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

Authors:
1. Gregory J. Fox, Woolcock Institute of Medical Research, University of Sydney

2. Simone E. Barry, Centenary Institute of Cancer Medicine and Cell Biology, University of Sydney

3. Warwick J Britton, Centenary Institute of Cancer Medicine and Cell Biology, and Discipline of Medicine, Sydney Medical School, University of Sydney

4. Guy B. Marks, Woolcock Institute of Medical Research, University of Sydney and Department of Respiratory Medicine, Liverpool Hospital.

Correspondence:

Dr Gregory Fox, Woolcock Institute of Medical Research, University of Sydney,

email: greg.fox@sydney.edu.au.

Abstract

Background: Investigation of contacts for patients with tuberculosis is a priority for tuberculosis 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.

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

Results: After screening 9555 titles, we included 203 published studies. In 95 studies from low and middle-income settings, the prevalence of active tuberculosis in all contacts was 3.1% (95% CI 2.2%-4.4%, I^2=99.4%), microbiologically proven tuberculosis 1.2% (95% CI 0.9-1.8%, I^2=95.9%), and latent tuberculosis infection 51.5% (95% CI 47.1-55.8%, I^2=98.9%). The prevalence of tuberculosis among household contacts was 3.1% (95% CI 2.1-4.5%, I^2=98.8%) and among contacts of patients with multi-drug resistant or extensively drug resistant tuberculosis 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.

Conclusions: Contacts of tuberculosis patients are a high-risk group for developing tuberculosis, particularly within the first year. Children under 5 years 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.

Introduction

Rationale

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 to social and economic development has been widely acknowledged including in the Millennium Development Goals. In this context, the WHO STOP TB Partnership has set two targets: (a) by 2015 to reduce prevalence and deaths by 50% relative to 1990 levels and (b) by 2050 to eliminate TB as a public health problem.[2] In order to achieve these targets, health-care systems will need to identify more cases of TB at an earlier stage of the illness.[3]

Contact investigation entails the systematic evaluation of the contacts of known TB patients to identify active disease or latent tuberculosis 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 contact,[6,7] and susceptibility of the contact.[8,9] The onset of disease may occur early, within six weeks, or up to 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 radiography, microbiological evaluation of sputum or a test to detect LTBI, such as a tuberculin skin test (TST) or an interferon-gamma release assay (IGRA). There has been a growing interest in contact investigation in resource-limited settings as national programs seek new methods for improving case detection.[12] The World Health Organization currently recommends contact investigation in two high-risk populations: children aged under five years[13] and people living with, or at high risk, of HIV infection.[14] However, there are no international standards for investigation of others in the population who are contacts of patients with TB.

One previous meta-analysis examined data from 41 household contact investigation studies in low-middle income countries up to 2005[15]. However, there has not yet been an analysis of contact investigation beyond the household setting or in high-income countries. Further, 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 five years following exposure. Nor has there been an analysis of key risk-groups, such as contacts of patients with multi-drug resistant 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[16] review for an Expert Panel that was convened to contribute to the development of international guidelines on contact investigation for the World Health Organization.

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.[17] First, we searched the literature for available systematic reviews and meta-analyses, identifying a Cochrane review,[18] a systematic review of household contact investigation,[19] 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 1st 2011. Our search included 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 a Web Appendix**.**

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 randomized controlled trials. We excluded editorials, conference abstracts and systematic reviews.

Data extraction and definitions

Two reviewers (GF and CD) 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 (WB) 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 (GF) extracted all data from all studies, and the other authors (SB, WB, GM) 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 the 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, the number of incident cases each year during the first five years. 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 multi-drug resistant or extensively drug resistant (M/XDR) TB. Subgroup data were also extracted for contacts that were known to be HIV-positive, household contacts, close contacts, casual contacts and for contacts from congregate settings.

We analyzed data on TB and LTBI for the following age groups: 5 years or below, >5 to <15 years and 15 years and above. Where the limits of the age range reported in studies were up to one year 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 were described thus 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 that were diagnosed during the baseline contact investigation or within the first 3 months after diagnosis of the index patient. Contacts who 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 analyzed by year after exposure to the index patient with incidence in year 1 being from 3 to 12 months after diagnosis of the index case, incidence in year 2 being between 13 months and 24 months, and so on up to the end of 5 years. Incidence data were not reported if annual incidence could not be determined. Incidence at 1 year 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 $\geq$ 10 mm at 48 to 72 hours. 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 World Bank definitions of high-income or low-middle income countries

based on gross national income (GNI) from 2010 or the latest preceding year for which data were available. Studies were also stratified by World Health Organization region. We stratified outcomes according 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 in 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 a Web Appendix.

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 by the method of Fleiss[22].

For the meta-analysis weighted average estimates of incidence rate and prevalence were calculated using the exact binomial method of Hamza et al[23] fitted using Proc NLMIXED in SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

The effect of study design and country income level (low-medium or high) on the estimates was tested using logistic regression fitted by generalized estimating equations (GEE) 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 for 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 mid-year of the study period or 1990, whichever was the later [24] 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.[25,26] Values of I^2 near 0% 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[25] and can be applied to all study designs.[25]

Portions of the code used for the analysis are included in a Web Appendix.

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 9555 unique publications, and included 108 studies (53.2%) performed in high-income countries and 95 studies (46.8%) performed 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, 2 case-control studies and 185 cohort studies and one randomized controlled trial in the analysis. The reasons for exclusion at each stage are summarized in the flow diagram 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.[27] 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,[28] others used expressions such as "intimate"[29] "sharing the air for a prolonged period",[30] or specifying a minimum duration of exposure in other closed spaces such as the workplace.[31] Some studies did not provide precise definitions of close contacts.[32]

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 five years 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 a Web appendix. There was
substantial heterogeneity between studies, indicated by high I^2 statistics. Tuberculin
skin testing (TST) was used as the primary measure of LTBI in all but six studies,
where only Heaf test results were available. [33,34,35,36,37,38]

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 Figure 3. 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 five years after exposure are shown in Figure 2, with additional
incidence data included in a Web appendix.

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, finding 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).[39] 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, 2 and 3. Outcomes for individual studies are included in a Web appendix.

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 a Web appendix. 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 both contacts born overseas compared to those born locally [OR = 3.39, 95% CI 3.10 to 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], with details in a Web appendix. 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, 2 and 3 provide data for contact sub-groups 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 in a Web appendix.

The median incidence rate ratio (IRR) among contacts during the first year among 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 summarizes 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 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 five years 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.[19] 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 generalizable to most circumstances in which contact investigations are considered. We used an exact binomial approach to meta-analysis, which does not make distributional assumptions nor 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 summarized. This heterogeneity exists even within the strata and sub-groups 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 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 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 randomized controlled trials or trials with matched controls[40,41] 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 in 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 BCG vaccination. It is likely 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 [42].

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 of the contact. 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.[43]

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 overestimate of the true prevalence and incidence of disease. This is particularly likely among child contacts, from whom it is 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 all isolates can be tested.[44] 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 [45]. This may 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.[46,47,48] The incidence in the first five years may be even higher that we have estimated, as many contacts from the included studies did not complete follow-up.

Policy implications for contact investigation

The studies we have reported here are almost all observational studies. In the absence of randomized controlled trials of contact tracing it is not possible to make strong recommendations for the implementation of specific interventions [16]. Nonetheless, this review provides support for the existing priority given in WHO recommendations[49] for screening children under 5 years and contacts with HIV infection. Our data also demonstrates that children between 5 and 14 years 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 [50].

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 modeling 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 years 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.[11,51,52]. 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 Programs in resource-limited settings should implement this intervention. Tuberculosis control programs in all countries need to consider the effectiveness and cost implications of any contact investigation policies carefully. Our finding that the incidence rate ratio 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 [53]. This will require evidence from randomized trials, such as cluster randomized controlled trials or 'step-wedge' trials [54] conducted in the appropriate settings.

Conclusion

In summarizing 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 the review 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 randomized studies conducted in relevant populations.

Conflict of interests

Author contributions

GF designed the protocol, designed the data extraction template, extracted data, helped to write the review and conduct the analysis.

GM helped to design the protocol, extract data, conduct the analysis and write the review.

SB and WB helped to extract data and write the review.

References

1. World Health Organization (2011) Global tuberculosis control 2011. Geneva: World Health Organization

2. World Health Organization (2006) The Stop TB Strategy: Building on and enhancing DOTS to meet the TB-related Millennium Development Goals. Geneva: World Health Organization.

3. The Stop TB Partnership (2010) The Global Plan to Stop TB 2011-2015. Geneva

4. Riechler HL (2003) Contacts of tuberculosis patients in high-incidence countries. International Journal of Tuberculosis & Lung Disease 7: S333-336.

5. Greenaway C, Palayew M, Menzies D (2003) Yield of casual contact investigation by the hour. Int J Tuberc Lung Dis 7: S479-485.

6. Fok A, Numata Y, Schulzer M, FitzGerald M (2008) Risk factors for clustering of tuberculosis cases: a systematic review of population-based molecular epidemiology studies. International Journal of Tuberculosis & Lung Disease 12: 480-492.

7. Kenyon TA, Valway SE, Walter WI, Onorato IM, Castro KG (1996) Transmission of Multidrug-Resistant *Mycobacterium tuberculosis* during a Long Airplane Flight. New England Journal of Medicine 334: 933-938.

8. Yim J, Selvaraj P (2010) Genetic susceptibility in tuberculosis. Respirology 15: 241-256.

9. Suggaravetsiri P, Yanai H, Chongsuvivatwong V, Naimpasan O, Akarasewi P (2003) Integrated counseling and screening for tuberculosis and HIV among household contacts of tuberculosis patients in an endemic area of HIV infection: Chiang Rai, Thailand. Int J Tuberc Lung Dis 7: S424-431.

10. Marks SM, Taylor Z, Qualls NL, Shrestha-Kuwahara RJ, Wilce MA, et al. (2000) Outcomes of contact investigations of infectious tuberculosis patients. Am J Respir Crit Care Med 162: 2033-2038.

11. Joint Tuberculosis Committee of the British Thoracic Society (2000) Control and prevention of tuberculosis in the United Kingdom: Code of Practice 2000. Thorax 55: 887-901.

12. Hwang TJ, Ottmani S, Uplekar M (2011) A rapid assessment of prevailing policies on tuberculosis contact investigation. Int J Tuberc Lung Dis 15: 1620-1623.

13. World Health Organization (2006) International Standards for Tuberculosis Care: Diagnosis, Treatment, Public Health. The Hague: Tuberculosis Coalition for Technical Assistance.

14. World Health Organization (2008) WHO Three I's Meeting. Geneva, Switzerland

15. Morrison J, Pai M, Hopewell PC (2008) Tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis. The Lancet Infectious Diseases 8: 359-368.

16. Guyatt GHG, Oxman A, Vist G, Kunz R, Falk-Ytter Y, et al. (2008) GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. British Medical Journal 336: 924-926.
17. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, et al. (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. British Medical Journal 339: b2700.
18. Fox GJ, Dobler CC, Marks GB (2011) Active case finding in contacts of people with tuberculosis. Cochrane Database of Systematic Reviews 7 Sept 2011.
19. Morrison J, Pai M, Hopewell D (2008) Tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis. Lancet Infect Dis 8: 359-368.
20. Liu E, Cheng S, Wang X, Hu D, Zhang T, et al. (2010) A systematic review of the investigation and management of close contacts of tuberculosis in China. J Public Health (Oxf) 32: 461-466.
21. Mulder C, Klinkenberg E, Manissero D (2009) Effectiveness of tuberculosis contact tracing among migrants and the foreign-born population. Euro Surveill 14.
22. Fleiss J (1981) Statistical methods for rates and proportions. 2nd ed. New York: John Wiley & Sons. pp. 14-15.
23. Hamza TH, van Houwelingen HC, Stijnen T (2008) The binomial distribution of meta-analysis was preferred to model within-study variability. Journal of clinical epidemiology 61: 41-51.
24. World Bank (2012) Data: Incidence of tuberculosis per 100,000 people. In: Bank W, editor.
25. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327: 557-560.
26. Riley RD, Higgins JPT, Deeks JJ (2009) Interpretation of random effects meta-analyses. British Medical Journal 342: d549.
27. Mixides G, Shende V, Teeter LD, Awe R, Musser JM, et al. (2005) Number of negative acid-fast smears needed to adequately assess infectivity of patients with pulmonary tuberculosis. Chest 128: 108-115.
28. Diel R, Loddenkemper R, Meywald-Walter K, Gottschalk R, Nienhaus A, et al. (2009) Comparative performance of tuberculin skin test, QuantiFERON-TB-Gold In Tube assay, and T-Spot.TB test in contact investigations for tuberculosis. Chest 135: 1010-1018.
29. van Geuns HA, Meijer J, Styblo K (1975) Results of contact examination in Rotterdam, 1967-1969. Bull Int Union Tuberc 50: 107-121.
30. Snider DE, Jr., Kelly GD, Cauthen GM, Thompson NJ, Kilburn JO (1985) Infection and disease among contacts of tuberculosis cases with drug-resistant and drug-susceptible bacilli. Am Rev Resp Dis 132: 125-132.
31. Carvalho AC, DeRiemer K, Nunes ZB, Martins M, Comelli M, et al. (2001) Transmission of *Mycobacterium tuberculosis* to contacts of HIV-infected tuberculosis patients. Am J Respir Crit Care Med 164: 2166-2171.
32. Zhang X, Wei X, Zou G, Walley J, Zhang H, et al. (2011) Evaluation of active tuberculosis case finding through symptom screening and

sputum microscopy of close contacts in Shandong, China. Trop Med Int Health.

33. Payne CR (1978) Surveillance of tuberculosis contacts: experience at Ealing Chest Clinic. Tubercle 59: 179-184.

34. Gilpin TP, Hammond M (1987) Active case-finding--for the whole community or for tuberculosis contacts only? S Afr Med J 72: 260-262.

35. Loudon RG, Williamson J, Johnson JM (1958) An analysis of 3,485 tuberculosis contacts in the city of Edinburgh during 1954-1955. Am Rev Tuberc 77: 623-643.

36. Rubilar M, Brochwicz-Lewinski MJ, Anderson M, Leitch AG (1995) The outcome of contact procedures for tuberculosis in Edinburgh, Scotland 1982-1991. Respir Med 89: 113-120.

37. Hussain SF, Watura R, Cashman B, Campbell IA, Evans MR (1992) Audit of a tuberculosis contact tracing clinic. BMJ 304: 1213-1215.

38. Ansari S, Thomas S, Campbell IA, Furness L, Evans MR (1998) Refined tuberculosis contact tracing in a low incidence area. Respiratory Medicine 92: 1127-1131.

39. Becerra MC, Appleton SC, Franke MF, Chalco K, Arteaga F, et al. (2011) Tuberculosis burden in households of patients with multidrug-resistant and extensively drug-resistant tuberculosis: a retrospective cohort study. Lancet 377: 147-152.

40. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. Biometrics 50: 1088-1101.

41. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315: 629-634.

42. Espinal MA, Perez EN, Baez J, Henriquez L, Fernandez K, et al. (2000) Infectiousness of *Mycobacterium tuberculosis* in HIV-1-infected patients with tuberculosis: a prospective study. Lancet 355: 275-280.

43. Aissa K, Madhi F, Ronsin N, Delarocque F, Lecuyer A, et al. (2008) Evaluation of a model for efficient screening of tuberculosis contact subjects. American Journal of Respiratory and Critical Care Medicine 177: 1041-1047.

44. Borrell S, Espanol M, Orcau A, Tudo G, March F, et al. (2009) Factors associated with differences between conventional contact tracing and molecular epidemiology in study of tuberculosis transmission and analysis in the city of Barcelona, Spain. J Clin Microbiol 47: 198-204.

45. Kranzer K, Houben RM, Glynn JR, Bekker L-G, Wood R, et al. (2010) Yield of HIV-associated tuberculosis during intensified case finding in resource-limited settings: a systematic review and meta-analysis. Lancet Infectious Diseases 10: 93-102.

46. Chee CB, Teleman MD, Boudville IC, Do SE, Wang YT (2004) Treatment of latent TB infection for close contacts as a complementary TB control strategy in Singapore. Int J Tuberc Lung Dis 8: 226-231.

47. Reichler MR, Reves R, Bur S, Ford J, Thompson V, et al. (2002) Treatment of latent tuberculosis infection in contacts of new tuberculosis cases in the United States. South Med J 95: 414-420.

48. Devadatta S, Dawson JJ, Fox W, Janardhanam B, Radhakrishna S, et al. (1970) Attack rate of tuberculosis in a 5-year period among close family contacts of tuberculous patients under domiciliary treatment with

isoniazid plus PAS or isoniazid alone. Bull World Health Organ 42: 337-351.

49. World Health Organization Stop TB Partnership Childhood TB Subgroup (2007) Chapter 4: childhood contact screening and management. International Journal of Tuberculosis & Lung Disease 11: 12-15.

50. Veen J (1992) Microepidemics of tuberculosis: the stone-in-the-pond principle. Tubercle & Lung Disease 73: 73-76.

51. Erkens CG, Kamphorst M, Abubakar I, Bothamley GH, Chemtob D, et al. (2010) Tuberculosis contact investigation in low prevalence countries: a European consensus. The European respiratory journal 36: 925-949.

52. Centers for Disease Control (2005) Guidelines for the investigation of contacts of persons with infectious tuberculosis. Recommendations from the National Tuberculosis Controllers Association and CDC. MMWR Recommendations and reports : Morbidity and mortality weekly report 54: 1-47.

53. Fox GJ, Dobler CC, Marks GB (2011) Active case finding in contacts of people with tuberculosis. Cochrane Database Syst Rev 9: CD008477.

54. Brown CA, Lilford RJ (2006) The stepped wedge trial design: a systematic review. BMC medical research methodology 6: 54.

55. Carvalho ACC, Deriemer K, Nunes ZB, Martins M, Comelli M, et al. (2001) Transmission of *Mycobacterium tuberculosis* to Contacts of HIV-infected Tuberculosis Patients. American Journal of Respiratory and Critical Care Medicine 164: 2166-2171.

56. Cailleaux-Cezar M, de AMD, Xavier GM, de Salles CL, de Mello FC, et al. (2009) Tuberculosis incidence among contacts of active pulmonary tuberculosis. Int J Tuberc Lung Dis 13: 190-195.

57. Lemos AC, Matos ED, Pedral-Sampaio DB, Netto EM (2004) Risk of tuberculosis among household contacts in Salvador, Bahia. Braz J Infect Dis 8: 424-430.

58. del Corral H, Paris SC, Marin ND, Marin DM, Lopez L, et al. (2009) IFNgamma response to *Mycobacterium tuberculosis,* risk of infection and disease in household contacts of tuberculosis patients in Colombia. PLoS One 4: e8257.

59. Hill PC, Jackson-Sillah DJ, Fox A, Brookes RH, de Jong BC, et al. (2008) Incidence of tuberculosis and the predictive value of ELISPOT and Mantoux tests in Gambian case contacts. PLoS Med 3: e1379.

60. Pai M, Joshi R, Dogra S, Zwerling AA, Gajalakshmi D, et al. (2009) T-cell assay conversions and reversions among household contacts of tuberculosis patients in rural India. Int J Tuberc Lung Dis 13: 84-92.

61. Ramakrishnan CV, Andrews RH, Devadatta S, Fox W, Radhakrishna S, et al. (1961) Influence of segregation to tuberculous patients for one year on the attack rate of tuberculosis in a 2-year period in close family contacts in South India. Bull World Health Organ 24: 129-148.

62. Kamat SR, Dawson JJ, Devadatta S, Fox W, Janardhanam B, et al. (1966) A controlled study of the influence of segregation of tuberculous patients for one year on the attack rate of tuberculosis in a 5-year period in close family contacts in South India. Bull World Health Organ 34: 517-532.

63. Egsmose T, Ang'awa JO, Poti SJ (1965) The use of isoniazid among household contacts of open cases of pulmonary tuberculosis. Bull World Health Organ 33: 419-433.
64. Crampin A, Kasimba S, Mwaungulu NJ, Dacombe R, Floyd S, et al. (2011) Married to M. tuberculosis: risk of infection and disease in spouses of smear-positive tuberculosis patients. Tropical Medicine & International Health 16: 811-818.
65. Hussain R, Talat N, Shahid F, Dawood G (2007) Longitudinal tracking of cytokines after acute exposure to tuberculosis: association of distinct cytokine patterns with protection and disease development. Clin Vaccine Immunol 14: 1578-1586.
66. Aziz A, Ishaq M, Akhwand R (1985) Infection risk of sputum positive tuberculosis patients to their family contacts with and without chemotherapy. J Pak Med Assoc 35: 249-252.
67. Bayona J, Chavez-Pachas AM, Palacios E, Llaro K, Sapag R, et al. (2003) Contact investigations as a means of detection and timely treatment of persons with infectious multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 7: S501-509.
68. Grandjean L, Crossa A, Gilman RH, Herrera C, Bonilla C, et al. (2011) Tuberculosis in household contacts of multidrug-resistant tuberculosis patients. International Journal of Tuberculosis and Lung Disease 15: 1164-1169.
69. Lienhardt C, Fielding K, Hane AA, Niang A, Ndao CT, et al. (2010) Evaluation of the prognostic value of IFN-gamma release assay and tuberculin skin test in household contacts of infectious tuberculosis cases in Senegal. PLoS One 5: e10508.
70. Bakir M, Millington KA, Soysal A, Deeks JJ, Efee S, et al. (2008) Prognostic value of a T-cell-based, interferon-gamma biomarker in children with tuberculosis contact. Ann Intern Med 149: 777-787.
71. Kilicaslan Z, Kiyan E, Kucuk C, Kumbetli S, Sarimurat N, et al. (2009) Risk of active tuberculosis in adult household contacts of smear-positive pulmonary tuberculosis cases. Int J Tuberc Lung Dis 13: 93-98.
72. Janssens JP, Roux-Lombard P, Perneger T, Metzger M, Vivien R, et al. (2008) Contribution of a IFN-gamma assay in contact tracing for tuberculosis in a low-incidence, high immigration area. Swiss Med Wkly 138: 585-593.
73. Moran-Mendoza O, Marion SA, Elwood K, Patrick D, FitzGerald JM (2010) Risk factors for developing tuberculosis: a 12-year follow-up of contacts of tuberculosis cases. Int J Tuberc Lung Dis 14: 1112-1119.
74. Diel R, Loddenkemper R, Meywald-Walter K, Niemann S, Nienhaus A (2008) Predictive value of a whole blood IFN-gamma assay for the development of active tuberculosis disease after recent infection with *Mycobacterium tuberculosis*. Am J Respir Crit Care Med 177: 1164-1170.
75. Vidal R, Miravitlles M, Cayla JA, Torrella M, de Gracia J, et al. (1997) Increased risk of tuberculosis transmission in families with microepidemics. Eur Respir J 10: 1327-1331.
76. Liippo KK, Kulmala K, Tala EO (1993) Focusing tuberculosis contact tracing by smear grading of index cases. Am Rev Respir Dis 148: 235-236.

77. Selby CD, Allen MB, Leitch AG (1989) Optimal duration of radiological follow-up for tuberculosis contacts. Respir Med 83: 353-355.
78. Teale C, Cundall DB, Pearson SB (1991) Time of development of tuberculosis in contacts. Respir Med 85: 475-477.
79. Neely F, Maguire H, Le Brun F, Davies A, Gelb D, et al. (2010) High rate of transmission among contacts in large London outbreak of isoniazid mono-resistant tuberculosis. J Public Health (Oxf) 32: 44-51.
80. Aspin J (1952) Spread of adult-type pulmonary tuberculosis in contact households. Lancet 1: 502-507.
81. Horne NW, Davies BH, Pines A (1978) A study of a standardised contact procedure in tuberculosis. Tubercle 59: 245-259.
82. Lees AW, Allan GW, Smith J, Tyrrell WF (1961) Pulmonary tuberculosis in contacts: a ten year survey. Dis Chest 40: 516-521.
83. Emerson PA (1959) Tuberculosis contacts in north-west London. Tubercle 40: 177-180.
84. Ormerod LP, Green RM, Broadfield E (2004) Outcome for adult contacts of smear-positive pulmonary tuberculosis in the absence of X-ray follow-up: 2000-03. Commun Dis Public Health 7: 132-133.
85. Esmonde TF, Petheram IS (1991) Audit of tuberculosis contact tracing procedures in south Gwent. Respir Med 85: 421-424.
86. Ormerod LP (1993) Results of tuberculosis contact tracing: Blackburn 1982-90. Respir Med 87: 127-131.
87. Ling DL, Liaw YP, Lee CY, Lo HY, Yang HL, et al. (2011) Contact investigation for tuberculosis in Taiwan contacts aged under 20 years in 2005. Int J Tuberc Lung Dis 15: 50-55.
88. Lee T, Kim N, Kim J (2010) Diagnosis of latent tuberculosis infection by using the QuantiFERON-TB Gold in-tube test in children whose household contact has contagious pulmonary tuberculosis disease. International Journal of Infectious Diseases 14: e307.
89. Ponticiello A, Perna F, Sturkenboom MC, Marchetiello I, Bocchino M, et al. (2001) Demographic risk factors and lymphocyte populations in patients with tuberculosis and their healthy contacts. Int J Tuberc Lung Dis 5: 1148-1155.
90. Yoshiyama T, Harada N, Higuchi K, Sekiya Y, Uchimura K (2010) Use of the QuantiFERON-TB Gold test for screening tuberculosis contacts and predicting active disease. Int J Tuberc Lung Dis 14: 819-827.
91. Bush OB, Jr., Sugimoto M, Fujii Y, Brown FA, Jr. (1965) Isoniazid prophylaxis in contacts of persons with known tuberculosis. Second report. Am Rev Respir Dis 92: 732-740.
92. Chen CH, Goh EH (1981) The management of household contacts of active pulmonary tuberculosis in Singapore. Ann Acad Med Singapore 10: 242-247.
93. Ferebee SH, Mount FW (1962) Tuberculosis morbidity in a controlled trial of the prophylactic use of isoniazid among household contacts. Am Rev Respir Dis 85: 490-510.
94. Mount FW, Ferebee SH (1962) The effect of isoniazid prophylaxis on tuberculosis morbidity among household contacts of previously known cases of tuberculosis. Am Rev Respir Dis 85: 821-827.

95. Swayne JB, Tepper L (1964) Tuberculosis contact follow-up in the Los Angeles City health department. Am J Public Health Nations Health 54: 1270-1281.

96. Pothukuchi M, Nagaraja SB, Kelamane S, Satyanarayana S, Shashidhar, et al. (2011) Tuberculosis contact screening and isoniazid preventive therapy in a South Indian district: operational issues for programmatic consideration. PLoS One 6: e22500.

97. Singh M, Mynak ML, Kumar L, Mathew JL, Jindal SK (2005) Prevalence and risk factors for transmission of infection among children in household contact with adults having pulmonary tuberculosis. Arch Dis Child 90: 624-628.

98. Warawdekar MS, Shah JR (1958) Pulmonary tuberculosis in the contacts: a mass miniature roentgenographic study. Indian J Med Sci 12: 797-801.

99. Kumar RA, Saran M, Verma BL, Srivastava RN (1984) Pulmonary tuberculosis among contacts of patients with tuberculosis in an urban Indian population. J Epidemiol Community Health 38: 253-258.

100. Dahiwale N, Rao S, Singh J, Rawat AK (2011) Significance of Family Survey of Index Case for Detection of Tuberculosis. Indian Pediatr.

101. Eckhoff CT (2000) Evaluation of a clinical index among adult contacts of children with tuberculosis in rural Haiti. Int J Tuberc Lung Dis 4: 1143-1148.

102. Klausner JD, Ryder RW, Baende E, Lelo U, Williame JC, et al. (1993) *Mycobacterium tuberculosis* in household contacts of human immunodeficiency virus type 1-seropositive patients with active pulmonary tuberculosis in Kinshasa, Zaire. J Infect Dis 168: 106-111.

103. Lin X, Chongsuvivatwong V, Lin L, Geater A, Lijuan R (2008) Dose-response relationship between treatment delay of smear-positive tuberculosis patients and intra-household transmission: a cross-sectional study. Trans R Soc Trop Med Hyg 102: 797-804.

104. Kenyon TA, Creek T, Laserson K, Makhoa M, Chimidza N, et al. (2002) Risk factors for transmission of *Mycobacterium tuberculosis* from HIV-infected tuberculosis patients, Botswana. International Journal of Tuberculosis and Lung Disease 6: 843-850.

105. Teixeira L, Perkins MD, Johnson JL, Keller R, Palaci M, et al. (2001) Infection and disease among household contacts of patients with multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 5: 321-328.

106. Cavalcante SC, Durovni B, Barnes GL, Souza FB, Silva RF, et al. (2010) Community-randomized trial of enhanced DOTS for tuberculosis control in Rio de Janeiro, Brazil. Int J Tuberc Lung Dis 14: 203-209.

107. Machado A, Jr., Emodi K, Takenami I, Finkmoore BC, Barbosa T, et al. (2009) Analysis of discordance between the tuberculin skin test and the interferon-gamma release assay. Int J Tuberc Lung Dis 13: 446-453.

108. Kritski AL, Marquez MJO, Rabahi MF, Silva Vieira MAM, Werneck-Barroso E, et al. (1996) Transmission of tuberculosis to close contacts of patients with multidrug- resistant tuberculosis. American Journal of Respiratory and Critical Care Medicine 153: 331-335.

109. Militao de Albuquerque Mde F, Ximenes RA, Campelo AR, Sarinho E, Cruz M, et al. (2004) Neonatal BCG vaccine and response to the

tuberculin test in BCG vaccinated children in contact with tuberculosis patients in Recife, Brazil. J Trop Pediatr 50: 32-36.

110. Alavi SM, Farahmand FM (2008) Pulmonary tuberculosis in household contact of patients with active tuberculosis in Ahwaz, Iran (2003-2005). Pakistan Journal of Medical Sciences 24: 780-785.

111. Khalilzadeh S, Masjedi H, Hosseini M, Safavi A, Masjedi MR (2006) Transmission of Mycoba cterium tuberculosis to households of tuberculosis patients: a comprehensive contact tracing study. Arch Iran Med 9: 208-212.

112. WHO Chemotherapy Centre Nairobi (1961) An investigation of household contacts of open cases of pulmonary tuberculosis amongst the Kikuyu in Kiambu, Kenya. Bull World Health Organ 25: 831-850.

113. Aluoch JA, Edwards EA, Stott H (1982) A fourth study of case-finding methods for pulmonary tuberculosis in Kenya. Transactions of the Royal Society of Tropical Medicine and Hygiene 76: 679-691.

114. Nunn P, Mungai M, Nyamwaya J, Gicheha C, Brindle RJ, et al. (1994) The effect of human immunodeficiency virus type-1 on the infectiousness of tuberculosis. Tuber Lung Dis 75: 25-32.

115. Aluoch JA, Karuga WK, Nsanzumuhire H, Edwards EA, Stott H, et al. (1978) A second study of the use of community leaders in case-finding for pulmonary tuberculosis in Kenya. Tubercle 59: 233-243.

116. Grounds JG (1964) The contacts of cases of open pulmonary tuberculosis in Kisii, Kenya. East Afr Med J 41: 20-25.

117. Nsanzumuhire H, Aluoch JA, Karuga WK, Edwards EA, Stott H, et al. (1981) A third study of case-finding methods for pulmonary tuberculosis in Kenya, including the use of community leaders. Tubercle 62: 79-94.

118. Nguyen TH, Odermatt P, Slesak G, Barennes H (2009) Risk of latent tuberculosis infection in children living in households with tuberculosis patients: a cross sectional survey in remote northern Lao People's Democratic Republic. BMC Infect Dis 9: 96.

119. Azar JE (1957) Source detection and contact investigation in tuberculosis control. Doc Med Geogr Trop 9: 45-51.

120. Ottmani S, Zignol M, Bencheikh N, Laasri L, Blanc L, et al. (2009) TB contact investigations: 12 years of experience in the National TB Programme, Morocco 1993-2004. East Mediterr Health J 15: 494-503.

121. Zachariah R, Spielmann MP, Harries AD, Gomani P, Graham SM, et al. (2003) Passive versus active tuberculosis case finding and isoniazid preventive therapy among household contacts in a rural district of Malawi. Int J Tuberc Lung Dis 7: 1033-1039.

122. Topley JM, Maher D, Mbewe LN (1996) Transmission of tuberculosis to contacts of sputum positive adults in Malawi. Arch Dis Child 74: 140-143.

123. Sinfield R, Nyirenda M, Haves S, Molyneux EM, Graham SM (2006) Risk factors for TB infection and disease in young childhood contacts in Malawi. Ann Trop Paediatr 26: 205-213.

124. Naing NN, Mohammad WZW, Salleh R, Ahmad N, Iyawoo K, et al. (2007) A multi-centered study of the influence of HIV on transmission of tuberculosis to household contacts in three states of Malaysia. International Medical Journal 14: 273-279.

125. Afonja AO, Labode MO, Edet EG (1973) Early yield of pulmonary tuberculosis among household contacts of known cases of open pulmonary tuberculosis in Lagos. East Afr Med J 50: 136-139.

126. Akenzua G, Oviawe O (1984) Cost-benefit of contact-tracing in a tuberculosis programme. Nigerian Journal of Paediatrics 11: 81-85.

127. Wares DF, Akhtar M, Singh S, Luitel H (2000) Is TB contact screening relevant in a developing country setting? Experiences from eastern Nepal, 1996-1998. Int J Tuberc Lung Dis 4: 920-924.

128. Bokhari SY, Ahmad A, Shaikh MY, Ahmad I (1987) A study of tuberculosis contacts. J Pak Med Assoc 37: 48-52.

129. Yad MI (1974) Observations on the examination of contacts of tuberculosis patients--a 15 year study (1953-67). Bull Int Union Tuberc 49 suppl 1: 261-266.

130. Whalen CC, Zalwango S, Chiunda A, Malone L, Eisenach K, et al. (2011) Secondary attack rate of tuberculosis in urban households in Kampala, Uganda. PLoS One 6: e16137.

131. van Zyl S, Marais BJ, Hesseling AC, Gie RP, Beyers N, et al. (2006) Adherence to anti-tuberculosis chemoprophylaxis and treatment in children. Int J Tuberc Lung Dis 10: 13-18.

132. Schaaf HS, Gie RP, Kennedy M, Beyers N, Hesseling PB, et al. (2002) Evaluation of young children in contact with adult multidrug-resistant pulmonary tuberculosis: a 30-month follow-up. Pediatrics 109: 765-771.

133. Elliott AM, Hayes RJ, Halwiindi B, Luo N, Tembo G, et al. (1993) The impact of HIV on infectiousness of pulmonary tuberculosis: a community study in Zambia. AIDS 7: 981-987.

134. Mtombeni S, Mahomva A, Siziya S, Sanyika C, Doolabh R, et al. (2002) A clinical evaluation of children under the age of five years who are household contacts of adults with sputum positive tuberculosis in Harare, Zimbabwe. Cent Afr J Med 48: 28-32.

135. Vella V, Racalbuto V, Guerra R, Marra C, Moll A, et al. (2011) Household contact investigation of multidrug-resistant and extensively drug-resistant tuberculosis in a high HIV prevalence setting. International Journal of Tuberculosis and Lung Disease 15: 1170-1175.

136. Kruk A, Gie RP, Schaaf HS, Marais BJ (2008) Symptom-based screening of child tuberculosis contacts: improved feasibility in resource-limited settings. Pediatrics 121: e1646-1652.

137. Saunders LD, Irwig LM, Wilson TD, Kahn A, Groeneveld H (1984) Tuberculosis management in Soweto. South African Medical Journal 66: 330-333.

138. Kasambira TS, Shah M, Adrian PV, Holshouser M, Madhi SA, et al. (2011) QuantiFERON-TB gold in-tube for the detection of *Mycobacterium tuberculosis* infection in children with household tuberculosis contact. Int J Tuberc Lung Dis 15: 628-634.

139. Beyers N, Gie RP, Schaaf HS, Van Zyl S, Talent JM, et al. (1997) A prospective evaluation of children under the age of 5 years living in the same household as adults with recently diagnosed pulmonary tuberculosis. Int J Tuberc Lung Dis 1: 38-43.

140. Marais BJ, Hesseling AC, Schaaf HS, Gie RP, van Helden PD, et al. (2009) *Mycobacterium tuberculosis* transmission is not related to

household genotype in a setting of high endemicity. J Clin Microbiol 47: 1338-1343.

141. Becerra MC, Pachao-Torreblanca IF, Bayona J, Celi R, Shin SS, et al. (2005) Expanding tuberculosis case detection by screening household contacts. Public Health Rep 120: 271-277.

142. Salazar-Vergara RM, Sia IG, Tupasi TE, Alcaneses MR, Orillaza RB, et al. (2003) Tuberculosis infection and disease in children living in households of Filipino patients with tuberculosis: a preliminary report. Int J Tuberc Lung Dis 7: S494-500.

143. Fuimaono A, Vince J (1997) Screening contacts of children with tuberculosis: an important and worthwhile part of case management. P N G Med J 40: 69-73.

144. Padungchan S, Konjanart S, Kasiratta S, Daramas S, ten Dam HG (1986) The effectiveness of BCG vaccination of the newborn against childhood tuberculosis in Bangkok. Bull World Health Organ 64: 247-258.

145. Soysal A, Millington KA, Bakir M, Dosanjh D, Aslan Y, et al. (2005) Effect of BCG vaccination on risk of *Mycobacterium tuberculosis* infection in children with household tuberculosis contact: a prospective community-based study. Lancet 366: 1443-1451.

146. Sia IG, Orillaza RB, St Sauver JL, Quelapio ID, Lahr BD, et al. (2010) Tuberculosis attributed to household contacts in the Philippines. Int J Tuberc Lung Dis 14: 122-125.

147. Dasgupta K, Schwartzman K, Marchand R, Tennenbaum TN, Brassard P, et al. (2000) Comparison of cost-effectiveness of tuberculosis screening of close contacts and foreign-born populations. Am J Respir Crit Care Med 162: 2079-2086.

148. Yeo IKT, Tannenbaum T, Scott AN, Kozak R, Behr MA, et al. (2006) Contact investigation and genotyping to identify tuberculosis transmission to children. Pediatric Infectious Disease Journal 25: 1037-1043.

149. MacIntyre CR, Plant AJ (1998) Impact of policy and practice on the effectiveness of contact screening for tuberculosis. Prev Med 27: 830-837.

150. Grzybowski S, Barnett GD, Styblo K (1975) Contacts of cases of active pulmonary tuberculosis. Bull Int Union Tuberc 50: 90-106.

151. Temple A (1935) The Results of Routine Examination of Tuberculosis Contacts. Can Med Assoc J 33: 507-509.

152. Lankensjold E, Herrmann FR, Luong BL, Rochat T, Janssen JP (2008) Contact tracing for tuberculosis and treatment for latent infection in a low incidence country. Swiss Medical Weekly 138: 78-84.

153. Casanova C, Gonzalez C, Perez M, Piqueras R, Estelles C, et al. (1996) Contact screening in tuberculous pediatric patients. Pediatric Infectious Disease Journal 15: 277.

154. del Castillo Otero D, Penafiel Colas M, Alvarez Gutierrez F, Soto Campos JG, Calderon Osuna E, et al. (1999) Investigation of tuberculosis contacts in a nonhospital pneumology practice. Eur J Clin Microbiol Infect Dis 18: 790-795.

155. Hortoneda M, Saiz C, Alfonso JI, Cortina P, Gonzalez JI, et al. (1996) Prevention and early detection of tuberculosis. Eur J Epidemiol 12: 413-419.
156. Uhari M, Linna O (1982) Close contact with tuberculosis in childhood. Eur J Respir Dis 63: 579-583.
157. Madhi F, Fuhrman C, Monnet I, Atassi K, Poirier C, et al. (2002) Transmission of tuberculosis from adults to children in a Paris suburb. Pediatr Pulmonol 34: 159-163.
158. Underwood BR, White VLC, Baker T, Law M, Moore-Gillon JC (2003) Contact tracing and population screening for tuberculosis - Who should be assessed? Journal of Public Health Medicine 25: 59-61.
159. Thompson BC (1946) Tuberculosis home contacts; a technique of routine examination at Ealing Chest Clinic. Nurs Times 42: 188.
160. Miller RF, Kent RJ, Uttley AHC, Stoker NG, Pozniak AL (1995) Transmission of tuberculosis in patients with HIV infection. British Medical Journal 310: 401.
161. Dick WP, Thompson BC (1946) Examination of home-contacts of tuberculous persons. Lancet 2: 791-793.
162. Davies PD (1961) The natural history of tuberculosis in children. A study of child contacts in the Brompton Hospital Child Contact Clinic from 1930 to 1952. Tubercle 42(Suppl): 1-40.
163. Capewell S, Leitch AG (1984) The value of contact procedures for tuberculosis in Edinburgh. Br J Dis Chest 78: 317-329.
164. Thomas B, Pugalenthi A, Patel H, Woltmann G, Bankart J, et al. (2011) Concordance between tuberculin skin test and interferon-gamma assay and interferon-gamma response to mitogen in pediatric tuberculosis contacts. Pediatr Pulmonol.
165. Wang PD, Lin RS (2000) Tuberculosis transmission in the family. J Infect 41: 249-251.
166. Noertjojo K, Tam CM, Chan SL, Tan J, Chan-Yeung M (2002) Contact examination for tuberculosis in Hong Kong is useful. Int J Tuberc Lung Dis 6: 19-24.
167. Huang YW, Shen GH, Lee JJ, Yang WT (2010) Latent tuberculosis infection among close contacts of multidrug-resistant tuberculosis patients in central Taiwan. Int J Tuberc Lung Dis 14: 1430-1435.
168. Lee MS, Leung CC, Kam KM, Wong MY, Leung MC, et al. (2008) Early and late tuberculosis risks among close contacts in Hong Kong. Int J Tuberc Lung Dis 12: 281-287.
169. Gaensbauer JT, Vandaleur M, O'Neil M, Altaf A, Ni Chroinin M (2009) BCG protects toddlers during a tuberculosis outbreak. Arch Dis Child 94: 392-393.
170. Attamna A, Chemtob D, Attamna S, Fraser A, Rorman E, et al. (2009) Risk of tuberculosis in close contacts of patients with multidrug resistant tuberculosis: a nationwide cohort. Thorax 64: 271.
171. Moro ML, Errante I, Infuso A, Sodano L, Gori A, et al. (2000) Effectiveness of infection control measures in controlling a nosocomial outbreak of multidrug-resistant tuberculosis among HIV patients in Italy. Int J Tuberc Lung Dis 4: 61-68.
172. Hirama T, Hagiwara K, Kanazawa M (2011) Tuberculosis screening programme using the QuantiFERON-TB Gold test and chest computed

tomography for healthcare workers accidentally exposed to patients with tuberculosis. Journal of Hospital Infection 77: 257-262.

173. Jin BW, Hong YP, Kim SJ (1989) A contact study to evaluate the BCG vaccination programme in Seoul. Tubercle 70: 241-248.

174. Verver S, van Loenhout-Rooyackers JH, Bwire R, Annee-van Bavel JA, de Lange HJ, et al. (2005) Tuberculosis infection in children who are contacts of immigrant tuberculosis patients. Eur Respir J 26: 126-132.

175. Kik SV, Franken WP, Arend SM, Mensen M, Cobelens FG, et al. (2009) Interferon-gamma release assays in immigrant contacts and effect of remote exposure to *Mycobacterium tuberculosis.* Int J Tuberc Lung Dis 13: 820-828.

176. Karalus NC (1988) Contact screening procedures for tuberculosis in Auckland. N Z Med J 101: 45-49.

177. Calder L, Priest P (1996) One year of tuberculosis in Auckland. N Z Med J 109: 164-167.

178. Chee CBE, Teleman MD, Boudville IC, Wang YT (2005) Contact screening and latent TB infection treatment in Singapore correctional facilities. International Journal of Tuberculosis and Lung Disease 9: 1248-1252.

179. Webb RM, Holcombe M, Pearson MM (2003) Tuberculosis contact investigation in a rural state. Int J Tuberc Lung Dis 7: S353-357.

180. Yun LW, Reves RR, Reichler MR, Bur S, Thompson V, et al. (2003) Outcomes of contact investigation among homeless persons with infectious tuberculosis. Int J Tuberc Lung Dis 7: S405-411.

181. Vennema A (1992) Contact investigation and isoniazid chemoprophylaxis in New York City, 1979-1987. N Y State J Med 92: 185-188.

182. Wells CD, Zuber PL, Nolan CM, Binkin NJ, Goldberg SV (1997) Tuberculosis prevention among foreign-born persons in Seattle--King County, Washington. Am J Respir Crit Care Med 156: 573-577.

183. Gross TP, Silverman PR, Bloch AB, Smith TY, Rogers GW (1989) An outbreak of tuberculosis in rural Delaware. Am J Epidemiol 129: 362-371.

184. Marienau KJ, Burgess GW, Cramer E, Averhoff FM, Buff AM, et al. (2010) Tuberculosis investigations associated with air travel : U. S. centers for disease control and prevention, January 2007 June 2008. Travel Medicine and Infectious Disease 8: 104-112.

185. Behr MA, Hopewell PC, Paz EA, Kawamura LM, Schecter GF, et al. (1998) Predictive value of contact investigation for identifying recent transmission of *Mycobacterium tuberculosis.* American Journal of Respiratory and Critical Care Medicine 158: 465-469.

186. Davidow AL, Mangura BT, Wolman MS, Bur S, Reves R, et al. (2003) Workplace contact investigations in the United States. Int J Tuberc Lung Dis 7: S446-452.

187. Driver CR, Balcewicz-Sablinska MK, Kim Z, Scholten J, Munsiff SS (2003) Contact investigations in congregate settings, New York City. Int J Tuberc Lung Dis 7: S432-438.

188. Moonan PK, Marruffo M, Manguia-Bayona G, Sahbazian B, Bayona M, et al. (2005) Tuberculosis: what is the yield of associate investigations

in non-BCG-immunized children with positive tuberculin skin tests? Int J Tuberc Lung Dis 9: 322-327.

189. Lofy KH, McElroy PD, Lake L, Cowan LS, Diem LA, et al. (2006) Outbreak of tuberculosis in a homeless population involving multiple sites of transmission. Int J Tuberc Lung Dis 10: 683-689.

190. Centers for Disease Control (2004) Tuberculosis outbreak in a low-incidence state--Indiana, 2001-2004. MMWR Morbidity and mortality weekly report 53: 1134-1135.

191. Gerald LB, Tang S, Bruce F, Redden D, Kimerling ME, et al. (2002) A decision tree for tuberculosis contact investigation. Am J Respir Crit Care Med 166: 1122-1127.

192. Cruz AT, Medina D, Whaley EM, Ware KM, Koy TH, et al. (2011) Tuberculosis among families of children with suspected tuberculosis and employees at a children's hospital. Infect Control Hosp Epidemiol 32: 188-190.

193. Jereb J, Etkind SC, Joglar OT, Moore M, Taylor Z (2003) Tuberculosis contact investigations: outcomes in selected areas of the United States, 1999. Int J Tuberc Lung Dis 7: S384-390.

194. Rose CE, Jr., Zerbe GO, Lantz SO, Bailey WC (1979) Establishing priority during investigation of tuberculosis contacts. Am Rev Respir Dis 119: 603-609.

195. Sprinson JE, Flood J, Fan CS, Shaw TA, Pascopella L, et al. (2003) Evaluation of tuberculosis contact investigations in California. Int J Tuberc Lung Dis 7: S363-368.

196. Gessner BD, Weiss NS, Nolan CM (1998) Risk factors for pediatric tuberculosis infection and disease after household exposure to adult index cases in Alaska. J Pediatr 132: 509-513.

197. Greenberg HB, Trachtman L, Thompson DH (1976) Finding recent tuberculous infection in New Orleans. Results of tuberculin skin tests on New Orleans children from the inner city and Contact Investigation Program. JAMA 235: 931-932.

198. Li J, Marks SM, Driver CR, Diaz FA, Castro AF, 3rd, et al. (2007) Human immunodeficiency virus counseling, testing, and referral of close contacts to patients with pulmonary tuberculosis: feasibility and costs. J Public Health Manag Pract 13: 252-262.

199. Geiger FL, Kuemmerer JM (1963) Tuberculosis casefinding among contacts in seven south carolina counties. Public Health Rep 78: 663-668.

200. Golub J, Bur S, Cronin WA, Gange S, Baruch N, et al. (2006) Delayed tuberculosis diagnosis and tuberculosis transmission. International Journal of Tuberculosis and Lung Disease 10: 24-30.

201. Ruben FL, Lynch DC (1996) Tuberculosis control through contact investigation. Pa Med 99: 22-23.

202. Reichler MR, Reves R, Bur S, Thompson V, Mangura BT, et al. (2002) Evaluation of investigations conducted to detect and prevent transmission of tuberculosis. JAMA 287: 991-995.

203. Lobato MN, Royce SE, Mohle-Boetani JC (2003) Yield of source-case and contact investigations in identifying previously undiagnosed childhood tuberculosis. Int J Tuberc Lung Dis 7: S391-396.

204. World Bank (2011) Data: Country classifications.

205. Akhtar S, Rathi SK (2009) Multilevel modeling of household contextual determinants of tuberculin skin test positivity among contacts of infectious tuberculosis patients, Umerkot, Pakistan. Am J Trop Med Hyg 80: 351-358.

206. Petrucci R, Abu Amer N, Gurgel RQ, Sherchand JB, Doria L, et al. (2008) Interferon gamma, interferon-gamma-induced-protein 10, and tuberculin responses of children at high risk of tuberculosis infection. Pediatr Infect Dis J 27: 1073-1077.

207. Nakaoka H, Lawson L, Squire SB, Coulter B, Ravn P, et al. (2006) Risk for tuberculosis among children. Emerg Infect Dis 12: 1383-1388.

208. Rakotosamimanana N, Raharimanga V, Andriamandimby SF, Soares JL, Doherty TM, et al. (2010) Variation in gamma interferon responses to different infecting strains of *Mycobacterium tuberculosis* in acid-fast bacillus smear-positive patients and household contacts in Antananarivo, Madagascar. Clin Vaccine Immunol 17: 1094-1103.

209. Narain R, Nair SS, Rao GR, Chandrasekhar P (1966) Distribution of tuberculous infection and disease among households in a rural community. Bull World Health Organ 34: 639-654.

210. Radhakrishna S, Frieden TR, Subramani R, Santha T, Narayanan PR (2007) Additional risk of developing TB for household members with a TB case at home at intake: a 15-year study. Int J Tuberc Lung Dis 11: 282-288.

211. Ramakrishnan CV, Andrews RH, Devadatta S, Fox W, Radhakrishna S, et al. (1961) Prevalence and early attack rate of tuberculosis among close family contacts of tuberculous patients in South India under domiciliary treatment with isoniazid plus PAS or isoniazid alone. Bull World Health Organ 26: 361-407.

212. Lienhardt C, Fielding K, Sillah J, Tunkara A, Donkor S, et al. (2003) Risk factors for tuberculosis infection in sub-Saharan Africa: a contact study in The Gambia. Am J Respir Crit Care Med 168: 448-455.

213. Lutong L, Bei Z (2000) Association of prevalence of tuberculin reactions with closeness of contact among household contacts of new smear-positive pulmonary tuberculosis patients. Int J Tuberc Lung Dis 4: 275-277.

214. Almeida LM, Barbieri MA, Da Paixao AC, Cuevas LE (2001) Use of purified protein derivative to assess the risk of infection in children in close contact with adults with tuberculosis in a population with high Calmette-Guerin bacillus coverage. Pediatr Infect Dis J 20: 1061-1065.

215. Raqib R, Kamal SM, Rahman MJ, Rahim Z, Banu S, et al. (2004) Use of antibodies in lymphocyte secretions for detection of subclinical tuberculosis infection in asymptomatic contacts. Clin Diagn Lab Immunol 11: 1022-1027.

216. Hussain R, Talat N, Shahid F, Dawood G (2009) Biomarker changes associated with Tuberculin Skin Test (TST) conversion: a two-year longitudinal follow-up study in exposed household contacts. PLoS One 4: e7444.

217. Madico G, Gilman RH, Checkley W, Cabrera L, Kohlstadt I, et al. (1995) Community infection ratio as an indicator for tuberculosis control. Lancet 345: 416-419.

218. Aziz N, Hasan S, Munir M, Tayyab M, Chaudrhy NA (2008) Risk to household contacts of tuberculous patients based on Mantoux test and antibody titre. J Ayub Med Coll Abbottabad 20: 47-50.
219. Mutsvangwa J, Millington KA, Chaka K, Mavhudzi T, Cheung YB, et al. (2010) Identifying recent *Mycobacterium tuberculosis* transmission in the setting of high HIV and TB burden. Thorax 65: 315-320.
220. Hesseling AC, Mandalakas AM, Kirchner HL, Chegou NN, Marais BJ, et al. (2009) Highly discordant T cell responses in individuals with recent exposure to household tuberculosis. Thorax 64: 840-846.
221. den Boon S, Verver S, Marais BJ, Enarson DA, Lombard CJ, et al. (2007) Association between passive smoking and infection with *Mycobacterium tuberculosis* in children. Pediatrics 119: 734-739.
222. Shanaube K, Hargreaves J, Fielding K, Schaap A, Lawrence KA, et al. (2011) Risk factors associated with positive quantiFERON-TB gold in-tube and tuberculin skin tests results in Zambia and South Africa. PLoS One 6.
223. Lewinsohn DA, Zalwango S, Stein CM, Mayanja-Kizza H, Okwera A, et al. (2008) Whole blood interferon-gamma responses to *Mycobacterium tuberculosis* antigens in young household contacts of persons with tuberculosis in Uganda. PLoS One 3: e3407.
224. Tornee S, Kaewkungwal J, Fungladda W, Silachamroon U, Akarasewi P, et al. (2004) Risk factors for tuberculosis infection among household contacts in Bangkok, Thailand. Southeast Asian J Trop Med Public Health 35: 375-383.
225. Kifai EJ, Bakari M (2009) Mantoux skin test reactivity among household contacts of HIV-infected and HIV un-infected patients with sputum smear positive TB in Dar es Salaam, Tanzania. East Afr J Public Health 6: 211-218.
226. CCDR (2006) Tuberculin skin testing of close contacts: recent or long-standing infection? Can Commun Dis Rep 32: 133-140.
227. Diel R, Loddenkemper R, Meywald-Walter K, Gottschalk R, Nienhaus A (2009) Comparative performance of tuberculin skin test, QuantiFERON-TB-Gold In Tube assay, and T-Spot.TB test in contact investigations for tuberculosis. Chest 135: 1010-1018.
228. Anibarro L, Trigo M, Villaverde C, Pena A, Gonzalez-Fernandez A (2011) Tuberculin skin test and interferon-gamma release assay show better correlation after the tuberculin 'window period' in tuberculosis contacts. Scand J Infect Dis.
229. Miller FJ (1947) Work of a tuberculosis contact clinic for young children, 1941-5. British Medical Journal 2: 91-94.
230. Johnson H, Lee B, Doherty E, Kelly E, McDonnell T (1995) Tuberculin sensitivity and the BCG scar in tuberculosis contacts. Tuber Lung Dis 76: 122-125.
231. Ward LJ, Hughes SE, Grabau JC (2004) The evaluation of school-based contact investigations in New York State, exclusive of New York City, 1997-2001. J Public Health Manag Pract 10: 308-315.
232. Zaki MH, Lyons HA, Robins AB, Brown EP (1976) Tuberculin sensitivity. Contacts of tuberculosis patients. N Y State J Med 76: 2138-2143.

233. Conover C, Ridzon R, Valway S, Schoenstadt L, McAuley J, et al. (2001) Outbreak of multidrug-resistant tuberculosis at a methadone treatment program. Int J Tuberc Lung Dis 5: 59-64.

234. Andre M, Ijaz K, Tillinghast JD, Krebs VE, Diem LA, et al. (2007) Transmission network analysis to complement routine tuberculosis contact investigations. American Journal of Public Health 97: 470-477.

235. Cauthen GM, Dooley SW, Onorato IM, Ihle WW, Burr JM, et al. (1996) Transmission of *Mycobacterium tuberculosis* from tuberculosis patients with HIV infection or AIDS. Am J Epidemiol 144: 69-77.

236. Cook VJ, Sun SJ, Tapia J, Muth SQ, Arguello DF, et al. (2007) Transmission network analysis in tuberculosis contact investigations. Journal of Infectious Diseases 196: 1517-1527.

237. MMWR (2003) Transmission of *Mycobacterium tuberculosis* associated with failed completion of treatment for latent tuberculosis infection-- Chickasaw County, Mississippi, June 1999-March 2002. MMWR 52: 222-224.

238. Centers for Disease Control (2001) Cluster of tuberculosis cases among exotic dancers and their close contacts--Kansas, 1994-2000. MMWR Morb Mortal Wkly Rep 50: 291-293.

239. Johnsen C (1993) Tuberculosis contact investigation: two years of experience in New York City correctional facilities. Am J Infect Control 21: 1-4.

240. Ames WR, Miles HC (1950) Apparent decline in tuberculous infection among household associates of sputum-positive cases of tuberculosis. American Journal of Public Health and the Nation's Health 40: 143-150.

241. Chapman JS, Dyerly MD (1964) Social and other factors in intrafamilial transmission of tuberculosis. American Review of Respiratory disease 90: 48-60.

242. Greenberg HB, Trachtman L, Thompson DH (1977) Investigating the contacts and suspected contacts of tuberculous patients in New Orleans. South Med J 70: 829-830.

243. Asghar RJ, Patlan DE, Miner MC, Rhodes HD, Solages A, et al. (2009) Limited utility of name-based tuberculosis contact investigations among persons using illicit drugs: Results of an outbreak investigation. Journal of Urban Health 86: 776-780.

244. LoBue PA, LeClair JJ, Moser KS (2004) Contact investigation for cases of pulmonary *Mycobacterium bovis*. Int J Tuberc Lung Dis 8: 868-872.

245. Beyers N (2003) Case finding in children in contact with adults in the house with TB. Int J Tuberc Lung Dis 7: 1013-1014.

Figure 1. Flow diagram for study selection.
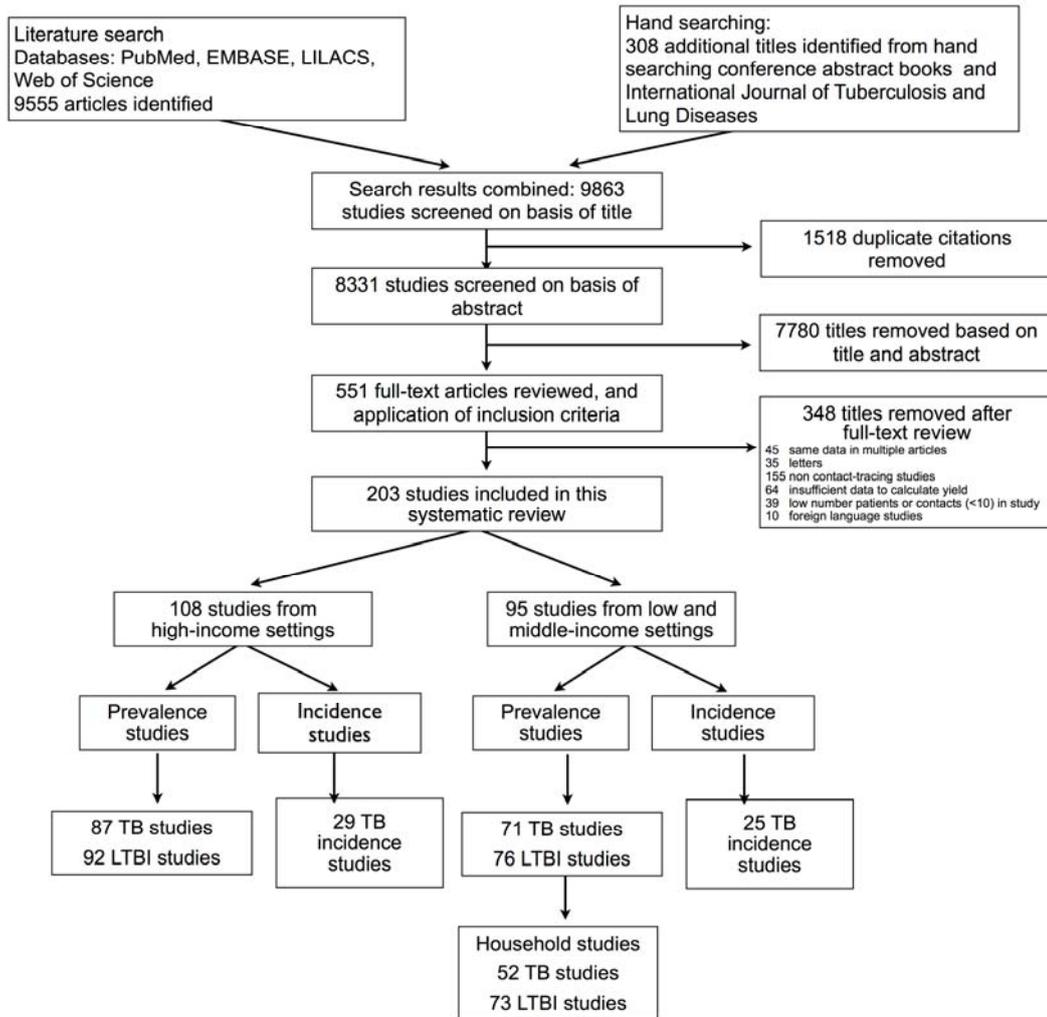
Figure 1: Flow diagram for study selection

Figure 2. Annual incidence rate of tuberculosis in contacts by year of follow-up, according to country income.

Years after exposure to index patient	1	2	3	4	5
Incidence rate in low-middle income countries (cases/100,000/y) (95% CI)	1,478 (897-2,427)	831 (624-1,106)	1,101 (757-1,599)	492 (344-704)	549 (415-726)
Incidence rate in high income countries (cases/100,000/y) (95% CI)	524 (336-816)	152 (74-314)	233 (80-673)	202 (69-593)	171 (49-598)
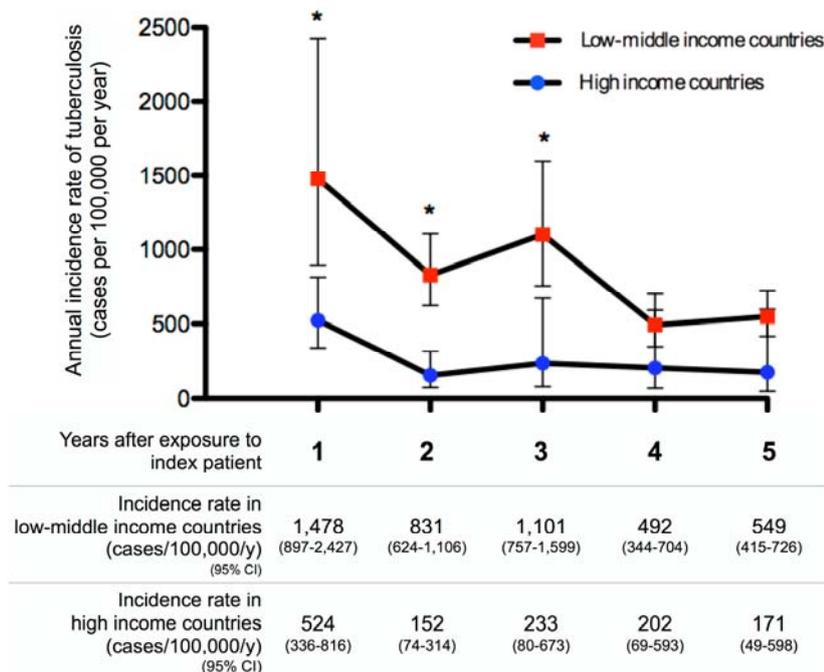
Figure 2. Annual incidence rate of tuberculosis in contacts by year of follow-up, according to country income. *Statistically significant difference between contacts from high compared to low-middle income countries, p<0.05

*Statistically significant difference between contacts from high compared to low-middle income countries, p<0.05

Study references for studies from low-middle income countries:
[31,33,35,36,37,38,39,42,48,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83, 84,85,86,87,88,89,90,91,92,93,94,95]

Study references for studies from high income countries:
[32, 34-37, 148, 154, 155, 159, 162, 163, 167-170, 172, 176, 182, 183, 191, 205, 206, 219, 221-226].

See web appendix for complete details of outcomes, estimates of heterogeneity and outcomes of individual included studies.

Figure 3. Forest plot of the prevalence of active tuberculosis among contacts of smear positive tuberculosis. Size of the symbols is proportional to the study sample size.

A Prevalence of active tuberculosis from studies from low-middle income countries
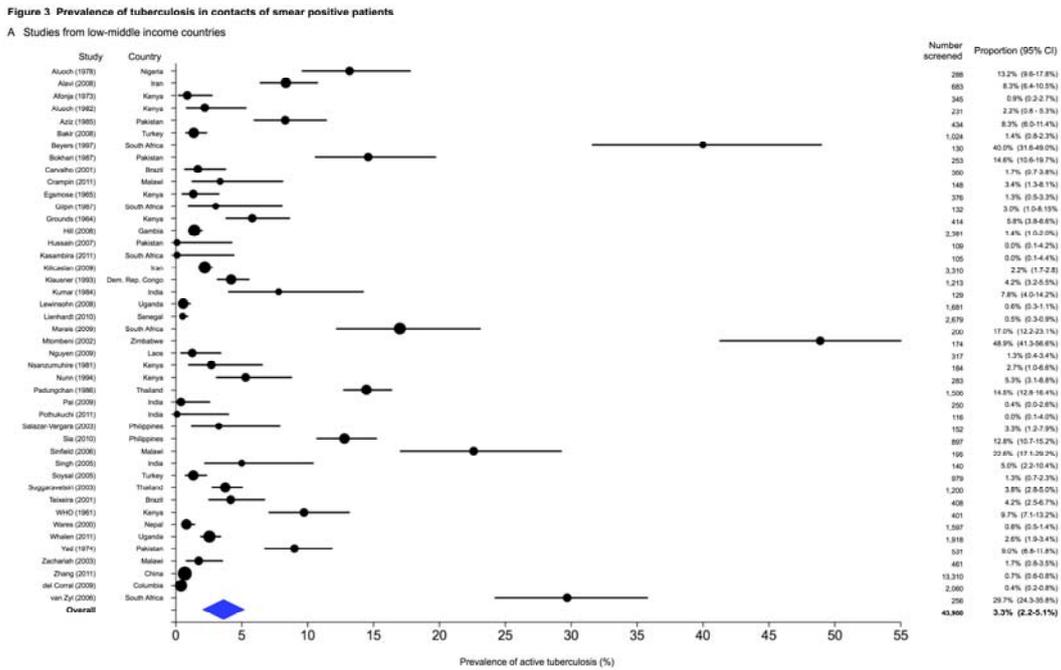
Figure 3 Prevalence of tuberculosis in contacts of smear positive patients
A Studies from low-middle income countries

B Prevalence of active tuberculosis from studies from low-middle income countries

B Studies from high income countries
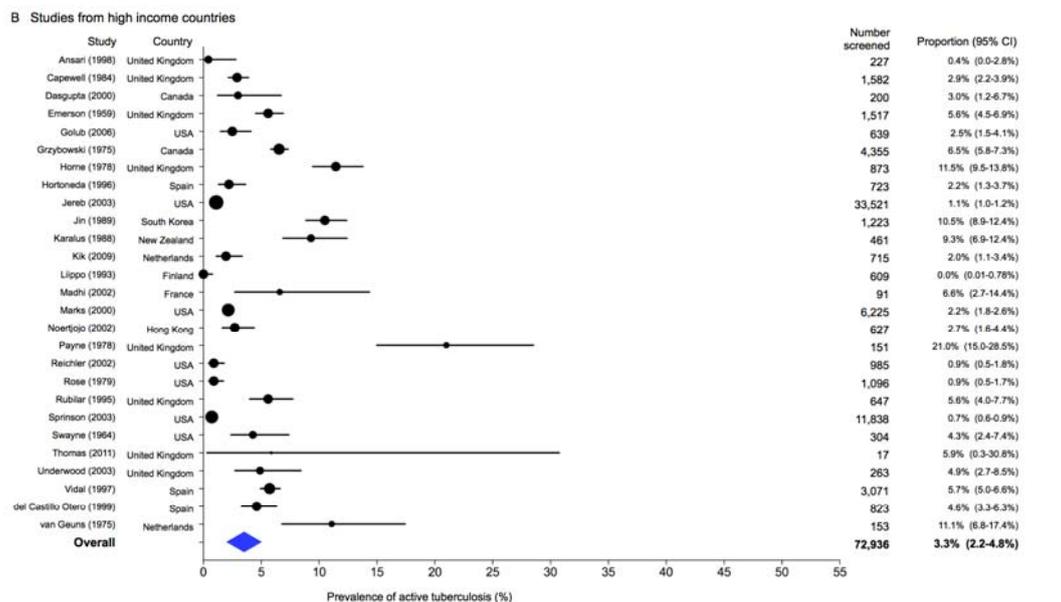
Table 1. Prevalence of active tuberculosis among contacts

A Prevalence of active tuberculosis among contacts in low-middle income countries

Age group	Sub-group	Included studies	Contacts with active TB	Contacts screened	Proportion	95% CI	τ²	I²
All ages	**All***	**71**	**24,799**	**878,724**	**3.1%**	**2.2% - 4.4%**	**2.18**	**99.4**
	Index patient smear positive	44	1,415	43,960	3.3%	2.2% - 5.1%	2.04	98.5
	Index patient with HIV	6	90	1,526	5.4%	2.2% - 12.4%	1.14	95.5
	Index patient X-MDR-TB	6	149	5,584	3.4%	0.8% - 12.6%	2.88	95.7
	Household contacts	68	22,390	858,422	3.1%	2.1% - 4.5%	2.35	98.8
	All close contacts	70	22,458	860,638	3.1%	2.2% - 4.4%	2.22	98.8
	Casual contacts only	1	34	1,492	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 years	**All**	18	754	5,112	10.0%	5.0% - 18.9%	2.35	97.8
5 to 14 years	**All**	9	155	1,643	8.4%	2.8% - 22.6%	2.51	92.5
≥15 years	**All**	11	127	3,614	3.2%	2.0% - 5.3%	0.53	87.1

* Study references:
[9,32,34,39,55,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146]

B Prevalence of active tuberculosis among contacts in high income countries

Age group	Sub-group	Included studies	Contacts with active TB	Contacts screened	Proportion	95% CI	τ²	I²
All ages	**All***	87	5,058	308,048	1.4%	1.1% - 1.8%	1.48	98.7
	Index patient smear positive	27	1,704	72,936	3.3%	2.2% - 4.8%	1.08	98.3
	Index patient with HIV	.	.	.	.	. .	.	.
	Index patient X-MDR-TB	2	0	554	0.0%	. .	0.00	99.9
	Household contacts	29	2,047	56,221	3.0%	2.0% - 4.4%	1.09	98.2
	All close contacts	45	3,053	127,699	1.9%	1.3% - 2.7%	1.42	98.7
	Casual contacts only	9	73	15,607	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 years	**All**	10	212	4,057	4.7%	3.4% - 6.4%	0.18	79.0
5 to 14 years	**All**	9	253	5,665	2.9%	1.7% - 5.1%	0.56	95.5
≥15 years	**All**	9	507	17,867	2.3%	1.1% - 4.8%	1.19	99.0

*Study references:
[10,29,30,33,35,36,37,38,43,44,46,72,75,76,77,78,79,81,83,84,85,86,87,90,91,92,93,94,95,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203]

Countries classified according to World Bank Income Gross National Income per capita: Low income (≤$1005/year), low-middle income ($1006 – $3,975 / year), upper-middle income ($3976-$12,275 / year) high-income (≥$12,276 / year)[204], na=not applicable, CI=confidence intervals, TB = tuberculosis, X-MDR-TB = extensively or multi-drug resistant tuberculosis. See web appendix for outcomes of individual included studies.

Table 2. Prevalence of latent tuberculosis infection in the contacts of tuberculosis patients

A Prevalence of latent tuberculosis infection among contacts in low-middle income countries

Age group	Sub-group	Included studies	Contacts with active TB	Contacts screened	Proportion	95% CI		τ²	I²
All ages	All*	76	35,788	60,557	51.5%	47.1% -	55.8%	0.58	98.9
	Index patient smear positive	51	19,003	33,875	52.9%	48.9% -	56.8%	0.32	97.7
	Index patient with HIV	12	1,138	2,376	45.7%	38.7% -	52.9%	0.22	90.9
	Index patient X-MDR-TB	6	431	684	61.3%	39.1% -	79.6%	1.21	95.2
	Household contacts	73	23,577	49,512	45.4%	40.7%-	50.2%	0.69	98.4
	All close contacts	73	23,577	49,643	45.3%	40.6% -	50.1%	0.69	98.4
	Casual contacts only	.	.	.	.	.	.	.	.
	Contacts with HIV infection	8	123	247	53.5%	40.6% -	66.0%	0.36	71.4
< 5 years	All	33	5,102	12,389	35.5%	30.3% -	41.1%	0.42	96.6
5 to 14 years	All	21	6,587	11,123	53.1%	42.0% -	63.9%	1.05	98.6
≥15 years	All	10	11,980	14,057	65.3%	35.5% -	86.5%	3.80	99.6

* Study references:
[9,31,34,42,48,56,57,58,59,60,62,63,64,65,66,69,70,97,100,102,103,104,105,107,108,109,110,111,112,114,116,118,119,122,123,124,126,128,129,130,131,132,133,134,136,138,139,140,142,143,144,145,146,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225]

B Prevalence of latent tuberculosis infection among contacts in high income countries

Age group	Sub-group	Included studies	Contacts with active TB	Contacts screened	Proportion	95% CI		τ²	I²
All ages	All*	92	79,511	284,505	28.1%	24.2% -	32.4%	0.99	99.5
	Index patient smear positive	34	25,910	78,784	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 X-MDR-TB	2	287	554	52.6%	49.5% -	55.7%	0.00	.
	Household contacts	33	20,960	67,175	30.0%	21.3% -	40.5%	1.80	99.6
	All close contacts	29	20,213	68,738	28.0%	18.9% -	39.4%	1.96	99.6
	Casual contacts only	7	5,779	27,383	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 years	All	17	2,093	6,900	16.3%	9.2% -	27.0%	1.73	99.2
5 to 14 years	All	10	1,407	4,871	18.4%	11.8% -	27.5%	0.64	98.4
≥15 years	All	8	6,221	12,633	41.9%	30.5% -	54.2%	0.50	99.4

* Study references
[10,27,29,30,33,35,37,43,46,72,73,74,75,79,81,85,87,89,90,91,92,93,147,148,149,150,151,152,153,154,155,156,157,161,162,163,164,166,167,168,169,170,171,172,173,174,175,176,178,179,180,181,182,183,184,185,186,187,188,189,190,191,193,194,195,196,197,198,199,200,201,202,203,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244] CI = confidence interval, TB = tuberculosis, X-MDR-TB = extensively or multi-drug resistant tuberculosis.

Table 3. Prevalence of microbiologically proven tuberculosis in the contacts of tuberculosis patients

A Prevalence of microbiologically proven tuberculosis in low-middle income settings

Age group	Sub-group	Included studies	Contacts with active TB	Contacts screened	Proportion	95% CI		τ^2	I^2
All ages	All*	38	8,633	841,721	1.2%	0.9% -	1.8%	1.00	95.9
	Index patient smear positive	17	150	10,241	1.2%	0.8% -	1.8%	0.47	87.4
	Index patient with HIV	4	35	1,317	1.9%	0.8% -	4.5%	0.53	89.7
	Index patient X-MDR-TB	2	2	1,056	0.2%	0.0% -	0.8%	0.00	82.7
	Household contacts	36	8,336	811,231	1.4%	1.0% -	2.1%	1.16	97.9
	All close contacts	37	8,426	824,541	1.4%	1.0% -	2.1%	1.14	97.8
	Casual contacts only	1	12	1,492	0.7%	0.4% -	1.3%	0.00	.

* Study references:
[9,32,34,59,63,64,65,66,67,99,101,102,103,105,107,108,111,112,113,115,116,117,118,120,121,124,127,129,130,13
3,135,136,140,142,144,145,146,245]

B Prevalence of microbiologically proven tuberculosis in high income settings

Age group	Sub-group	Included studies	Contacts with active TB	Contacts screened	Proportion	95% CI		τ^2	I^2
All ages	All*	21	264	45,897	0.4%	0.2% -	0.7%	1.56	96.1
	Index patient smear positive	6	108	5,970	0.7%	0.3% -	1.9%	1.08	97.6
	Index patient with HIV	.	.	.	.	.	.	.	.
	Index patient X-MDR-TB	2	0	554	0.0%	.	.	0.00	99.9
	Household contacts	6	116	5,459	1.4%	0.8% -	2.5%	0.33	92.6
	All close contacts	14	187	30,269	0.4%	0.2% -	0.9%	1.35	96.9
	Casual contacts only	1	0	275	0.0%	.	.	1.87	.

*Study references: [29,30,75,76,77,81,85,86,90,153,154,156,157,167,168,169,173,184,185,189,196]. CI = Confidence interval, TB = tuberculosis, X-MDR-TB = extensively or multi-drug resistant tuberculosis.

Table 4. Prevalence of LTBI among foreign and locally born contacts in high-income countries

Country of origin	Included studies	Contacts with LTBI	Contacts screened	Proportion (%)	95% CI (%)	τ²	I²	Odds ratio (95% I)	p-value
Contacts born locally	6	1,536	7,576	17.0%	11-8-24.0%	0.28	98.5	1.0	--
Contacts born overseas	6	1.849	4.298	39.2%	30.0-49.3%	0.24	97.9	3.39 (3.10-3.71)	<0.0001

Study references: [10,43,74,152,164,187,227].

Table 5. Outcomes of contact investigation studies in congregate settings in high-income countries

Study	Country	Location of contact	Number of contacts tested	Prevalence active TB (%)	Prevalence LTBI (%)
Gaensbauer (2009)[169]	Ireland	Child care centre	268	**6.7%**	N/A
Lofy (2006)[189]	USA	Homeless facilities	425	**3.1%**	**23.3%**
Marienau (2010)[184]	USA	Aeroplane flight	861	0	**24%**
Conover (2001)[233]	USA	Methadone clinic	393	N/A	**22.3%**
MMWR (2001)[238]	USA	Clubs with exotic dancers	344	N/A	**29.8%**
Davidow (2003)[186]	USA	Workplaces	724	**0.2%**	**22.0%**