Contact investigation for tuberculosis: a systematic review and meta-analysis

Gregory J. Fox*, Simone E. Barry#, Warwick J. Britton#,¶ and Guy B. Marks*,+

ABSTRACT: Investigation of contacts of patients with tuberculosis (TB) is a priority for TB control in high-income countries, and is increasingly being considered in resource-limited settings. This review was commissioned for a World Health Organization Expert Panel to develop global contact investigation guidelines.

We performed a systematic review and meta-analysis of all studies reporting the prevalence of TB and latent TB infection, and the annual incidence of TB among contacts of patients with TB.

After screening 9,555 titles, we included 203 published studies. In 95 studies from low- and middle-income settings, the prevalence of active TB in all contacts was 3.1% (95% CI 2.2–4.4%, I^2=99.4%), microbiologically proven TB was 1.2% (95% CI 0.9–1.8%, I^2=95.9%), and latent TB infection was 51.5% (95% CI 47.1–55.8%, I^2=98.9%). The prevalence of TB among household contacts was 3.1% (95% CI 2.1–4.5%, I^2=98.8%) and among contacts of patients with multidrug-resistant or extensively drug-resistant TB was 3.4% (95% CI 0.8–12.6%, I^2=95.7%). Incidence was greatest in the first year after exposure. In 108 studies from high-income settings, the prevalence of TB among contacts was 1.4% (95% CI 1.1–1.8%, I^2=98.7%), and the prevalence of latent infection was 28.1% (95% CI 24.2–32.4%, I^2=99.5%). There was substantial heterogeneity among published studies.

Contacts of TB patients are a high-risk group for developing TB, particularly within the first year. Children <5 yrs of age and people living with HIV are particularly at risk. Policy recommendations must consider evidence of the cost-effectiveness of various contact tracing strategies, and also incorporate complementary strategies to enhance case finding.

KEYWORDS: Contact tracing, early diagnosis, human, *Mycobacterium tuberculosis*, systematic review, tuberculosis

Tuberculosis (TB) remains a major global health challenge, affecting 8.8 million people each year, most of whom live in low- and middle-income countries [1]. The importance of TB control in social and economic development has been widely acknowledged, including in the Millennium Development Goals. In this context, the World Health Organization (WHO) STOP TB Partnership has set two targets: 1) to reduce prevalence and deaths by 50% by 2015, relative to 1990 levels; and 2) to eliminate TB as a public health problem by 2050 [2]. In order to achieve these targets, healthcare systems will need to identify more cases of TB at an earlier stage of the illness [3].

Contact investigation involves the systematic evaluation of the contacts of known TB patients to identify active disease or latent TB infection (LTBI). It is one of a number of active case-finding strategies that have been proposed to increase case detection [4]. Active case finding may be worthwhile in contacts of patients with TB because they are at higher risk of exposure to the causative organism than members of the general population [5]. After exposure to airborne droplets containing *Mycobacterium tuberculosis*, some contacts will be infected and some of these will go on to develop disease. The risk of a contact becoming infected relates to the infectiousness of the TB patient, the duration and proximity of the contact [6, 7], and susceptibility of the contact [8, 9]. The onset of disease may occur early, within 6 weeks, or many years later [10]. Contact investigations are undertaken to prevent or detect these cases.

Contact investigation has been standard practice for decades in high-income countries, where the incidence of TB in the general population is low [11]. It may involve clinical assessment, chest

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radiography, microbiological evaluation of sputum or a test to detect LTBI, such as a tuberculin skin test (TST) or an interferon-γ release assay. There has been a growing interest in contact investigation in resource-limited settings as national programmes seek new methods for improving case detection [12]. The WHO currently recommends contact investigation in two high-risk populations: children aged <5 yrs [13] and people living with, or at high risk of, HIV infection [14]. Recently, the WHO has also launched the first international standards for the investigation of contacts of patients with infectious TB [15].

One previous meta-analysis examined data from 41 household contact investigation studies in low–middle-income countries up to 2005 [16]. However, there has not yet been an analysis of contact investigation beyond the household setting or in high-income countries. Furthermore, the previous meta-analysis was limited to cases of TB that were diagnosed at the time of the initial contact investigation. There has not yet been a meta-analysis of data on the incidence of TB among contacts during the 5 yrs following exposure. Nor has there been an analysis of key risk groups, such as contacts of patients with multidrug-resistant (MDR)-TB. Therefore, the aim of the analysis presented here is to systematically review and quantify data on the prevalence of TB and LTBI and the subsequent incidence of TB in contacts of patients with TB in household and non-household settings in high-, middle- and low-income countries and in various risk groups.

This systematic review and meta-analysis was conducted as a part of a GRADE (Grading of Recommendations Assessment, Development and Evaluation) [17] review for an Expert Panel that was convened to contribute to the development of international guidelines on contact investigation for the WHO [15].

METHODS
Search strategy and study selection
This review followed the methods described in the PRISMA statement for the reporting of systematic reviews and meta-analyses [18]. First, we searched the literature for available systematic reviews and meta-analyses, identifying a Cochrane review [19], a systematic review of household contact investigation [16], and two reviews focusing on specific populations [20, 21]. We then designed a search for all published studies that provided a measure of prevalence or incidence of TB or LTBI among contacts of patients with new or recurrent TB. We conducted the search using PubMed, EMBASE, LILACS and Web of Science for all studies up to October 1, 2011. Our search included the terms: ''tuberculosis'', ''*Mycobacterium tuberculosis*'', ''tuberculosis, pulmonary'', and ''contact tracing'', ''disease outbreaks'', ''contact'', ''spread'', ''contact screen*'', ''disease transmission'', ''case find'', ''cluster analysis'', ''household'', ''household contact'', ''case finding" or ''case detection''. The full search strategy is available in the supplementary material.

All titles and abstracts were assessed for inclusion according to the following agreed criteria. We included all English language studies that reported a quantitative measure of the TB or LTBI diagnosed among contacts of patients with TB. We only included studies where the number of cases tested was also reported, and where specific source patients with TB (index

patients) had been identified before screening was conducted. We excluded studies where the diagnosis of TB was not made according to clinical, radiological or microbiological criteria or where there were less than 10 index patients or contacts identified in the study.

Cross-sectional, case–control studies and cohort studies were included. We also sought evidence from any published randomised controlled trials. We excluded editorials, conference abstracts and systematic reviews.

Data extraction and definitions
Two reviewers (G.J. Fox and C. Dobler (Woolcock Institute of Medical Research, University of Sydney, Sydney, Australia)) independently screened all titles identified in the database searches. The full-text of all articles included by either reviewer on the basis of abstract was obtained. To determine eligibility for inclusion, one author reviewed all full-text articles. A second author (W.J. Britton) repeated this assessment independently for a random selection of 10% of full-text articles and there was complete agreement about excluded articles.

Two authors independently extracted data from all of the included studies. One author (G.J. Fox) extracted all data from all studies, and the other authors (S.E. Barry, W.J. Britton and G.B. Marks) independently re-extracted data for six key data fields from all of the included studies between them. Disagreements were resolved by consensus.

Where data from the same contact cohort were included in multiple papers, we included the study with the most complete data. If the reviewers were certain the two studies had the same participants and there were different sets of data in two papers then the results were merged into one entry. If a paper described outcomes in two countries, the data from each were reported separately.

Data extracted from selected studies included: 1) study design, country, location of exposure, selection criteria for index patients and contacts; 2) screening methods employed; and 3) outcomes including number of contacts screened, the number of cases of TB and microbiologically proven disease among contacts, the number of contacts with LTBI, and the number of incident cases each year during the first 5 yrs. Subgroup data were extracted for outcomes of TB, microbiologically proven TB and LTBI among contacts of acid-fast bacilli (AFB) smear-positive and AFB smear-negative source patients (index patients), index patients with HIV, and MDR- or extensively drug-resistant (XDR)-TB. Subgroup data were also extracted for contacts that were known to be HIV positive, household contacts, close contacts, casual contacts and contacts from congregate settings.

We analysed data on TB and LTBI for the following age groups: ≤5 yrs, 5–14 yrs and ≥15 yrs. Where the limits of the age range reported in studies were up to 1 yr higher or lower than our pre-defined age range, data were included in the pre-defined range for analysis. Otherwise, the age-specific data were not extracted. Where children were identified as ''index patients'', then data were included for all screened ''contacts'' even if an undiagnosed adult might have been the source case.

Household contacts were those living in the same household as the index patient. Contacts were defined as ''close'' if they
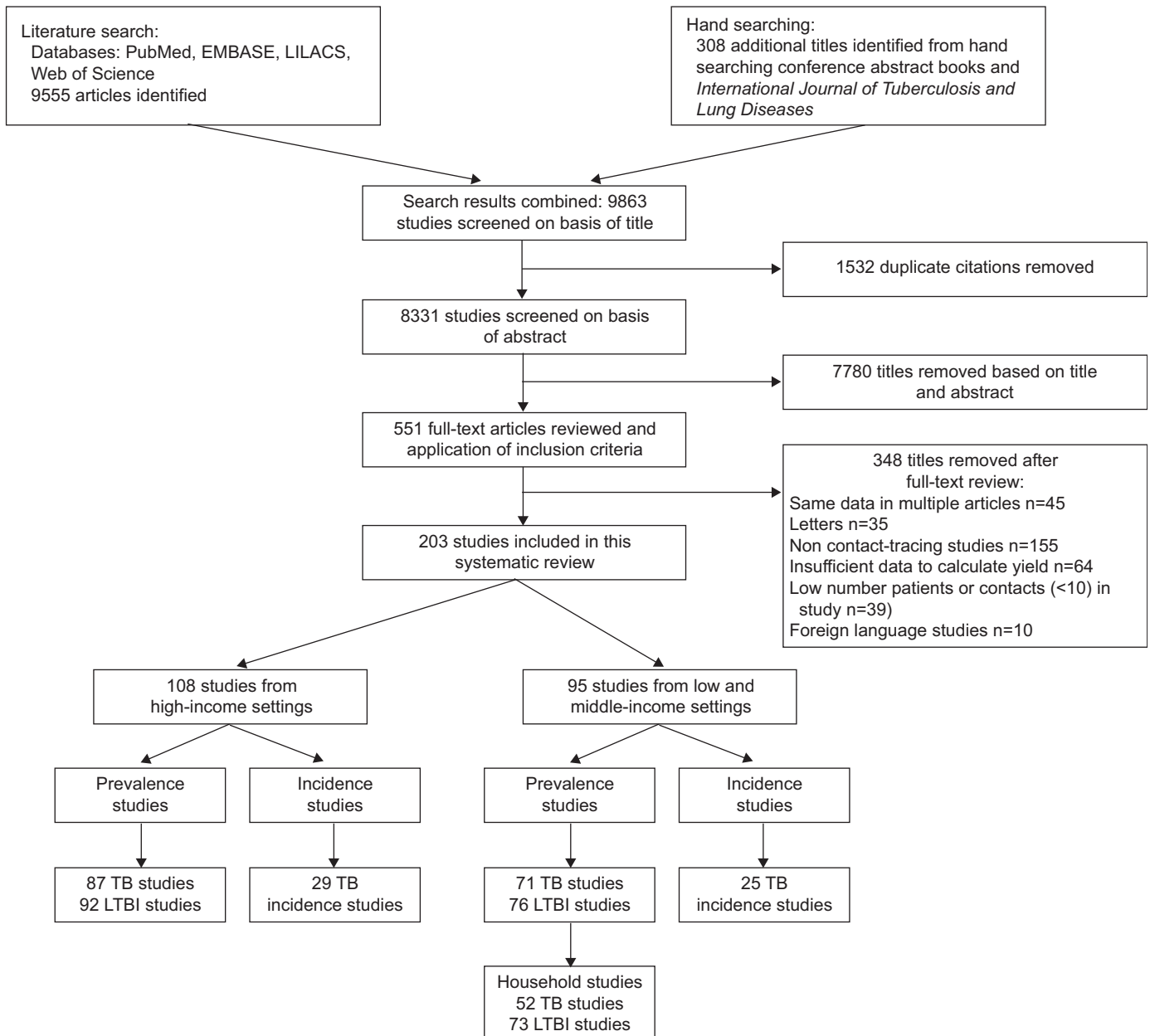
FIGURE 1. Flow diagram for study selection. TB: tuberculosis; LTBI: latent tuberculosis infection.

were described as this in the manuscript, or if they were household contacts.

Prevalent cases of TB among the screened contacts were defined as previously undiagnosed cases of TB among contacts diagnosed during the baseline contact investigation or within the first 3 months after diagnosis of the index patient. Contacts that had been diagnosed with TB prior to the contact investigation were not considered prevalent cases because the identification of these cases could not be attributed to the contact investigation. Incident cases of TB were separately analysed by year after exposure to the index patient with incidence in the first year being from 3–12 months after diagnosis of the index case, incidence in the second year being between 13 and 24 months, and so on up to the end of 5 yrs. Incidence data were not reported if annual incidence

could not be determined. Incidence at 1 yr was calculated excluding the prevalent cases identified during the initial investigation. Contacts were included in the "at risk" population for analysis if they attended the first reported screening procedure and had not already been diagnosed with TB prior to that screening procedure. This at risk population was the denominator for the estimation of prevalence and subsequent incidence.

We defined LTBI as having a TST $\geqslant 10$ mm at 48–72 h. Where these data were not available we used the definition applied in the paper.

Studies were stratified by income level of the country in which they were conducted by applying the World Bank definitions of high-income or low–middle-income countries based on gross national income from 2010 or the latest preceding year

TABLE 1	Prevalence of active tuberculosis (TB) among contacts in low–middle- and high-income countries						
	Included studies	Contacts with active TB	Contacts screened	Proportion %	95% CI	τ^2	I^2
Low–middle income							
All ages							
All[#]	71	24799	878724	3.1	2.2–4.4	2.18	99.4
Index patient smear positive	44	1415	43960	3.3	2.2–5.1	2.04	98.5
Index patient with HIV	6	90	1526	5.4	2.2–12.4	1.14	95.5
Index patient XDR/MDR-TB	6	149	5584	3.4	0.8–12.6	2.88	95.7
Household contacts	68	22390	858422	3.1	2.1–4.5	2.35	98.8
All close contacts	70	22458	860638	3.1	2.2–4.4	2.22	98.8
Casual contacts only	1	34	1492	2.2	1.6–3.0	0.00	
Contacts with HIV infection	8	96	391	21.6	8.8–44.1	2.04	92.3
⩽5 yrs	21	754	5112	10.0	5.0–18.9	2.35	97.8
5–14 yrs	9	155	1643	8.4	2.8–22.6	2.51	92.5
⩾15 yrs	11	127	3614	3.2	2.0–5.3	0.53	87.1
High income							
All ages							
All[¶]	87	5058	308048	1.4	1.1–1.8	1.48	98.7
Index patient smear positive	27	1704	72936	3.3	2.2–4.8	1.08	98.3
Index patient XDR/MDR-TB	2	0	554	0.0		0.00	99.9
Household contacts	29	2047	56221	3.0	2.0–4.4	1.09	98.2
All close contacts	45	3053	127699	1.9	1.3–2.7	1.42	98.7
Casual contacts only	9	73	15607	0.4	0.2–0.6	0.30	79.9
Contacts with HIV infection	2	15	133	11.4	7.0–18.0	0.00	9.0
⩽5 yrs	10	212	4057	4.7	3.4–6.4	0.18	79.0
5–14 yrs	9	253	5665	2.9	1.7–5.1	0.56	95.5
⩾15 yrs	9	507	17867	2.3	1.1–4.8	1.19	99.0

Data are presented as n, unless otherwise stated. XDR: extensively drug resistant; MDR: multidrug resistant. Countries were classified according to World Bank Income Gross National Income per capita: low income (⩽$1,005 per yr); lower-middle income ($1,006 to $3,975 per yr); upper-middle income ($3,976 to $12,275 per yr); high income (⩾$12,276 per yr) [22]. [#]: [9, 32–101]; [¶]: [10, 30, 31, 102–184]. Refer to supplementary material for outcomes of individual included studies.

for which data were available [22]. Studies were also stratified by WHO region. We stratified outcomes according to proximity of exposure (household, close and casual), age group, HIV status of the index patient, HIV status of the contact, smear positivity of the index patient and a diagnosis of MDR-TB in the index patient. We stratified outcomes according to whether contacts and index patients participating in contact investigation were foreigners or born locally. We planned to assess the risk of bias of studies at the level of outcome level. We also planned to determine whether study design was independently associated with yield and, if so, to conduct separate analyses for cross-sectional and cohort studies. More detailed definitions of the diagnostic and stratification criteria are included in the supplementary material.

Summary measures and methods of analysis

For each study, incidence rate was calculated as the number of incident cases per year divided by the population at risk and prevalence was calculated as the number of prevalent cases expressed as a proportion of the size of the at-risk population. Asymptotic 95% confidence intervals were calculated using the method of FLEISS [23].

For the meta-analysis weighted average estimates of incidence rate and prevalence were calculated using the exact binomial method of HAMZA et al. [24] fitted using Proc NLMIXED in SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

The effect of study design and country income level (low–middle or high) on the estimates was tested using logistic regression fitted by generalised estimating equations with an unstructured covariance matrix in Proc Genmod. Since local and foreign born contacts were assessed and reported in the same study, we used a matched pair analysis to estimate the odds ratios for LTBI and TB among foreign-born contacts compared to local-born contacts. This was performed using Proc Logistic with strata statement.

Incidence rate ratio was calculated for each study that reported incidence in the first year as the ratio of the TB incidence rate during the first year of follow-up, divided by the estimated general population incidence of TB in the mid-year of the study period or in 1990, whichever was the later [25]. For all studies, and for studies classified by income group and by study design, the median and interquartile range for the incidence rate ratio was estimated for the first and second years.

We estimated between study inconsistency as I^2, representing the percentage of total variation across studies that was attributable to heterogeneity, using the method proposed by HIGGINS et al. [26] and RILEY et al. [27]. Values of I^2 near 0%
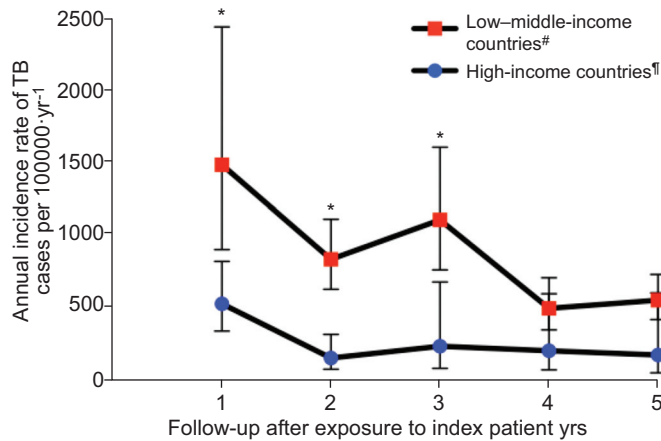
FIGURE 2. Annual incidence rate of tuberculosis (TB) in contacts by year of follow-up, according to country income. World Bank Income Gross National Income per capita: low income (≤$1,005 per yr); lower-middle income ($1,006 to $3,975 per yr); upper-middle income ($3,976 to $12,275 per yr); high income (≥$12,276 per yr) [22]. *: p<0.05, statistically significant difference between contacts from high compared to low–middle-income countries. #: [25, 32, 36–50, 102–106, 110–127, 185–193]; ¶: [33, 34, 103–105, 129, 135, 136, 140, 143, 144, 148–151, 153, 157, 163, 164, 172, 194–202]. Refer to the supplementary material for complete details of outcomes, estimates of heterogeneity and outcomes of individual included studies.

indicates no observed heterogeneity and larger values show increasing heterogeneity. This measure does not inherently depend upon the number of studies in the meta-analysis and can be applied to all study designs [26]. Portions of the code used for the analysis are included in the supplementary material.

Role of the funding source
No funding bodies had any role in the study design, data collection, data analysis, data interpretation or writing of the report. The authors had access to all study data and are responsible for the decision to submit for publication.

RESULTS
Study selection and study characteristics
We identified 9,555 unique publications, and included 108 (53.2%) studies performed in high-income countries and 95 (46.8%) studies performed in low- and middle-income countries. These 203 studies included 158 studies reporting data on TB disease status of 1,186,772 contacts and 168 studies reporting LTBI status on 345,062 contacts. We included 15 cross-sectional studies, two case–control studies, 185 cohort studies and one randomised controlled trial in the analysis. The reasons for exclusion at each stage are summarised in figure 1. There were an average of 3.8 (95% CI 2.3–5.0) contacts per index patient in studies from low–middle-income countries and an average of 5.1 (95% CI 3.1–10.4) contacts per index patients in studies from high-income countries.

Definitions used in studies
The definitions of ''household contact'' varied considerably between studies. Some described household based on location, such as a common eating or sleeping area, while some studies stipulated a minimum duration of exposure or degree of

proximity [28]. Definitions of close contact also varied considerably in the requisite intensity of exposure to patients. Some studies had a broad definition, with close including any known exposure [29], others used expressions such as intimate [30], sharing the air for a prolonged period [31], or specifying a minimum duration of exposure in other closed spaces such as the workplace [32]. Some studies did not provide precise definitions of close contacts [33].

Low and middle-income countries
Table 1 shows the summary estimates for prevalence of previously undiagnosed TB. Figure 2 shows the incidence of TB for the first 5 yrs after exposure to the index patient. Table 2 shows the prevalence of LTBI in contacts and table 3 shows the prevalence of microbiologically proven TB. The findings of the individual studies that form the basis of these summary estimates are shown in the supplementary material. There was substantial heterogeneity between studies, indicated by high I^2 statistics. TST was used as the primary measure of LTBI in all but six studies, where only Heaf test results were available [34, 102–104].

The estimated overall prevalence of TB (clinically and/or microbiologically diagnosed) in all contacts in low- and middle-income countries was 3.1% (95% CI 2.2–4.4, I^2=99.4%). In these countries, the prevalence of TB in household contacts was 3.1% (95% CI 2.1–4.5, I^2=98.8%). Prevalence according to setting of exposure is shown in figures 3 and 4. The prevalence of LTBI among contacts is shown in table 2, and prevalence of microbiologically proven TB is shown in table 3. The incidence rates for TB up to 5 yrs after exposure are shown in figure 2, with additional incidence data included the supplementary material.

Among contacts of smear-positive index patients the prevalence of TB was 3.3% (95% CI 2.2–5.1, I^2=98.5%) and the prevalence of LTBI was 52.9% (95% CI 48.9–56.8, I^2=97.7%). Among contacts of MDR- or XDR-TB, the prevalence of TB was 3.4% (95% CI 0.8–12.6, I^2=95.7%) and the prevalence of LTBI was 61.3% (95% CI 39.1–79.6, I^2=95.2%). Only one study, from Peru, compared the effect of exposure to XDR-TB to MDR-TB and found that the odds of TB among contacts of patients with XDR-TB was 1.88-fold higher than the odds of TB among contacts exposed to MDR-TB (95% CI 1.1–3.21) [35]. Among contacts of index patients with known HIV, the prevalence of TB was 5.4% (95% CI 2.2–12.4, I^2=95.5%) and prevalence of LTBI was 45.7% (95% CI 38.7–52.9, I^2=90.9%).

The prevalence of TB and LTBI among sub-groups including child contacts, close contacts, household contacts and casual contacts are shown in tables 1–3. Outcomes for individual studies are included in the supplementary material.

High-income countries
The reported prevalence of previously undiagnosed active TB among all contacts from high-income countries was 1.4% (95% CI 1.1–1.8, I^2=98.7%) (table 1). The prevalence of disease in household contacts was 3.0% (95% CI 2.0–4.4, I^2=98.2%). The prevalence of LTBI among contacts is shown in table 2. The prevalence of microbiologically proven disease is shown in table 3. Incidence rates of TB among contacts are shown in

figure 2, with additional details in the supplementary material. For the 11 studies from high-income countries that reported the country of origin of screened subjects, an average of 36.2% of screened contacts were born overseas. Table 4 shows the weighted prevalence of LTBI was significantly higher among contacts born overseas compared to those born locally (OR 3.39, 95% CI 3.10–3.71, p<0.0001). Similarly, contacts of foreign born index patients were more likely to be infected than contacts of locally born index patients (OR 2.27, 95% CI 2.08–2.38, p<0.0001) (refer to supplementary material). There were insufficient data to validly estimate the odds ratio for TB disease.

Among contacts of smear-positive patients in high-income settings, the prevalence of TB was 3.3% (95% CI 2.2–4.8, I^2=98.3%) and the prevalence of LTBI was 34.8% (95% CI 27.6–42.7, I^2=99.1%). Tables 1–3 provide data for contact subgroups including contacts of patients with MDR- or XDR-TB, contacts of patients living with HIV, child contacts and contacts with known HIV infection. Outcomes for individual studies are included in the supplementary material.

The median incidence rate ratio (IRR) among contacts during the first year in 29 studies from high-income countries (ratio 46.6, interquartile range (IQR) 3.2–68.0) was substantially higher than that for 25 studies in low–middle-income countries (ratio 15.9, IQR 2.6–21.4). During the second year after exposure, the median IRR for contacts was 9.7 (IQR 2.3–28.6) for 18 high-income and 6.0 (IQR 1.8–105) for 19 low–middle-income countries.

Congregate settings and casual contacts
We identified no studies of contact investigation from low–middle-income countries in congregate settings or among only casual contacts. Table 5 summarises the outcomes of the contact investigation for published studies from congregate settings in high-income countries.

Effect of study design and country income status
The study design had no significant effect on the estimates for either active disease or LTBI, overall or in any population subgroup. Compared to case–control studies, the odds of prevalent disease were 0.88 (95% CI 0.68–1.13, p=0.31) in cohort studies and 1.24 (95% CI 0.65–2.37, p=0.51) in cross-sectional studies. There was a significantly lower prevalence of TB overall among all studies from high-income countries

TABLE 2	Prevalence of latent tuberculosis (TB) infection in the contacts of TB patients in low–middle- and high-income countries						
	Included studies	Contacts with active TB	Contacts screened	Proportion %	95% CI	τ^2	I^2
Low–middle income							
All ages							
All[#]	76	35788	60557	51.5	47.1–55.8	0.58	98.9
Index patient smear positive	51	19003	33875	52.9	48.9–56.8	0.32	97.7
Index patient with HIV	12	1138	2376	45.7	38.7–52.9	0.22	90.9
Index patient XDR/MDR-TB	6	431	684	61.3	39.1–79.6	1.21	95.2
Household contacts	73	23577	49512	45.4	40.7–50.2	0.69	98.4
All close contacts	73	23577	49643	45.3	40.6–50.1	0.69	98.4
Contacts with HIV infection	8	123	247	53.5	40.6–66.0	0.36	71.4
≤5 yrs	33	5102	12389	35.5	30.3–41.1	0.42	96.6
5–14 yrs	21	6587	11123	53.1	42.0–63.9	1.05	98.6
≥15 yrs	10	11980	14057	65.3	35.5–86.5	3.80	99.6
High income							
All ages							
All[¶]	92	79511	284505	28.1	24.2–32.4	0.99	99.5
Index patient smear positive	34	25910	78784	34.8	27.6–42.7	0.96	99.1
Index patient with HIV	1	131	363	36.0	31.2–41.0	0.00	
Index patient XDR/MDR-TB	2	287	554	52.6	49.5–55.7	0.00	
Household contacts	33	20960	67175	30.0	21.3–40.5	1.80	99.6
All close contacts	29	20213	68738	28.0	18.9–39.4	1.96	99.6
Casual contacts only	7	5779	27383	18.7	11.8–28.5	0.52	99.4
Contacts with HIV infection	3	28	151	25.0	11.4–46.4	0.53	86.6
≤5 yrs	17	2093	6900	16.3	9.2–27.0	1.73	99.2
5–14 yrs	10	1,407	4,871	18.4	11.8–27.5	0.64	98.4
≥15 yrs	8	6221	12633	41.9	30.5–54.2	0.50	99.4

Data are presented as n, unless otherwise stated. XDR: extensively drug resistant; MDR: multidrug resistant. World Bank Income Gross National Income per capita: low income (≤$1,005 per yr); lower-middle income ($1,006 to $3,975 per yr); upper-middle income ($3,976 to $12,275 per yr); high income (≥$12,276 per yr) [22]. #: [9, 32, 34, 36–39, 41–43, 48, 49, 52, 55, 57–60, 62–67, 69, 71, 73, 74, 77–79, 81, 83–89, 91, 93–95, 97–101, 185–187, 194–196, 199–201 203–215]; ¶: [10, 28, 30, 31, 102, 103, 105, 107, 109–111, 115, 116, 119, 121–125, 128–138, 142–145, 147–157, 159–184, 188, 189, 193, 202, 216–233].

compared to all studies from low–middle income countries (OR 0.57, 95% CI 0.39–0.84, p=0.005). However, there were no associations between disease prevalence and country income level for either household contacts (OR 1.40, 95% CI 0.93–2.08, p=0.10) or close contacts (OR 0.55, 95% CI 0.37–0.81, p=0.29).

DISCUSSION

Contacts exposed to patients with TB, in a variety of settings, are at substantial risk of LTBI and active TB. The incidence of new cases is highest in the first year and remains above background incidence for at least 5 yrs after exposure to a patient with TB. The prevalence of LTBI and TB among contacts is significantly less in high-income countries than in low–middle-income countries, although this difference was not evident among household contacts. Foreign-born contacts are significantly more likely to have LTBI than locally born contacts in high-income countries.

This systematic review and meta-analysis is broader in scope than a previous meta-analysis on this topic [16]. The inclusion of data from low-, middle- and high-income countries, as well as data on prevalence and incidence in household, close contacts and congregate settings means that the findings are generalisable to most circumstances in which contact investigations are considered. We used an exact binomial approach to meta-analysis, which does not make distributional assumptions or rely on the normal approximation. Hence, our methods are broad in scope and robust in application.

A major limitation on the interpretation of the meta-analysis is the substantial heterogeneity among the studies summarised. This heterogeneity exists even within the strata and subgroups we have investigated and, therefore, must be attributable to factors that we have not investigated in this analysis. These factors may include the background prevalence of disease in the study population and differences in aspects of the study methodologies, such as inclusion criteria for contacts, time of screening relative to the time of diagnosis of the index case, methods of recruiting contacts for investigation, and diagnostic tests implemented during screening. Furthermore, some studies merged incident and prevalent cases, consequently overestimating prevalence. The confidence intervals derived from the random effects meta-analysis reflect the increased uncertainty consequent upon this heterogeneity. Nevertheless, this heterogeneity means that the summary estimates shown here need to be interpreted with caution.

There are other reasons for caution when interpreting the results. The recruitment of contacts in contact investigations is almost always incomplete and is subject to selection bias. Symptomatic contacts may be more likely than those without symptoms to comply with contact investigation. Hence, the measured prevalence of TB among contacts may overestimate the true prevalence of disease among contacts. Nevertheless, it does reflect the likely yield in contact investigations.

There is substantial risk of bias in each of the reported outcomes, owing to the observational design of most studies

TABLE 3	Prevalence of microbiologically proven tuberculosis (TB) in the contacts of TB patients in low–middle- and high-income countries						
	Included studies	Contacts with active TB	Contacts screened	Proportion %	95% CI	τ^2	I^2
Low–middle income							
All ages							
All[#]	38	8633	841721	1.2	0.9–1.8	1.00	95.9
Index patient smear positive	17	150	10241	1.2	0.8–1.8	0.47	87.4
Index patient with HIV	4	35	1317	1.9	0.8–4.5	0.53	89.7
Index patient XDR/MDR-TB	2	2	1056	0.2	0.0–0.8	0.00	82.7
Household contacts	36	8336	811231	1.4	1.0–2.1	1.16	97.9
All close contacts	37	8426	824541	1.4	1.0–2.1	1.14	97.8
Casual contacts only	1	12	1492	0.7	0.4–1.3	0.00	
High income							
All ages							
All[¶]	21	264	45897	0.4	0.2–0.7	1.56	96.1
Index patient smear positive	6	108	5970	0.7	0.3–1.9	1.08	97.6
Index patient XDR/MDR-TB	2	0	554	0.0		0.00	99.9
Household contacts	6	116	5459	1.4	0.8–2.5	0.33	92.6
All close contacts	14	187	30269	0.4	0.2–0.9	1.35	96.9
Casual contacts only	1	0	275	0.0		1.87	

Data are presented as n, unless otherwise stated. XDR: extensively drug resistant; MDR: multidrug resistant. World Bank Income Gross National Income per capita: low income (⩽$1,005 per yr); lower-middle income ($1,006 to $3,975 per yr); upper-middle income ($3,976 to $12,275 per yr); high income (⩾$12,276 per yr) [22]. [#]: [9, 33, 34, 38, 42–46, 54, 56–58, 60, 62, 63, 66–68, 70–73, 75, 76, 79, 82, 84, 85, 88, 90, 91, 95, 97, 99–101, 234]; [¶]: [30, 31, 111–113, 116, 119, 120, 122, 134, 135, 137, 138, 148–150, 154, 165, 166, 170, 177].

and the lack of suitably matched control populations in almost all studies. Publication bias is also an important consideration in all meta-analyses. However, the usual methods for assessing bias using visual or statistical tests are only applicable to randomised controlled trials or trials with matched controls [236, 237] and not to observational studies. Therefore, we were unable to apply the formal assessments of publication bias to this analysis. It is important to consider the possibility that contact investigation with low yield may have been withheld from publication and those reporting higher prevalence of TB may be more likely to be available in the public domain. This possible cause for over-estimation of the prevalence of TB in contacts should be considered when interpreting these results.

The reported data on prevalence of LTBI are subject to all of the known limitations of methods for identifying LTBI in population studies including problems due to anergy, exposure to environmental mycobacteria, and bacilli Calmette–Guérin vaccination. It is probable that the estimate of the prevalence of LTBI among HIV infected contacts is an underestimate as tests for LTBI are more likely to be falsely negative in the presence of HIV infection [185].

Interpreting the findings

Many of the patterns of TB disease and LTBI observed among contacts reflect those observed in the general population. These include findings of a higher prevalence of TB among child contacts compared with adults, and a higher prevalence of TB among contacts in low–middle-income countries compared with high-income countries. This explanation is also supported by the observation that there is no difference between low–middle- and high-income countries when analyses are limited to household contacts, because we would expect the risk in more distant, non-household contacts to be less influenced by the recent exposure to the index case and more influenced by general population risk factors.

The location of exposure to an infectious index patient is one factor that is likely to influence the risk of infection. Another is the contact's prior risk of exposure. The high prevalence of TB and LTBI among household contacts in high-income countries is likely to be explained, in part, by our finding that 36.7% of contacts investigated in high-income countries were foreign born. This is supported by other research that showed an association between the prevalence of LTBI among migrants and the prevalence of TB in the country of origin [107].

The prevalence of clinically diagnosed TB among contacts was substantially higher than the prevalence of microbiologically proven disease. It is likely that prevalence and incidence estimates based on clinically diagnosed TB are an over-estimate of the true prevalence and incidence of disease. This is particularly likely among child contacts, from whom it is
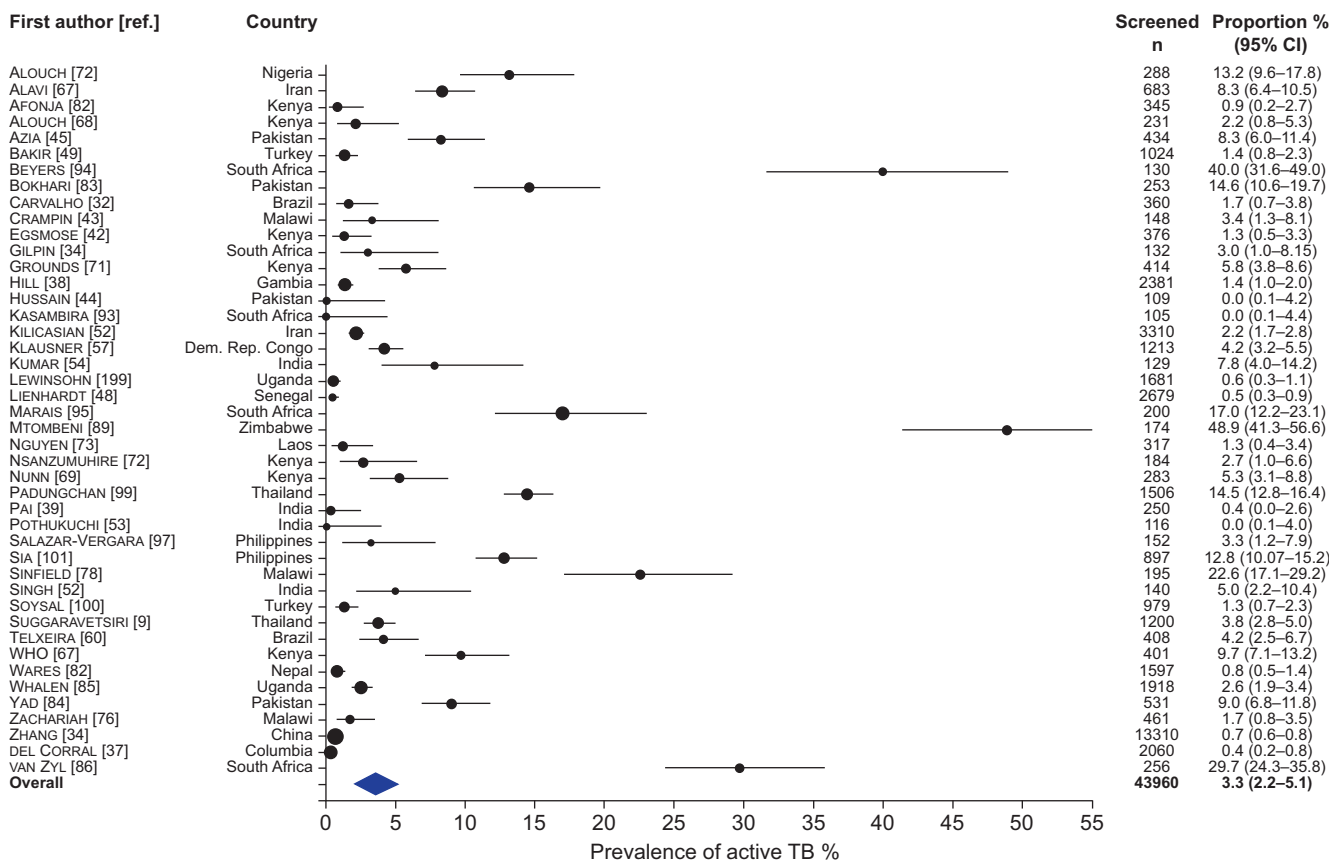

First author [ref.]	Country	Screened n	Proportion % (95% CI)
ALOUCH [72]	Nigeria	288	13.2 (9.6–17.8)
ALAVI [67]	Iran	683	8.3 (6.4–10.5)
AFONJA [82]	Kenya	345	0.9 (0.2–2.7)
ALOUCH [68]	Kenya	231	2.2 (0.8–5.3)
AZIA [45]	Pakistan	434	8.3 (6.0–11.4)
BAKIR [49]	Turkey	1024	1.4 (0.8–2.3)
BEYERS [94]	South Africa	130	40.0 (31.6–49.0)
BOKHARI [83]	Pakistan	253	14.6 (10.6–19.7)
CARVALHO [32]	Brazil	360	1.7 (0.7–3.8)
CRAMPIN [43]	Malawi	148	3.4 (1.3–8.1)
EGSMOSE [42]	Kenya	376	1.3 (0.5–3.3)
GILPIN [34]	South Africa	132	3.0 (1.0–8.15)
GROUNDS [71]	Kenya	414	5.8 (3.8–8.6)
HILL [38]	Gambia	2381	1.4 (1.0–2.0)
HUSSAIN [44]	Pakistan	109	0.0 (0.1–4.2)
KASAMBIRA [93]	South Africa	105	0.0 (0.1–4.4)
KILICASIAN [52]	Iran	3310	2.2 (1.7–2.8)
KLAUSNER [57]	Dem. Rep. Congo	1213	4.2 (3.2–5.5)
KUMAR [54]	India	129	7.8 (4.0–14.2)
LEWINSOHN [199]	Uganda	1681	0.6 (0.3–1.1)
LIENHARDT [48]	Senegal	2679	0.5 (0.3–0.9)
MARAIS [95]	South Africa	200	17.0 (12.2–23.1)
MTOMBENI [89]	Zimbabwe	174	48.9 (41.3–56.6)
NGUYEN [73]	Laos	317	1.3 (0.4–3.4)
NSANZUMUHIRE [72]	Kenya	184	2.7 (1.0–6.6)
NUNN [69]	Kenya	283	5.3 (3.1–8.8)
PADUNGCHAN [99]	Thailand	1506	14.5 (12.8–16.4)
PAI [39]	India	250	0.4 (0.0–2.6)
POTHUKUCHI [53]	India	116	0.0 (0.1–4.0)
SALAZAR-VERGARA [97]	Philippines	152	3.3 (1.2–7.9)
SIA [101]	Philippines	897	12.8 (10.07–15.2)
SINFIELD [78]	Malawi	195	22.6 (17.1–29.2)
SINGH [52]	India	140	5.0 (2.2–10.4)
SOYSAL [100]	Turkey	979	1.3 (0.7–2.3)
SUGGARAVETSIRI [9]	Thailand	1200	3.8 (2.8–5.0)
TELXEIRA [60]	Brazil	408	4.2 (2.5–6.7)
WHO [67]	Kenya	401	9.7 (7.1–13.2)
WARES [82]	Nepal	1597	0.8 (0.5–1.4)
WHALEN [85]	Uganda	1918	2.6 (1.9–3.4)
YAD [84]	Pakistan	531	9.0 (6.8–11.8)
ZACHARIAH [76]	Malawi	461	1.7 (0.8–3.5)
ZHANG [34]	China	13310	0.7 (0.6–0.8)
DEL CORRAL [37]	Columbia	2060	0.4 (0.2–0.8)
VAN ZYL [86]	South Africa	256	29.7 (24.3–35.8)
Overall		**43960**	**3.3 (2.2–5.1)**

FIGURE 3. Forest plot of the prevalence of active tuberculosis (TB) among contacts of smear-positive TB in low–middle-income countries. The size of the symbols is proportional to the study sample size.
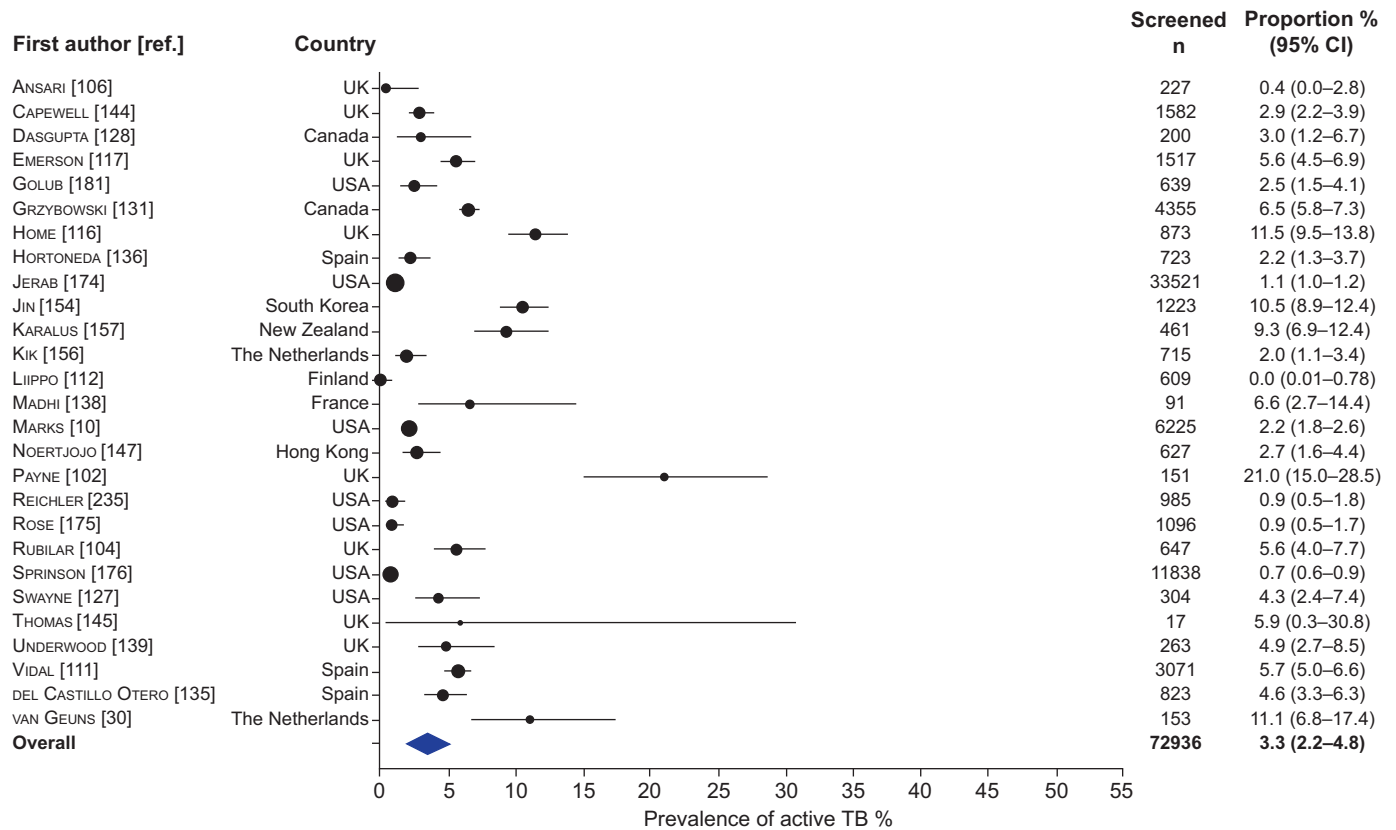
FIGURE 4. Forest plot of the prevalence of active tuberculosis (TB) among contacts of smear-positive TB in high-income countries. The size of the symbols is proportional to the study sample size.

often difficult to obtain specimens. The true burden of disease probably lies somewhere between the estimate based on clinical criteria and the estimate based on microbiological criteria.

In the absence of accurate measures of disease prevalence in the general community, it is difficult to estimate the relative contribution that transmission from index patients makes to the TB prevalence among contacts. Modern molecular epidemiology combined with conventional contact tracing has substantially clarified this issue in low-prevalence settings, where a high proportion of all isolates can be tested [108]. However, in high-prevalence countries there may be considerable difficulty in using this technique, as an insufficient proportion of cases may be captured for testing [6].

The estimated prevalence of TB among HIV infected contacts in this meta-analysis was higher than in another recent systematic review [238]. This may be because the previous review included patients "at risk" of HIV, as well as those known to be infected with HIV in the risk group. This is likely to have diluted the estimated prevalence of TB in that review.

Our analysis also shows there is a substantial ongoing risk of developing TB after the contact intervention at baseline, particularly during the first year. This risk is significantly higher in low–middle-income countries than high-income settings. This difference may be explained by the lower risk of ongoing transmission within the community in high-income countries and also the greater likelihood that contacts will have been treated for LTBI in high-income countries [109, 186, 235].

TABLE 4	Prevalence of latent tuberculosis infection (LTBI) among foreign and locally born contacts in high-income countries[#]								
Country of origin	Included studies	Contacts with LTBI	Contacts screened	Proportion %	95% CI	τ^2	I^2	OR (95% CI)	p-value
Contacts born locally	6	1536	7576	17.0	11–8–24.0	0.28	98.5	1.0	
Contacts born overseas	6	1849	4298	39.2	30.0–49.3	0.24	97.9	3.39 (3.10–3.71)	<0.0001

Data are presented as n, unless otherwise stated. [#]: [10, 107, 133, 145, 168, 189, 216].

TABLE 5	Outcomes of contact investigation studies in congregate settings in high-income countries				
Frist author [ref.]	Country	Location of contact	Contacts tested	Prevalence of active TB %	Prevalence of LTBI %
GAENSBAUER [149]	Ireland	Child care centre	268	6.7	NA
LOFY [169]	USA	Homeless facilities	425	3.1	23.3
MARIENAU [164]	USA	Aeroplane flight	861	0	24
CONOVER [221]	USA	Methadone clinic	393	NA	22.3
Centers for Disease Control [226]	USA	Clubs with exotic dancers	344	NA	29.8
DAVIDOW [166]	USA	Workplaces	724	0.2	22.0

Data are presented as n, unless otherwise stated. TB: tuberculosis; LTBI: latent tuberculosis infection; NA: not available.

The incidence in the first 5 yrs may be even higher than we have estimated, as many contacts from the included studies did not complete follow-up.

Policy implications for contact investigation

The studies we reported herein are almost all observational studies. In the absence of randomised controlled trials of contact tracing it is not possible to make strong recommendations for the implementation of specific interventions [17]. Nonetheless, this review provides support for the existing priority given in WHO recommendations [239] for screening children aged <5 yrs and contacts with HIV infection. Our data also demonstrates that children between 5 and 14 yrs of age are at a relatively high risk of active disease and latent infection, hence this group may also benefit from additional interventions. The finding that the prevalence of TB decreases with more remote exposure lends support to the current practice of progressively implementing contact screening in concentric circles starting with household contacts and progressing through other close contacts to more remote contacts [240].

The primary goal of contact investigation is to identify disease and infection among high-risk individuals near the time of exposure. However, the contribution of contact tracing to reducing the burden of disease in the population as a whole is unclear at this time. Although recent infection is more likely to lead to disease, all individuals with latent TB infection, including those who acquired infection at a much earlier time, are at risk of reactivation. Further research, including detailed mathematical modelling applied to different epidemiological settings, will be required to estimate the impact of contact investigation on the burden of TB disease over time.

The substantial incidence of TB disease during the 5 yrs after exposure, and particularly within the first 12 months, highlights the potential importance of serial screening for TB in contacts that do not receive treatment for LTBI. An alternative to repeated screening, for low resource settings, may be providing comprehensive information to contacts about their ongoing risk of developing disease even after the index case is treated and facilitating referral in the case of contacts developing symptoms.

Contact investigation is a central component of the public health response to TB in most high-income countries [11, 241,

242]. In recent years there has been an increasing trend in low–middle-income countries to implement contact investigation in some form but considerable heterogeneity in the practice of it [12]. Although we have shown that the estimated prevalence of TB and LTBI is higher in low–middle-income countries than in high-income countries, it does not necessarily follow that National Tuberculosis Programmes in resource-limited settings should implement this intervention. Tuberculosis control programmes in all countries need to consider the effectiveness and cost implications of any contact investigation policies carefully. Our finding that the IRR for screening contacts in high-income settings is substantially higher than in low–middle income settings supports the current priority placed upon contact investigation in high-income countries. In order to show that contact investigation is effective in high-prevalence settings, studies must compare contact investigation to case-finding alone [19]. This will require evidence from randomised trials, such as cluster randomised controlled trials or ''step-wedge'' trials [243] conducted in the appropriate settings.

Conclusion

In summarising the available data on the burden of TB and LTBI among contacts of patients with TB we have highlighted the substantial heterogeneity in available estimates. Although this article does provide evidence that contacts are a high-risk group for developing TB, policy recommendations must consider evidence of the cost-effectiveness of various contact tracing strategies, and also incorporate alternative strategies to enhance case finding. These will require investment in well-designed, robust randomised studies conducted in relevant populations.

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