

Systematic review of factors associated with the yield of tuberculosis among household contacts

Running Head: Undiagnosed TB among household contacts

Kavindhran Velen^{1, 2}, Piotr Hippner¹, James J Lewis³, N. Sarita Shah⁴, Laura J. Podewils⁴,
Salome Charalambous^{1, 2}

Affiliations: ¹ The Aurum Institute, Johannesburg, South Africa, ² The School of Public Health, University of Witwatersrand, Johannesburg, South Africa, ³ MRC Tropical Epidemiology Group, London School of Hygiene and Tropical Medicine, London, United Kingdom, ⁴ Division of Global HIV and TB, US Centers for Disease Control and Prevention, Atlanta, USA

Keywords: TB; contact tracing; contact investigation; case finding; HIV

Corresponding author: Kavindhran Velen, The Aurum Institute, The Ridge, 29 Queens Road, Parktown, Johannesburg, South Africa, 2193. Tel: +27 11 590 1391; E-mail: kvelen@auruminstitute.org

Disclaimer: The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the U.S. Department of Health and Human Services.

Word Count: 3,007 (excluding abstract and references)

Abstract word count: 213

References: 59

Tables and Figures: 3 and 4

21 **Abstract**

22 **Objective:** To identify factors which may account for the heterogeneity in the yield of TB
23 among household contact tracing (HHCT) studies.

24 **Design:** We searched PubMed, Google Scholar and Global Index Medicus for studies
25 conducted up to 30th June 2017. Univariable random effects meta-regression models were
26 developed to regress the proportion of TB identified among household contacts by study
27 characteristics.

28 **Results:** 3,631 citations were identified of which 37 were evaluated with a median of 802
29 household contacts (interquartile range [IQR], 461-1,918) from a median 307 index TB
30 patients (IQR, 137-648). The pooled yield was 2.3% (95% CI, 2.0%-2.7%, $I^2=96.5\%$) among
31 household contacts. Factors contributing to differences were 1) background TB incidence
32 {odds ratio (OR) 1.10 [95% CI, 0.97-1.27]} with every 100 cases per 100,000 population
33 increase in the background TB incidence); 2) HIV burden (OR 1.9 [95% CI, 0.9-3.7])
34 comparing high burden settings with those in low burden); and 3) proportion of contacts <5
35 years old (OR 2.0 [95% CI 0.98-4.0]) with every 10% increase in the proportion of <5 years
36 old contacts screened; 15 studies).

37 **Conclusions:** The TB yield from HHCT is higher in settings with a high background TB
38 incidence and HIV prevalence. Paediatric contacts should be targeted as they have an
39 increased risk for acquiring TB in a household and are therefore a high-yield group.

Introduction

The 2017 Global TB report suggests that despite the global decline in TB incidence at a rate of approximately 1.4%, further acceleration is needed if we are to reach the first milestones of the End TB Strategy particularly in high-burden countries ¹. The World Health Organization estimates 3.9 million TB cases were undiagnosed last year; India, Indonesia and Nigeria accounting for about half of these missed cases ¹. Finding and treating missed cases is essential for improving individual patient outcomes and curbing ongoing transmission in communities.

Household Contact Tracing (HHCT) is a well-established method for detecting and preventing additional TB cases ². Public health program support for this intervention in high-burden settings has been mixed, in part due to the varying yield of undiagnosed TB reported in HHCT studies ³⁻⁶, ranging from 1.5% to 7.8% among contacts ≥ 5 years old who could provide sputum for testing. In these studies, yield appeared to differ based on the type of HHCT strategy implemented. These variations would suggest that it is still unclear which approaches work best to improve HHCT ⁷. A 2013 systematic review by Fox *et al* reported significant heterogeneity in TB yield from HHCT studies of index TB patients ⁸; it also specifically evaluated the effect of income-setting (low, middle and high) on observed heterogeneity, as well as differences in yield for latent TB infection and active TB disease. However, there are still many unknown factors that may be associated with differences in yield of TB cases diagnosed as a result of HHCT, in addition, the yield of TB from HHCT might differ now compared to previous years due the rapidly evolving changes in TB and HIV incidence and prevalence and changes in laboratory testing practices. If programs are to

62 implement the optimal HHCT strategy, further data are needed about factors that may
63 account for this differences in TB yield.

64 We conducted a systematic review and meta-regression to expand on previous reviews,
65 specifically providing updated estimates of yield and heterogeneity among HHCT studies,
66 but also evaluating additional factors that may account for the differences in the yield of TB.

Methods

Search strategy and selection of papers

We conducted literature searches within 3 databases: 1) PubMed; 2) Google Scholar; and 3) Global Index Medicus, and limited to papers describing studies published in English up to the 30th June 2017. Search terms included *mycobacterium tuberculosis*, *contact tracing* and *case finding*. To maximize the literature search, citations found in retrieved papers were used to identify additional papers not identified in the original search. The complete search strategy is detailed in Appendix I.

Initial review of studies

We combined search outputs from all databases and imported eligible citations into a citation management program. After removing duplicates, K.V., and P.H. individually screened titles and abstracts of the remaining citations to identify full-text papers to be included based on four criteria: 1) contact tracing was initiated from an index TB patient, 2) conducted TB screening among household contacts, 3) ≥ 50 household contacts enrolled, and 4) diagnosed microbiologically confirmed TB amongst household contacts.

Disagreements on full-text papers were resolved by reaching a consensus between reviewers. Papers were excluded if contacts were linked retrospectively with index patients and not actually traced (i.e. contacts were linked with index patients from a national TB database), or if TB infection was reported as the outcome instead of TB disease.

Data Abstraction from eligible papers

A data extraction tool was designed (Appendix II) using Microsoft Excel™ (2010) which K.V. and P.H. piloted. During piloting, data extraction for five papers were compared for consistency to finalise the tool. These reviewers independently extracted data from the studies and where there was disagreement, a consensus was reached on the data to be included. Specific data elements were included in the extraction tool for each study and for index and household contacts.

We used the annual WHO Global TB Report ⁹ for the year in which the study was conducted to describe the background incidence of TB and classify the country setting as having a “high” or “low TB burden” and a “high” or “low HIV burden”. During the period 1998–2015, the concept of a “high TB burden” country became widely used in the context of TB and was defined in 1998, based on the burden of TB in absolute terms; its purpose was to allow focused interventions in the countries responsible for 80% of the global burden, with the rationale that progress in these countries would translate into global impact ¹⁰. In 2015, a new “high TB burden list was defined to be used for the period 2016–2020; contains 30 countries, defined as the top 20 in terms of absolute numbers of cases plus the additional 10 countries with the most severe burden in terms of case rates per capita that do not already appear in the “top 20” and that meet a minimum threshold in terms of absolute numbers of cases (10 000 per year for TB ¹⁰

Evaluating the quality of selected studies

We evaluated the quality of the selected studies using a standardized tool which was modified from the Newcastle-Ottawa Scale (NOS) specifically for cohort and cross-sectional

studies ¹¹. We assessed the following characteristics for each study: selection bias (representativeness of the sampled population), detection bias (ascertainment of the exposure and outcome), reporting bias (reported outcomes match the assessed outcomes), and confounding (described and/or adjusted in the analysis). Each of these individual criteria was assigned a score with the overall highest possible score being 6.5. Studies with an overall score of ≥ 4.5 were considered to be of good quality.

Data Analysis

Statistical analyses were done using STATA[®] 14 (Stata Corporation, College Station, Texas, USA). We computed the overall pooled yield of active TB disease among household contacts for all studies using the “metaprop” command in Stata: this is based on a random effects model and calculates 95% confidence intervals using Wilson’s method. The prevalence of HIV among household contacts was described where available. Univariable analyses were done using random effects meta-regression models using the “metareg” command in to regress the study-level log odds of TB cases identified among households contacts by the pre-specified study characteristics of timing of sputum specimen, diagnostic test used, proportion of paediatric contacts, TB incidence and HIV burden in that country at the time of the study. Within-study standard errors were calculated as the square-root of the sum of the inverse of the number of contacts with TB and the inverse of the number of contacts without TB. Heterogeneity was measured using the I^2 statistic and statistical significance was determined using the Q-statistic ¹².

Results

Description of the papers included

We identified 3,631 citations; 37 papers were selected for final inclusion (Figure 1) evaluating 186,765 household contacts with a median of 802 (interquartile range [IQR], 461-1,918) from 39,036 index TB patients with a median of 307 (IQR, 137-648) (Table 1). We found 33/37 (89.2%) studies conducted within “high TB burden” settings and 22/37 (59.5%) within “high HIV burden” settings.

Study Quality

The median quality score was 5.0 (IQR, 4.5-5.5) for the evaluated studies (Table 2). There were 9 studies with a score of <4.5 which were deemed low quality; however these were not excluded from the analysis. The majority of the papers (28/37 studies, 75.7%) were considered to be of good quality (score ≥ 4.5).

Household contact tracing procedures

HHCT procedures differed among the evaluated studies (Table 3). Smear status of the index patient was reported in 27/37 (73.0%) studies; 27/27 (100%) were of an index patient with sputum smear-positive TB. Symptom screening of household contacts was included in 35/37 (94.6%) studies to identify persons suspected of having TB; 20/37 (54.1%) studies also included a tuberculin skin test (TST) as part of initial screening.

Amongst those who reported timing of sputum collection (n=23), 16 (69.6%) collected a spot sputum while 6 (26.1%) collected both a spot and early morning sputum. Laboratory testing to microbiologically confirm TB included at least one of the following tests (n=37):

AFB microscopy in 34 (91.9%); Mycobacterial culture in 22 (59.5%); Gene Xpert MTB/RIF in 5 (13.5%); and Chest Radiography in 24 (64.9%) studies.

Twelve (32.4%) studies reported offering HIV testing to household contacts. In these 12 studies, 13,174/16,026 (82.2%) participants were tested, of whom 1,293 (9.8%) were newly diagnosed as HIV positive.

Yield of active TB diagnosed among household contacts

There were 2,458 cases diagnosed among 186,765 contacts (1.3% ignoring study weighting), with an overall pooled yield of TB cases diagnosed as a result of HHCT of 2.3% (95% CI, 2.0%-2.7%, $I^2=96.5\%$) and a median yield of 2.2% (IQR, 0.9%-3.5%) (Table1). The pooled yield of TB when stratified by HIV burden was 3.3% (95% CI, 2.6%-4.1%, $I^2=97.4\%$) for high HIV settings (n=22) and 1.4% (95% CI, 1.0%-1.8%, $I^2=90.3\%$) for low HIV settings (n=15) (Figure 2). The numbers of paediatric (≤ 5 years old) contacts and the number of TB cases among children ≤ 5 was reported in 11/37 (29.7%) studies (four studies did not report paediatric TB cases and two additional studies reported not including paediatric contacts). These eleven studies collectively screened 2,218 paediatric contacts, among whom 109 TB cases were diagnosed, giving a pooled yield in paediatric contacts across the eleven studies of 7.4% (95% CI: 4.0%-10.9%, $I^2=96.1\%$) in comparison to the pooled yield amongst contacts >5 years old within the same eleven studies of 2.4% (95% CI: 1.5%-3.2%, $I^2=91.3\%$).

The pooled yield of TB in the studies which used smear only (n=13) was 1.7% (95% CI: 1.2%, 2.2%, $I^2=97.2\%$), and in the 21 studies that used both culture and smear the yield was 2.8% (95% CI: 2.1%, 3.5%, $I^2=94.5\%$). The odds of diagnosing TB was two times more likely in studies which included culture as part of the testing algorithm (n=22, pooled yield= 3.1%

[95% CI: 2.4%-3.9, $I^2=95.2\%$]) compared to the 15 studies (pooled yield=1.5% [95% CI: 1.1-2.0, $I^2=96.8\%$]) that used smear and/or Xpert MTB/RIF without culture (OR=1.8 [95% CI, 0.9-3.7], p-value=0.09). The pooled yield of TB in the 16 studies with spot sputum collection only was 2.4% (95% CI: 1.7%, 3.0%, $I^2=97.5\%$); 2.7% (95% CI: 1.3%, 4.2%) in the six studies with both spot and morning sputum collection; 0.7% (95% CI: 0.4%, 1.4% in the one study with early morning sputum collection; and 3.4% (95% CI: 2.4%, 4.4%, $I^2=93.3\%$) in the 14 studies with unknown timing. There was no significant difference in the odds of diagnosing TB in the 16 studies with spot sputum collection compared to the six studies with both spot and morning sputum collection (OR=1.0 [95% CI, 0.3-2.9], p-value=1.0), although the confidence intervals were very wide.

Factors associated with TB disease among household contacts

The odds ratio for diagnosing TB among the household contacts was 1.9 (95% CI, 0.9-3.7) in settings with a high HIV burden compared with low HIV burden settings. The proportion of contacts who were paediatric was available for 15 studies and the odds ratio for diagnosing TB among household contacts of all ages in these 15 studies was 2.0 (95% CI 0.98-4.0) with every 10% increase in the proportion of contacts that were paediatric (Figure 3). Using the background TB incidence for the study period as reported by the WHO, the odds ratio was 1.10 (95% CI, 0.97-1.27) with every 100 cases per 100,000 population increase in the background TB incidence (Figure 4).

Discussion

We derived a pooled yield of 2.3% (95% CI, 2.0%–2.7%, $I^2=96.5\%$) of contacts diagnosed with TB based on HHCT in our systematic review and meta-analysis, lower than a recent systematic review by Fox *et al* which reported a TB prevalence of 3.1% (95% CI, 2.1%–4.5%, $I^2=98.8\%$)⁸. The difference in our pooled estimate compared to Fox *et al* is explained by the fact that three of our 37 included studies accounted for 78.8% of evaluated contacts, however only diagnosed a yield of 0.9% and thus skewed the overall pooled result downwards; in the absence of these studies, the pooled yield is 2.8% (95% CI: 2.3%–3.4%), $I^2=94.8\%$. Nevertheless, the high yield of TB cases diagnosed through HHCT expands upon the evidence supporting the importance of contact tracing as a TB case-detection strategy. Our findings also support the 2012 WHO recommendations for the investigation of contacts of known index patients with TB who are symptomatic, HIV positive, or <5 years old¹³.

Higher incidence rates of TB in the general population of the country was associated with a higher yield of TB among household contacts. The odds of diagnosing a household contact with TB disease was 10% higher for every 100 cases per 100,000 population increase in the background incidence of TB for that country. We expect naturally higher transmission of TB in “high TB burden” settings¹⁴ as individuals are more prone to be latently infected. Contact with a smear-positive TB patient in the household or community results in an increase in the transmission and incidence of TB^{15,16}. Our findings provide further evidence of the need to implement contact tracing activities in “high TB burden” countries².

The pooled yield was higher in settings with a high HIV burden compared to low HIV burden settings (3.3% versus 1.4%). This is consistent with the abundance of research published about the greater risk of developing and dying from TB among people living with HIV (PLHIV)

214 ¹⁷⁻¹⁹. The added finding of 9.8% of those tested for HIV as part of HHCT being diagnosed
215 with HIV supports the need for integrating TB/HIV activities within HHCT by being able to
216 diagnose two diseases early on in an individual²⁰.

217 The pooled TB yield among paediatric contacts was high (7.4%) and is consistent with a
218 previous systematic review which found them to have the highest yield of any subgroup ²¹.
219 Children are often overlooked during HHCT activities ²², however from our meta-regression
220 model we found that for every 10% increase in the proportion of paediatric contacts
221 screened, the odds of diagnosing TB among household contacts was 1.8. These findings
222 support previous evidence for targeting this age group and are consistent with the current
223 recommendation by WHO ^{21,23}. It further emphasizes HHCT as potentially the best strategy
224 to identify undiagnosed childhood cases of TB.

225 Among studies included in our review, smear microscopy still remained the mainstay of TB
226 testing; culture testing closely followed. There was no statistical difference between the
227 yield of undiagnosed TB in studies which included culture as part of the testing algorithm
228 compared to those that used smear only. In addition, none of the studies which reported
229 the use of culture and smear reported the yield by diagnostic test to determine the basis for
230 TB diagnosis which made it difficult to establish which test contributed to the highest yield
231 for a given study. Only five studies included the Xpert MTB/RIF assay in its testing strategy
232 and thus we couldn't compare its diagnostic benefit based on its limited use. Nonetheless,
233 its emergence as a TB diagnostic in routine settings has important implications for future
234 algorithms used in HHCT. A recent TB prevalence survey found that the yield of Xpert
235 MTB/RIF was higher than smear microscopy but lower than culture ²⁴, however, more

236 operational research is required in the context of HHCT to understand if this reported
237 finding still holds true among household contacts.

238 We observed substantial differences between studies, particularly around testing
239 procedures; therefore pooled yield estimates must be interpreted with caution. We
240 attempted to overcome this using random-effect models; however, the magnitude of the
241 heterogeneity meant that we could not account for all the factors which might explain the
242 difference in yield across studies. These differences likely introduced a level of
243 ascertainment bias. For instance, smear status of index cases was not consistently reported,
244 so we were unable to determine how smear status may have influenced the yield among
245 household contacts; we assume that a smear-positive patient would be more infectious
246 than a smear-negative patient and therefore pose a higher risk for transmission within the
247 household. Systematic reviews such as this one provide an opportunity for synthesizing
248 evidence from the literature, however without particular aspects consistently reported
249 among studies, it makes it difficult to evaluate certain factors; we thus recommend that
250 studies report a minimum set of characteristics that include index TB identification, timing
251 of household visits, screening and laboratory testing algorithms, stratification of laboratory
252 results by diagnostic tests, HIV status of household contact and previous TB history.

253 Large variations in HHCT practices prevented us from determining screening and testing
254 modalities worked best for identifying undiagnosed TB. Timing of sputum collection was
255 reported in around two-thirds of evaluated studies so we could not make a firm conclusion
256 from this however, according to the available data, there was no statistical difference in the
257 yield of TB diagnosed regardless of whether the sputum was collected on the spot or with
258 both spot and morning collection. Chest radiography was reported in approximately two-

259 thirds of included studies; however, we focused this review on microbiologically confirmed
260 TB and thus haven't elaborated on its value in identifying TB among household contacts.

261 Our review was restricted to papers published in English and hence generalizability of
262 findings may not account for results reported in the literature produced in other languages.

263 Our study has provided an updated systematic review and pooled yield of HHCT for TB
264 among household contacts of people with drug-susceptible TB, as well as factors that
265 influence differences in the yield. Although we did not fully examine the independent
266 contributions of each factor to the heterogeneity in the yield of TB, we were able to show
267 that TB household contact tracing yield is higher in settings with high TB incidence and high
268 background HIV prevalence.

269 Our findings emphasize the benefit of household contact tracing as an effective approach
270 for finding undiagnosed TB, a necessary strategy if we are to meet the milestones of the End
271 TB Strategy. The high TB yield identified in this review should be particularly considered in
272 settings with high TB and high HIV settings. More research is needed to identify an optimal
273 approach for household contact tracing, particularly as new diagnostics such as Xpert
274 MTB/RIF become increasingly accessible to TB programs worldwide.

275 **Funding:** This work has been supported in part by the President's Emergency Plan for AIDS
276 Relief (NSS, LJP) through the Centers for Disease Control and Prevention and by the US
277 National Institute of Allergy and Infectious Diseases, National Institutes of Health
278 R01AI089349 (NSS).

Potential conflicts of Interest: All authors declare they have no conflicts of interest related to this work. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Disclaimer: The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the U.S. Department of Health and Human Services.

References

1. WHO. *Global Tuberculosis Report 2017*. Geneva 2017.
2. Shah NS, Yuen CM, Heo M, Tolman AW, Becerra MC. Yield of contact investigations in households of patients with drug-resistant tuberculosis: systematic review and meta-analysis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Feb 2014;58(3):381-391.
3. Zachariah R, Spielmann MP, Harries AD, et al. Passive versus active tuberculosis case finding and isoniazid preventive therapy among household contacts in a rural district of Malawi. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*. Nov 2003;7(11):1033-1039.
4. Jackson-Sillah D, Hill PC, Fox A, et al. Screening for tuberculosis among 2381 household contacts of sputum-smear-positive cases in The Gambia. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. Jun 2007;101(6):594-601.
5. Thind D, Charalambous S, Tongman A, Churchyard G, Grant AD. An evaluation of 'Ribolola': a household tuberculosis contact tracing programme in North West Province, South Africa. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*. Dec 2012;16(12):1643-1648.
6. Shapiro AE, Variava E, Rakgokong MH, et al. Community-based targeted case finding for tuberculosis and HIV in household contacts of patients with tuberculosis in South Africa. *American journal of respiratory and critical care medicine*. May 15 2012;185(10):1110-1116.
7. Borgdorff MW, Yew WW, Marks G. Active tuberculosis case finding: why, when and how? *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*. Mar 2013;17(3):285.
8. Fox GJ, Barry SE, Britton WJ, Marks GB. Contact investigation for tuberculosis: a systematic review and meta-analysis. *The European respiratory journal*. Jan 2013;41(1):140-156.
9. WHO. *Global Tuberculosis Report*. Geneva: World Health Organization;2013.
10. WHO. *Use of high burden country lists for TB by WHO in the post-2015 era*. Switzerland 2015.
11. Wells GA, Shea B, O'Connell D, et al. *The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis*. The Ottawa Hospital Research Institute;2010.
12. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. Sep 6 2003;327(7414):557-560.
13. Organization WH. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. WHO Press; 2011.

14. Van Wyk SS, Mandalakas AM, Enarson DA, Gie RP, Beyers N, Hesselning AC. Tuberculosis contact investigation in a high-burden setting: house or household? *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*. Feb 2012;16(2):157-162.
15. Radhakrishna S, Frieden TR, Subramani R, Santha T, Narayanan PR. Additional risk of developing TB for household members with a TB case at home at intake: a 15-year study. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*. Mar 2007;11(3):282-288.
16. Verver S, Warren RM, Munch Z, et al. Proportion of tuberculosis transmission that takes place in households in a high-incidence area. *Lancet (London, England)*. Jan 17 2004;363(9404):212-214.
17. Corbett EL, MacPherson P. Tuberculosis screening in high human immunodeficiency virus prevalence settings: turning promise into reality. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*. Sep 2013;17(9):1125-1138.
18. Cox JA, Lukande RL, Lucas S, Nelson AM, Van Marck E, Colebunders R. Autopsy causes of death in HIV-positive individuals in sub-Saharan Africa and correlation with clinical diagnoses. *AIDS Rev*. Oct-Dec 2010;12(4):183-194.
19. Cohen T, Murray M, Wallengren K, Alvarez GG, Samuel EY, Wilson D. The prevalence and drug sensitivity of tuberculosis among patients dying in hospital in KwaZulu-Natal, South Africa: a postmortem study. *PLoS medicine*. Jun 2010;7(6):e1000296.
20. Ayles H, Muyoyeta M, Du Toit E, et al. Effect of household and community interventions on the burden of tuberculosis in southern Africa: the ZAMSTAR community-randomised trial. *Lancet (London, England)*. Oct 5 2013;382(9899):1183-1194.
21. Morrison J, Pai M, Hopewell PC. 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*. Jun 2008;8(6):359-368.
22. Swaminathan S, Rekha B. Pediatric tuberculosis: global overview and challenges. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. May 15 2010;50 Suppl 3:S184-194.
23. Enarson DA, Arnadottir T, Trebucq A. *Management of tuberculosis: a guide for low income countries*. 5th ed: International Union Against TB and Lung Disease; 2000.
24. Dorman SE, Chihota VN, Lewis JJ, et al. Performance characteristics of the Cepheid Xpert MTB/RIF test in a tuberculosis prevalence survey. *PloS one*. 2012;7(8):e43307.
25. Becerra MC, Pachao-Torreblanca IF, Bayona J, et al. Expanding tuberculosis case detection by screening household contacts. *Public health reports*. 2005;120(3):271.
26. Beyers N, Gie R, Schaaf H, et al. A prospective evaluation of children under the age of 5 years living in the same household as adults with recently diagnosed pulmonary tuberculosis. *The International Journal of Tuberculosis and Lung Disease*. 1997;1(1):38-43.
27. Borraccino A, Migliore E, Piccioni P, Baussano I, Carosso A, Bugiani M. Yield of tuberculosis contact investigation in a low-incidence country. *The Journal of infection*. May 2014;68(5):448-454.
28. Chakhaia T, Magee MJ, Kempker RR, et al. High utility of contact investigation for latent and active tuberculosis case detection among the contacts: a retrospective cohort study in Tbilisi, Georgia, 2010–2011. *PloS one*. 2014;9(11):e111773.
29. Chheng P, Nsereko M, Malone LL, et al. Tuberculosis case finding in first-degree relative contacts not living with index tuberculosis cases in Kampala, Uganda. *Clinical epidemiology*. 2015;7:411.

- 369 **30.** de Lima LM, Schwartz E, Gonzales RI, Harter J, de Lima JF. [The tuberculosis control program
370 in Pelotas/RS, Brazil: home contact investigations]. *Revista gaucha de enfermagem*. Jun
371 2013;34(2):102-110.
- 372 **31.** Deery C, Hanrahan C, Selibas K, Bassett J, Sanne I, Van Rie A. A home tracing program for
373 contacts of people with tuberculosis or HIV and patients lost to care. *The International*
374 *Journal of Tuberculosis and Lung Disease*. 2014;18(5):534-540.
- 375 **32.** Egere U, Togun T, Sillah A, et al. Identifying children with tuberculosis among household
376 contacts in The Gambia. *The International Journal of Tuberculosis and Lung Disease*.
377 2017;21(1):46-52.
- 378 **33.** Gashu Z, Jerene D, Ensermu M, et al. The Yield of Community-Based “Retrospective”
379 Tuberculosis Contact Investigation in a High Burden Setting in Ethiopia. *PloS one*.
380 2016;11(8):e0160514.
- 381 **34.** Gupta M, Saibannavar AA, Kumar V. Household symptomatic contact screening of newly
382 diagnosed sputum smears positive tuberculosis patients-An effective case detection tool.
383 *Lung India: official organ of Indian Chest Society*. 2016;33(2):159.
- 384 **35.** Guwatudde D, Nakakeeto M, Jones-Lopez EC, et al. Tuberculosis in household contacts of
385 infectious cases in Kampala, Uganda. *American journal of epidemiology*. Nov 01
386 2003;158(9):887-898.
- 387 **36.** Gyawali N, Gurung R, Poudyal N, et al. Prevalence of tuberculosis in household contacts of
388 sputum smears positive cases and associated demographic risk factors. *Nepal Med. Coll. J*.
389 2012;14:303-307.
- 390 **37.** Hill PC, Jackson-Sillah DJ, Fox A, et al. Incidence of tuberculosis and the predictive value of
391 ELISPOT and Mantoux tests in Gambian case contacts. *PLoS One*. Jan 02 2008;3(1):e1379.
- 392 **38.** Jaganath D, Zalwango S, Okware B, et al. Contact investigation for active tuberculosis among
393 child contacts in Uganda. *Clinical infectious diseases*. 2013:cit645.
- 394 **39.** Khalilzadeh S, Masjedi H, Hosseini M, Safavi A, Masjedi MR. Transmission of *Mycobacterium*
395 tuberculosis to households of tuberculosis patients: a comprehensive contact tracing study.
396 *Archives of Iranian medicine*. Jul 2006;9(3):208-212.
- 397 **40.** Khan TR, Ahmed Z, Zafar M, Nisar N, Qayyum S, Shafi K. Active case finding of sputum
398 positive pulmonary tuberculosis in household contacts of tuberculosis patients in Karachi,
399 Pakistan. *The Journal of Association of Chest Physicians*. 2014;2(1):25.
- 400 **41.** Khaparde K, Jethani P, Dewan PK, et al. Evaluation of TB Case Finding through Systematic
401 Contact Investigation, Chhattisgarh, India. *Tuberculosis research and treatment*. 2015;2015.
- 402 **42.** Kumar V, Kalaiselvan G, Dongre A. Prevalence of Tuberculosis among Household Contacts in
403 Pondicherry: Active Case Finding Among New Smear Positive Cases. *Online J Health Allied*
404 *Scs*. 2016;15(1):4.
- 405 **43.** Lala SG, Little KM, Tshabangu N, et al. Integrated Source Case Investigation for Tuberculosis
406 (TB) and HIV in the Caregivers and Household Contacts of Hospitalised Young Children
407 Diagnosed with TB in South Africa: An Observational Study. *PloS one*. 2015;10(9):e0137518.
- 408 **44.** Lebina L, Fuller N, Osoba T, et al. The Use of Xpert MTB/Rif for Active Case Finding among TB
409 Contacts in North West Province, South Africa. *Tuberculosis Research and Treatment*.
410 2016;2016.
- 411 **45.** Liippo KK, Kulmala K, Tala EO. Focusing tuberculosis contact tracing by smear grading of
412 index cases. *The American review of respiratory disease*. Jul 1993;148(1):235-236.
- 413 **46.** Loredó C, Cailleaux-Cezar M, Efron A, de Mello FCQ, Conde MB. Yield of close contact
414 tracing using two different programmatic approaches from tuberculosis index cases: a
415 retrospective quasi-experimental study. *BMC pulmonary medicine*. 2014;14(1):1.
- 416 **47.** Maciel EL, Vieira LW, Molina LP, Alves R, Prado TN, Dietze R. Juvenile household contacts
417 aged 15 or younger of patients with pulmonary TB in the greater metropolitan area of
418 Vitória, Brazil: a cohort study. *Jornal brasileiro de pneumologia : publicação oficial da*
419 *Sociedade Brasileira de Pneumologia e Tisiologia*. Apr 2009;35(4):359-366.

- 420 **48.** Noertjojo K, Tam C, Chan S, Tan J, Chan-Yeung M. Contact examination for tuberculosis in
421 Hong Kong is useful. *The International Journal of Tuberculosis and Lung Disease*.
422 2002;6(1):19-24.
- 423 **49.** Ntinginya EN, Squire SB, Millington KA, et al. Performance of the Xpert(R) MTB/RIF assay in
424 an active case-finding strategy: a pilot study from Tanzania. *The international journal of*
425 *tuberculosis and lung disease : the official journal of the International Union against*
426 *Tuberculosis and Lung Disease*. Nov 2012;16(11):1468-1470.
- 427 **50.** Puryear S, Seropola G, Ho-Foster A, et al. Yield of contact tracing from pediatric tuberculosis
428 index cases in Gaborone, Botswana. *The International Journal of Tuberculosis and Lung*
429 *Disease*. 2013;17(8):1049-1055.
- 430 **51.** Salazar-Vergara RM, Sia IG, Tupasi TE, et al. Tuberculosis infection and disease in children
431 living in households of Filipino patients with tuberculosis: a preliminary report. *The*
432 *international journal of tuberculosis and lung disease : the official journal of the International*
433 *Union against Tuberculosis and Lung Disease*. Dec 2003;7(12 Suppl 3):S494-500.
- 434 **52.** Shah SA, Qayyum S, Abro R, Baig S, Creswell J. Active contact investigation and treatment
435 support: an integrated approach in rural and urban Sindh, Pakistan. *The international journal*
436 *of tuberculosis and lung disease : the official journal of the International Union against*
437 *Tuberculosis and Lung Disease*. Dec 2013;17(12):1569-1574.
- 438 **53.** Shapiro AE, Variava E, Rakgokong MH, et al. Community-based targeted case finding for
439 tuberculosis and HIV in household contacts of patients with tuberculosis in South Africa.
440 *American journal of respiratory and critical care medicine*. 2012;185(10):1110-1116.
- 441 **54.** Singh J, Sankar MM, Kumar S, et al. Incidence and prevalence of tuberculosis among
442 household contacts of pulmonary tuberculosis patients in a peri-urban population of South
443 Delhi, India. *PLoS One*. 2013;8(7):e69730.
- 444 **55.** Thanh THT, Ngoc SD, Viet NN, et al. A household survey on screening practices of household
445 contacts of smear positive tuberculosis patients in Vietnam. *BMC public health*.
446 2014;14(1):1.
- 447 **56.** Thind D, Charalambous S, Tongman A, Churchyard G, Grant AD. An evaluation of 'Ribolola': a
448 household tuberculosis contact tracing programme in North West Province, South Africa.
449 *The International Journal of Tuberculosis and Lung Disease*. 2012;16(12):1643-1648.
- 450 **57.** Togun T, Egere U, Sillah A, et al. Contribution of Xpert® MTB/RIF to the diagnosis of
451 pulmonary tuberculosis among TB-exposed children in The Gambia. *The International*
452 *Journal of Tuberculosis and Lung Disease*. 2015;19(9):1091-1097.
- 453 **58.** Whalen CC, Zalwango S, Chiunda A, et al. Secondary attack rate of tuberculosis in urban
454 households in Kampala, Uganda. *PLoS One*. Feb 14 2011;6(2):e16137.
- 455 **59.** Zhang X, Wei X, Zou G, et al. Evaluation of active tuberculosis case finding through symptom
456 screening and sputum microscopy of close contacts in Shandong, China. *Tropical Medicine &*
457 *International Health*. 2011;16(12):1511-1517.

Table 1. Study characteristics of studies selected for inclusion in the evaluation (n=37).

Author	Country	Year	WHO TB Incidence per 100k (At time of study) †	WHO defined HIV Burden †	TB Index patients	Household contacts evaluated for active TB	Number of contacts with microbiologically confirmed TB (%)
Becerra <i>et al</i> ²⁵	Peru	2005	153	High	191	1094	8 (0.7)
Beyers <i>et al</i> ²⁶	South Africa	1997	360	High	80	309	69 (22.3)
Borraccino <i>et al</i> ²⁷	Italy	2014	5.8	Low	833	3123	28 (0.9)
Chakhaia <i>et al</i> ²⁸	Georgia	2014	106	Low	396	869	23 (2.6)
Chheng <i>et al</i> ²⁹	Uganda	2015	202	High	31	125	13 (10.4)
de Lima <i>et al</i> ³⁰	Brazil	2013	43	High	68	163	3 (1.8)
Deery <i>et al</i> ³¹	South Africa	2014	834	High	172	67	1 (1.5)
Egere <i>et al</i> ³²	Gambia	2017	173	High	551	4042	19 (0.5)
Fox <i>et al</i> ⁸	Vietnam	2012	147	Low	212	545	5 (0.9)
Gashu <i>et al</i> ³³	Ethiopia	2016	192	High	19235	116324	861 (0.7)
Gupta <i>et al</i> ³⁴	India	2016	217	High	133	521	5 (1.0)
Guwatudde <i>et al</i> ³⁵	Uganda	2003	502	High	302	1206	51 (4.2)
Gyawali <i>et al</i> ³⁶	Nepal	2012	161	Low	184	802	13 (1.6)
Hill <i>et al</i> ³⁷	Gambia	2008	183	Low	317	2381	33 (1.4)
Jaganath <i>et al</i> ³⁸	Uganda	2013	203	High	351	761	79 (10.4)
Khalilzadeh <i>et al</i> ³⁹	Iran	2006	16	Low	68	224	17 (7.6)
Khan <i>et al</i> ⁴⁰	Pakistan	2014	270	High	135	750	88 (11.7)
Khaparde <i>et al</i> ⁴¹	India	2015	217	High	312	1490	11 (0.7)
Kumar <i>et al</i> ⁴²	India	2016	217	High	157	472	3 (0.6)
Lala <i>et al</i> ⁴³	South Africa	2015	834	High	576	1826	66 (3.6)
Lebina <i>et al</i> ⁴⁴	South Africa	2016	834	High	768	863	23 (2.7)
Liippo <i>et al</i> ⁴⁵	Finland	1992	16	Low	134	136	4 (2.9)
Loredo <i>et al</i> ⁴⁶	Brazil	2014	41	High	193	609	9 (1.5)

† Specific for this country in the year the study was conducted

Author	Country	Year	WHO TB Incidence per 100k (At time of study) †	HIV Burden †	TB Index patients	Household contacts evaluated for active TB	Number of contacts with microbiologically confirmed TB (%)
Maciel <i>et al</i> ⁴⁷	Brazil	2008	43	High	137	155	5 (3.2)
Noertjojo <i>et al</i> ⁴⁸	Hong Kong	2002	105	Low	903	1859	37 (2.0)
Ntinginya <i>et al</i> ⁴⁹	Tanzania	2012	378	High	80	219	5 (2.3)
Puryear <i>et al</i> ⁵⁰	Botswana	2013	414	High	163	548	12 (2.2)
Salazar-Vergara <i>et al</i> ⁵¹	Philippines	2003	349	Low	62	153	5 (3.3)
Shah <i>et al</i> ⁵²	Pakistan	2013	275	High	3037	19191	490 (2.6)
Shapiro <i>et al</i> ⁵³	South Africa	2011	922	High	727	2843	169 (5.9)
Singh <i>et al</i> ⁵⁴	India	2013	228	High	432	1608	52 (3.2)
Thanh <i>et al</i> ⁵⁵	Vietnam	2014	140	Low	1091	474	20 (4.2)
Thind <i>et al</i> ⁵⁶	South Africa	2011	922	High	732	3627	127 (3.5)
Togun <i>et al</i> ⁵⁷	Gambia	2015	174	Low	622	3298	21 (0.6)
Whalen <i>et al</i> ⁵⁸	Uganda	2011	207	High	497	1918	49 (2.6)
Zachariah <i>et al</i> ³	Malawi	2003	397	High	189	461	2 (0.4)
Zhang <i>et al</i> ⁵⁹	China	2011	77	Low	4965	11709	40 (0.3)

† Specific for this country in the year the study was conducted

Table 2. Summary of study quality criteria for selected publications (n=37).

Criteria	n (%)
1. Selection bias <i>Were inclusion and exclusion criteria described for the household contact?</i> <i>Was the recruitment strategy clearly stated?</i>	32 (84.2%) 32 (84.2%)
2. Information/Detection bias <u>Ascertainment of Exposure</u> <i>Was the index patient clearly defined?</i> <u>Assessment of outcome</u> <i>Was mycobacterial culture used a gold standard for laboratory confirmation of TB?</i> <i>Were radiological methods used to diagnose TB?</i>	30 (78.9%) 22 (59.5%) 25 (65.8%)
3. Reporting bias <i>Did the reported outcomes match the assessed outcomes?</i>	38 (100%)
4. Confounding <i>Was confounding described and/or adjusted for in the analysis?</i>	15 (39.5%)
Overall study quality score (median, IQR)	5.5 (4.5-6)
Studies with quality score ≥ 4.5	14 (82.4%)
Studies with low quality, defined as score < 4.5	3 (17.6%)

Table 3. TB household contact tracing testing practices utilized in studies included in the evaluation (n=37).

	Any of these used to determine persons suspected of TB		Any of these tests used to diagnose a TB case				
Author	Symptom Screening	Tuberculin Skin Test	Smear Microscopy	Culture	Xpert MTB/RIF	Chest Radiography	Timing of specimen collected
Becerra <i>et al</i>	Yes	No	Yes	Yes	No	No	Early morning
Beyers <i>et al</i>	Yes	Yes	No	Yes	No	Yes	Unknown
Borraccino <i>et al</i>	Yes	Yes	Yes	Yes	No	Yes	Unknown
Chakhaia <i>et al</i>	Yes	Yes	Yes	Yes	No	Yes	Unknown
Chheng <i>et al</i>	Yes	Yes	Yes	Yes	No	Yes	Unknown
de Lima <i>et al</i>	Yes	Yes	Yes	No	No	Yes	Unknown
Deery <i>et al</i>	Yes	No	No	No	Yes	No	Spot
Egere <i>et al</i>	Yes	Yes	No	No	Yes	Yes	Spot
Fox <i>et al</i>	Yes	No	Yes	Yes	No	Yes	Spot and Early morning
Gashu <i>et al</i>	Yes	No	Yes	No	No	Yes	Spot and Early morning
Gupta <i>et al</i>	Yes	No	Yes	No	No	Yes	Spot
Guwatudde <i>et al</i>	Yes	Yes	Yes	Yes	No	Yes	Spot
Gywali <i>et al</i>	No	No	Yes	No	No	No	Spot and Early morning
Hill <i>et al</i>	Yes	Yes	Yes	Yes	No	Yes	Spot
Jaganath <i>et al</i>	Yes	Yes	Yes	Yes	No	Yes	Unknown
Khalilzadeh <i>et al</i>	Yes	Yes	Yes	No	No	Yes	Spot
Khan <i>et al</i>	Yes	No	Yes	No	No	No	Spot and Early morning
Khaparde <i>et al</i>	Yes	Yes	Yes	No	No	Yes	Unknown
Kumar <i>et al</i>	Yes	No	Yes	No	No	No	Spot and Early morning
Lala <i>et al</i>	Yes	No	Yes	Yes	No	No	Spot

	Any of these used to determine persons suspected of TB		Any of these tests used to diagnose a TB case				
Author	Symptom Screening	Tuberculin Skin Test	Smear Microscopy	Culture	Xpert MTB/RIF	Chest Radiography	Timing of specimen collected
Lebina <i>et al</i>	Yes	No	Yes	Yes	Yes	No	Spot
Liippo <i>et al</i>	No	Yes	Yes	No	No	Yes	Unknown
Loredo <i>et al</i>	Yes	Yes	Yes	Yes	No	Yes	Unknown
Maciel <i>et al</i>	Yes	Yes	Yes	Yes	No	Yes	Unknown
Noertjojo <i>et al</i>	Yes	Yes	Yes	Yes	No	Yes	Unknown
Ntinginya <i>et al</i>	Yes	No	Yes	Yes	Yes	No	Spot
Puryear <i>et al</i>	Yes	Yes	Yes	Yes	No	Yes	Unknown
Salazar-Vergara <i>et al</i>	Yes	Yes	Yes	Yes	No	Yes	Unknown
Shah <i>et al</i>	Yes	No	Yes	No	No	No	Spot
Shapiro <i>et al</i>	Yes	No	Yes	Yes	No	No	Spot
Singh <i>et al</i>	Yes	Yes	Yes	Yes	No	No	Spot
Thanh <i>et al</i>	Yes	No	Yes	No	No	Yes	Spot
Thind <i>et al</i>	Yes	No	Yes	Yes	No	No	Spot and Early morning
Togun <i>et al</i>	Yes	Yes	Yes	Yes	Yes	Yes	Spot
Whalen <i>et al</i>	Yes	Yes	Yes	Yes	No	Yes	Unknown
Zachariah <i>et al</i>	Yes	No	Yes	No	No	Yes	Spot
Zhang <i>et al</i>	Yes	No	Yes	No	No	No	Spot

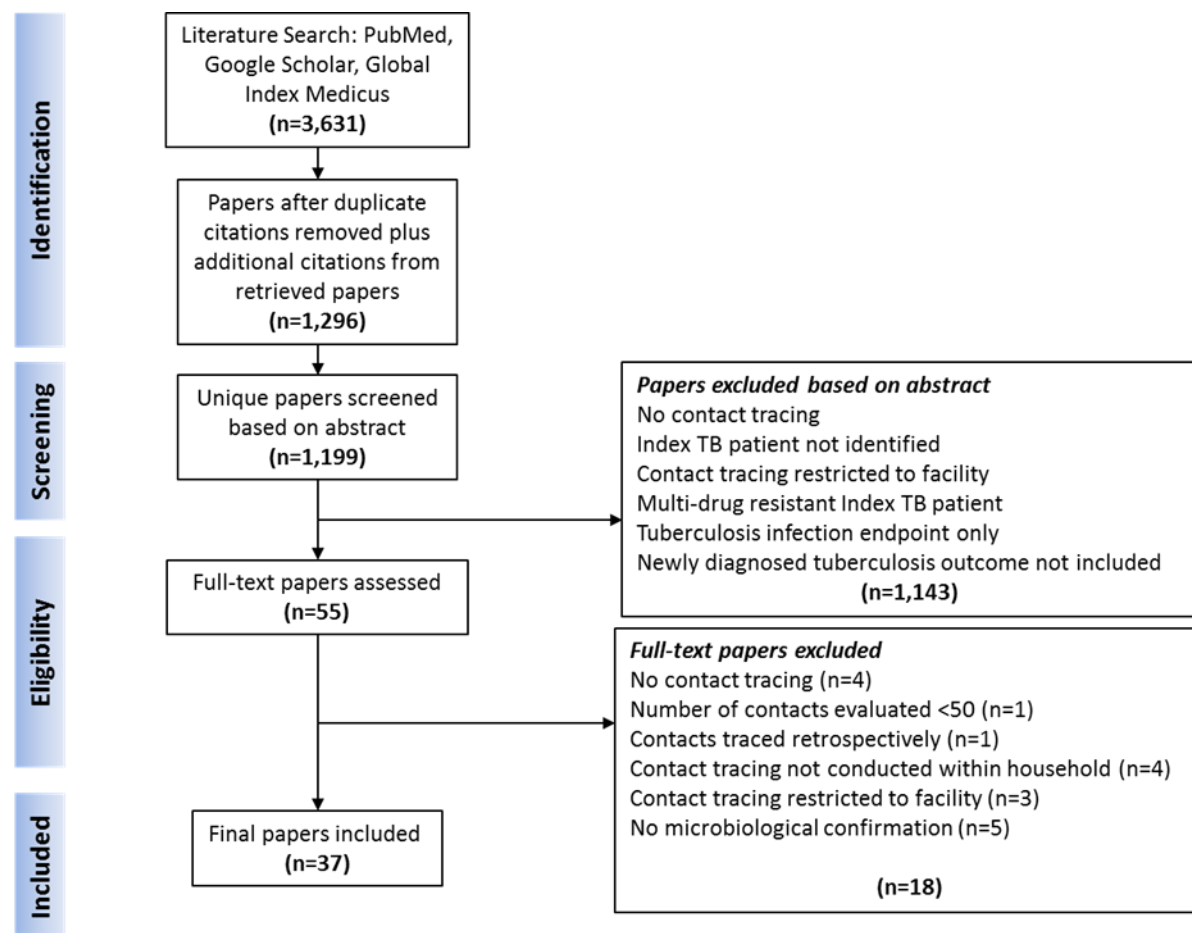


Figure 1: Flow diagram for study selection. Abbreviations: WHO, World Health Organization

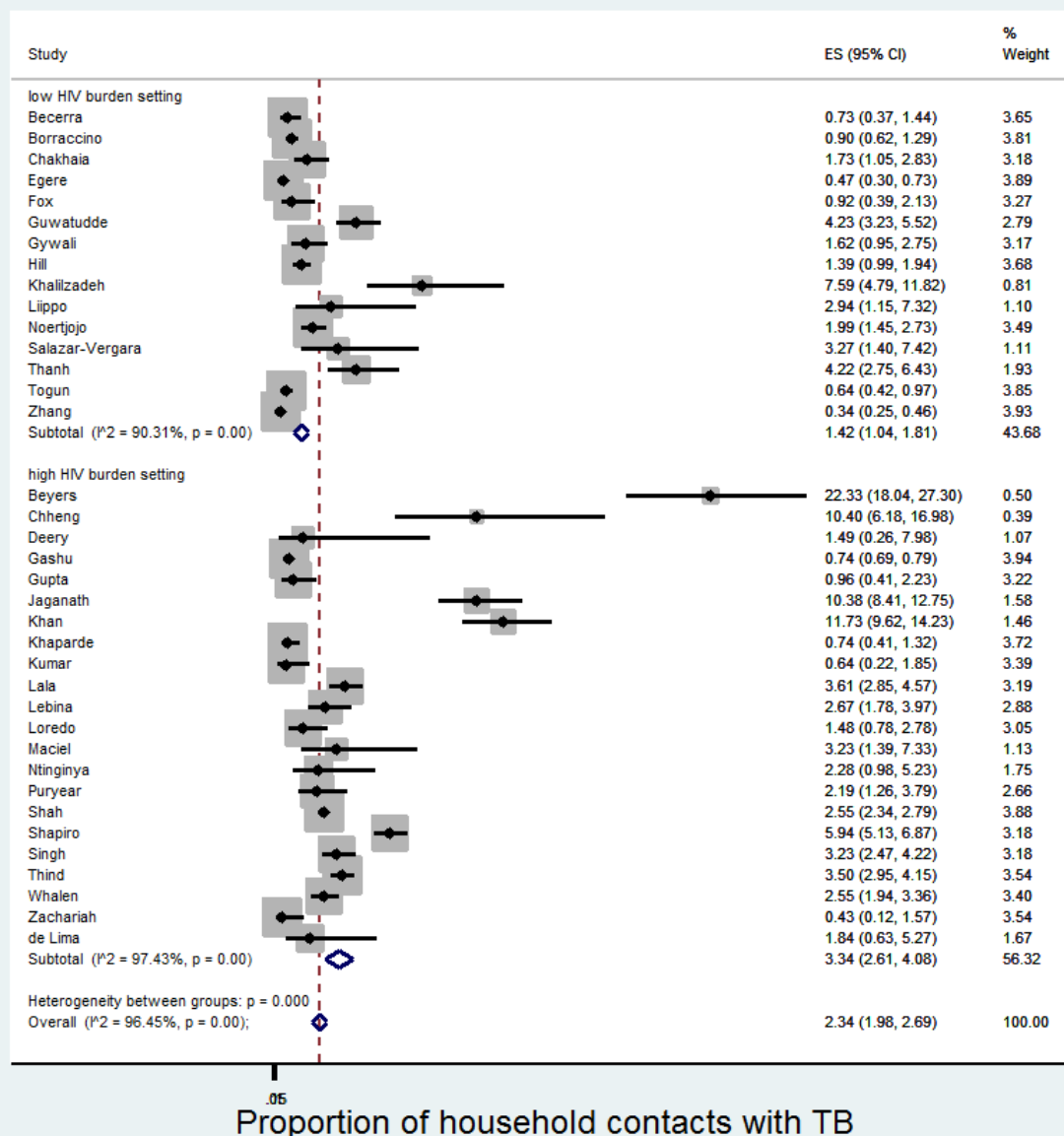


Figure 2: Forest plot for active TB diagnosed among household contacts of known TB index patients stratified by background country HIV burden (ES = estimated proportion of contacts with TB)

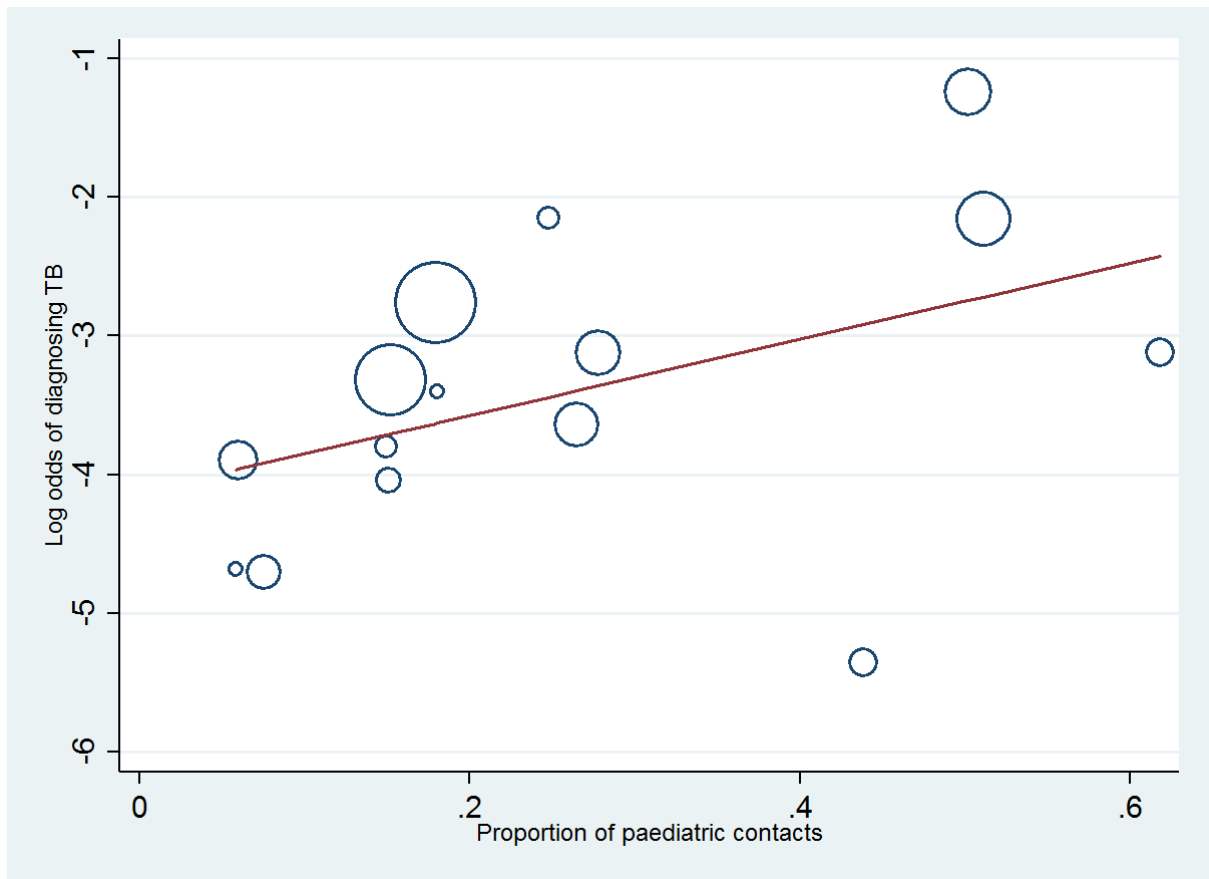


Figure 3: Random-effects meta-regression graph for diagnosing active TB among household contacts stratified by proportion of paediatric contacts (n=15)

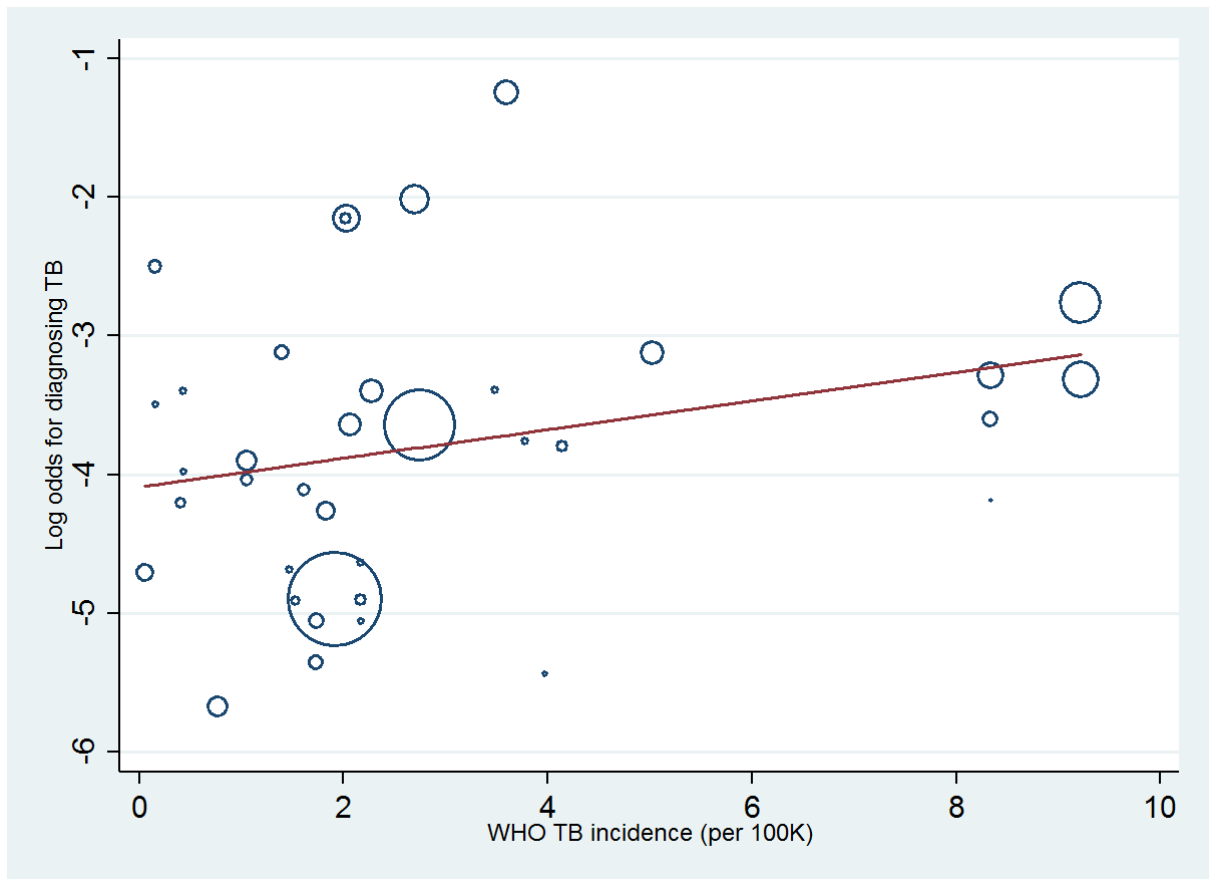


Figure 4: Random-effects meta-regression graph for diagnosing active TB among household contacts stratified by WHO TB incidence per 100,000 cases.

Appendix I: Search strategy

For PubMed

We conducted searches using MeSH terms: 1) “mycobacterium tuberculosis” AND “contact tracing;” 2) “mycobacterium tuberculosis” AND “case finding;” 3) “mycobacterium tuberculosis” AND “household contact;” 4) “mycobacterium tuberculosis” AND “case detection;” 5) “mycobacterium tuberculosis” AND “yield.”

Google Scholar

We used the following keywords “mycobacterium tuberculosis” AND “case finding” OR “yield” AND “household contact.”

Global Index Medicus

We searched all regional indices using keywords “contact tracing” AND “tuberculosis.”

Appendix II: Data Extraction Tool

<i>Year</i>	<i>Study</i>	<i>Country</i>	<i>TB burden (High/Low)</i>	<i>HIV burden (High/Low)</i>	<i>Special Populations (Yes/No)</i>	<i>Selection criteria for Index</i>	<i>Selection criteria for Contact</i>	<i>Screening tests</i>	<i>Screening Procedures</i>	<i>Total number of Index patients</i>	<i>Number of Index patients with Previous TB</i>	<i>How long after Index diagnosis is household visited</i>	<i>Total number of household contacts</i>	<i>Household contacts (Male)</i>	<i>Household contacts (Female)</i>
-------------	--------------	----------------	---------------------------------	--------------------------------------	---	---	---	----------------------------	---------------------------------	---	--	--	---	--	--

<i>Symptom screening (Yes/No)</i>	<i>Smear Microscopy</i>	<i>Culture</i>	<i>Chest Radiography</i>	<i>Tuberculin Skin Test</i>	<i>GXP</i>	<i>Timing of Specimen</i>	<i>Household contacts screened</i>	<i>TB suspects</i>	<i>Contacts <5years old</i>	<i>Total number of microbiologi- cally confirmed TB cases</i>	<i>Proportion of paediatric TB cases</i>	<i>Contacts tested for HIV</i>	<i>Contacts eligible for HIV testing</i>	<i>Known HIV positive contacts</i>	<i>HIV positive contacts (Tested)</i>
---	-----------------------------	----------------	------------------------------	---------------------------------	------------	-------------------------------	--	------------------------	--	---	--	--	--	--	---