The effectiveness of contact investigation among contacts of tuberculosis patients: a systematic review and meta-analysis

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Contact investigation is associated with increased case detection, reduced mortality and decreased community prevalence of TB, and resulted in a high yield of co-prevalent, incident and latent TB infection among contacts https://bit.ly/3h9jW2H

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Abstract

Background We aimed to evaluate the effectiveness of contact investigation in comparison with passive case detection alone, and estimate the yield of co-prevalent and incident tuberculosis (TB) and latent TB infection (LTBI) among contacts of patients with TB.

Methods A systematic search was undertaken of studies published between 1 January 2011 and 1 October 2019 in the English language. The proportion of contacts diagnosed with co-prevalent TB, incident TB and/or LTBI was estimated. Evaluation of the effectiveness of contact investigation included randomised trials, while the yield of contact investigation (co-prevalent/incident TB and LTBI) was assessed in nonrandomised studies.

Results Data were extracted from 244 studies, of which 187 studies measured the proportion of contacts diagnosed with TB disease and 135 studies measured LTBI prevalence. Individual randomised trials demonstrated that contact investigation increased TB case notification (relative risk 2.5, 95% CI 2.0–3.2) and TB case detection (OR 1.34, 95% CI 0.43–4.24) and decreased mortality (relative risk 0.6, 95% CI 0.4–0.8) and population TB prevalence (risk ratio 0.82, 95% CI 0.64–1.04). The overall pooled prevalence of TB was 3.6% (95% CI 3.3–4.0%; I^2=98.9%, 181 studies). The pooled prevalence of microbiologically confirmed TB was 3.2% (95% CI 2.6–3.7%; I^2=99.5%, 106 studies). The pooled incidence of TB was highest in the first year after exposure to index patients (2.0%, 95% CI 1.1–3.3%; I^2=96.2%, 14 studies) and substantially lower 5 years after exposure to index patients (0.5%, 95% CI 0.3–0.9%; one study). The pooled prevalence of LTBI among contacts was 42.4% (95% CI 38.5–46.4%; I^2=99.8%, 135 studies).

Conclusions This systematic review and meta-analysis found that contact investigation was effective in high-burden settings. The higher pooled prevalence estimates of microbiologically confirmed TB compared with previous reviews suggests newer rapid molecular diagnostics contribute to increased case detection.

Introduction

Tuberculosis (TB) remains a major global public health challenge owing to its high morbidity and mortality rates. In 2018, 10 million people fell ill with the airborne respiratory infection caused by *Mycobacterium tuberculosis*; however, only 7 million of these cases were diagnosed [1]. This substantial case detection gap leads to substantial morbidity and mortality [1]. Consequently, the scale-up of strategies to identify people with TB disease and increase access to TB preventive therapy (TPT) is urgently required [2]. Targeted active case finding is a top priority for healthcare providers and policy makers [3].

Contacts of patients with TB have a substantially increased risk of developing TB compared with the general population [4]. This is reflected by the high prevalence of latent TB infection (LTBI) among contacts. Contact investigation entails screening for TB, with or without screening for LTBI. This typically includes a combination of symptom screening, chest radiography and/or the tuberculin skin test (TST).

Microbiological tests used to confirm the diagnosis of TB include direct sputum smear, culture or the nucleic acid amplification test (NAAT). Contact investigation is also a priority for drug-resistant TB patients and scale-up of NAATs enables the rapid detection of drug-resistant TB. Contact investigation has been shown to increase case detection [5], facilitate earlier treatment initiation, and enable the diagnosis and treatment of LTBI in low- and high-incidence settings [6, 7]. Contact investigation may also reduce *M. tuberculosis* transmission in the community [8]. Recent randomised trials have provided new insights into the effectiveness of contact investigation for individuals and communities [5, 9]. Furthermore, the scale-up of rapid molecular diagnostic tests, such as GeneXpert MTB/RIF and Truenat, has been increasingly used to increase the sensitivity of screening algorithms to detect TB [10].

This systematic review and meta-analysis was undertaken to inform updated World Health Organization (WHO) guidelines regarding TB screening among contacts of TB patients. This review aimed to 1) evaluate evidence for the effectiveness of contact investigation, 2) estimate co-prevalent and incident TB and the prevalence of LTBI among contacts, and 3) evaluate the sensitivity of alternative algorithms for identifying co-prevalent TB among contacts of patients with TB.

Methods

Search strategy and study eligibility

We conducted a systematic review and meta-analysis of study-level observational data and reported these according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines [11, 12]. A review protocol was developed and approved by the WHO secretariat. We searched four databases: MEDLINE (*via* PubMed), Embase, LILACS and Web of Science. A database-specific search strategy was used that included MeSH (Medical Subject Headings) terms or free-text words such as "*Mycobacterium tuberculosis*", "tuberculosis", "contact tracing", "contact screening", "disease outbreaks" and "case finding". The complete search strategy is listed in the supplementary material. We searched the reference lists of included studies to identify additional papers for consideration.

Included studies were published between 1 January 2011 and 1 October 2019 in the English language, and provided a quantitative measure of the proportion of contacts diagnosed with co-prevalent TB, incident TB or LTBI. The evaluation of the effectiveness of contact investigation included randomised trials in which contact investigation was compared with standard "passive" approaches to case detection. The evaluation of the yield of contact investigation (co-prevalent and incident TB and LTBI) included nonrandomised studies. Studies were excluded if <10 index cases were evaluated, if index patients had not been identified as the starting point for contact investigation, the number of contacts screened was not reported (*i.e.* no denominator data was available), or TB among contacts was not diagnosed on microbiological or standard clinical grounds (*e.g.* suitable grounds include screening algorithms such as chest radiography plus symptoms and microbiology plus chest radiography). Conference abstracts were excluded.

Screening and data extraction

Each title and abstract identified in the literature search was independently screened by two reviewers (R.V.S. and M.V.). When the two reviewers' assessments of eligibility differed, a third reviewer (K.V.) made a final decision. Manuscripts considered for full-text review were uploaded onto Endnote X8 (https://endnote.com) and independently screened for inclusion by two reviewers (R.V.S. and K.V.). Cohen's κ was used to measure inter-coder agreement at each screening phase; a poor correlation was defined as a $\kappa<0.5$.

A standardised data extraction form in REDCap [13] captured data elements from each included manuscript. Data extraction was completed by three reviewers (R.V.S., J.H. and K.V.). Extracted data included: 1) assessment of eligibility criteria and study design; 2) methods used for screening (timing of TB screening in relation to the diagnosis of the index case, TB screening and diagnostic testing modalities, and location of exposure); and 3) screening outcomes (characteristics of the index case, number of index cases in the study, number of contacts evaluated for TB disease and LTBI, number of contacts tested for TB or LTBI and number of contacts diagnosed with TB or LTBI, and HIV prevalence).

Definitions

An index case was defined as the initially identified case of new or recurrent TB, in a person of any age, in a specific household or other comparable setting in which others may have been exposed [14].

A contact was defined as any person who had been exposed to an index case [14]. A household contact was defined as any person who shared the same enclosed living space for 7 nights, or for frequent or

extended periods during the day, with the index case during the 3 months before commencement of the current treatment episode [14]. A "close" contact was defined as any person who was not in the household but shared an enclosed space with the index case (such as a place of social gathering, workplace or facility) for extended time periods during the 3 months prior to the index commencing the current treatment episode [14].

The income classification of the country in which studies were conducted was classified by World Bank criteria for Gross National Income per capita: high, upper-middle, lower-middle and low income [15]. Countries were classified as low (<20 cases per 100 000 population), medium (20–99 cases per 100 000 population) or high (⩾100 cases per 100 000 population) incidence for TB [1].

"Co-prevalent TB" was defined as TB that was diagnosed clinically and/or microbiologically (using any combination of smear microscopy, mycobacterial culture, NAAT, chest radiography and clinical grounds) among contacts during the baseline contact investigation, usually within 3 months of index patient diagnosis. "Incident TB" was defined as TB diagnosed clinically and/or microbiologically (using any combination of smear microscopy, mycobacterial culture, NAAT, chest radiography and clinical grounds) among contacts at any time, post the initial baseline contact investigation. Where co-prevalent and incident TB could not be separated based on available data, these were regarded as co-prevalent TB. Where a study separated the contacts into co-prevalent and incident TB, we allocated TB as either co-prevalent or incident.

LTBI was defined as a positive TST or interferon-γ release assay (IGRA) result (where TST was not available); if the study reported both results, TST was used.

Assessment of study quality

A risk-of-bias assessment was performed for all included studies using the Newcastle–Ottawa Scale (NOS), as described in the supplementary material [16].

Data synthesis and analysis

Characteristics of included studies were analysed using descriptive statistics. A meta-analysis was performed where two or more studies were included that evaluated similar outcomes. Effectiveness was measured at the level of the general population and of contacts, and outcome measures included TB case notification, TB case detection, mortality and TB prevalence. Outcomes of individual randomised studies are presented when meta-analyses were not possible.

Pooled estimates of co-prevalent TB, incident TB and LTBI among contacts were calculated for nonrandomised studies using a random effects model. Pooled estimates were weighted by the number of included participants and 95% confidence intervals calculated using Wilson's method. Within-study standard errors were calculated as the square root of the sum of the inverse of the number of contacts with each outcome of interest and the inverse of the number of contacts without that outcome. Pooled estimates were also calculated for specific subpopulations described in supplementary table E1. TB incidence estimates among contacts were stratified by the number of years between the diagnosis of the index case and the onset of TB diagnosed in contacts, up to 5 years.

Publication bias was investigated using funnel plots and the Egger test [17, 18]. Between-study heterogeneity was measured using the I^2 statistic. A statistical significance threshold of $p<0.05$ was used [19].

Statistical analyses were performed using Stata version 16 (StataCorp, College Station, TX, USA).

Results

Study characteristics

Between January 2011 and October 2019, 244 eligible papers were identified (figure 1). Of these, 187 papers measured the proportion of contacts diagnosed with TB disease, comprising 1 404 453 individuals from 61 countries (table 1). The prevalence of LTBI was measured in 135 studies, comprising 473 075 individuals. Among studies evaluating TB disease (n=187), the median (interquartile range (IQR)) number of included contacts per study was 646 (255–2666). The majority of studies (62.6%) were conducted in countries with a high incidence of TB. Six randomised studies (3.2%) and 181 nonrandomised studies (96.8%) were identified. A summary of included studies, grouped by the country incidence of TB, is shown in table 1.

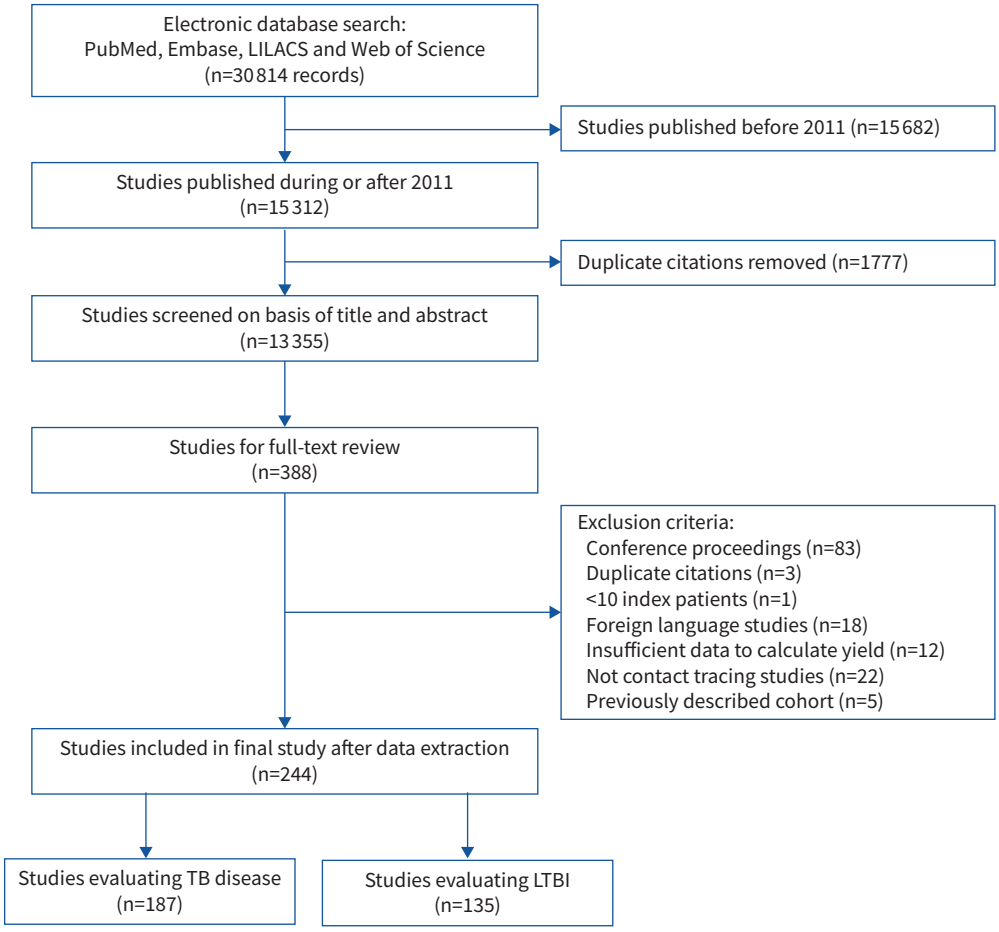

FIGURE 1 Flow diagram for study identification and selection. TB: tuberculosis; LTBI: latent TB infection.

Evidence for the effectiveness of contact investigation

Three randomised control trials met the eligibility criteria for the assessment of effectiveness of contact investigation [5, 9, 20]. A meta-analysis was not performed for these studies owing to heterogeneity in their methods and outcome measures (supplementary table E2). Three other randomised controlled trials were excluded for reasons outlined in supplementary table E3 [21–23].

The effect of household contact investigation upon TB case detection was reported in one randomised trial, performed in Uganda [20]. This study found that seven out of 471 individuals were diagnosed with TB in the intervention group *versus* five out of 448 individuals in the control group (OR 1.34, 95% CI 0.43–4.24).

A second randomised trial evaluated the effect of household contact investigation, integrated with HIV care, upon TB prevalence in the general community [9]. The study found that 443 out of 43 941 individuals were diagnosed with TB with household screening compared with 451 out of 45 763 individuals in the control group (risk ratio 0.82, 95% CI 0.64–1.04).

TB case notification was reported in a third randomised trial performed in Vietnam. In this study, 180 out of 10 069 screened household contacts developed TB *versus* 110 out of 15 638 contacts in the control group in which passive case finding alone was performed. In the screening group, the relative risk of notified TB was 2.5 (95% CI 2.0–3.2) compared with the control group [5]. Additionally, 160 out of 10 069 individuals in the intervention group developed microbiologically confirmed TB *versus* 39 out of 15 638 individuals in the control group (relative risk 6.4, 95% CI 4.5–9.0). The screening intervention was associated with 40% reduction in mortality compared with the control group (relative risk 0.6, 95% CI 0.4–0.8) in a *post hoc* analysis.

TABLE 1 Summary characteristics of 187 included studies, grouped by tuberculosis (TB) incidence setting

	TB incidence setting[#]			Total
	Low	Medium	High	
Studies	37 (19.8)	33 (17.7)	117 (62.6)	187 (100)
Study type				
Randomised	0 (0)	0 (0)	6 (5.1)	6 (3.2)
Nonrandomised	37 (100)	33 (100)	111 (94.9)	181 (96.8)
Nonrandomised study design type				
Case–control	0 (0)	0 (0)	1 (0.9)	1 (0.6)
Cross-sectional	14 (37.8)	13 (39.4)	52 (46.8)	79 (43.6)
Retrospective cohort	13 (35.1)	7 (21.2)	7 (6.3)	27 (14.9)
Prospective cohort	10 (27.1)	13 (39.4)	51 (46.0)	74 (40.9)
Index case				
Smear-positive	7 (18.9)	11 (33.3)	42 (35.9)	127 (67.9)
Any microbiological confirmation	14 (37.8)	16 (48.5)	74 (63.3)	104 (55.6)
MDR/XDR-TB	2 (5.4)	1 (3.0)	17 (14.5)	20 (10.7)
Selection of index case				
Consecutive	6 (16.2)	7 (21.2)	32 (27.4)	45 (24.1)
Random	1 (2.7)	1 (3.0)	2 (1.7)	4 (2.1)
Based on convenience	12 (32.4)	5 (15.2)	30 (25.6)	47 (25.1)
Not stated	20 (48.8)	30 (61.2)	64 (45.1)	114 (49.1)
Selection of contacts				
Consecutive	6 (16.2)	9 (27.3)	35 (29.9)	50 (26.7)
Random	1 (2.7)	2 (6.1)	1 (0.9)	4 (2.1)
Based on convenience	13 (35.1)	6 (18.2)	34 (29.1)	53 (28.3)
Not stated	17 (46.0)	16 (48.5)	47 (40.2)	80 (42.8)
Timing of contact diagnosis				
Co-prevalent TB				
Any TB	37 (100)	33 (100)	117 (100)	187 (100)
Microbiologically confirmed TB	15 (40.5)	15 (45.5)	80 (68.4)	110 (58.8)
Incident TB				
At year 1	3 (8.1)	2 (6.1)	8 (6.9)	13 (7.0)
At year 2	4 (10.8)	1 (3.0)	3 (2.6)	8 (4.3)
At year 3	1 (2.7)	0 (0)	1 (0.9)	2 (1.1)
At year 4	1 (2.7)	0 (0)	1 (0.9)	2 (1.1)
At year 5	0 (0)	0 (0)	1 (0.9)	1 (0.5)
Age group				
<5 years	5 (13.5)	7 (21.2)	29 (24.8)	41 (21.9)
5–14 years	5 (13.5)	7 (21.2)	29 (24.8)	41 (21.9)
⩾15 years	7 (19.0)	8 (24.2)	34 (29.1)	49 (26.2)
HIV-infected contacts	0 (0)	2 (6.1)	16 (13.7)	18 (9.6)
Location of contact exposure				
Household	23 (62.2)	30 (91.0)	93 (79.5)	146 (78.1)
School	1 (2.7)	2 (6.1)	0 (0)	3 (1.6)
Work	5 (13.5)	4 (12.1)	0 (0)	9 (4.8)
Screening tests included				
Symptoms	19 (51.4)	19 (57.6)	75 (64.1)	113 (60.4)
Chest radiography	26 (70.3)	23 (69.7)	54 (46.2)	103 (55.1)
TST/IGRA	35 (94.6)	25 (75.8)	45 (38.5)	105 (56.2)
Initial screening test(s)				
Symptoms only	4 (10.8)	3 (9.1)	3 (2.6)	10 (5.3)
Chest radiography only	11 (29.7)	6 (18.2)	8 (6.8)	25 (13.4)
Symptoms+chest radiography	15 (40.5)	12 (36.4)	29 (24.8)	56 (29.9)
Microbiological TB testing				
Smear	5 (13.5)	14 (42.4)	72 (61.5)	91 (48.6)
NAAT	0 (0)	1 (3.0)	29 (24.8)	30 (16.0)
Culture	4 (10.8)	6 (18.2)	37 (31.6)	47 (25.1)
Diagnostic combinations used for diagnosing TB				
Smear only	2 (5.4)	8 (24.2)	23 (19.7)	33 (17.6)
NAAT only	0 (0)	0 (0)	4 (3.4)	4 (2.1)
Culture only	1 (2.7)	0 (0)	0 (0)	1 (0.5)

Continued

TABLE 1 Continued

	TB incidence setting[#]			Total
	Low	Medium	High	
Smear+NAAT	0 (0)	0 (0)	14 (12.0)	14 (7.5)
Smear+culture	3 (8.1)	5 (15.2)	28 (23.9)	36 (19.3)
NAAT+culture	0 (0)	0 (0)	2 (1.7)	2 (1.1)
Smear+NAAT+culture	0 (0)	1 (3.0)	7 (6.0)	8 (4.3)
Any microbiological test	6 (16.2)	14 (42.4)	78 (66.7)	98 (52.4)

Data are presented as n (%). MDR: multidrug-resistant; XDR: extensively drug-resistant; TST: tuberculin skin test; IGRA: interferon-γ release assay; smear: sputum smear microscopy; NAAT: nucleic acid amplification test; culture: liquid or solid mycobacterial culture. [#]: TB incidence per 100 000 population of <20 (low incidence), 20–99 (medium incidence) or ⩾100 (high incidence).

The included randomised trials were assessed as having "good" quality (supplementary table E4).

Co-prevalent and incident TB in nonrandomised studies

We included 181 nonrandomised studies that evaluated the proportion of patients with co-prevalent or incident TB. Table 2 shows the pooled estimates of co-prevalent TB detected among contacts, stratified by subgroups of index cases and contacts. Figure 2 shows the pooled estimates for incident TB detected among contacts up to 5 years after exposure to the index patient. Among the 181 nonrandomised studies, the median (IQR) NOS score was 4 (3–5), out of a maximum of 9 for cohort studies and 7 for cross-sectional studies. Using the Agency for Healthcare Research and Quality scale, only 37 studies (19%) were considered "good" quality (supplementary table E5).

Co-prevalent TB detected among contacts

The overall pooled TB prevalence (clinically and/or microbiologically diagnosed) was 3.6% (95% CI 3.3–4.0%; I^2=98.9%, 181 studies). The pooled TB prevalence of microbiologically confirmed TB was 3.2% (95% CI 2.6–3.7%; I^2=99.5%, 106 studies). The pooled TB prevalence was 3.8% (95% CI 3.3–4.3%; I^2=98.4%, 100 studies) among contacts of microbiologically confirmed index patients and 4.1% (95% CI 2.8–5.6%; I^2=98.1%, 20 studies) among contacts of multidrug-resistant (MDR)/extensively drug-resistant (XDR)-TB index patients (table 2).

Pooled prevalence estimates, stratified by income classification and TB incidence of the country in which studies were performed, are shown in table 2. Studies conducted in low-income countries had a pooled TB prevalence of 5.0% (95% CI 4.0–6.1%; I^2=98.7%, 35 studies), while high-income countries had a pooled TB prevalence of 1.8% (95% CI 1.3–2.3%; I^2=98.8%, 42 studies). Studies conducted in low-incidence countries had a pooled TB prevalence of 1.9% (95% CI 1.5–2.4%; I^2=97.7%, 37 studies), while high-incidence countries had a pooled TB prevalence of 5.0% (95% CI 4.5–5.5%; I^2=99.0%, 111 studies).

Pooled TB prevalence was highest among contacts infected with HIV (11.6%, 95% CI 8.2–15.4%; I^2=81.7%, 17 studies), followed by contacts ⩾15 years old (5.2%, 95% CI 3.7–6.8%; I^2=99.0%, 24 studies) (table 2).

Symptom screening as part of an initial algorithm was included in 113 studies (60.4%), while smear microscopy was the most reported microbiological test used (n=91 (48.6%)). The pooled TB prevalence among contacts varied according to the initial diagnostic test performed and the confirmatory microbiological test used to detect TB (table 3 and supplementary table E8).

Incident TB detected among contacts

The pooled annual TB incidence was highest in the first year after exposure to index patients (2.0%, 95% CI 1.1–3.3%; I^2=96.2%, 14 studies) and significantly reduced 5 years after exposure to index patients (0.5%, 95% CI 0.3–0.9%, one study) (figure 2).

LTBI prevalence among contacts

We identified 135 studies which reported on LTBI testing and prevalence, comprising 473 075 individuals (table 4). The overall pooled prevalence of LTBI among contacts was 42.4% (95% CI 38.5–46.4%; I^2=99.8%, 135 studies). When stratified by TB incidence of study setting, pooled LTBI prevalence was 28.6% (95% CI 22.7–34.8%; I^2=99.8%, 37 studies) in low-incidence settings, 44.7% (95% CI 36.5–

TABLE 2 Meta-analyses of co-prevalent tuberculosis (TB) detected among contacts, grouped by selected index patient, contact and study characteristics

	Studies n	Contacts with active TB n	Contacts screened n	Pooled prevalence % (95% CI)	I^2 %
Any TB	181	19 277	1 308 612	3.6 (3.3–4.0)	98.9
Microbiologically confirmed TB	106	14 495	955 733	3.2 (2.6–3.7)	99.5
Index TB type					
All forms of TB	181	19 277	1 308 612	3.6 (3.3–4.0)	98.9
Smear-positive TB	58	4417	264 782	3.7 (3.0–4.5)	98.6
Microbiologically confirmed TB	100	10 157	586 980	3.8 (3.3–4.3)	98.4
MDR/XDR-TB	20	4911	275 332	4.1 (2.8–5.6)	98.1
Country income classification[#]					
Low	35	4155	356 605	5.0 (4.0–6.1)	98.7
Low-middle	53	8404	522 718	4.4 (3.8–5.1)	98.6
Upper-middle	51	3563	89 024	3.9 (2.9–5.1)	98.4
High	42	3155	340 265	1.8 (1.3–2.3)	98.8
TB incidence setting[¶]					
Low	37	2949	187 411	1.9 (1.5–2.4)	97.7
Medium	33	1029	196 264	1.9 (1.3–2.6)	97.6
High	111	15 299	924 937	5.0 (4.5–5.5)	99.0
Year of study publication					
2011–2013	30	6246	326 407	3.6 (2.7–4.7)	98.8
2014–2016	37	6889	485 715	4.1 (2.8–5.6)	99.7
2017–2019	39	1360	143 611	2.1 (1.5–2.8)	98.1
Contact age group					
<5 years	28	799	48 805	3.9 (2.5–5.4)	97.0
5–14 years	18	277	14 501	2.4 (1.6–3.4)	84.5
⩾15 years	24	3740	222 362	5.2 (3.7–6.8)	99.0
Contact with HIV infection	17	287	2941	11.6 (8.2–15.4)	81.7
Contact type					
Any contact	181	19 277	1 308 612	3.6 (3.3–4.0)	98.9
Household contact	146	15 042	994 755	3.5 (3.2–3.9)	98.4
Casual contact	9	1294	84 074	1.9 (1.0–3.1)	99.0

MDR: multidrug-resistant; XDR: extensively drug-resistant. [#]: annual per capita Gross National Income of ⩽USD 1035 per year (low income), USD 1036–4045 per year (low-middle income), USD 4046–12 535 per year (upper-middle income) or >USD 12 535 per year (high income) [15]; [¶]: TB incidence per 100 000 population of <20 (low incidence), 20–99 (medium incidence) or ⩾100 (high incidence).

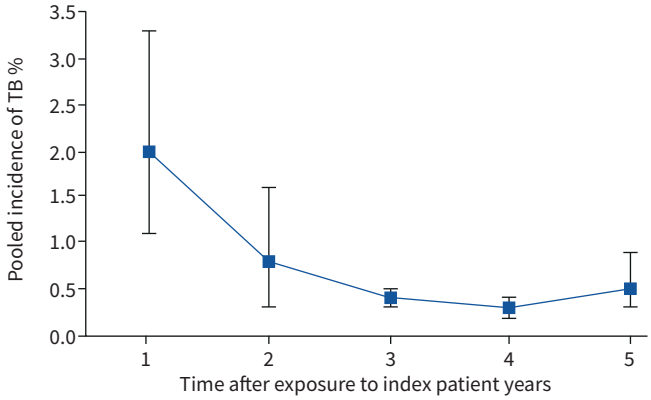

FIGURE 2 Meta-analyses of incident tuberculosis (TB) detected among contacts by year of follow-up after exposure to index patient.

TABLE 3 Meta-analyses of co-prevalent tuberculosis (TB) detected among contacts, by initial screening and microbiological test(s) used to diagnose TB

	Studies n	Contacts identified with active TB n	Contacts screened n	Pooled proportion of contacts with TB % (95% CI)	I^2 %
Initial screening test					
Symptoms only	9	153	20 118	1.7 (0.7–3.2)	95.2
Chest radiography only	25	1893	88 103	3.6 (2.6–4.8)	98.4
Symptoms+chest radiography	56	6411	366 508	4.4 (3.8–5.2)	97.9
Test(s) used to diagnose TB					
Smear only	33	4630	398 561	3.3 (2.6–4.0)	98.6
NAAT only	3	41	5374	0.9 (0.1–2.2)	77.5
Culture only	1	55	2136	2.6 (2.0–3.3)	NA
Smear+NAAT	12	1627	162 172	3.4 (2.2–4.9)	99.1
Smear+culture	35	7183	346 318	4.3 (3.5–5.3)	98.6
NAAT+culture	2	65	546	11.6 (9.0–14.5)	NA
Smear+NAAT+culture	8	684	17 334	6.6 (0.3–19.5)	99.7
Any microbiological test	94	14 285	932 441	3.9 (3.5–4.4)	99.0

Smear: sputum smear microscopy; NAAT: nucleic acid amplification test; culture: liquid or solid mycobacterial culture; NA: not available.

53.1%; I^2=99.4%, 39 studies) in medium-incidence settings and 50.5% (95% CI 46.7–54.3%; I^2=99.2%, 59 studies) in high-incidence settings.

Evaluation of algorithms for identifying co-prevalent TB among contacts

The pooled TB prevalence by initial screening and microbiological test(s) is shown in table 3. Studies which reported the use of symptom screening and chest radiography had the highest pooled prevalence at

TABLE 4 Prevalence of latent tuberculosis infection (LTBI) among contacts of patients with TB, stratified according to contact and index patient characteristics

	Studies n	Contacts tested for LTBI n	Contacts with LTBI n	Pooled prevalence % (95% CI)	I^2 %
All ages	135	473 075	185 171	42.4 (38.5–46.4)	99.8
Contact age group					
<5 years	17	3459	1207	37.1 (25.9–48.9)	97.7
5–14 years	13	4800	2405	50.2 (42.6–57.8)	95.5
⩾15 years	10	20 060	6513	42.7 (22.5–64.3)	99.9
Country income classification[#]					
Low	21	13 693	7250	60.3 (46.8–73.1)	99.6
Low-middle	29	264 795	124 439	45.0 (40.3–49.8)	98.1
Upper-middle	40	39 629	19 232	47.8 (40.5–55.1)	99.4
High	45	154 958	34 250	28.7 (23.5–34.2)	99.8
TB incidence setting[¶]					
Low	37	146 096	31 621	28.6 (22.7–34.8)	99.8
Medium	39	25 530	10 087	44.7 (36.5–53.1)	99.4
High	59	301 449	143 463	50.5 (46.7–54.3)	99.2
Index TB type					
All forms of TB	135	473 075	185 171	42.4 (38.5–46.4)	99.8
Microbiologically confirmed	82	342 361	154 473	46.6 (42.9–50.4)	99.5
Smear-positive	80	336 826	153 187	46.8 (43.1–50.4)	99.5
MDR/XDR-TB	12	257 696	120 445	42.9 (33.4–52.7)	98.8

Smear: sputum smear microscopy; MDR: multidrug-resistant; XDR: extensively drug-resistant. [#]: annual per capita Gross National Income ⩽USD 1035 per year (low income), USD 1036–4045 per year (low-middle income), USD 4046–12 535 per year (upper-middle income) or >USD 12 535 per year (high income) [15]; [¶]: TB incidence per 100 000 population <20 (low incidence), 20–99 (medium incidence) or ⩾100 (high incidence).

4.4% (95% CI 3.8–5.2%; I^2=97.9%, 56 studies). Variations in pooled TB prevalence were observed by microbiological test(s) used to diagnose TB, with the combination of NAAT and culture reporting the highest prevalence at 11.6% (95% CI 9.0–14.5%; two studies).

Assessment of publication bias

A visual inspection of funnel plots for nonrandomised studies reporting on TB disease and LTBI illustrated significant asymmetry indicating an under-reporting of studies with low case detection (supplementary figures E1 and E2). Evidence of publication bias was noted for studies reporting TB disease ($p<0.001$ using the Egger test) but not LTBI prevalence ($p<0.2$ using the Egger test).

Discussion

This systematic review and meta-analysis found evidence that contact investigation was effective and associated with increased case detection [5], reduced mortality and decreased community prevalence of TB [9]. Contact investigation also resulted in a high yield of cases of co-prevalent and incident TB, as well as a high prevalence of LTBI. The prevalence of TB among contacts was found to be high, particularly in low-income and high TB incidence settings, and among contacts of MDR/XDR-TB index patients, contacts ⩾15 years old and contacts infected with HIV.

An accurate estimate of the effectiveness of contact investigation requires both an intervention group and also a comparator group where systematic screening was not performed. Randomised trials provide the most robust evidence of effectiveness, accounting for both measured and unmeasured confounding. Despite identifying a large number of studies in this review, most lacked a valid comparison group where screening was not performed, *i.e.* nonrandomised studies, which likely overestimate the benefits of contact investigation. Only three randomised controlled studies included a valid comparison group [5, 9, 20]. Differences in the outcome measures precluded the ability to conduct a meta-analysis of the outcomes of these three studies, of which two demonstrated effectiveness. In the first, a study from sub-Saharan Africa, a high-prevalence setting for TB and HIV, the community prevalence of TB was reduced by 18% owing to the intervention [9]. The second study from Vietnam, a high-incidence setting with a low prevalence of HIV [5], found that notification of TB and microbiologically confirmed TB increased, while all-cause mortality decreased. This study provides high certainty that contact investigation increases case detection. Together, these randomised trials provide strong evidence for the effectiveness of contact investigation in high-prevalence settings.

The prevalence of TB among contacts was shown to be high. The overall pooled prevalence of any TB in contacts included in this review was 3.6%, slightly higher than the 3.1% estimate in a previous meta-analysis of studies published between 1946 and 2011 [24]. Our findings may reflect scaling up of more sensitive diagnostic tests, particularly GeneXpert MTB/RIF, over the past decade [25]. Stratified estimates demonstrated a high pooled prevalence among certain groups of contacts, including contacts of MDR/XDR-TB index patients, in keeping with the prolonged duration of infectiousness of these patients [26]. Although this finding suggests that contacts of MDR/XDR-TB index patients may be at higher risk for developing TB, few studies have compared transmission of drug-susceptible *versus* drug-resistant TB [27]. While drug-resistant TB accounts for only 5% of the total TB burden globally, its high morbidity and mortality coupled with high costs associated with treatment make it necessary to investigate contacts exposed to drug-resistant index patients. The results from ongoing TPT trials [28, 29] will also provide important insights into selection of regimens and other implementation issues for this group of contacts.

The yield of contact investigation varied considerably between settings. We found the prevalence of TB detected among contacts was highest in high-incidence and low-income settings, consistent with high levels of community transmission [30]. Studies conducted in high-incidence settings had the highest pooled TB prevalence compared with low-incidence settings (5.0% and 1.9%, respectively). There are several possible explanations for this finding, including earlier TB screening and treatment of LTBI among contacts to prevent disease in low-incidence settings [31] and the lower risk of transmission to contacts from sources outside of the household [31]. This highlights the value of implementing strategies such as contact investigation in high-incidence settings. The higher TB prevalence among contacts in high-incidence settings suggests that transmission outside of the household plays an important role in household infection [30]. This indicates the need to expand case finding beyond known household contacts in order to reduce transmission in these settings. We also note a trend in increased case detection from 2011 to 2016 reported in studies; however, a reduction in prevalence was found for the period 2017–2019. These estimates may represent the scale-up of NAATs and the subsequent global decline in TB incidence, respectively.

Individuals who are HIV-infected are also known to be at high risk for developing TB [32]. We found the pooled prevalence of TB in this population was 11.6%, the highest among any subgroup. This finding confirms and supports the current recommendations for early TB screening and preventive therapy in this population [33]. Regardless of exposure to a known TB patient, HIV-infected individuals should always be targeted for ongoing screening, particularly in high TB incidence settings where the likelihood of infection remains high.

The use of highly sensitive screening and diagnostic algorithms provides important predictors of increased yield of contact investigation. In our review, studies that combined symptom screening and chest radiography for identifying presumptive TB patients had a higher pooled prevalence of TB detected than those which used symptoms only (4.4% *versus* 1.7%). Smear microscopy was used to confirm a diagnosis of TB in most studies. Rapid NAATs such as GeneXpert MTB/RIF were used in just 16% of studies, reflecting limited dissemination of this more sensitive, but also more costly, technology [34]. Importantly, the pooled prevalence of microbiologically confirmed TB among contacts of 3.2% in our study was substantially higher than reviews of studies before 2011 [24, 35], suggesting a potential benefit from using molecular rapid diagnostics for contact screening. We found that pooled prevalence of TB increased considerably when GeneXpert MTB/RIF was combined with mycobacterial culture. This suggests that if a more sensitive confirmatory test(s) is used, the yield and impact of contact investigation might be further improved. New-generation NAATs with increased sensitivity [36] may further strengthen active case finding. Finding contacts with paucibacillary TB is an expected outcome from contact investigation. Therefore, the selection of sensitive test algorithms must ensure that results are available rapidly while maintaining detection capabilities.

Our finding that TB incidence remained high throughout the first 5 years following exposure indicates that TPT and/or serial screening are both important for the management of contacts. Repeat screening has the advantage of detecting missed prevalent cases [5, 37]; however, it may not be necessary if effective TPT is given. We also found a prevalence of LTBI among contacts of 42.4%, slightly lower than previous reviews [24, 35]. It is possible that these differences reflect temporal changes in TB incidence over the past 20 years or the increased use of the IGRA, which is less likely to cause false positives compared with the TST. The expansion of screening to include contacts at a lower risk of infection, such as contacts of patients with culture-positive and smear-negative TB, may also explain the observed fall in prevalence of LTBI in low- and middle-income settings since 2011. In contrast, we found LTBI prevalence among contacts remained similar in high-income settings. Nevertheless, these findings highlight the high risk of LTBI among contacts, and the importance of TPT for contacts, to prevent incident TB. This supports recommendations to combine scale-up of contact investigation combined with TPT in high-incidence settings [38]. The included studies also demonstrate the feasibility of the TST and IGRA in high- and low-resource settings [39]. Efforts to increase access to tuberculin, coupled with health systems strengthening and staff training in the management of LTBI, can help to support the widespread adoption of TPT in resource-limited settings [40].

This systematic review and meta-analysis has several limitations. First, high levels of heterogeneity were observed among nonrandomised studies, as reflected by the I^2 statistic. This is consistent with previous meta-analyses of contact investigation [24, 35]. Our study does characterise several factors which may explain inter-study variability, including variations in contact and index patient characteristics, screening algorithms employed, and differences in the epidemiology of TB between settings. However, the substantial heterogeneity precluded further subgroup analyses. Second, there is known attrition prior to completing screening of contacts during contact investigation, likely resulting in an underestimation of TB prevalence. In addition, contacts with symptoms are usually the only contacts evaluated, thus true prevalence is underestimated in most studies where this occurs. Third, the classification of TB among contacts as co-prevalent or incident depends upon whether TB is detected at the time of initial contact screening. A higher proportion of cases will be co-prevalent if delays in contact investigation occur, since contacts with LTBI may develop active disease prior to screening. Hence, contacts with co-prevalent or incident TB may be misclassified as a result of local differences in the performance of screening algorithms.

Our study has important policy implications. First, we have identified evidence for the effectiveness of contact investigation. Randomised trials published in the last decade provide greater confidence in the benefit of contact investigation for contacts. Second, despite limitations in using nonrandomised studies, we identified specific settings and specific subgroups at an increased risk of TB. Third, our comprehensive search strategy identified a large number of recent studies to evaluate LTBI among contacts. This provides a lower, and likely more robust, estimate compared with a recent review including 27 studies [41]. Our

study also provides further support for why contacts of active TB patients should be prioritised for TPT, as part of wider TB control efforts.

In light of the existing data from randomised trials showing a benefit for contact investigation, it is unlikely to be ethical to conduct future randomised trials of contact investigation that include no screening as a comparator. Further operational research is now required to optimise the delivery of contact investigation in different settings (*e.g.* ensuring maximal enrolment and follow-up of contacts). High-quality studies comparing different screening and confirmatory testing modalities on the detection of TB among contacts are lacking. Priorities for future research include the evaluation of interventions to improve the accuracy of chest radiography interpretation [42], use of molecular diagnostics (including whole-genome sequencing) for the timely detection of drug-resistant TB among high-risk contacts, and evaluation of interventions that expand access to testing and treatment for LTBI.

Conclusions

Recent randomised controlled trials have shown that contact investigation is an effective intervention for increasing TB case detection among contacts, reducing mortality and decreasing community prevalence of TB. The pooled prevalence estimate of microbiologically confirmed TB from our study is higher than previous reviews [24, 35], suggesting that newer rapid molecular diagnostics have improved case detection. The scale-up of contact investigation promises to increase early diagnosis and prevention, contributing to global TB elimination efforts.

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