components of the cascade of care that could have contributed to heterogeneity in LTBI estimates and TPT outcomes. These factors can also inform strategies to improve the effectiveness of LTBI management. No single factor or intervention can be considered pre-eminent to improve the LTBI cascade, and many incremental strategic adjustments will be needed to reduce losses that can occur throughout the LTBI cascade of care [71].

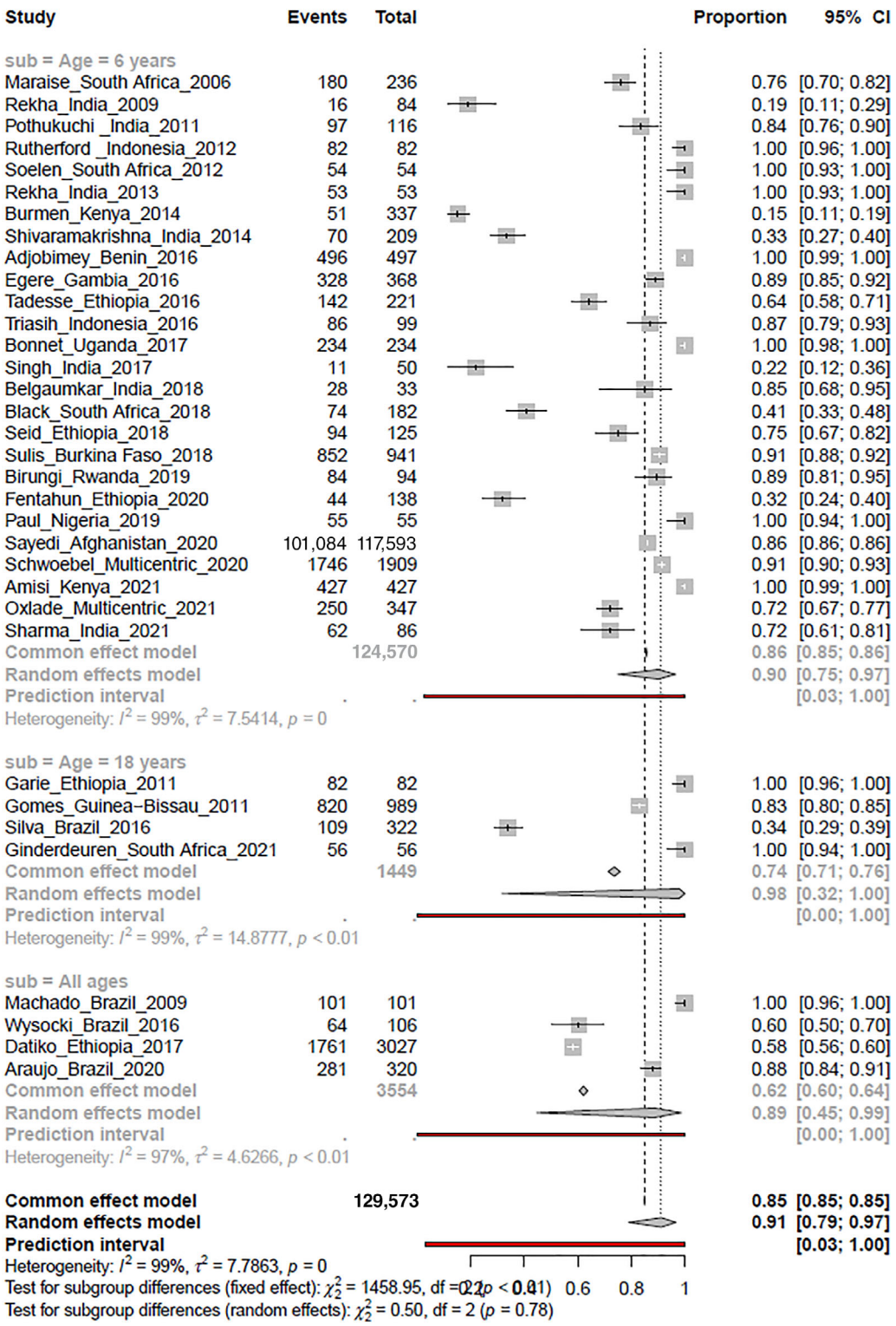

FIGURE 3 Forest plot of the proportions initiating tuberculosis preventive treatment sub-grouped by the age of household contacts

Limitations

A major limitation in this review was the lack of adequate details provided in the included studies regarding the processes used in screening, testing or treatment initiation due to which we were unable to adequately assess the quality of implementation of LTBI management strategies. The variety of included study designs precluded valid assessments of the risk of bias uniformly applicable across these designs. The possibility of reporting biases is also high with systematic reviews using observational data.

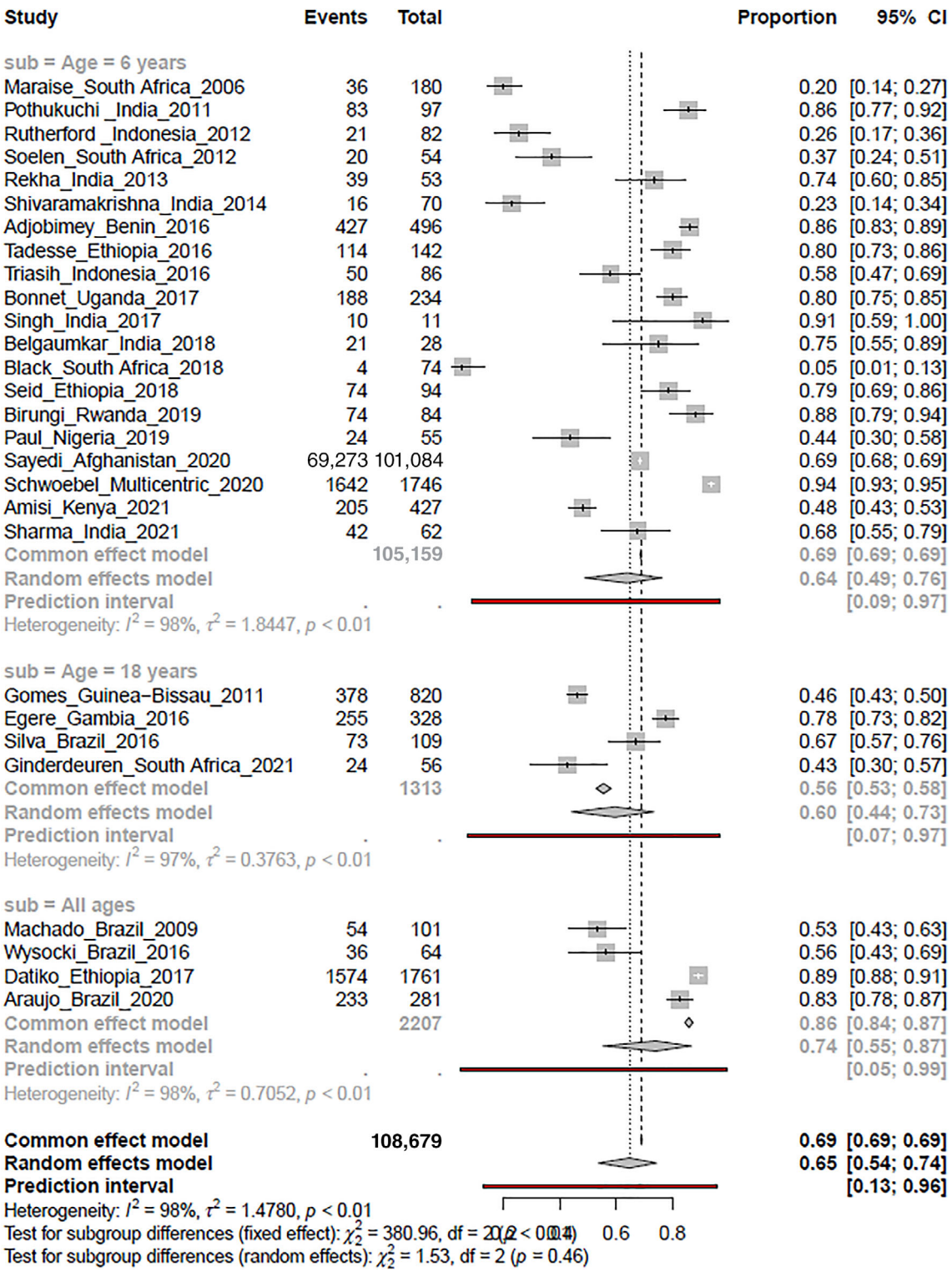

FIGURE 4 Forest plot of the proportions completing tuberculosis preventive treatment sub-grouped by the age of household contacts

Another major limitation was the significant heterogeneity in the pooled estimates from meta-analysis for the diagnostic yield. This was not explained in subgroup analyses based on the diagnostic tests used and the place of testing. Additional post hoc sub-group analyses based on the study designs employed and geographical differences in the countries where the studies were conducted also did not explain the heterogeneity. Significant heterogeneity in the estimates for TPT outcomes was also a serious limitation that was not explained in pre-stated subgroup analyses based on the age of the household contacts. The prevalence of TB (and LTBI) varies across different populations within

TABLE 7 Factors reported to affect the TPT care cascade

Factors	Description	Study reference
Duration of follow-up	Short duration of follow-up could have affected the assessment of TPT effectiveness and the magnitude of the true burden of *Mycobacterium tuberculosis* infection.	[17, 26, 59]
Type of test used	Using TST could have resulted in low yield for *M. tuberculosis* infection, since IGRA correlates better with recent *M. tuberculosis* exposure and has higher accuracy in diagnosing infection in children.	[18, 23]
Timing of tests	The timing of conducting tests could have affected the results in terms of LTBI positivity as the average time for developing hypersensitivity reactions is 4–12 weeks, thus some household contacts who might have been incubating the infection might have tested negative on the tests.	[24, 29]
Inadequate documentation	Retrospective studies and studies on programmatic data reported that the lack of proper documentation on the care cascade for TB management could have affected their assessment and findings. Collecting data from the programme registers and from reports that lack rigour in documenting the information could lead to selection bias for the number of household contacts.	[32, 38, 52, 53, 62]
Adherence to TPT	The common factors related to TPT adherence included: higher cost of transportation, medication palatability, longer treatment duration, social support, and the knowledge and beliefs of HCWs and carers. Further, treatment adherence reported in the studies could be an overestimation as it depended on pill count or on the monthly collection of prescriptions.	[37, 39, 42, 48, 66]
Risk perception of the participants	Parents' or caregivers' own experience concerning TB disease and its long-term health consequences was reported as a motivating factor for TPT initiation and completion. Further, participants' perception regarding the risk related to LTBI influences the treatment initiation and adherence among HH contacts, especially among child contacts. Parents were unable to comprehend the relevance of initiating TPT among asymptomatic children.	[40, 41, 55, 60]
Recall bias	Studies that ascertained information on the care cascade from the participants reported that recall bias or the tendency to provide socially desirable answers could have resulted in under- or over-estimation of the results in the study.	[12, 43, 51, 60, 70]
Participants' characteristics	One study reported that HIV positivity reduces the likelihood of completing testing, whereas in another, it was reported that HIV-infected participants were more likely to get their contacts screened as they visit the health facility regularly and are aware of the benefits of early contact screening. Another study mentioned that subjects' immunological status could also impact the testing outcomes as the T-SPOT.TB assay was based on the individual activated T cell.	[20, 30, 60]
HCWs' related	In one study, the high patient to health worker ratio was thought to have compromised the quality of care, whereas another reported that the working hours of the HCWs could have resulted in under-representation of certain age group (especially school-going children).	[40, 57]

Abbreviations: HCWs, healthcare workers; HH, house-to-house; IGRA, interferon-gamma release assay; IPT, isoniazid preventive therapy; LTBI, latent tuberculosis infection; TB, tuberculosis; TST, tuberculin skin test.

and between countries and between geographical regions, as was also evident in other systematic reviews and meta-analysis of TB contact tracing [3, 6, 14, 15]; their results were similar to the estimates in this review. This highlights the inherent difficulty in accurately estimating, with the available data, the effects of strategies like TB contact tracing among diverse populations.

Anticipating that meta-analysis of studies of disease prevalence would result in significant heterogeneity, we chose to use the random-effects model for meta-analysis. The random-effects model adjusts the weights assigned to each study to account for within-study and between-study variability, and results in wider 95% CIs for the prevalence estimates. With the magnitude of heterogeneity observed ($I^2 > 95\%–100\%$), the weights assigned to each study in random-effects meta-analysis are nearly equal, regardless of the sample size and study variance. Therefore, the point estimates for LTBI and TPT outcomes in these studies generated through random-effects meta-analysis only represent the mean of a wide range of possible estimates [72]. In spite of the significant heterogeneity, we chose to retain the meta-analysis estimates in order to explore heterogeneity, but caution against relying on these pooled estimates alone. The median estimates (with the IQR) that accompany each analysis offer a more conservative interpretation of LTBI positivity and TPT outcomes in the included studies.

Recommendations for LTBI management scale up

In spite of these limitations, the evidence synthesised in this review provides important information that can inform the national TB programmes in high TB burden countries while scaling up LTBI management.

Firstly, a more systematic approach is needed for screening TB symptoms (to exclude active TB). There are already comprehensive guidelines on contact investigations provided by WHO that most programmes have integrated into their systems. However, the recording and reporting for TPT eligibility need to be strengthened. Information regarding the personnel doing the screening and their training;

details on the timing and frequency of screening, particularly in relation to the timing since the index case was diagnosed, also need to be documented as these can impact detection and implementation. Screening should not depend only on verbal screening of symptoms to rule out active TB, and imaging and molecular tools should be optimally utilised.

Secondly, diagnostic testing for LTBI among the household contacts should be mandatory and TPT should not be initiated without a positive result (except for those <5 years and for those with HIV infection, or on the recommendation of a consulting physician), since, on an average, only a third to a little more than half of household contacts may have LTBI. Irrespective of the diagnostic test used or considered feasible, ensuring consistent protocols and adequately trained staff in administrating the tests will result in better outcomes.

Thirdly, mechanisms to ensure better integration of TPT initiation with mechanisms to encourage and monitor adherence, detect and manage adverse events, provide counselling, to record treatment completion and follow-up after TPT are required. Many of these problems already exist in national TB programmes for active TB case finding, and common solutions are needed for LTBI and TB case detection and management [73]. For optimum utilisation of resources, adherence mechanisms integrated with active TB management may work well, however real-world experience indicates that this may overburden health workers who support TB treatment.

TPT scale-up, as recommended by WHO and the commitments at UNHLM, is important. However, in high-TB burden, resource-constrained countries, this would require attending to approximately four-times more people than the total number of TB patients diagnosed. Integrating TPT in the current active TB programmes, without providing additional human resources, risks overburdening of existing staff, while leaving large numbers without completing their treatment, and wasting already limited resources in terms of free testing and treatment provided under the programmes. While shorter treatment regimens may aid in treatment completion, the systems to support this need to be in place for this to work. Follow-up mechanisms for those household contacts who complete TPT to document any further episodes of TB also need to be in place.

CONCLUSION

The results of this systematic review and meta-analysis provide updated data on LTBI positivity, TPT initiation and completion among household contacts in high TB burden countries. The common strategies used to identify those eligible were contact investigation either at home or at health facility, mostly using verbal screening. The proportions detected with LTBI varied considerably in the studies, but the median positivity for LTBI was 44%. While the proportions initiated on TPT were reassuringly high, treatment completion proportions were worryingly lower. The qualitative data collected alongside the quantitative data provide heuristic insights about factors that could reduce losses in the LTBI cascade of care.

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SUPPORTING INFORMATION

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

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