

WEB MATERIAL

Transmission of *Mycobacterium tuberculosis* in Households and the Community:

A Systematic Review and Meta-Analysis

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Table of Contents

| | |
|--|----|
| Web Appendix 1. PRISMA Checklist | 3 |
| Web Appendix 2. Search Strategy | 6 |
| Web Table 1. List of Characteristics Extracted from Selected Studies. | 8 |
| Web Table 2. Selection of community controls in 26 included studies..... | 10 |
| Web Table 3. Methods of tuberculosis diagnosis in index case and classification of exposure amongst 26 included studies..... | 13 |
| Web Table 4. Definitions and recruitment of household contacts and community controls in all studies . | 16 |
| Web Table 5. Odds ratios of 26 included studies..... | 20 |
| Web Table 6. Sensitivity Analysis: Crude versus Adjusted Odds Ratios..... | 21 |
| Web Figure 1. Funnel plot (with pseudo confidence intervals) of 26 studies investigating the association between latent tuberculosis infection amongst children exposed and unexposed to a tuberculosis case in their household ^a | 22 |
| REFERENCES. | 23 |



Web Appendix 1. PRISMA Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---------------------------|---|---|--------------------|
| TITLE | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | Title |
| ABSTRACT | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | Abstract |
| INTRODUCTION | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 1; Appendix |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 1; Appendix |
| METHODS | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | NA |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | Table 1; Appendix |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 5; Appendix |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 5; Appendix |

| | | | |
|------------------------------------|----|--|----------|
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | Appendix |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | Appendix |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | Appendix |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 8 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 7 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis. | 8 |

| | | | |
|-------------------------------|----|--|-----------------------|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 12-13 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 10; Appendix |
| RESULTS | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 9; Figure 1; Appendix |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 6-7 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | NA |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Figure 2; 9-10 |

| | | | |
|-----------------------------|----|--|-------|
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 9-10 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | NA |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 10 |
| DISCUSSION | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 11-12 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 12-13 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 13-14 |
| FUNDING | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 15 |

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. (1)

Web Appendix 2. Search Strategy

Pubmed.

Search used:

("mycobacterium tuberculosis"[Mesh] OR "tuberculosis"[Mesh] OR TB[tiab] OR "tuberculin test"[Mesh])

AND

("contact tracing"[Mesh] OR "household*"[All Fields] OR "family contact*"[WORD] OR "household contact*"[All Fields] OR "childhood contact*"[TI] OR "Disease Transmission, Infectious"[Mesh] OR "Household transmission"[WORD] OR "community controls" [All Fields])

Results: 2719 hits

Biosis.

Search used:

[(Topic="Mycobacterium tuberculosis") OR (Topic=tuberculosis) OR (Topic="tuberculin") OR (Topic=TB)]

AND

[(Topic="contact tracing") OR (Topic="household contact") OR (Topic="childhood contact") OR (Topic="Household transmission") OR (Topic="community controls") OR (Topic="family contact*") OR (Topic="close contact*") OR (Topic="tuberculosis transmission")]

Results: 838 hits

Web of Science.

Search used:

[(Topic="Mycobacterium tuberculosis") OR (Topic=tuberculosis) OR (Topic="tuberculin") OR (Topic=TB)]

AND

[(Topic="contact tracing") OR (Topic="household contact") OR (Topic="childhood contact") OR (Topic="Household transmission") OR (Topic="community controls") OR (Topic="family contact*") OR (Topic="close contact*") OR (Topic="tuberculosis transmission")]

Results: 1252 hits

Embase.

Search used:

('Mycobacterium tuberculosis'/exp OR 'tuberculosis'/exp OR 'tuberculosis':ti,ab OR 'TB':ti,ab)
AND
('contact tracing'/exp OR 'contact examination'/exp OR 'family contact*'/ti,ab OR 'household transmission'/ti,ab OR 'household*':ti OR 'contact*':ti)

Results: 1314

Web Table 1. List of Characteristics Extracted from Selected Studies.

| Characteristic | Details of Extraction |
|---------------------------------|--|
| Author | First and last name of first author |
| Publication | Year of publication |
| Time Period | Year the study started and ended |
| Country | Country in which study was performed |
| Type of Test | Which type of test was used to measure latent TB infection? Were multiple tests used? |
| Definition of Latent Infection | Number of millimeters of skin induration study defined latent TB infection |
| Study Design | Name the study design used |
| Journal | Name the journal the paper was published in |
| Recruitment of Contacts | How were household contacts recruited? |
| Recruitment of Controls | How were community controls recruited? |
| Age of Index Cases | What was the age range of the TB index cases? |
| Number of Index Cases | Were the number of TB index cases reported? If so, how many were present? |
| Age Range of Contacts | What age range among household contacts was reported by the study? |
| Number of Contacts | How many household contacts were reported in the study? |
| Age Stratification of Contacts | Was age stratified into multiple groups among household contacts in the study? If so, what groups? |
| Age Range of Controls | What age range among community controls was reported by the study? |
| Number of Controls | How many community controls were reported in the study? |
| Age Stratification of Controls | Was age stratified into multiple groups among controls in the study? If so, what groups? |
| Crude Odds Ratio | Was a crude odds ratio given comparing infection among HHC and CC groups in children ≤ 14 ? |
| Adjusted Odds Ratio | Was an adjusted odds ratio provided among HHC and CC groups in children ≤ 14 ? |
| Definition of Household | Was a definition provided of household in the paper? If so, report this. |
| Definition of Household Contact | Was a definition provided of HHC in the paper? If so, report this. |
| Definition of Community Control | Was a definition provided of CC in the paper? If so, report this. |
| Matching Characteristics | In which ways were HHC and CC groups matched (i.e. sex, age, neighborhood, etc.)? |
| HIV Participants | Did any contacts or controls have HIV? |
| HIV Index Cases | Did any index cases have HIV? Was the proportion of HIV-infected index cases provided? |
| Treatment of TB Index Cases | Were TB index cases on treatment when infection on contacts was measured? If so, how long? |
| TB Disease in Contacts | Was TB disease measured amongst contacts? If so, how many contact children had TB disease? |
| TB Disease in Controls | Was TB disease measured amongst controls? If so, how many control children had TB disease? |

| | |
|--|--|
| Participation Rate | What proportion of individuals joined the study out of the total recruited? |
| Location of Recruitment of Contact | Where contacts were recruited (i.e. hospital, passive case finding, local clinic, etc.) |
| Location of Recruitment of Controls | Where controls were recruited (i.e. hospital, neighborhood, local clinic, etc.) |
| Infected Contacts | How many contacts within the eligible age range were latent TB infected? |
| Infected Controls | How many controls within the eligible age range were latent TB infected? |
| Healthy Contacts | How many contacts within the eligible age range were without latent TB infection? |
| Healthy Controls | How many controls within the eligible age range were without latent TB infection? |
| Prevalence of TB Infection in Contacts | What was the proportion of contacts with latent TB infection? |
| Prevalence of TB Infection in Controls | What was the proportion of controls with latent TB infection? |
| Risk Difference | What was the risk difference in latent TB infection between contacts and controls? |
| Diagnosis of TB | How was diagnosis of TB performed? |
| Sputum+, Culture+ Diagnosis | If index cases were diagnosed with sputum, how many sputum+, culture+ TB cases were reported? |
| Sputum-, Culture+ Diagnosis | If index cases were diagnosed with sputum, how many sputum-, culture+ TB cases were reported? |
| Sputum-, Culture- Diagnosis | If TB Index cases with diagnosed with x-ray, how many index cases were x-ray positive? |
| Multiple Methods of Diagnoses | Were multiple methods of TB diagnoses used? |
| Contacts of Sputum+, Culture+ TB Cases | Prevalence of latent TB infection among household contacts of sputum+, culture+ TB index cases |
| Contacts of Sputum-, Culture+ TB Cases | Prevalence of latent TB infection among household contacts of sputum-, culture+ TB index cases |
| Contacts of Sputum-, Culture- TB Cases | Prevalence of latent TB infection among household contacts of sputum-, culture- TB index cases |

Web Table 2. Selection of community controls in 26 included studies.

| First author, Year (Reference No.)^a | Study design | Methods of selection of community controls | Notes |
|---|-------------------------|--|---|
| Narasimhan, 2012 (2) | CC | Visited the house on the right and left if one existed. If houses existed on both the right and left the left house was selected. | NA |
| Almeida, 1998 (3) | CC | Randomly selected household in the same neighborhoods. All households were situated at least 200 meters away from an index household to avoid potential cross-infection | Control household were selected to complete a nutritional survey commissioned by UNICEF and were expected to be representative of the neighborhoods |
| Blahd, 1946 (4) | CC | Recruitment of control household was not specified and is unclear | NA |
| Brailey, 1928–1937 (5) | CC | Recruitment of control household was not specified and is unclear | NA |
| Den Boon, 2002 (6) | CS | 837 addresses were selected randomly. Households with TB and without were later ascertained from this representative sample. | Selection of control household is assumed to be random. |
| Dogra, 2004 – 2005 (7) | CS | Randomly selected participants and then later designated participants as exposed or unexposed | Selection of control household is assumed to be random. |
| Dow, 1931 (8) | CS | Recruitment of control household was not specified and is unclear | Selection of control household is assumed to be random. |
| Gilpin, 1984 (9) | CC | A compass was used to indicate all the homes inside a reading northwest to northeast from the home of an index patient. The nearest in that range was then selected. Every household member was included. | The distance between contact and non-contact households varied from a few meters to a kilometer. |
| Gustafson, 1999 – 2000 (10) | CC | Randomly selected household in the neighborhood of the index case. Family members of case and control household were investigated in the same way. | Controls were matched into 10-year age bands with contacts. |
| Hill, 2002–2004 (11) | CC | Controls were selected by choosing a random direction from the cases home by spinning a pen in the air and visiting the second compound on the right. These households were checked for any history of TB among household members. | Controls were age matched by 5-year bands for children <15 years old |

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|---------------------------------|----|--|---|
| Hoang, 2006 – 2007 (12, 13) | CS | Randomly selected participants and then later designated participants as exposed or unexposed through a previously completed TB disease prevalence study (laboratory diagnosed) | Selection of control household is assumed to be random. |
| Hossain, 2007 – 2009 (14, 15) | CS | Randomly selected participants and then later designated participants as exposed or unexposed through a previously completed TB disease prevalence study (laboratory diagnosed) | Selection of control household is assumed to be random. |
| Kenyon, 1997 (16, 17) | CC | Controls were recruited from a separate household cluster survey from 1996 (cases were recruited in 1997). The same study personnel was used in each study. | Controls were age- and neighborhood-matched to contacts |
| Lienhardt, 1999 – 2001 (18, 19) | CC | Controls were selected randomly in the neighborhood of the TB case's household by choosing a random direction from the cases' home and visiting the third dwelling on the right. | If several household lived in the same dwelling one household was selected by drawing lots. |
| Madico, 1990 (20, 21) | CS | A control household close to the contacts was designated a near control; a house located a street away from the contacts was designated as a far control | Two controls were paired with each contact household |
| Mandalakas, 2015 (22, 23) | CC | Children with no documented TB exposure were recruited from neighboring households. No other recruitment information is given. | Controls were age-matched to contacts. |
| McPhedran, 1935 (24) | CC | Recruitment of control household was not specified and is unclear | NA |
| Nakaoka, 2005 (25) | CC | A control household was selected if situated at least 100 meters from an index case patient's household to avoid potential cross-infection. Individuals were inspected for TB symptoms. If none were found children in the household were included in the study. | 46 control children were selected compared to 161 exposed children. |
| Narain, 1960 – 1961 (26) | CS | Randomly selected participants and then later designated participants as exposed or unexposed through a previously completed TB disease prevalence study (laboratory diagnosed) | Selection of control household is assumed to be random. |
| Olender, 1997 – 2000 (27-30) | CS | Randomly selected participants and then later designated participants as exposed or unexposed | Selection of control household is assumed to be random. |
| Roelsgaard, 1955 – 1960 (31) | CS | Randomly selected participants and then later designated participants as exposed or unexposed | Selection of control household is assumed to be random. |
| Radhakrishna, 1968 – 1983 (32) | CS | Randomly selected participants and then later designated participants as exposed or unexposed | Selection of control household is assumed to be random. |

| | | | |
|-----------------------------|----|--|--|
| Rutherford, 2012 (33, 34) | CC | A social worker identified and recorded all matching children from a neighborhood register and then randomly selected one child's name from a hat. If that child could not participate another child was selected. For all children who lived with a TB case were excluded | Controls were age-matched within 1 year from contacts. They were also sex and neighborhood matched. Controls called "neighborhood-exposed" even though no exposure was identifiable. |
| Schlesinger, 1929 (35) | CC | Control children were tested over the same period and evaluated by the same investigator. No other recruitment information is given. | Control children were age- and neighborhood-matched. |
| Shaw, 1948 – 1952 (36) | CC | Control children were selected at random over the same time period. No other information is provided. | Control children were age- and neighborhood-matched. |
| Whalen, 1995 – 2006 (37-39) | CC | Control household were eligible if no case of TB was present in the household for at least one year and the household contained two or more members. | Controls were age-matched within 5 years of age of the index case, |

Abbreviations: CC, Case-control; CS, Cross-Sectional; TB, tuberculosis; NA, not applicable; No., number.

^a Year refers to the dates in which the study was implemented. If study implementation was not specified the date of publication was used. Multiple citations may be present for one study because methods for selecting controls may be available from several manuscripts and we attempted to retrieve all potentially relevant information. If the study group published multiple articles with the same cohort more than one manuscript was inspected to ensure all recruitment methods were collected.

Web Table 3. Methods of tuberculosis diagnosis in index case and classification of exposure amongst 26 included studies.

| First Author, Year (Reference No.)^a | Study design | Exposure | Methods of tuberculosis diagnosis in index cases |
|---|---------------------|-----------------|---|
| Narasimhan, 2012 (2) | CC | Current | TB patients visiting the DOTS centers who were classified as new cases, diagnosed with sputum smear positive or negative. |
| Almeida, 1998 (3) | CC | Current | Adults with TB were identified from the Reference Centre for TB in Sergipe, northeast Brazil. A potential index case was defined as any adult attending the clinic in 1998 who had acid-fast bacilli in sputum bacilloscopy |
| Blahd, 1946 (4) | CC | Current | Adults with TB from the Tice Laboratory and Clinic in Chicago, USA. TB was inspected through chest x-rays and smear laboratory testing. |
| Brailey, 1928 – 1937 (5) | CC | Current | Every household registered in the clinic in which a definite intrafamilial contact of some or all of the children with an adult with pulmonary TB was included. |
| Den Boon, 2002 (6) | CS | Current or Past | Household contacts consisted of children living in households where at least 1 adult ever had TB; community controls were children living in households where no adult ever had TB. |
| Dogra, 2004 – 2005 (7) | CS | Current | Defined as any child who lived in a household with an adult taking anti-TB therapy. |
| Dow, 1931 (8) | CS | Current | Manuscript uses terminology throughout stating that contact children were living with index cases. Methods of recruitment of index cases or household contacts not detailed or explicit. |
| Gilpin, 1984 (9) | CC | Current | All patients admitted to the TB ward were assessed by a specially trained nurse and on that basis either included in the study or not. All patients aged 15 years and over with pulmonary TB confirmed by a smear-positive sputum result were included in the study. In the clinic, a date was arranged with each patient for a home visit. |
| Gustafson, 1999 – 2000 (10) | CC | Current | Adults aged 15 years and older with newly diagnosed pulmonary TB were recruited and investigated at Hospital Raoul Follereau, the national referral hospital. Confirmed with smear laboratory testing. |
| Hill, 2002 – 2004 (11) | CC | Current | Sputum smears from TB cases were prepared, stained, cultured, identified and confirmed |
| Hoa, 2006 – 2007 (12, 13) | CS | Current | "Current", "TB cases in the past 2 years", and "TB cases in the past 2 years but no current case" are stratified out. Only "Current cases" was used. |
| Hossain, 2007 – 2009 (14, 15) | CS | Current | Contacts were "children from a household where a smear-positive TB case was detected during the 2007–2009 survey" |
| Kenyon, 1997 (16, 17) | CC | Current | Adults with TB were identified from a cohort of hospitalized patients with lung disease in Gaborone and Francistown. Confirmed with smear laboratory results |

| | | | |
|---------------------------------|----|-----------------|---|
| Lienhardt, 1999 – 2001 (18, 19) | CC | Current | TB cases were recruited at three major urban health centers in The Gambia. All newly detected smear-positive pulmonary TB patients older than 15 years who have been living at the same address for more than 3 months were eligible. Pulmonary TB was confirmed by two consecutive sputum smears positive for acid-fast bacilli and/or a positive culture. |
| Madico, 1990 (20, 21) | CS | Current | A contact household was defined by the presence of a pulmonary TB patient identified by a positive sputum smear at the clinical laboratory. Cases were confirmed with smear laboratory results. |
| Mandalakas, 2015 (22, 23) | CC | Current | Children with documented TB exposure were recruited within 3 months of the source case starting treatment. Source case sputum specimens underwent smear and culture. |
| McPhedran, 1935 (24) | CC | Current | Manuscript uses terminology throughout stating that contact children were living with index cases. Methods of recruitment of index cases or household contacts not detailed or explicit. |
| Nakaoka, 2005 (25, 40) | CC | Current | Households of adults with TB who were diagnosed at enrollment in a separate study of TB diagnosis. These index adults had undergone HIV counseling and testing and had a diagnosis of TB. TB cases were confirmed with smear laboratory results. |
| Narain, 1960 – 1961 (26) | CS | Current | Households with a current case of either bacteriologically or radiographically confirmed TB. |
| Olender, 1997 – 2000 (27-30) | CS | Current or Past | Household contacts consisted of children living in households where at least 1 adult ever had TB; community controls were children living in households where no adult ever had TB. |
| Roelsgaard, 1955 – 1960 (31) | CS | Current | Manuscript uses terminology throughout stating that contact children were living with index cases. Methods of recruitment of index cases or household contacts not detailed or explicit. |
| Radhakrishna, 1968 – 1983 (32) | CS | Current | Those with an abnormal CXR or symptoms had sputum examined for acid-fast bacilli and culture for MTB. |
| Rutherford, 2012 (33, 34) | CC | Current | All newly diagnosed sputum smear and chest X-ray positive adult TB patients were invited to have children in their household evaluated for TB infection and disease. |
| Schlesinger, 1929 (35) | CC | Current | All currently exposed children. All suspect or definite cases of TB amongst contacts were excluded. Methods of recruitment not explicit or detailed. |
| Shaw, 1948 – 1952 (36) | CC | Current | All tuberculin tests were done as soon as practicable after diagnosis and, in many instances, before the final sputum status of the source case was established. All persons with contacts who had previously been in contact with a known case of TB were excluded. All index cases were bacteriologically confirmed. |
| Whalen, 1995 – 2006 (37-39) | CC | Current | TB cases were identified at the TB Treatment Center of Mulago Hospital. Household contacts were identified within 4 weeks of the initial diagnosis of the index case. |

Abbreviations: CC, Case-control; CS, Cross-Sectional; HIV, human immunodeficiency virus; CXR, chest x-ray; DOTS, directly observed therapy; TB, tuberculosis; MTB, *Mycobacterium tuberculosis*.

^a Year refers to the dates in which the study was implemented. If study implementation was not specified the date of publication was used. Multiple citations may be present for one study because methods for selecting controls may be available from several manuscripts and we attempted to retrieve all potentially

relevant information. If the study group published multiple articles with the same cohort more than one manuscript was inspected to ensure all recruitment methods were collected.

Web Table 4. Definitions and recruitment of household contacts and community controls in all studies

| First Author, Year (Reference No.) ^a | Enrollment of Each Group | Definition of Household | Definition or Recruitment Method of Community Control |
|--|---|---|---|
| Almeida, 1998 (3) | Contact investigation with a separately recruited community control group | -- | "All children between the ages of 1 and 15 years living in the selected households were included until at least three children had been enrolled for each exposed child" |
| Blahd, 1946 (4) | Contact investigation with a separately recruited community control group | -- | -- |
| Brailey, 1928 – 1937 (5) | Contact Investigation; Some children were found to have no contact at intake. | "Persons associated more or less permanently in the same home, taking their meals together, and sleeping under the same roof." | -- |
| Den Boon, 2002 (6) | Tuberculin Survey; randomly sampled | -- | -- |
| Dogra, 2004 – 2005 (7) | Hospital-based tuberculin survey | -- | -- |
| Dow, 1931 (8) | Tuberculin Survey; randomly sampled | -- | -- |

| | | | |
|---------------------------------|--|--|---|
| Gustafson, 1999 – 2000 | Contact investigation with a separately recruited community control group | "Houses in the study area are 1-storey, unattached, rectangular buildings, usually with 6-8 rooms and inhabited by 2-4 families. The house is usually owned by 1 of these families. The majority of houses do not have an internal ceiling; this leaves a gap between the internal walls and the roof allowing air to circulate freely among all the rooms." | -- |
| Gilpin, 1984 (9) | Contact investigation with a separately recruited community control group | "defined as people living in the same group of huts .of a patient's kraal or in the same home" | "defined as people living outside the kraal or home of the patient" |
| Hoa, 2006 – 2007 (12, 13) | Nationally representative tuberculin Survey; randomly sampled | -- | -- |
| Hossain, 2007 – 2009 (14, 15) | Nationally representative tuberculin Survey; randomly sampled | -- | -- |
| Kenyon, 1997 (16, 17) | Contact investigation with a separately recruited community control group | "This included children who reportedly lived at the same address or had a close personal relationship with the index case." | -- |
| Lienhardt, 1999 – 2001 (18, 19) | Contact investigation with a separately recruited community control group | "The extended family living together in the same area and eating from the same pot" | -- |
| Madico, 1990 (20, 21) | Began as a tuberculin survey* and then later children in contact with TB in the household were followed up and index cases were evaluated. | -- | "Living in a household free of tuberculosis" |

| | | | |
|--------------------------------|---|---|---|
| McPhedran, 1935 (24) | Contact investigation with a separately recruited community control group | -- | -- |
| Nakaoka, 2005 (25) | Contact investigation with a separately recruited community control group | "Eligible children were defined as any relative in the household <15 years of age who ate food prepared in the same cooking facilities as the index patient." | "A separate group of children <15 years of age who were not exposed to adults with TB was selected to assess the prevalence of asymptomatic infections in the community." |
| Narain, 1960 – 1961 (26) | Tuberculin Survey | -- | -- |
| Narasimhan, 2012 (2) | Contact investigation with a separately recruited community control group | -- | -- |
| Olender, 1997 – 2000 (27-30) | Community-based tuberculin survey from a Peruvian shantytown | -- | -- |
| Radhakrishna, 1968 – 1983 (32) | Secondary analysis of baseline data from a large clinical trial evaluating BCG effectiveness. In this paper, groups were separated into two separate groups and analyzed. | "A household was defined as a group of persons living together and sharing food from the same kitchen." | -- |
| Roelsgaard, 1955 – 1960 (31) | Tuberculin Survey | "A household constitutes a group of people who live and eat together." | -- |
| Rutherford, 2012 (33, 34) | Contact investigation with a separately recruited community control group | These children were required to have been living with the case ≥ 3 months prior to diagnosis. | "Community Contact" |
| Schlesinger, 1929 (35) | Contact investigation with a separately recruited community control group | -- | -- |
| Shaw, 1948 – 1952 (36) | Contact investigation with a separately recruited community | -- | -- |

control group

| | | | |
|-----------------------------|--|---|---|
| Whalen, 1995 – 2006 (37-39) | Longitudinal contact investigation with separately recruited community control | "A household was defined as a group of people living within one residence who share meals together and identified a head of family who made decisions for the household." | "Households were eligible to be controls if no case of tuberculosis was present in the household for at least one year, at least one member in the household was within 5 years of age as the index case, and the household contained two or more members." |
|-----------------------------|--|---|---|

Abbreviations: No., number.

^a Year refers to the dates in which the study was implemented. If study implementation was not specified the date of publication was used. Multiple citations may be present for one study because methods for selecting controls may be available from several manuscripts and we attempted to retrieve all potentially relevant information. If the study group published multiple articles with the same cohort more than one manuscript was inspected to ensure all recruitment methods were collected.

Web Table 5. Odds ratios of 26 included studies.

| First Author, Year (Reference No.)^a | Total Contacts | Infected Contacts (%) | Total Controls | Infected Controls (%) | Odds Ratio (95% CI), p-value |
|---|-----------------------|------------------------------|-----------------------|------------------------------|-------------------------------------|
| Almeida, 1998 (3) | 141 | 67 (47.5) | 506 | 18 (3.6) | 24.6 (13.8 – 43.6), <0.0001 |
| Blahd, 1946 (4) | 143 | 32 (22.4) | 3589 | 133 (3.7) | 7.49 (4.9 – 11.5), <0.0001 |
| Brailey, 1928 – 1937 (5) | 789 | 523 (66.3) | 111 | 38 (34.2) | 3.78 (2.5 – 5.7), <0.0001 |
| Den Boon, 2002 (6) | 401 | 179 (44.6) | 943 | 253 (26.8) | 2.2 (1.7 – 2.8), <0.0001 |
| Dogra, 2004 – 2005 (7) | 16 | 3 (18.8) | 89 | 7 (7.9) | 2.7 (0.6 – 11.8), 0.1859 |
| Dow, 1931 (8) | 279 | 102 (60.0) | 507 | 140 (27.6) | 3.93 (2.7 – 5.7), <0.0001 |
| Gilpin, 1984 (9) | 80 | 24 (30.0) | 94 | 12 (12.8) | 2.93 (1.4 – 6.3), 0.0064 |
| Gustafson, 1999 – 2000 (10) | 482 | 134 (30.5) | 541 | 59 (10.9) | 3.59 (2.6 – 5.0), <0.0001 |
| Hill, 2002 – 2004 (11) | 255 | 68 (26.6) | 18 | 1 (5.5) | 6.18 (0.8 – 47.3), 0.08 |
| Hoa, 2006 – 2007 (13) | 189 | 51 (27.0) | 21055 | 3699 (17.6) | 1.73 (1.3 – 2.4), 0.0008 |
| Hossain, 2007 – 2009 (14) | 19 | 9 (47.4) | 17530 | 2934 (16.7) | 4.48 (1.8 – 11.0), 0.0011 |
| Kenyon, 1997 (16) | 107 | 13 (12.2) | 697 | 43 (6.2) | 2.24 (1.2 – 4.3), 0.016 |
| Lienhardt, 1999 – 2001 (18) | 1105 | 352 (31.9) | 967 | 59 (6.1) | 7.19 (5.4 – 9.6), <0.0001 |
| Madico, 1990 (20) | 175 | 97 (55.4) | 382 | 129 (33.8) | 2.44 (1.7 – 3.5), <0.0001 |
| Mandalakas, 2015 (23) | 824 | 378 (45.9) | 501 | 151 (30.1) | 1.96 (1.6 – 2.5), <0.0001 |
| McPhedran, 1935 (24) | 1342 | 970 (72.3) | 705 | 255 (36.2) | 4.60 (3.8 – 5.6), <0.0001 |
| Nakaoka, 2006 (25) | 158 | 52 (32.9) | 48 | 6 (12.5) | 3.43 (1.4 – 8.6), 0.008 |
| Narain, 1960 – 1961 (26) | 790 | 191 (24.2) | 9186 | 1102 (12) | 2.34 (2.0 – 2.8), <0.0001 |
| Narasimhan, 2012 (2) | 53 | 18 (34.0) | 53 | 12 (22.6) | 1.76 (0.7 – 4.2), 0.1981 |
| Olender, 1997 – 2000 (27) | 61 | 14 (23.0) | 563 | 29 (5.2) | 5.49 (2.7 – 11.1), <0.0001 |
| Radhakrishna, 1968 – 1983 (32) | 3191 | 1173 (37.2) | 106717 | 16960 (15.9) | 3.13 (2.9 – 3.4), <0.0001 |
| Roelsgaard, 1955 – 1960 (31) | 1010 | 111 (11.0) | 7295 | 528 (7.2) | 1.58 (1.3 – 2.0), <0.0001 |
| Rutherford, 2012 (33) | 299 | 144 (48.2) | 72 | 7 (9.7) | 8.63 (3.8 – 19.4), <0.0001 |
| Schlesinger, 1929 (35) | 68 | 42 (61.8) | 438 | 80 (18.3) | 7.23 (4.2 – 12.5), <0.0001 |
| Shaw, 1948 – 1952 (36) | 823 | 344 (41.8) | 709 | 157 (22.1) | 2.53 (2.0 – 3.2), <0.0001 |
| Whalen, 1995 – 2006 (37) | 1199 | 795 (65.3) | 564 | 78 (13.8) | 11.74 (9.0 – 15.3), <0.0001 |

Abbreviations: No., number; CI, confidence interval.

^a Year refers to the dates in which the study was implemented. If study implementation was not specified the date of publication was used.

Web Table 6. Sensitivity Analysis: Crude versus Adjusted Odds Ratios

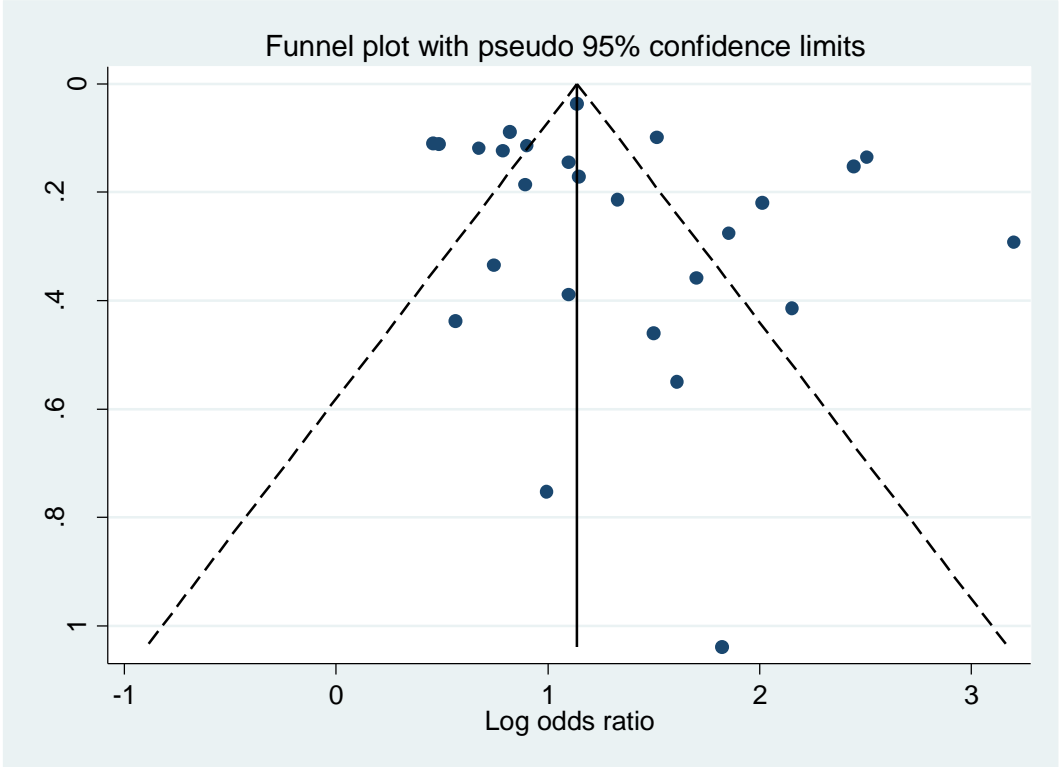
In our paper we used crude odds ratios (OR) for various reasons. These include the fact that few studies adjusted for confounders and that studies adjusted for different risk factors in their multivariate model. Due to this each adjusted OR was different. However, we sought to assess any potential bias from using crude versus adjusted ORs. Among five studies that used adjusted ORs we assessed any change from the crude OR and in which direction this occurred. We found amongst five studies the adjusted OR was very similar to the crude with a mean difference of approximately 0.36. Therefore we feel confident that using crude rates did not bias our conclusions.

| First Author, Year (Reference No.) ^a | Unadjusted OR | Adjusted OR | Difference between Unadjusted and Adjusted OR | Factors Adjusted in Multivariate Model |
|---|---------------|-------------|---|--|
| Madico, 1990 (20) | 2.44 | 2.5 | 0.06 | Age, Sex, Within-Household Correlation, Household Size |
| Dogra, 2004 – 2005 (7) | 2.7 | 2.48 | -0.22 | Age, Sex, Nutritional Status, BCG Scar Status |
| Den Boon, 2002 (6) | 2.2 | 2.01 | -0.19 | Age, Average Household Income, Household Clustering |
| Radhakrishna, 1968 – 1983 (32) | 3.13 | 2.8 | -0.33 | Sex |
| Gustafson, 1999 – 2000 (10) | 3.59 | 2.47 | -1.12 | Age, Sex, Ethnic Group, BCG Scar, Personal History of TB, Season for TST, History of Family TB, Bacterial Load, HIV Status of Case/Control, Animals Indoor during Night, Physical Size of Dwelling, Presence of Ceiling, Ownership of House, Age of Case/Control, Sex of Case/Control, Proximity |
| Mean | 2.81 | 2.45 | -0.36 | |

Abbreviations: Ref., Reference; OR, Odds Ratio; HHC, household contact; No., Number; TST, tuberculin skin test; BCG, bacille Calmette–Guérin; TB, tuberculosis; HIV, human immunodeficiency virus

^a Year refers to the dates in which the study was implemented. If study implementation was not specified the date of publication was used.

Web Figure 1. Funnel plot (with pseudo confidence intervals) of 26 studies investigating the association between latent tuberculosis infection amongst children exposed and unexposed to a tuberculosis case in their household^a



^aThe Harbord test for publication bias was not significant (P=0.841)

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