The Effectiveness of Isoniazid Preventive Treatment among Contacts of Multidrug-Resistant Tuberculosis: A Systematic Review and Individual-Participant Meta-Analysis

Leonardo Martinez, Ph.D.[1,*], Jeffrey I Campbell, M.D.[2], Lauren Linde, M.P.H.[1], Fadila Boulahbal, M.D.[3], Joan A Cayla, M.D.[4], Tsira Chakhaia, Ph.D.[5], Pei-Chun Chan, Ph.D.[6-8], Cheng Chen, Ph.D.[9], Chi-Tai Fang, Ph.D.[8,10], Greg Fox, Ph.D.[11], Louis Grandjean, Ph.D.[12], Djohar Hannoun, M.D.[13], Anneke Hesseling, M.D.[14], C. Robert Horsburgh, M.D.[1], Li-Min Huang, Ph.D.[15], Qiao Liu, Ph.D.[9], Rufaida Mazahir, Ph.D.[16], Chih-Hsin Lee[17,18], Li-Na Lee[19], Rutger Bennet, M.D.[20], Sahar Nejat, M.D.[20], Amita Gupta, M.D.[21], Mrinalini Das, Ph.D.[22], Megan Murray, Ph.D.[23-25], Chuan-Chin Huang, Sc.D.[23,24], Helena del Corral, Ph.D.[26], Dione Benjumea-Bedoya, Ph.D.[26], Ye Shen, Ph.D.[27], Mercedes Becerra, Sc.D.[24], Vicky Chang, Ph.D.[28,29], Sonya Krishnan, M.D.[21], Petra Heinmueller[30], Timothy Brewer, M.D.[31], Petros Isaakidis, Ph.D.[32], Anja M. Hauri, M.D.[33], Lena Shah, Ph.D.[34], Lisa Trieu, M.P.H.[35], James A Seddon, M.D.[14,36]

Affiliations:

1. Department of Epidemiology, School of Public Health, Boston University, Boston, Massachusetts, United States

2. Section of Pediatric Infectious Diseases, Boston Medical Center, Boston, Massachusetts, United States

3. Groupe de recherche sur la tuberculose latente, Laboratoire National de Référence pour la Tuberculose, Institut Pasteur d'Algérie, Algiers, Algeria

4. Barcelona Tuberculosis Research Unit Foundation, Barcelona, Spain

5. National Center for Tuberculosis and Lung Diseases, Tbilisi, Georgia

6. Division of Chronic Infectious Disease, Taiwan Centers for Disease Control, Taipei, Taiwan

7. Department of Pediatrics, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan

8. Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan

9. Department of Chronic Communicable Disease, Center for Disease Control and Prevention of Jiangsu Province, Nanjing, Jiangsu Province, China

10. Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

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11. Sydney Medical School, Camperdown, NSW, Australia

12. Department of Infection, Inflammation and Immunity, Institute of Child Health, University College London, London, United Kingdom

13. Department of Information, National Institute of Public Health, Algiers, Algeria

14. Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Stellenbosch University, Stellenbosch, South Africa

15. Department of Pediatrics, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan

16. Department of Pediatrics, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, India

17. Pulmonary Research Center, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan.

18. Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

19. Department of Laboratory Medicine, Fu Jen Catholic University Hospital, Fu Jen Catholic University, New Taipei City, Taiwan

20. Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden

21. Department of Medicine, Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States

22. Médecins Sans Frontières, Mumbai, India

23. Division of Global Health Equity, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, United States

24. Department of Global Health and Social Medicine, Harvard Medical School, Boston, Massachusetts, United States

25. Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, United States

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26. Grupo de Epidemiologia, Universidad de Antioquia, Medellin, Colombia; On behalf of Centro Colombiano de Investigacion en Tuberculosis, Medellin, Colombia

27. Department of Epidemiology and Biostatistics, College of Public Health, University of Georgia, Athens, Georgia, United States

28. Faculty of Medicine and Health, University of Sydney, New South Wales

29. Sutherland Hospital, Caringbah, New South Wales

30. Hessisches Landesamt für Gesundheit und Pflege (HLfGP)

31. Professor of Medicine and Epidemiology University of California, Los Angeles, United States

32. Southern Africa Medical Unit (SAMU), Médecins Sans Frontières, Cape Town, South Africa

33. Helmholtz Centre for Infection Research, Braunschweig, Germany

34. Department of Epidemiology, Biostatistics & Occupational Health, McGill University, Montreal, Quebec, Canada

35. Division of Disease Control, New York City Department of Health and Mental Hygiene, Queens, New York, United States

36. Department of Infectious Disease, Imperial College London, United Kingdom

***Correspondence:** leomarti@bu.edu

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Contributors

All authors contributed to data acquisition. LM and JAS conceived the study. LM and JAS were members of the primary writing group and wrote the first draft of the manuscript. LM and JAS edited subsequent versions of the manuscript until dissemination to the broader author group. All

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authors read and edited the drafted manuscript for important intellectual content and assisted in data interpretation. All authors approved the final version of the manuscript. All authors contributed data to the large, merged individual participant dataset, but some of the data were not accessible to all authors due to data sharing agreements and restrictions by each study group. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

At a Glance Commentary

Scientific Knowledge on the Subject: Individuals exposed to drug-resistant tuberculosis are a priority group for tuberculosis prevention efforts. Initial empirical evidence has suggested that isoniazid may be effective, however no large effectiveness studies have been performed.

What This Study Adds to the Field: In over 6,500 close contacts of individuals with MDR tuberculosis followed for over 14,643 person-years, we found that isoniazid significantly reduced the risk of incident tuberculosis by 57%. This association was especially apparent in high tuberculosis burden settings and protection persisted for up to two years after exposure.

Artificial Intelligence Disclaimer: No artificial intelligence tools were used in writing this manuscript.

Some of the results of these studies have been previously reported in the form of a preprint (medRxiv, 23 Nov 2014, https://doi.org/10.1101/2024.11.21.24317060).

This article has an online data supplement, which is accessible at the Supplements tab.

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Abstract

Rationale

Recent empirical research suggests isoniazid may lead to a risk reduction of incident tuberculosis among close tuberculosis contacts of multi-drug resistant (MDR) tuberculosis.

Objectives

To evaluate the association between isoniazid tuberculosis preventive treatment (TPT), compared to no treatment, upon incident tuberculosis in household contacts of MDR tuberculosis cases using a large global consortium of tuberculosis contact tracing studies.

Methods

We conducted a systematic review and individual-participant meta-analysis among observational studies of household contact tracing studies. Participants were included if they were exposed to someone with MDR-tuberculosis and were given either 6 months of isoniazid TPT or no TPT. Our primary outcome was incident tuberculosis in contacts exposed to tuberculosis. We derived adjusted hazard ratios (aHRs) using mixed-effects, multivariable survival regression models with study-level random effects. The effectiveness of isoniazid TPT against incident tuberculosis was estimated through propensity score matching. We stratified our results by contact age, background tuberculosis burden, and *Mycobacterium tuberculosis* infection status.

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Measurements and Main Results

We included participant-level data from 6,668 contacts exposed to multidrug-resistant tuberculosis from 17 countries. The effectiveness of isoniazid TPT against incident tuberculosis in contacts of multidrug-resistant tuberculosis was 57% (aHR, 0.43; 95% CI, 0.26–0.71) and did not appreciably change with adjustment for additional potential confounders. The reduction in incident tuberculosis was marginally greater among child (<20 years old) contacts (0.51; 95% CI, 0.28–0.92) compared to adult contacts (0.69; 95% CI, 0.22–2.20). The reduction in incidence was 73% (0.27; 95% CI, 0.11–0.70) in the first year of follow-up; effectiveness dropped to 60% (0.40; 95% CI, 0.15–1.06) from 12–23 months of follow-up and was non-significant after two years (28% effectiveness; 0.72; 95% CI, 0.33–1.54).

Conclusions

Among over 6,500 contacts of MDR-tuberculosis, isoniazid TPT was highly effective in preventing incident tuberculosis. The reduction was greatest in high-burden countries and waned after 2 years of follow-up.

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Introduction

Following exposure to an individual with infectious tuberculosis, some contacts will develop *Mycobacterium tuberculosis* (*Mtb*) infection.[1,2] *Mtb* infection is defined as having immunological sensitization to *Mtb* as measured by an interferon gamma release assay or tuberculin skin test.[3] Following infection, some individuals will progress to tuberculosis, characterized by symptoms and signs consistent with tuberculosis, frequently accompanied by radiological features and microbiological confirmation of the presence of *Mtb*. For over fifty years, drug treatment has been provided to individuals either with confirmed or suspected *Mtb* infection to prevent progression to disease, known as tuberculosis preventive treatment (TPT).[5,6] There is a substantial evidence base for the efficacy and safety of isoniazid, rifamycins or a combination of isoniazid and a rifamycin to prevent disease progression in those exposed to drug-susceptible tuberculosis.[6,7] The World Health Organization and most national tuberculosis guidelines advocate for the provision of TPT to contacts of tuberculosis who are judged to be at high risk of disease progression.[8] This includes young children (<5 years), individuals living with HIV and those deemed to be likely recently infected, where the risk of disease progression is highest.[9]

Multidrug-resistant (MDR) tuberculosis is defined as disease caused by *Mtb* resistant to at least isoniazid and rifampicin. Each year an estimated 500,000 individuals develop MDR tuberculosis, with several million of their close contacts subsequently exposed to, and infected with, MDR-*Mtb*.[10,11] As MDR tuberculosis is, by definition, resistant to the two main drug classes used for drug-susceptible TPT, it is unclear what drug should be given to prevent tuberculosis progression in exposed persons. The World Health Organization recommends MDR-TPT for high-risk MDR tuberculosis contacts.[8,12] Two recent clinical trials have evaluated the efficacy of daily levofloxacin

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given for six months to prevent disease progression in household contacts of MDR tuberculosis. V-QUIN recruited tuberculin skin test-positive adults and children exposed in their household to MDR tuberculosis while TB-CHAMP took place in South Africa and recruited mainly child contacts <5 years, irrespective of their *Mtb* status.[13,14] Individually, neither trial reached a threshold of precision that met statistical significance.[13,14] A pre-planned meta-analysis of the two trials demonstrated significant efficacy of levofloxacin at 12 months.[15]

Unlike isoniazid and the rifamycins, levofloxacin is a broad-spectrum antibiotic that is not only effective against *M. tuberculosis*, but is also commonly used to treat a wide range of Gram-positive and Gram-negative bacteria. Long-term use has the potential to substantially disrupt the gut and respiratory microbiome with unknown implications.[16-19] In addition, there is potential to drive resistance to the fluoroquinolone class of antibiotics in non-tuberculosis bacteria which could make treatment of serious, life-threatening infections more challenging.[20] Levofloxacin may not be appropriate for all high-risk contacts due to contraindications, levofloxacin resistance, or cost. For these reasons, it is important to consider alternative drug options when embarking upon preventive therapy for MDR tuberculosis contacts.

Recent empirical research has suggested that isoniazid may lead to a risk reduction of incident tuberculosis among close tuberculosis contacts of MDR tuberculosis.[21] To evaluate the impact of isoniazid on incident tuberculosis in household contacts of MDR tuberculosis cases, we carried out an analysis within a large individual participant dataset of individuals with close exposure to persons with multidrug-resistant tuberculosis.

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Methods

Search strategy and selection criteria

In this project, we used the same data collection and data collation methods as previously published systematic reviews and individual participant meta-analyses from this consortium investigating the development of tuberculosis among persons closely exposed to tuberculosis.[22-25] Briefly, this systematic review and individual participant data meta-analysis follows Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for individual patient data meta-analyses. We searched MEDLINE, Web of Science, BIOSIS, and Embase without language restrictions for case-contact cohort studies of tuberculosis contacts published between Jan 1, 1998, and April 7, 2018. The 20-year timeframe was chosen on the basis of the expected availability of individual participant data. We subsequently conducted an update of this systematic review to include articles from April 8, 2018 to August 28, 2023. To prioritize an incident tuberculosis outcome, we restricted our search to cohort studies only. Both case-control studies and outbreak reports were excluded. Search terms included "*Mycobacterium tuberculosis*", "TB", "tuberculosis", and "contact" and can be found in full in the appendix. Partnered with our systematic review, we also reviewed other systematic reviews and review articles of tuberculosis contact investigations. We inspected their reference lists for eligible articles. We included data that were unpublished (found through discussions with authors and data experts, with data located in data storage repositories, conference abstracts, and dissertations) if eligible.

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Two independent reviewers assessed the quality of each study using a modified rubric of the Newcastle-Ottawa scale (Appendix). Each study was judged based on a 9-point scale using three broad criteria: selection of participants (4 points), comparability of studies (2 points), and ascertainment of outcome of interest (3 points). High study quality was defined as a score of 6 or greater, moderate quality as 3 to 6 points, and low quality as below 3 points. Discrepancies were resolved by re-evaluating the study for consensus. This study follows PRISMA-IPD guidelines for individual-participant data reporting. The study protocol is registered with PROSPERO (CRD42018087022).

Study definitions

Participants were characterized as being exposed to tuberculosis if they were reported to be a close contact (either living in the same household or having substantial interaction outside the household) of a person with microbiologically or radiologically diagnosed pulmonary tuberculosis. Investigators from each study defined exposure and index case diagnoses; we used the study definitions assigned to each cohort. We used each study's classification of tuberculosis. Prevalent tuberculosis was defined as any diagnosis of tuberculosis at the initial visit or within 90 days of baseline evaluation. Incident tuberculosis was defined as a new tuberculosis case diagnosed more than 90 days after the initial evaluation. We restricted to only contacts of MDR tuberculosis (which was diagnosed based on culture status) and only included TPT regimens using isoniazid for six months. Tuberculosis infection was defined by a positive QuantiFERON-TB Gold In-Tube test (IFNγ nil value ≥0.35 IU/mL), T-SPOT.TB test (nil spots minus antigen spots ≥8), or tuberculin skin test (≥10 mm induration). Countries were classified into income levels by use of World Bank 2020 definitions (high-income, upper-middle-income, lower-middle-income, and low-income countries). MDR

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tuberculosis was defined as resistant to, at a minimum, rifampin and isoniazid, the two most potent tuberculosis-related drugs.

Data analysis

Individual participant data for a prespecified list of variables, including the characteristics of the exposed contact, the index case, and the environment, were requested from authors of all eligible studies. We pooled individual participant-level data from all included cohorts. The primary aim of our analysis was to estimate the overall and adjusted effectiveness of six months of isoniazid TPT in preventing incident tuberculosis in MDR tuberculosis contacts. Therefore, our primary outcome was incident tuberculosis diagnosed more than 90 days from baseline. All participants developing tuberculosis before this time point (including at baseline) were excluded. We calculated follow-up time from the first baseline visit to development of tuberculosis, loss to follow-up, death, or study completion

For the primary analyses, we derived adjusted hazard ratios (aHRs) using mixed-effects, binary, multivariable Cox regression and parametric survival-time models incorporating study-level random effects into each model. We assumed a conditional Bernoulli distribution of the response given the random effects. We conducted a propensity score analysis when evaluating the protective effect of TPT. In this analysis, propensity score matching was done based on individual-level covariates of contact age, contact sex, and whether data were collected prospectively or retrospectively. Additional propensity score were also done including contact prior tuberculosis. We matched contacts who began isoniazid TPT with individuals who did not receive any TPT using a nearest neighbor matching algorithm. In this matched cohort, we estimated covariate-adjusted risk of incident

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tuberculosis between groups when examining the protective effectiveness of isoniazid TPT. We conducted secondary multivariable regression analyses into key subgroups to assess whether effectiveness was modified by risk profile. We further stratified our analysis by contact age, *M tuberculosis* infection status, contact prior tuberculosis, World Health Organization region, and background tuberculosis incidence levels.

To assess the durability of the treatment effect, follow-up time was split into three time groups (<12 months, 12–23 months, and 24 months and after). We specified the effects of isoniazid by follow-up time and derived adjusted hazard ratios (aHRs) for each time interval.

Results

Parent Systematic Review

We conducted two systematic reviews in this study, using the same methodology. The first from 1998–2018 and the second an updated review from 2019 to 2023 (**Figure 1**). In total from both reviews, 20,386 original study reports from our database searches were identified. We screened 15,212 through an exclusionary keyword algorithm. We tested the exclusionary words approach for accuracy by implementing it on a random list of 100 titles that were also manually screened for eligibility to our study. Our exclusionary algorithm eliminated all articles that were excluded by manual screening with 100% specificity. We reviewed 981 full text articles published on or after

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January 1, 1998. 155 study groups were contacted for individual participant data and study groups from 77 studies agreed to share their data, which were collated into a single database.

Studies and Participants from the Parent Systematic Review into this Study

For this specific research question, we only included a subset of the larger parent consortium studies with eligible data. 60 studies were excluded because they lacked data on the drug resistance status of the index case, had no index cases detected with drug resistance, or did not provide information on whether TPT was provided to contacts of drug-resistant tuberculosis. In total, 17 cohort studies from our larger parent consortium was included in this meta-analysis.

Nine (53%) of the 17 cohorts used a prospective cohort study design. 14 (82%) of the 17 cohorts performed either IGRA or TST on contacts. Overall, study quality was considered for 14 of 17 studies (two studies were conference abstracts and one other was unpublished and not reviewable); all 14 studies were considered at either a moderate (N_{cohort}=6; 43%) or high (N_{cohort}=8; 57%) study quality (Appendix). In total, 6,668 participants were followed for incident tuberculosis for 14,643 person-years (**Table 1**).

Demographic and Clinical Information of Participants and Tuberculosis Progressors

The median age of MDR tuberculosis contact participants was 25 years (IQR, 11–44). A majority of participants were younger than 30 years and older (N=3,812; 57%). Among 4,676 contacts tested for HIV, 284 (6%) were positive. Less than half of participants were evaluated with a test for *M. tuberculosis* infection (N=2,798; 42%). Most participants ($N_{participants}$=4,860; 72%) were in settings with

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a background tuberculosis incidence >100 cases per 100 thousand persons. Among all participants 1,020 (15%) were given isoniazid TPT while 5,648 were not given any TPT.

Over 14,643 person-years of follow-up, 187 persons exposed to MDR developed tuberculosis (1.3 cases per 100 person-years). Among contacts developing tuberculosis, 167 were not given TPT and 20 were given isoniazid TPT. Of these, 89/187 [46%] were diagnosed in the first year of follow-up. 48 (26%) cases developed tuberculosis in the second year while 50 (27%) cases developed disease subsequently after year 2.

Among the 187 progressors, 71 (38%) had information on drug-susceptibility status. Among these, 68 were not given TPT; 52 (76%) of these progressors developed MDR tuberculosis while 7 (10%) developed drug-susceptible tuberculosis. The remaining cases were either mono-resistant to either rifampin or isoniazid (n=2; 3%) or polyresistant (n=7; 10%). Among the three progressors with drug-susceptibility status who were given isonaizid TPT, all three developed MDR tuberculosis.

Statistical Analysis

In an age-adjusted mixed-effects model, the effectiveness of isoniazid TPT against tuberculosis in contacts of multidrug-resistant tuberculosis ($N_{participants}$=6,668) was 57% (aHR, 0.43; 95% CI, 0.26–0.70) compared to no treatment (**Table 2**). This protection did not appreciably change with adjustment for additional potential confounders. For example, when this model was additionally adjusted for sex, incident tuberculosis was reduced by 59% (aHR , 0.41; 95% CI, 0.25–0.68). In a fully adjusted model, protection remained at 59% (aHR, 0.41; 95% CI, 0.25–0.68).

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Effectiveness was marginally higher among child contacts (<20 years old) compared to adult contacts (aHR, 0.51 [95% CI, 0.28–0.92] versus 0.69 [95% CI, 0.22–2.20]). Among 728 children <5 years old, three developed incident tuberculosis among the isoniazid TPT group (3/291; 1%) while nine developed incident tuberculosis among children that were not given TPT (9/437; 2%). The effect of isoniazid TPT was highest in settings with a background tuberculosis incidence >100 cases per 100 thousand persons (aHR, 0.40; 95% CI, 0.24–0.67). In settings with a background tuberculosis incidence of 50–100 cases per 100 thousand persons, there were no incident cases among the group given isoniazid TPT and therefore a measure of effect could not be calculated. In settings with a background tuberculosis incidence of <50 cases per 100 thousand persons, there was no statistically significant effect of isoniazid TPT (0.90; 95% CI, 0.11–7.29). Other covariates of interest did not modify the effectiveness of isoniazid TPT.

Although assessing an effect of isoniazid TPT was difficult to show in any one cohort, the effect was largely consistent across the largest cohorts. For example, in the three largest included cohorts, the increased risk difference of incident tuberculosis among contacts without TPT versus contacts taking isoniazid TPT was 3.7% (95% CI, 2.5–4.9), 2.9% (95% CI, 0.9–4.8), and 1.2% (95% CI, 0.5–1.9), respectively.

The effect of isoniazid on the risk of tuberculosis was greatest in the first year of follow-up (aHR 0.27; 95% CI, 0.11–0.70). The effect decreased over follow-up time (**Figure 2**). At 12–23 months of follow-up, effectiveness was 60% (aHR, 0.40; 95% CI, 0.15–1.06). From 24–60 months of follow-up, effectiveness was 28% but was no longer statistically significant (aHR, 0.72; 95% CI, 0.33–1.54).

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Discussion

We analyzed the impact of isoniazid on the risk of incident tuberculosis in over 6,500 household contacts of individuals with MDR tuberculosis, assessed over 14,643 participant years of follow up. Our study demonstrated that isoniazid significantly reduced the risk of incident tuberculosis by 57% and the reduction was slightly greater reduction among children than adults. This association was especially apparent among contacts in high tuberculosis burden settings. Importantly, the duration of protection persisted for up to two years after exposure.

We found that overall isoniazid was 57% effective in protecting against incident tuberculosis among contacts of MDR tuberculosis. A previous cohort study in Rio de Janeiro had retrospectively assessed 218 adult and child contacts of MDR tuberculosis, of whom 45 had been given isoniazid.[26] This study failed to find any protective effect of isoniazid with two of 45 contacts who had been given isoniazid developing disease (1.2 per 1,000 person-years), compared to 13 of 145 who did not receive isoniazid progressing (1.7 per 1,000 person-years; p=0.47). There have been isolated examples of individuals exposed to MDR tuberculosis progressing to disease, despite preventive treatment with first-line drugs.[27] Given the *in vitro* resistance implicit in the definition of MDR tuberculosis, most national and international guidelines have, for many years, advised against isoniazid as TPT for individuals exposed to MDR tuberculosis.

With the data available, it is not possible to interrogate underlying mechanisms for the results seen in this study. However, several are plausible. First, in high tuberculosis incidence contexts, individuals are exposed to *Mtb* frequently. Many individuals will have been exposed to, and infected by, *Mtb*

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originating from another person outside of the household, before or after someone in their household has been diagnosed with MDR tuberculosis. Given that drug-susceptible tuberculosis is more common than MDR tuberculosis in almost all contexts, it is more likely that this exogenous infection would have been with a drug-susceptible strain. Successful treatment of this drug-susceptible isolate with isoniazid would therefore reduce the incidence of incident tuberculosis. Our finding that effectiveness was highest in studies with a high background tuberculosis burden supports this hypothesis. Furthermore, even in households where MDR tuberculosis is diagnosed, a significant proportion of contacts who develop disease have drug-susceptible tuberculosis.[28] However, the low sample sizes (and disease events) in settings with a lower burden of tuberculosis from our consortium makes it difficult to definitively exclude low statistical power as a reason for a lack of effect in these settings. Further research is needed to understand whether isoniazid is effective against progression among contacts exposed to MDR tuberculosis in settings with a low burden of tuberculosis. Second, isoniazid resistance is mediated through multiple resistance mechanisms, encoded for by several genetic mutations to the *Mtb* genome.[29,30] Distinct mutations in the *katG* gene and *inhA* promoter region lead to resistance, but the resulting minimum inhibitory concentration can be highly variable depending on exact site of mutation and isoniazid can still be effective against some of these strains.[31] Finally, the detection of *in vitro* resistance, either through genotypic or phenotypic evaluation, does not always translate into the drug being ineffective *in vivo*. Novel mechanisms of action for isoniazid have been proposed in which the drug has efficacy not only by killing *Mtb*, but also by interacting with the host immune system to promote *Mtb* death.[32]

An increasing body of empirical data has demonstrated the efficacy and safety of a second-line antibiotic, levofloxacin, as TPT for contacts of MDR tuberculosis.[33] Two recent trials – V-QUIN and TB-CHAMP – provide compelling evidence for fluoroquinolone TPT for MDR tuberculosis

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contacts.[13-15] Despite this, there may be an important role for isoniazid in contexts where fluoroquinolones are unavailable, too expensive, contraindicated for a particular individual. Alternatively, tuberculosis programmes, individual clinical staff, or patients, may be unwilling to endorse fluoroquinolone usage in some cases. There may be some advantages to using isoniazid as MDR-TPT, given fewer non-specific effects on non-tuberculous antimicrobial resistance and less disruption to the microbiome. Isoniazid may also be more available at lower levels of care and appropriate formulations may be stocked more regularly in remote health facilities. Importantly, isoniazid may be an important option for contacts of fluoroquinolone-resistant MDR tuberculosis. Having more than one option as TPT for contacts exposed to MDR tuberculosis is likely to be useful for most tuberculosis programs and clinical staff.[33,34]

An important finding from this analysis is the differential protection of isoniazid TPT over follow-up. We found that effectiveness was especially high in the first year after exposure (73%) and then dipped to 60% from 1-2 years, and 28% (although not statistically significant), from years 3 to 5. To our knowledge, this finding has not been described previously in studies of TPT among close contacts of individuals with tuberculosis. However, it is congruent to results among other vulnerable populations in high-incidence settings where *Mtb* reinfection is thought to occur after sufficient follow-up. For example, among people with HIV from a trial in South Africa, effectiveness of nine months of isoniazid was 48%, 39%, and 12% from <1, 1–2, and after two years of follow-up.[35] In South Africa, continuous isoniazid was as effective at preventing tuberculosis compared to shorter regimens; however, toleration of the regimen for long durations of time was difficult.[36] Other explanations of this finding include differing and/or diminishing statistical power over time and selection biases.[37] How to manage long-term protection of contacts, including those exposed to drug-resistant disease, is an ongoing discussion.[38] Despite the waning duration of protection to

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contacts of MDR tuberculosis seen in our study, the observation that protection was high (>60%) for up to 2 years after primary exposure provides important justification to provide TPT in this context.

Our work has limitations. While the dataset is large and from a diverse geographical spread, all studies contributing data were observational. This brings limitations in missing data and potential confounding by indication, given that the choice to give isoniazid was not randomly assigned but decided either at a study level or by clinician decision on an individual basis. For example, we found that a higher proportion of children, who have a higher risk of tuberculosis after exposure than adults,[22,39,40] in the isoniazid TPT group. Although we stratified our results by children and adults and additionally used propensity score matching to account for differential risk profiling among those receiving and not receiving TPT, residual confounding remains possible. However, if present, this bias is likely to have driven our results towards the null as persons given TPT are likely to have a higher risk profile. Some of the studies contributing data were retrospective. In included studies, differing case definitions were used to define close exposure, and different screening and follow-up procedures for tuberculosis were employed. Some data was not congruently collected across cohorts; therefore, it was not possible to assess the impact of other, potentially important confounders, which may have included cigarette smoking, crowding, socioeconomic status, N-acetyltransferase 2 (i.e., NAT2) genotype status of contacts, body mass index, amongst others. Lastly, other differences between studies may also contribute to between-study heterogeneity.

In conclusion, using a combined analysis of 17 cohort studies comprising over 6,500 close contacts of individuals with MDR tuberculosis, isoniazid substantially and significantly reduced the risk of developing incident tuberculosis, as compared to no treatment. This effect was greater in children

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than in adults and most apparent in high-burden settings. The duration of protection persisted for two years and then subsequently waned. When developing guidance for MDR-TPT, isoniazid should be considered as a preventive treatment option, alongside fluoroquinolones.

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References.

1. 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*. 2008 Jun 1;8(6):359-68.

2. Martinez L, Shen Y, Mupere E, Kizza A, Hill PC, Whalen CC. Transmission of *Mycobacterium tuberculosis* in households and the community: a systematic review and meta-analysis. *American Journal of Epidemiology*. 2017 Jun 15;185(12):1327-39.

3. Coussens A, Zaidi A, Allwood BA, Dewan P, Gray G, Kohli M, Kredo T, Marais B, Marks G, Martinez L, Ruhwald M, Scriba T, Seddon J, Tisile P, Warner D, Wilkinson RJ, Esmail H, Houben RM on behalf of the International Consensus for Early TB (ICE-TB) group. A new disease framework for tuberculosis to guide research towards improved care and prevention - an International Consensus for Early TB (ICE-TB). *The Lancet Respiratory Disease*. [In-Press]. October 2023.

4. Pai M, Behr MA, Dowdy D, Dheda K, Divangahi M, Boehme CC. *Nature Reviews Disease Primers. Tuberculosis*. 2016; 2: 16076.

5. Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis. *Adv Tuberc Res*. 1969; 17: 28-106.

6. Salazar-Austin N, Dowdy DW, Chaisson RE, Golub JE. Seventy years of tuberculosis prevention: efficacy, effectiveness, toxicity, durability, and duration. *American Journal of Epidemiology*. 2019 Dec 31; 188 (12): 2078-85.

7. Shah R, Khakhkhar T, Modi B, Patel P. Efficacy and Safety of Different Drug Regimens for Tuberculosis Preventive Treatment: A Systematic Review and Meta-Analysis. *Cureus*. 2023 Apr 26; 15 (4).

8. World Health Organization. WHO operational handbook on tuberculosis. Module 1: prevention-tuberculosis preventive treatment. World Health Organization; 2024 Sep 2.

9. da Costa FB, Nicol MP, Botha M, et al. *Mycobacterium tuberculosis* infection and tuberculosis disease in the first decade of life: a South African birth cohort study. *The Lancet Child & Adolescent Health*. 2024 Dec 1;8(12):891-9.

10. Global tuberculosis report 2024. Geneva: World Health Organization; 2023. Licence: CC BY-NC-SA 3.0 IGO.

AJRCCM Articles in Press. Published September 23, 2025 as 10.1164/rccm.202411-2340OC

11. Knight GM, McQuaid CF, Dodd PJ, Houben RM. Global burden of latent multidrug-resistant tuberculosis: trends and estimates based on mathematical modelling. *The Lancet Infectious Diseases*. 2019 Aug 1; 19 (8): 903-12.

12. Kherabi Y, Tunesi S, Kay A, Guglielmetti L. Preventive Therapy for Contacts of Drug-Resistant Tuberculosis. *Pathogens*. 2022 Oct 15; 11 (10): 1189.

13. Fox GJ, Nhung NV, Cam Binh N, et al. Levofloxacin for the prevention of multidrug-resistant tuberculosis in Vietnam. *New England Journal of Medicine*. 2024 Dec 19; 391 (24): 2304-14.

14. Hesseling AC, Purchase SE, Martinson NA, et al. Levofloxacin preventive treatment in children exposed to MDR tuberculosis. *New England Journal of Medicine*. 2024 Dec 19; 391 (24): 2315-26.

15. Duong T, Brigden J, Simon Schaaf H, et al. A Meta-analysis of levofloxacin for contacts of Multidrug-resistant tuberculosis. *NEJM evidence*. 2025 Jan 1; 4 (1): EVIDoa2400190.

16. Ziegler M, Han JH, Landsburg D, Pegues D, Reesey E, Gilmar C, Gorman T, Bink K, Moore A, Kelly BJ, CDC Prevention Epicenters Program. Impact of levofloxacin for the prophylaxis of bloodstream infection on the gut microbiome in patients with hematologic malignancy. In Open forum infectious diseases 2019 Jul (Vol. 6, No. 7, p. ofz252). US: Oxford University Press.

17. Rashidi A, Kaiser T, Holtan SG, Rehman TU, Weisdorf DJ, Khoruts A, Staley C. Levaquin gets a pass. *Biology of Blood and Marrow Transplantation*. 2020 Apr 1;26(4):778-81.

18. Schito AM, Schito GC. Levofloxacin, a broad spectrum anti-infective: from Streptococcus pneumoniae to Pseudomonas aeruginosa. Journal of Chemotherapy. 2004 Mar 1;16(sup2):3-7.

19. Wimer SM, Schoonover L, Garrison MW. Levofloxacin: a therapeutic review. Clinical Therapeutics. 1998 Nov 1; 20 (6): 1049-70.

20. Saxena S, Spaink HP, Forn-Cuní G. Drug resistance in nontuberculous mycobacteria: mechanisms and models. Biology. 2021 Jan 29; 10 (2): 96.

21 Huang CC, Becerra MC, Calderon R, Contreras C, Galea J, Grandjean L, Lecca L, Yataco R, Zhang Z, Murray M. Isoniazid preventive therapy in contacts of multidrug-resistant tuberculosis. *American Journal of Respiratory and Critical Care Medicine*. 2020 Oct 15;202(8):1159-68.

22. Martinez L, Cords O, Horsburgh CR, et al. The risk of tuberculosis in children after close exposure: a systematic review and individual-participant meta-analysis. *The Lancet*. 2020 Mar 21;395(10228):973-84.

AJRCCM Articles in Press. Published September 23, 2025 as 10.1164/rccm.202411-2340OC

23. Martinez L, Cords O, Liu Q, et al. Infant BCG vaccination and risk of pulmonary and extrapulmonary tuberculosis throughout the life course: a systematic review and individual participant data meta-analysis. *The Lancet Global Health*. 2022 Sep 1; 10 (9): e1307-16.

24. Martinez L, Seddon JA, Horsburgh CR, Lange C, Mandalakas AM, TB Contact Studies Consortium. Effectiveness of preventive treatment among persons with differing age and Mycobacterium tuberculosis infection status: A systematic review and individual-participant meta-analysis of contact tracing studies. *The Lancet Respiratory Health*. 2024 Aug 1; 12 (8): 633-41.

25. Pelzer PT, Stuck L, Martinez L, et al. Effectiveness of the primary Bacillus Calmette-Guérin vaccine against the risk of Mycobacterium tuberculosis infection and tuberculosis disease: a meta-analysis of individual participant data. *The Lancet Microbe*. 2025 Feb 1; 6 (2).

26. Teixeira L, Perkins MD, Johnson JL, Keller R, Palaci M, do Valle Dettoni V, Canedo Rocha LM, Debanne S, Talbot E, Dietze R. Infection and disease among household contacts of patients with multidrug-resistant tuberculosis. *The International Journal of Tuberculosis and Lung Disease*. 2001 Apr 1; 5 (4): 321-8.

27. Sneag DB, Schaaf HS, Cotton MF, Zar HJ. Failure of chemoprophylaxis with standard antituberculosis agents in child contacts of multidrug-resistant tuberculosis cases. *Pediatric Infectious Diseases Journal*. 2007; 26: 1142-1146.

28. 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*. 2014 Feb 1;58(3):381-91.

29. Seifert M, Catanzaro D, Catanzaro A, Rodwell TC. Genetic mutations associated with isoniazid resistance in *Mycobacterium tuberculosis*: a systematic review. *PloS One*. 2015 Mar 23; 10 (3): e0119628.

30. Lempens P, Meehan CJ, Vandelannoote K, Fissette K, de Rijk P, Van Deun A, Rigouts L, de Jong BC. Isoniazid resistance levels of Mycobacterium tuberculosis can largely be predicted by high-confidence resistance-conferring mutations. *Scientific Reports*. 2018 Feb 19; 8 (1): 3246.

31. Dooley KE, Miyahara S, von Groote-Bidlingmaier F, Sun X, Hafner R, Rosenkranz SL, Ignatius EH, Nuermberger EL, Moran L, Donahue K, Swindells S. Early bactericidal activity of different isoniazid doses for drug-resistant tuberculosis (INHindsight): a randomized, open-label clinical trial. *American Journal of Respiratory and Critical Care Medicine*. 2020 Jun 1; 201 (11): 1416-24.

32. Khan SR, Manialawy Y, Siraki AG. Isoniazid and host immune system interactions: A proposal for a novel comprehensive mode of action. *Br J Pharmacol*. 2019 Dec; 176 (24): 4599-4608.

AJRCCM Articles in Press. Published September 23, 2025 as 10.1164/rccm.202411-2340OC

33. Seddon JA, Achar J, Malik AA, et al. Management of individuals exposed to multidrug-resistant or rifampicin-resistant tuberculosis. *The Lancet Infectious Diseases*. 2025 Jun 6 [Online Only].

34. Schluger NW. Prevention of Multidrug-Resistant Tuberculosis in Close Contacts. Back to the Future?. *American Journal of Respiratory and Critical Care Medicine*. 2020 Oct 15; 202 (8): 1077-8.

35. Rangaka MX, Wilkinson RJ, Boulle A, Glynn JR, Fielding K, Van Cutsem G, Wilkinson KA, Goliath R, Mathee S, Goemaere E, Maartens G. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. *The Lancet*. 2014 Aug 23; 384 (9944): 682-90.

36. Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, McIntyre JA, Gray GE, Chaisson RE. New regimens to prevent tuberculosis in adults with HIV infection. *New England Journal of Medicine*. 2011; 365: 11–20.

37. Hernán MA. The hazards of hazard ratios. *Epidemiology*. 2010 Jan 1; 21 (1): 13-5.

38. Churchyard G, Cárdenas V, Chihota V, Mngadi K, Sebe M, Brumskine W, Martinson N, Yimer G, Wang SH, Garcia-Basteiro AL, Nguenha D. Annual tuberculosis preventive therapy for persons with HIV infection: a randomized trial. *Annals of Internal Medicine*. 2021 Oct;174(10):1367-76.

39. Martinez L, le Roux DM, Barnett W, et al. Tuberculin skin test conversion and primary progressive tuberculosis disease in the first 5 years of life: a birth cohort study from Cape Town, South Africa. *The Lancet Child & Adolescent Health*. 2018 Jan 1; 2 (1): 46-55.

40. Mandalakas AM, Hesseling AC, Kay A, et al. Tuberculosis prevention in children: a prospective community-based study in South Africa. *European Respiratory Journal*. 2021 Apr 22; 57 (4).

AJRCCM Articles in Press. Published September 23, 2025 as 10.1164/rccm.202411-2340OC

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Tables and Figures

Table 1. Demographic characteristics of included participants exposed to an individual with multidrug-resistant tuberculosis from included studies.

Table 2. Effectiveness of isoniazid on risk of incident tuberculosis in household contacts of multidrug-resistant tuberculosis cases.

Figure 1. Flowchart of Systematic Search Process.

Figure 2. Effectiveness of isoniazid preventive treatment against incident tuberculosis among contacts exposed to MDR tuberculosis, by time period of follow-up.

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Table 1. Demographic characteristics of included participants exposed to an individual with multidrug-resistant tuberculosis from included studies.

Characteristic	N	Percent
Total individuals evaluated for incidence	6,668	100
Total person-years follow-up	14,468	
Median follow-up time (IQR)	1.8 (1.0 – 3.3)	
Age, years		
Median (IQR)	25 (11, 44)	
Mean (SD)	28 (20.0)	
Age group, years		
<10	1,441	21.6
10-19	1,308	19.6
20-29	1,063	15.9
30 and over	2,856	42.8
Sex		
Male	3,106	47.3
Female	3,466	52.7
QuantiFERON, T-SPOT, or tuberculin skin tested	2,798	42.0
HIV tested	4,676	70.1
Tested HIV positive (Percent of tested)	284	6.0
Prior tuberculosis	365	7.0
Isoniazid preventive treatment		
Given isoniazid TPT	1,020	15.3
Not given TPT	5,648	84.7

Data are n or n (%) unless otherwise specified.

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Table 2. Effectiveness of isoniazid on risk of incident tuberculosis in household contacts of multidrug-resistant tuberculosis cases.

	Total N		Person-years of follow-up	N, contacts	N, progressing to disease	Age-adjusted HR (95% CI)	Fully-adjusted HR (95% CI)
All participants	6,668	Not given TPT	12,471	5,648	167	1 (Referent)	1 (Referent)
		Given INH	1,998	1,020	20	0.43 (0.26–0.70)	0.41 (0.25–0.68)
Child <20 years	2,749	Not given TPT	3,526	1,847	50	1 (Referent)	1 (Referent)
		Given INH	1,596	902	17	0.54 (0.30–0.97)	0.51 (0.28-0.92)

INH, Isoniazid; HR, hazard ratio; TPT, tuberculosis preventive treatment. Fully-adjusted models are adjusted for contact age, sex, prior tuberculosis status, the study design, and the individual study.

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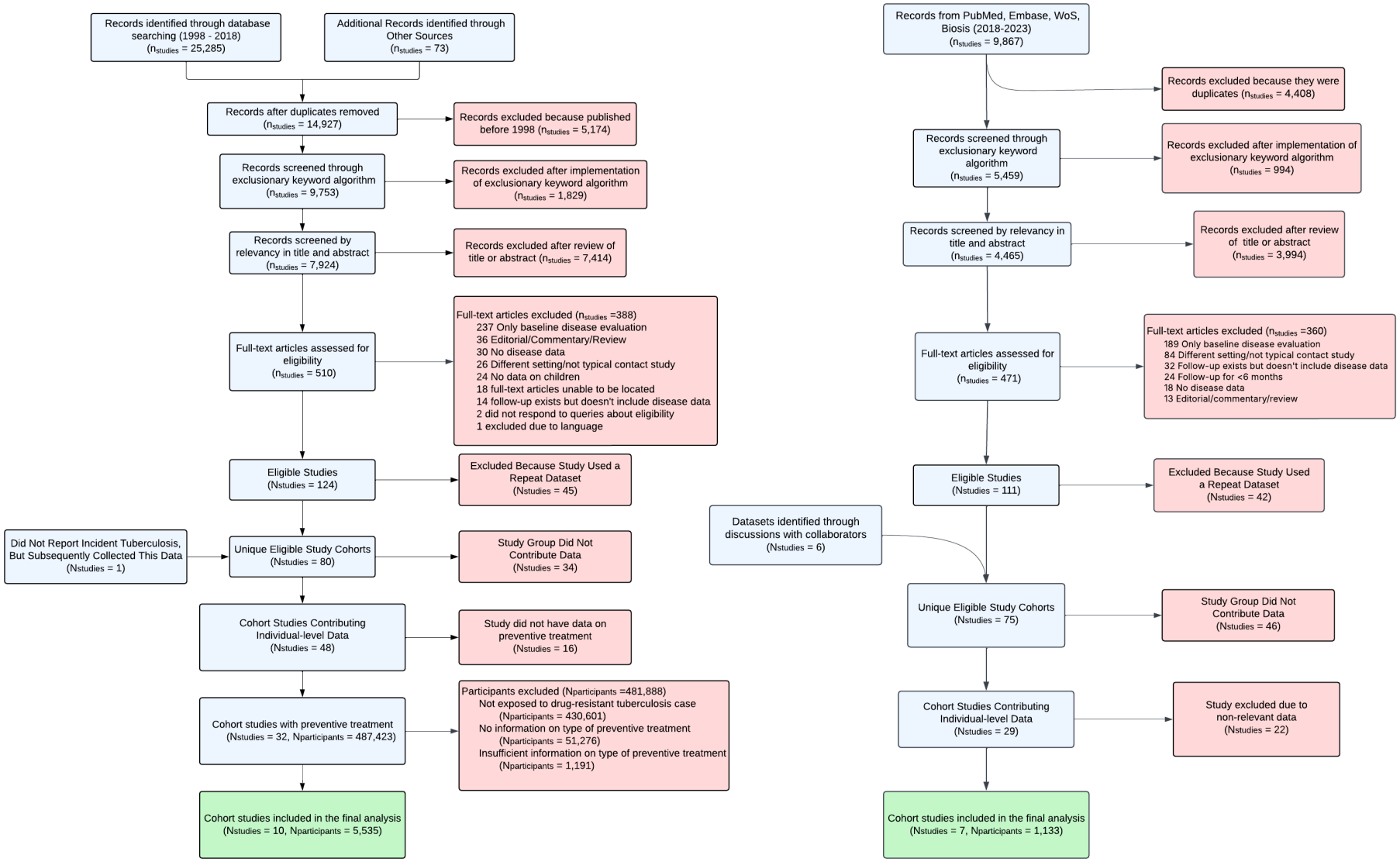
Figure 1. Flowchart of Systematic Search Process.



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Excluded full-text articles may have had more than one reason for exclusion, but only one reason for exclusion was listed for each excluded manuscript. Exclusionary keyword algorithm is described in the Supplementary Appendix.

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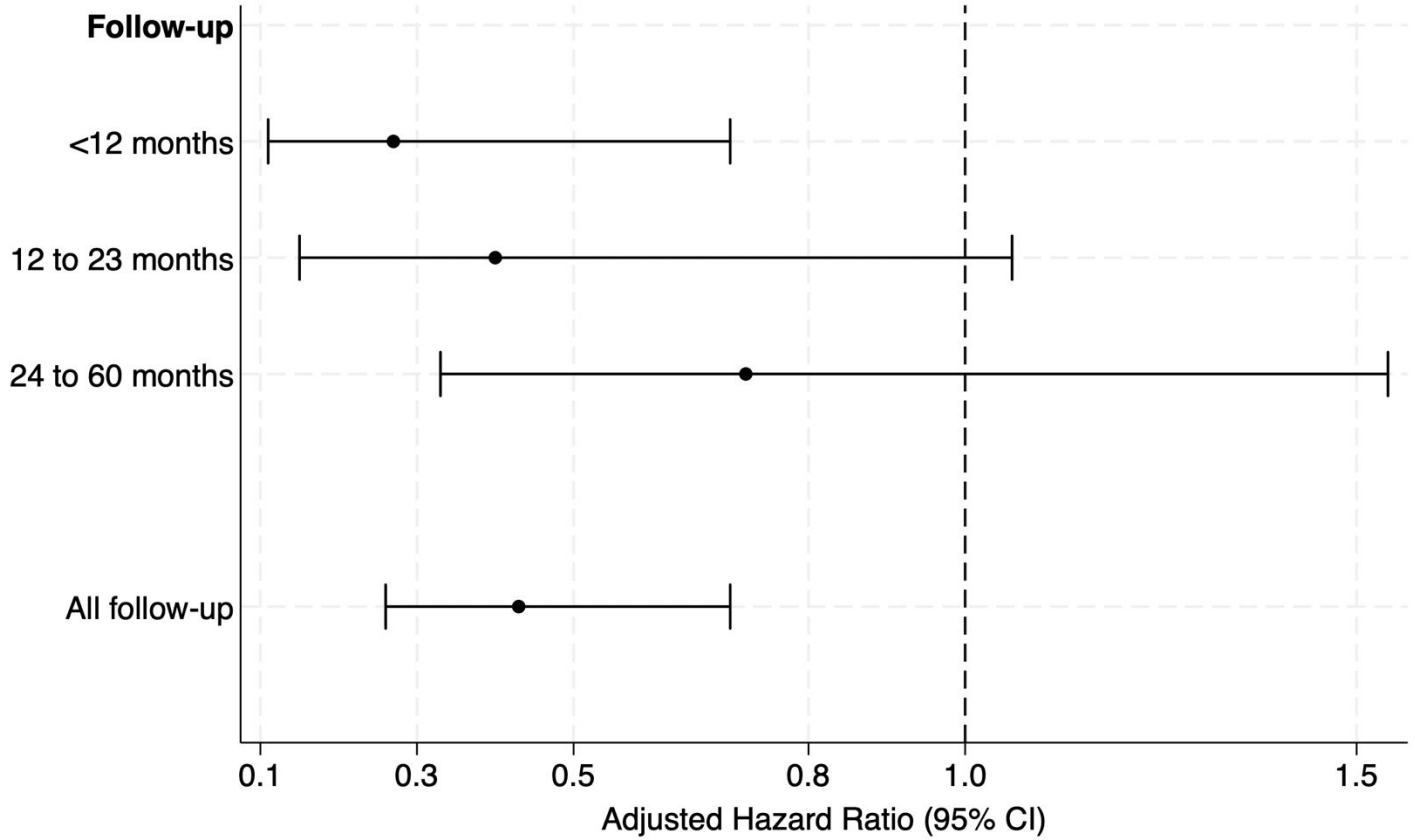
Figure 2. Effectiveness of isoniazid preventive treatment against incident tuberculosis among contacts exposed to multidrug-resistant tuberculosis, by period of follow-up.



To assess the durability of the treatment effect, follow-up time was split into three-time groups (<12 months, 12–23 months, and 24 to 60 months). We specified the effects of isoniazid by follow-up time and derived adjusted hazard ratios (aHRs) for each time interval. Models integrated a study-level random effect and adjusted for contact age, contact sex, and study design.

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The Effectiveness of Isoniazid Preventive Treatment among Contacts of Multidrug-Resistant Tuberculosis: A Systematic Review and Individual-Participant Meta-Analysis

Leonardo Martinez, Ph.D., Jeffrey I Campbell, M.D., Lauren Linde, M.P.H., Fadila Boulahbal, M.D., Joan A Cayla, M.D., Tsira Chakhaia, Ph.D., Pei-Chun Chan, Ph.D., Cheng Chen, Ph.D., Chi-Tai Fang, Ph.D., Greg Fox, Ph.D., Louis Grandjean, Ph.D., Djohar Hannoun, M.D., Anneke Hesseling, M.D., C. Robert Horsburgh, M.D., Li-Min Huang, Ph.D., Qiao Liu, Ph.D., Rufaida Mazahir, Ph.D., Chih-Hsin Lee, Li-Na Lee, Rutger Bennet, M.D., Sahar Nejat, M.D., Amita Gupta, M.D., Mrinalini Das, Ph.D., Megan Murray, Ph.D., Chuan-Chin Huang, Sc.D., Helena del Corral, Ph.D., Dione Benjumea-Bedoya, Ph.D., Ye Shen, Ph.D., Mercedes Becerra, Sc.D., Vicky Chang, Ph.D., Sonya Krishnan, M.D., Petra Heinmueller, Timothy Brewer, M.D., Petros Isaakidis, Ph.D., Anja M. Hauri, M.D., Lena Shah, Ph.D., Lisa Trieu, M.P.H., James A Seddon, M.D.

ONLINE DATA SUPPLEMENT

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Tables and Figures.

Additional Methodological Information.

Table S1. Demographic characteristics of included cohort studies

Table S2. Study results with information on multi-drug resistant status of index cases.

Table S3. Incidence rate ratios among subgroups of children exposed to multidrug-resistant tuberculosis, stratified by the age of the child.

Table S4. Incidence rate ratios among subgroups of participants exposed to multidrug-resistant tuberculosis, stratified by the background tuberculosis incidence of the country.

Table S5. Assessment of Quality of the Included Studies.

Table S6. Demographic characteristics of participants administered and not administered preventive treatment.

Figure S1. Map of Location of Included Studies.

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Additional Methodological Information.

Further enrollment and follow-up from original consortium data

Following the publication of the manuscript Anger et al, 2012, the New York City Department of Health continued to expand their dataset as part of routine programmatic activities. Contact tracing and follow-up data from 2007 to 2019 were added to the New York City cohort for the purposes of this analysis. Although contact tracing was done by the same group (New York City Department of Health), exact methods throughout this time period are not exactly the same. For example, IGRAs were used in later years of the study time period.

Event Ascertainment

Events were ascertained using several strategies selected by each cohort's investigator group. For tuberculosis diagnosis events, cohorts either diagnosed cases prospectively or used data linkage to national or sub-national tuberculosis registries. Most prospective studies used some type of microbiological test, either as a baseline evaluation or a triage test. Diagnosis of tuberculosis in all prospective studies included either a positive microbiological test or a physical examination and subsequent clinical diagnosis. Some prospective studies used diagnostic tests as part of their study procedures and also used national or sub-national tuberculosis registries.

Systematic Search.

Case-control studies and outbreak reports were excluded, as were reviews, editorials, letters, or studies for which individual outcomes were not reported. We did not restrict articles by language and reviewed manuscripts written in English, Chinese, French, German, Japanese, Korean, Persian, Portuguese, Russian, and Turkish. To facilitate the review process, a list of 'exclusionary words' was developed, based on words in titles highly suggestive of irrelevant content (see below for complete explanation and list). Manuscripts were excluded if their titles contained any of these exclusionary words. Two reviewers independently reviewed articles in two stages: evaluation of titles and abstracts followed by full-text review. After the review of titles and abstracts, the two reviewers discussed discrepancies and re-evaluated articles until consensus was reached. During this stage, if an abstract was in a language other than English the manuscript was advanced to the full-text review stage. Relevant articles were subject to a full-text review by both reviewers and any discrepancies were again resolved by reviewer discussion and consensus. If eligibility could not be assessed from the full-text manuscript because of missing information, we contacted authors for clarification. We evaluated eligible articles for duplication of data on the same individuals and excluded manuscripts if necessary.

Preventive Treatment

Preventive treatment was assigned to participants according to each study's protocol or local guidelines and practices.

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Study Quality.

Each study was judged based on a 9-point scale using three broad criteria: selection of participants (4 points), comparability of studies (2 points), and ascertainment of outcome of interest (3 points). High study quality was defined as >66.6%, moderate quality as 33.3-66.6%, and low quality as <33.3%. Discrepancies between the two reviewers were resolved by re-evaluating the study for consensus.

Study-level characteristics.

Country-level tuberculosis incidence data was collected from World Health Organization databases for each study. This variable was used as a continuous variable. Studies were categorized into "high-burden" country as classified by the World Health Organization. Studies were also grouped into World Health Organization global regions and World Bank country-level economies (high- income, upper-middle-income, lower-middle-income, and low-income) as of October 2018.

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Search Strategy.

Original search.
Search conducted on April 7, 2018

Pubmed/MEDLINE – 6252
Search conducted on April 7, 2018
(tuberculosis OR (mycobacterium tuberculosis[MeSH Terms]) OR tuberculosis[MeSH Terms])
AND
(contact tracing[MeSH Terms] OR infectious disease contact tracing[MeSH Terms] OR household*[Title/Abstract] OR contact*[Title/Abstract])

Embase – 8525
Search conducted on April 7, 2018
(tuberculosis OR 'mycobacterium tuberculosis')
AND
('contact examination'/de OR contact*)

Biosis – 3971
Search conducted on April 7, 2018
((TS=tuberculosis) OR (TS='mycobacterium tuberculosis') OR (TI=TB))
AND
((TS='contact examination') OR (TS=contact*) OR (TS='contact tracing') OR (TS=outbreak*))

Web of Science – 6537
Search conducted on April 7, 2018
((TS=tuberculosis) OR (TS='mycobacterium tuberculosis') OR (TI=TB))
AND
((TS='contact examination') OR (TS=contact*) OR (TS='contact tracing') OR (TS=outbreak*))

Total from Search: 25285.

Total from Search after Exclusion by Duplicates: 14927

Total from Search after Exclusion by Timeframe (pre-1998): 9753

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2023 Update
Search conducted on April 8, 2018 – August 28, 2023

Pubmed – 2417
Search conducted on August 28, 2023
Date range: April 8, 2018 – August 28, 2023
(tuberculosis OR (mycobacterium tuberculosis[MeSH Terms]) OR tuberculosis[MeSH Terms]) AND (contact tracing[MeSH Terms] OR infectious disease contact tracing[MeSH Terms] OR household*[Title/Abstract] OR contact*[Title/Abstract])

Embase – 3549
Search conducted August 28, 2023
Date range: April 8, 2018 – August 28, 2023
('tuberculosis'/exp OR tuberculosis OR 'mycobacterium tuberculosis'/exp OR 'mycobacterium tuberculosis') AND ('contact examination'/exp OR 'contact examination' OR contact*) AND [08-04-2018]/sd NOT [29-08-2023]/sd

Biosis – 946
Search conducted August 28, 2023
Date range: April 8, 2018 – August 28, 2023
((TS=tuberculosis) OR (TS='mycobacterium tuberculosis') OR (TI=TB)) AND ((TS='contact examination') OR (TS=contact*) OR (TS='contact tracing') OR (TS=outbreak*))

Web of Science – 2955
Search conducted August 28, 2023
Date range: April 8, 2018 – August 28, 2023
((TS=tuberculosis) OR (TS='mycobacterium tuberculosis') OR (TI=TB)) AND ((TS='contact examination') OR (TS=contact*) OR (TS='contact tracing') OR (TS=outbreak*))

Total from search: 9867

Total from search after exclusion by deduplication: 5459

Total after applying exclusionary words: 4465

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Exclusionary Keyword Algorithm for Study Titles.

i. Description of the Algorithm.

We wrote a script parsing titles into individual words. We selected words highly suggestive that an article was unrelated to our study objectives. Articles were then eliminated based on whether their titles contained these words.

In order to validate this process, we implemented the algorithm on the first 100 titles and manually screened them for eligibility in the study. Our exclusionary algorithm eliminated all articles that were screened out by manual screening with 100% specificity. This suggested that our selected words were appropriate. Out of the 9,243 articles disqualified at the title stage, 1,829 (19.7%) were eliminated based on whether they contained one of the exclusionary words. The code for exclusion words and article elimination, as well as the entire list of exclusionary words can be found below.

ii. Python script:

```
'''
Script parsing tokens for excluding titles and matching the tokens to the original word counterpart to each token.

Each title is normalized to lower-case letters and numbers with no punctuation. Excluding tokens use this format.
A list of exclusion tokens is used to eliminate all matching titles.
'''
import pandas as pd
import string
from difflib import SequenceMatcher

import sys
reload(sys)
sys.setdefaultencoding('utf8')

def remove_punctuations(text):
    """Removes punctuation from the string text.

    :param text: string
    :return: string, with punctuation removed.
    """
    if isinstance(text, float): return text
    for punctuation in string.punctuation:
        text = text.replace(punctuation, '')
    return text
```

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```
def similar(a, b):
    """
    Returns ratio of similarity between a and b in the range [0, 1].
    :param a: string
    :param b: string
    :return: float, between 0 and 1 inclusive
    """
    return SequenceMatcher(None, a, b).ratio()


def find_ex_word(ex_words_set, r):
    """
    Matches title words to exclusionary words.

    :param ex_words_set: set<string> of exclusionary words.
    :param r: pandas row
    :return: [(fraction, exclusion_word, title_word)] or 'No match' for no matches. The list contains all
possible matches.
    """
    candidates = []
    if isinstance(r['Title_punctuations'], float):
        return 'No match'
    for word in r['Title_punctuations'].split(' '):
        if word in ex_words_set:
            for original in r['Title'].split(' '):
                candidate = (similar(word, original.lower()), word, original)
                candidates.append(candidate)
    candidates.sort(key=lambda x: x[0], reverse=True)
    candidates = [c for c in candidates if c[0] > 0.0]
    if not candidates:
        return 'No match'
    else:
        return candidates

def run():
    '''Main driver function '''
    all_articles_read = pd.read_csv('endnote_oliviasearch_0411.csv')  # read File containing
titles
    all_articles_read = all_articles_read.dropna(subset=['Title'])  # remove blanks
    all_articles_read['Title_punctuations'] =
all_articles_read['Title'].apply(remove_punctuations)
    all_articles_read['Title_punctuations'] =
all_articles_read['Title_punctuations'].str.lower()  # make lowercase
    title_word_count =
```

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```
(all_articles_read['Title_punctuations'].str.split(expand=True).stack().value_counts(
    ascending=True))  # list of title with corresponding number of occurrences

  # Sheet of words and counts across titles.
  (pd.DataFrame(title_word_count).to_excel('title_word_count.xlsx', index=True))  #
export title_word_count

  # Read in file of exclusion words. Filter out titles that contain them.
  exclusion_words = pd.read_excel('exclusion_words.xlsx')  # read File containing words to
exclude

  exclusion_word_delim = [r'\b' + item + r'\b' for item in exclusion_words.word]
  exclusion_words_str = '|'.join(exclusion_word_delim)
  filtered = all_articles_read[all_articles_read['Title_punctuations'].str.contains(
    exclusion_words_str) == False]  # remove article titles if they contain exclusion words
  (pd.DataFrame(filtered).to_excel('907_exclude_test.xlsx', index=True))  # export
remaining titles

  ex_words_set = set()

  for word in exclusion_words['word']:
    ex_words_set.add(word)

  # List of tuples of match ratio (0-1), token, original_word
  matches = all_articles_read.apply(lambda x: find_ex_word(ex_words_set, x), axis=1)

  # build a dictionary from token to the best possible match
  ex_dict = dict()
  for match in matches:
    if match != 'No match':
      for n in match:
        key = n[1]
        if key not in ex_dict:
          ex_dict[key] = n
        else:
          ex_dict[key] = max(n, ex_dict[key])

  # mapping from token to original word
  matched_dict = dict()
  for value in ex_dict.values():
    if value[0] > 0:
      matched_dict[value[1]] = value[2]

  # see if any of the exclusion words were never matched to an original title word
```

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```
    words_not_found = []
    for w in ex_words_set:
        if w not in matched_dict:
            words_not_found.append(w)

    original_words = [x[2] for x in ex_dict.values()] + words_not_found # write all words out
    serialized = ', '.join(original_words)
    f = open('/Users/ocords/Desktop/original_words_test.txt', 'w')  # creates text files
words as appear in original titles
    f.write(serialized)
    f.close()


if __name__ == '__main__':
    run()
```

iii. List of words:

anti-coronavirus, A(2)CoMnO(6), Sulfhydrylase, influenza, polypeptides, lysosome, Thermococcus, YMn6-xTixSn6, amphotericin, reductoisomerase, porcine, Enteric, cryptococcosis, milk, cytokines, langurs, perianal, Birthplace, benzoquinone:, dichloroacetate, penile, polyunsaturated, Protein-RNA, peanut, squirrels:, Halogen, dairy, 3-(pyrazin-2-ylcarbonyl)dithiocarbazic, choliangiopancreatography, leukocytes, rhesus, ppe38, dermatophytosis, heme, Biofilms, extremophiles, UDP-galactopyranose, D-3-phosphoglycerate, peafowl, Salmonella, monkeys, ESAT-6-dependent, O-Acetylserine, mongooses, Primate, spoligofamily, (+1188A/C), Nicotinamide, vitrectomy, Isoniazid/Rifampicin/Poly, Shiga, Trypanosoma, A/H3N2, brucellosis, veterinarians, wild-boar, phosphorylated, Amoeba-Resistant, Cyclodestructive, pJHCMW1, miliary, subspecies, prostatitis, enterocolitica, hydrolysis, hematology-oncology, prisons, histone-like, macrophages, vampire, Pseudoaneurysm, lovebird, celiac, Guanine-Cytosine-Rich, phosphatase, Hsp70, factor-microRNA, osteoporosis, bovis, Bird, S12-S7, actinobacterial, CRF08_BC]., Corynebacteriurn, raccoons, brucei, ribose, kangaroo, herd, PD-1/PD-L2, beta-cyclocitral, alphaA-crystallin,, water-soluble, Ag85B, PCR-restriction, helicase, CXCL10/IP-10, inter-species, beta-semialdehyde, Asp299Gly, host-parasitoid, corynebacterium, Paracoccidioides, cinnamon,, Orang-Utan, metal-induced, raccoon, military, lymphadenitis, calf-to-calf, Lanthanide(III)-Phthalocyanine, sacroiliitis, Pseudomonas, extremophile:, mct1Delta, MD-2, Anions, glutaraldehyde, earth-nickel-indides, Coxsackievirus, transplant, arthropod, obliterans, catalase-peroxidase, Dy5Ni2In4, petroleum, Frog, oryx, low-molecular-mass, Automata, microbiota, electroelution, phytopathogen, (P631H), IL-17RA, psoriasis, Shiga-toxin-producing, staphylococcus, Microaggregates, 49-year-old, SAT6-CFP10, E-coli, chimpanzee, Metalloprotease-1, Adenosine, biotin, rabbit, radiculomyelitis, penis, Rv0753c, flora, animals, GC1237, K182G, PstS-1(285-374):CFP10, Death-Ligand, cat, mammalian, Arg753Gln, oxide, ligase, MDP-1, C1858T, proteasomal, Helicobacter, aminoglycoside, neurosarcoidosis, nursing, gingiva., Rv1737c, ferrets, pelvic, camelids, keratitis, CYP121-fluconazole, alpacas, gingivalis, cows,

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Oligosaccharides, confocal, hydrogen, species, Lamb, ribokinase, Lumbricidae), jails, paleopathological, pharyngitis-a, Cryoannealing-induced, rhinoceros, Micelle-based, animal, elephant, oropharyngeal, goat, ligand-independent, fever, aureus, Bacteriophages:, canker, fungus, possum, pigs, M2e.HSP70c, MVA85A,, prostate:, Leishmania, Bloodstream, calves, immune-endocrine, macrolide,, crystallin, disposable-sheath, jail, methadone, ID83/GLA-SE, Channel-Forming, crystallographic, Association-of-Primate-Veterinarians,, CD127-cells, antelope, phagocytosis, cryptosporidiosis, albicans, RE4Ni11In20, ulcerans, epilepsy, brucellosis--a, avium, PD-Ligand, Game-Theoretic, nitrogen, gonadal, Carnivores, 1-deoxy-D-xylulose-5-phosphate, badger, FMO2, leprae, antigen/N-trimethylaminoethylmethacrylate, ligand, botanical, protein-3, transferase, Cryptosporidium, m(1)A58, flavins, Rv1735c,, conspecific, Foxp3, coffee., cholera, food, diphosphate, osteolytic, Tb-2(SO4)(3), hypoxic, chemokines, phagocytes, exon, (Giraffa, metabolite, nematodes, DT104, ClpP1P2,, meat, aeruginosa, thymus., hemagglutinin, neoformans, esat-6, phytopathogenic, coronavirus, 33-year-old, amphiphilic, pyrimidine, CFP21-MPT64, bed-nets, sulfoglycolipids, D543N, chlamydial, Animal-Derived, myelin, elephants, Enterobacteriaceae, fish, sugars, bovine, 11p14-15, oncological, Quantum, lysis, protein-II, C(-159)T, semen, heme-degrading, metagenome, MPT51, phosphoryl, CD8+T, wildlife-pathogen, anorexia, (sIL-7R), cyber-gaming, c.1770-1900, arthritis, zoological, alkynes., lipopolysaccharide-induced, O3157, oligonucleotide, pre-ulcer, mammal, substrate-binding, host-microbial, agarose, monkey, phage-based, equine, SLC11A1, H1N1, braziliensis, Pseudo-septic, ostrich, Opiate-Driven, G354R, swine, Cyanide, osteomyelitis, phagosomes, ionic, raptors, borreliosis, sympatric, helix-turn-helix, buffaloes, leishmaniosis, 6-kilodalton, small-bowel, malonyl-CoA:AcpM, exostosis:, TLR4, antirheumatic, mammary, Earthworms, b-cell, sheep, ESAT-6/CFP-10, RMn6X6-x, pyrophosphatase., leptospirosis, sapiens, chimaera, Variable-Number-Tandem-Repeats, fragment-length, dyskinesia, leprae-specific, 4-Sulfamoylphenyl-omega-aminoalkyl, amines, pylori-Associated, Variant-Repeat, Carotenoids, human-livestock-wildlife, cytokine--IL-12,, resuscitation-promoting, Endoluminal, rickshaw, inmates, herds, Caulobacter, pheasants, non-contact-lens, vulvar, hemangiopericytoma:, mannose-binding, H-2K(k), IS6110, microglial, vulval, IL1B, flavin-binding, apiospermum, tubules, A0248:, mink, macaw, Legionella, fowl, kDa/MPT-64,, phosphoantigen-mediated, foodborne, phosphoribosyltransferase, lymphoblastic, rat, menstruus), dendritic, CD4+CD25, IS6110-fAFLP, glycopeptidolipid, MyD88, 30/31-kDa, smallpox, aeruginosan, amphibious, Crystallography, Tattoo-Related, clonality, DNA-probes, Xanthium, zoo, endangered, heat-shock, bullfrogs, serine, HLA-A*0201-Restricted, Chromosomes, botulinum, EGGS., protein-10, cytokines/chemokines, free-ranging, host-parasite, Hsp16.5, carcinoma, Brucella, vitro-selected, Elk-Fetus, ranavirus, Rv0081,, hemothoraces, Adenine, minisatellites, hydrocephalus, phospholipase, mannose, kDa/CFP-10,, socioepidemiologic, H-2-rich, fungal, bioarchaeology, cholerae, coli, human-wildlife, macaque, Rv1498A., pseudodiphtheriticum, aviary, ulcer, 30-kDa, hemangioendothelioma-case, (RE)(12)Co5Bi, G2109A), bronchoscopy-a, camelopardalis), kinase, GlfT2,, otorhinolaryngology, ESAT-6/MPT-64, Wood, Demodecidosis, salmonellosis, N-acetyl-gamma-glutamyl-phosphate, glycolipid, slit-lamp, Methylisothiazolinone, Nanocluster, palaeopathological, (10.1016/S1473-3099(17)30447-4)), histone, asbestos, Orang, endocarditis:, Cytokine-based, cyclopropane, cervids, cj0183, chrysomya, primates, CD8, Campylobacter, sarcoidosis,

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CD14-159C/T, spondyloarthritides, KIR3DL1/S1:, faeciuml,d-transpeptidase, abortus, dUTPases, tumors, heterocyclic, O157:H7/H-strains, chitotriosidase, lymphokine, IL-12Rbeta2, PENGUINS, bison, cyanobacterial, Hydrogen-bonding, aegypti, Synechococcus, pseudokinase, uveitis, 10.1093/cid/ciw694), Thymidylyltransferase, alanine, supramolecular, L-isoleucine, anthropozoonotic, chondrosarcoma, 2,3-Naphthalocyaninato, ionization-time-of-flight, CD1d-dependent, cattle, Salmonellae, thrombocytopenic, thrombocytopenia, IL12RB1, Neurobrucellosis:, House-Roosting, CHIMPANZEES, nucleoside, pets, zebrafish, ebola, CD1-mediated, chaperonin, (S1473309917304474), CD8-positive, gonorrhoeae, lymphocyte, (T874A, Clavibacter, Chihuahua, zoonoses, bushbuck, cervical, exomes, STAT3, Cow, hantavirus, cruzi, gyrase-fluoroquinolone, peptidoglycan, androgens, filariasis., CCR4, single-amino-acid, Ms6564,, lipases, Arg677Trp,, Tattoo-associated, Dysphagia, cancer, CRISPRs, Synthases,, Cryptogenic, peptide-binding, Clostfdium, thermophilus, crystalline, grazing, amino, myeloid-derived, Rv3802c, beef, Enterococci, (-362g/c), intracellular, benzaldehydes:, tracheobronchopathia, macaques, chromatography-tandem, interleukins, hydrolase, SrCl2-Promoted, pseudogene, Rv1057, isomerase, CD41, Lipid-Polymer, chain-binomial, CD40, Hydrogels, 1,2,4-triazoles,, ophthalmic, actinomycetemcomitans, Otolaryngological, miR-26a,, species-history, Apoptosis-associated, (S0140673615001518), tortoise,, cytotoxic, MazF-mt6, haematobium, Toxoplasma, Herpesvirus, CYP2E1, MS0006, leprosy, wild, cell-entry, interleukin-4, galactofuranosyltransferase, interleukin-1, cell-wall, CD1-presented, methyltransferases, glycaemic, Strongyloidiasis:, PstS1(285-374):CPF10:, ducks, polymerase, Proteolytic, eczema, sarcoma, beta-Lactamases:, Upregulated, 5-Phosphate, Nonsyphilitic, (CD11b/CD18), hyodysenteriae, ribosome, larva, Ccr2, helicases, Dengue/Zika, palsies, rrs491, cytolysis, Chromolaena, proleukin, IS3-based, chickenpox, Neutron, alcohol-resistant, zoonosis, 3-Deoxy-D-manno-octulosonate, difficile-associated, gastroenterology, nicotinohydrazide, typhoid, Anesthesiology, streptococcus, epizooties, ML2331, transposon, hydroxylase, poultry, 3-dioxygenase, C-24-methyltransferase, cytosolic, Th1/Th2, (IL)-12p70, chickens, vertebra:, chemokine, giraffe, post-implantkeratoprosthesis, 8-Phosphate, brasiliensis, streptomycin, lambs, mechanism-based, biochip, livestock, Glycine, ORS571, Lentivirus-control, Carboxylic, scabies, super-oxidized, mutase, sarcoidosis, Chagas, Mongoose, dpp3, macroscopic, Pyrazinamidase, cervix, boars, catalytic, RD1-epitopes, ML1419c, swine-origin, papulonecrotic, lattice, matricellular, prison, lymphocytes, nitrocellulose-bound, murine, IL-17-producing, parenchymal, apnea., scrofuloderma, nanofilters, prosthesis-free, Ospedalieri., wavelength, '-[(E)-2,6-Dichlorobenzylidene]pyrazine-2-carbohydrazide, C8G, Dy(III)-Phthalocyanine, furanoside, lymphoma, bioterrorism-related, Glucose-1-Phosphate, Sulfonyl-hydrazones, glycolipid-I, qualitative, spelunking:, brachiocephalic, Kuala, nosocomial, Estriol, Amoebae, antiprotozoal, leucoryx,, partridges, CeFeSi-type, ulcers, EMRSA-15, 38-kDa, CD56+CD3+, CYP121:, (H5N1), Protein-Ligand, CXCL10, Transcriptome, Gonococcal, pestis, gastrostomy, ungulate, pet, veterinary, fox, anti-leishmanial, goats, e59414,, syphilis, H7N9, wild-caught, zoonotic, IS6110-RFLP, metal/metal, core, Rv2721c), Tetrakis(4-chlorophenyl)borate, abattoirs, squirrel, CFP10, CCL18, dental, p38, autophagosomes, nanoliter, leukocyte-leukocyte, tetramer, wildlife, Autophosphorylation, Rv2628, tumor, Lynx, tannic, alpha-Substituted-2-Phenylcyclopropane, ribose-5-phosphate, Posttraumatic, badgers, pH-dependent, CYP51.,

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aortic, protease, F15/LAM4/KZN, haplotype, D2EHPA, (pyrazinecarbonyl)hydrazones, mitochondrial, sow., ex-vivo, non-ruminant, dehydrogenase, MCP-2, neutrophil-mediated, larvae., reticulum-related, crystallization, herbivores, Larval, Oligomycin, polymerization, cats, nitric, PPE39, 5q31.1, ML0405, CD1-lipid, CD4+CD45RO+T-Cells, tyrosine, metaproteomics., helminths, Convex-probe, chikungunya, mammals, keratinocyte, chromosomal, vivax, PCC7942., phenylalanine, Zika, PTPN22, CYP125:, Enterovirus, malate, Peppermint, apes, Octahydrocyclopenta[c]pyrrol-2-yl, aneurysm, 38kDa-antigen, polymorphisms, 'Zebra', rabbits, Cpn60.2, kinetics, Cytokine-Induced, deer, Enterococcus, Rv1733c,, pig, demethylase, lichen, Hypercalcemia, ticks, NOS2A, CFP10ESAT6, Rv0183, 14alpha-sterol, Lgn1, tandem-repeat, keratoplasty, Coxiella, N-(4-Bromophenyl)pyrazine-2-carboxamide, peptides, UVB-irradiated, snakes, photoluminescence, nanopore, thromboendarterectomy, actinorhodin, Glycosaminoglycans, IS1106, arthritis-associated, carboxylase, Vibrio, diesters, N-(2-Chloroethyl)pyrazine-2-carboxamide, peptide-25, inguinal, macrophage, non-methylated, cellulose-targeting, PCR-single-strand, camelus)., Flavohemoglobin, RegX3, Neuropilin-1, gonorrhea, Bartonella, citrate, electroretinographic, tnf_il2, bovus, antitnf_, v_11, guinea pig, 5_untranslated

AJRCCM Articles in Press. Published September 23, 2025 as 10.1164/rccm.202411-2340OC

References for All Individual Studies in Analysis.

Altet, N., Dominguez, J., Souza-Galvão, M.L.D., Jiménez-Fuentes, M.Á., Milà, C., Solsona, J., Soriano-Arandés, A., Latorre, I., Lara, E., Cantos, A. and Ferrer, M.D., 2015. Predicting the development of tuberculosis with the tuberculin skin test and QuantiFERON testing. *Annals of the American Thoracic Society*, 12(5), pp.680-688.

Anger, H.A., Proops, D., Harris, T.G., Li, J., Kreiswirth, B.N., Shashkina, E. and Ahuja, S.D., 2012. Active case finding and prevention of tuberculosis among a cohort of contacts exposed to infectious tuberculosis cases in New York City. *Clinical Infectious Diseases*, 54(9), pp.1287-1295.

Bennet R, Nejat S, Eriksson M. Effective tuberculosis contact investigation using interferon-gamma release assays. *The Pediatric Infectious Disease Journal*. 2019 Apr 1;38(4):e76-8.

Chakhaia, T., Magee, M.J., Kempker, R.R., Gegia, M., Goginashvili, L., Nanava, U. Blumberg, H.M., 2014. 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*, 9(11), p.e111773.

Chan, P.C., Shinn-Forng Peng, S., Chiou, M.Y., Ling, D.L., Chang, L.Y., Wang, K.F., Fang, C.T., Huang, L.M., 2014. Risk for tuberculosis in child contacts. Development and validation of a predictive score. *American Journal of Respiratory and Critical Care Medicine*, 189(2), pp.203-213.

Chang V, Ling RH, Velen K, Fox GJ. Latent tuberculosis infection among contacts of patients with multidrug-resistant tuberculosis in New South Wales, Australia. *ERJ Open Research*. 2021 Sep 20;7(3).

Grandjean, L., Gilman, R.H., Martin, L., Soto, E., Castro, B., Lopez, S., Coronel, J., Castillo, E., Alarcon, V., Lopez, V. and San Miguel, A., 2015. Transmission of multidrug-resistant and drug susceptible tuberculosis within households: a prospective cohort study. *PLoS Medicine*, 12(6), p.e1001843.

Grandjean, L., Crossa, A., Gilman, R.H., Herrera, C., Bonilla, C., Jave, O., Cabrera, J.L., Martin, L., Escombe, A.R. and Moore, D.A.J., 2011. Tuberculosis in household contacts of multidrug resistant tuberculosis patients. *The International Journal of Tuberculosis and Lung Disease*, 15(9), pp.1164-1169.

Hannoun, D. and Boulahbal, F., 2016. Incidence of tuberculosis among children living in contact with smear-positive tuberculosis: Advantages and limits of the Quantiferon TB gold in tube test. *International Journal of Mycobacteriology*, 5, p.S3.

Hauri AM, Bettge-Weller G, Westbrock HJ, Geis S, Goetsch U. Development of active Tuberculosis among TB Contact Persons with a positive IGRA, Hessen, 2008-2017. In GESUNDHEITSWESEN 2019 Mar 1 (Vol. 81, No. 3). RUDIGERSTR 14, D-70469 STUTTGART, GERMANY: GEORG THIEME VERLAG KG

AJRCCM Articles in Press. Published September 23, 2025 as 10.1164/rccm.202411-2340OC

Huang CC, Becerra MC, Calderon R, Contreras C, Galea J, Grandjean L, Lecca L, Yataco R, Zhang Z, Murray M. Isoniazid preventive therapy in contacts of multidrug-resistant tuberculosis. *American Journal of Respiratory and Critical Care Medicine*. 2020 Oct 15;202(8):1159-68.

Krishnan S, Wu X, Kim S, et al. 1-year incidence of tuberculosis infection and disease among household contacts of rifampin-and multidrug-resistant tuberculosis. *Clinical Infectious Diseases*. 2023 Sep 15;77(6):892-900

Lu P, Ding X, Liu Q, Lu W, Martinez L, Sun J, Lu F, Zhong C, Jiang H, Miao C, Zhu L. Mediating effect of repeated tuberculosis exposure on the risk of transmission to household contacts of multidrug-resistant tuberculosis patients. *The American Journal of Tropical Medicine and Hygiene*. 2018 Feb; 98 (2): 364.

Mazahir, R., Beig, F.K., Ahmed, Z. and Alam, S., 2017. Burden of tuberculosis among household children of adult multi drug resistant patients and their response to first line anti tubercular drugs. *Egyptian Pediatric Association Gazette*, 65(4), pp.122-126.

Paryani RH, Gupta V, Singh P, Verma M, Sheikh S, Yadav R, Mansoor H, Kalon S, Selvaraju S, Das M, Laxmeshwar C. Yield of systematic longitudinal screening of household contacts of Pre-Extensively Drug Resistant (PreXDR) and Extensively Drug Resistant (XDR) tuberculosis patients in Mumbai, India. *Tropical Medicine and Infectious Disease*. 2020 May 26; 5 (2): 83.

Shah L, Pena MR, Mori O, Zamudio C, Kaufman JS, Otero L, Gotuzzo E, Seas C, Brewer TF. A pragmatic stepped-wedge cluster randomized trial to evaluate the effectiveness and cost-effectiveness of active case finding for household contacts within a routine tuberculosis program, San Juan de Lurigancho, Lima, Peru. *International Journal of Infectious Diseases*. 2020 Nov 1; 100: 95-103.

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Table S1. Demographic characteristics of included cohort studies

Study or participant characteristics	Studies (n=17)	Proportion
Prospective study design	10	59
Background burden, >100 incident cases per 100 thousand people	7	41
Country-level tuberculosis incidence (per 100 000 people)†		
Below 50	6	35
50–100	4	24
>100–200	5	29
Above 200	3	18
World Health Organization region		
African	1	6
Americas	6	
Eastern Mediterranean	0	0
European	4	25
South-East Asia	2	13
Western Pacific	3	19
HIV status of participant reported	8	47
Cohort size		
Less than 1000	15	88
1000 or greater	2	12
QuantiFERON or tuberculin skin testing	14	82

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Table S2. Study results with information on multi-drug resistant status of index cases.

Characteristic	$N_{treated}/N_{total}$	Adjusted Hazard Ratio (95% CI)
All participants (Model 1)	1,020/6,668	0.43 (0.26-0.70)
All participants (Model 2)	1,020/6,668	0.41 (0.25–0.68)
All participants (Model 3)	939/5,242	0.44 (0.26–0.77)
Age group, years		
Child	901/2,749	0.51 (0.28–0.92)
Adult	119/3,919	0.69 (0.22–2.20)
HIV status		
Positive	8/289	Undefined
Negative	881/4,401	0.42 (0.26-0.70)
Prior tuberculosis		
Yes	12/366	0.55 (0.13-2.36)
No	927/4,925	0.47 (0.26-0.84)
TST or IGRA status		
Positive	195/1,570	0.78 (0.17–3.88)
Negative	218/1,271	Undefined

Model 1 includes all contacts and is adjusted for age and has a random study-level effect.
Model 2 includes all contacts and is adjusted for age, sex, the study design and has a random study-level effect.
Model 3 includes contacts and is adjusted for age, sex, prior tuberculosis, the study design, and has a random study-level effect.

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Table S3. Incidence rate ratios among subgroups of children exposed to multidrug-resistant tuberculosis, stratified by the age of the child.

	Incidence rate ratios	95% confidence interval
Age, years		
0 to 4	0.69	0.17 – 2.75
5 to 9	0.93	0.19 – 4.61
10 to 19	0.49	0.23 – 1.04

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Table S4. Incidence rate ratios among subgroups of participants exposed to multidrug-resistant tuberculosis, stratified by the background tuberculosis incidence of the country.

	Given INH TPT		Not given TPT		Hazard Ratio (95% CI)
	$N_{participants}$	N_{events}	$N_{participants}$	N_{events}	
Background incidence (per 100K persons)					
<50	117	1	980	10	0.90 (0.11–7.29)
50 to 100	36	0	728	1	Undefined
>100	867	19	3,993	156	0.40 (0.24–0.67)

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Table S5. Assessment of Quality of the Included Studies.

We assessed the quality of each study based on a modified version of Newcastle-Ottawa scale (Wells, 2012)†. We assessed each study's selection process, comparability, and outcome for a maximum total of 9 points. Studies were ranked high if they had a score of greater than 66.6%, moderate if they had a score greater than 33.3 and less than or equal to 66.6%, and low if they had a score of less than or equal to 33.3%.

Study†	**Selection**			**Comparability**	**Outcome**			**Rating**		**Quality**
	Represent-ativeness of sample[a]	**Ascertainment of exposure status - How was index case diagnosed?[b]**	**Demonstration that TB in contacts was not present at baseline. [c]**	**Comparability of cohorts (2 points)[d]**	**Assessment of tuberculosis (2 points)[e]**	**Was follow up long enough for outcomes to occur?[f]**	**Adequacy of follow up of exposed contactsf**	**Rating**	**PERCENT SCORE (X/9)**	
Grandjean, 2010	A	A	C	BC	AC	A	E	5	0.56	moderate
Grandjean, 2015	C	A	A	AB	AB	A	E	7	0.78	high
Chan, 2014	A	A	A	BC	AB	A	E	7	0.78	high
Chakhaia, 2014	C	A	A	CD	AB	A	E	5	0.56	moderate
Altet, 2015	A	A	A	AB	AB	A	B	9	1	high
Mazahir, 2017	A	A	A	AD	AB	A	A	8	0.89	high
Lu, 2015	B	A	B	B	D	A	C	6	0.67	moderate
Anger, 2012	B	A	A	CB	B	A	C	7	0.78	high
Gounder, 2015	A	A	A	CB	B	A	C	7	0.78	high
Bedoya, 2019	A	A	C	AB	AB	A	B	7	78%	high
Bennet, 2019	A	A	A	AD	AB	A	A	8	89%	high
Chang, 2021	A	A	A	CD	C	A	D	4	44%	moderate
Hauri, 2019	C	C	C	CD	D	A	D	1	11%	low
Krishnan, 2023	B	A	A	AD	AB	A	D	7	78%	high
Paryani, 2020	B	C	A	CD	B	A	D	4	44%	moderate
Shah. 2020	B	A	C	A	AB	A	A	6	67%	moderate

†Hannoun, 2016 was a conference abstract and therefore was not included in the assessment.

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[a] A*- Representative of the average TB case/TB contact in the community; B*- Somewhat representative of the average TB case/TB contact in the community; C - Selected group of TB cases/TB contacts, chance of bias; D - No description of the derivation of the cohort;
[b] A*- Microbiological (smear, culture, Xpert) testing of TB cases was done for all tuberculosis index cases; B - Chest radiographical/clinical diagnosis of tuberculosis index cases without microbiological testing; C - No description of the derivation of the cohort;
[c] A*- Reported testing for and numbers of tuberculosis cases in children at baseline; B*- Reported prevalent tuberculosis as an exclusion criteria for incident tuberculosis; C - No demonstration of lack of tuberculosis disease at baseline visit
[d] A*- Prospective Cohort; B* - Adjusted odds ratio; C - Retrospective Cohort; D - Adjusted Odd Ratio not specified; E - nothing specified;
[e] A*- Microbiological testing; B* - Radiographical and clinical (must have both); C - Radiographical or clinical (only 1); D - No description;
[f] A* - Yes (at least 3 months) after exposure to infectious patient with mycobacterium tuberculosis*; B - No; C - Information not provided;
[g] A* - If prospective, all children exposed were evaluated for tuberculosis during follow-up; B* - If prospective, <= 10% of children exposed lost to follow up; C* - If retrospective, number of children lost to follow-up or excluded is reported and <=10%; D - If retrospective or prospective, greater than 10% lost to follow up; E - If prospective or retrospective, number of children lost to follow up not reported.

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Table S6. Demographic characteristics of participants administered and not administered isoniazid preventive treatment.

Characteristic	Not administered INH preventive treatment	Administered INH preventive treatment
	n, %	n, %
Total individuals evaluated for incidence	5,648	1,020
Total person-years follow-up	12,470	1,997
Median, follow-up time (IQR)	1.8 (1.0 – 3.4)	1.6 (1.0 – 2.9)
Age group, years		
<10	923 (16)	518 (51)
10-19	925 (16)	383 (38)
20-29	1,023 (18)	40 (4)
30 and over	2,777 (49)	79 (8)
Sex		
Male	2,609 (47)	494 (50)
Female	2,972 (53)	497 (50)
Tested with QuantiFERON, T-SPOT, or TST (% tested among all participants)	2,385 (42)	413 (40)

QFT, QuantiFERON. TST, tuberculin skin test. INH, isoniazid. IQR, interquartile range.

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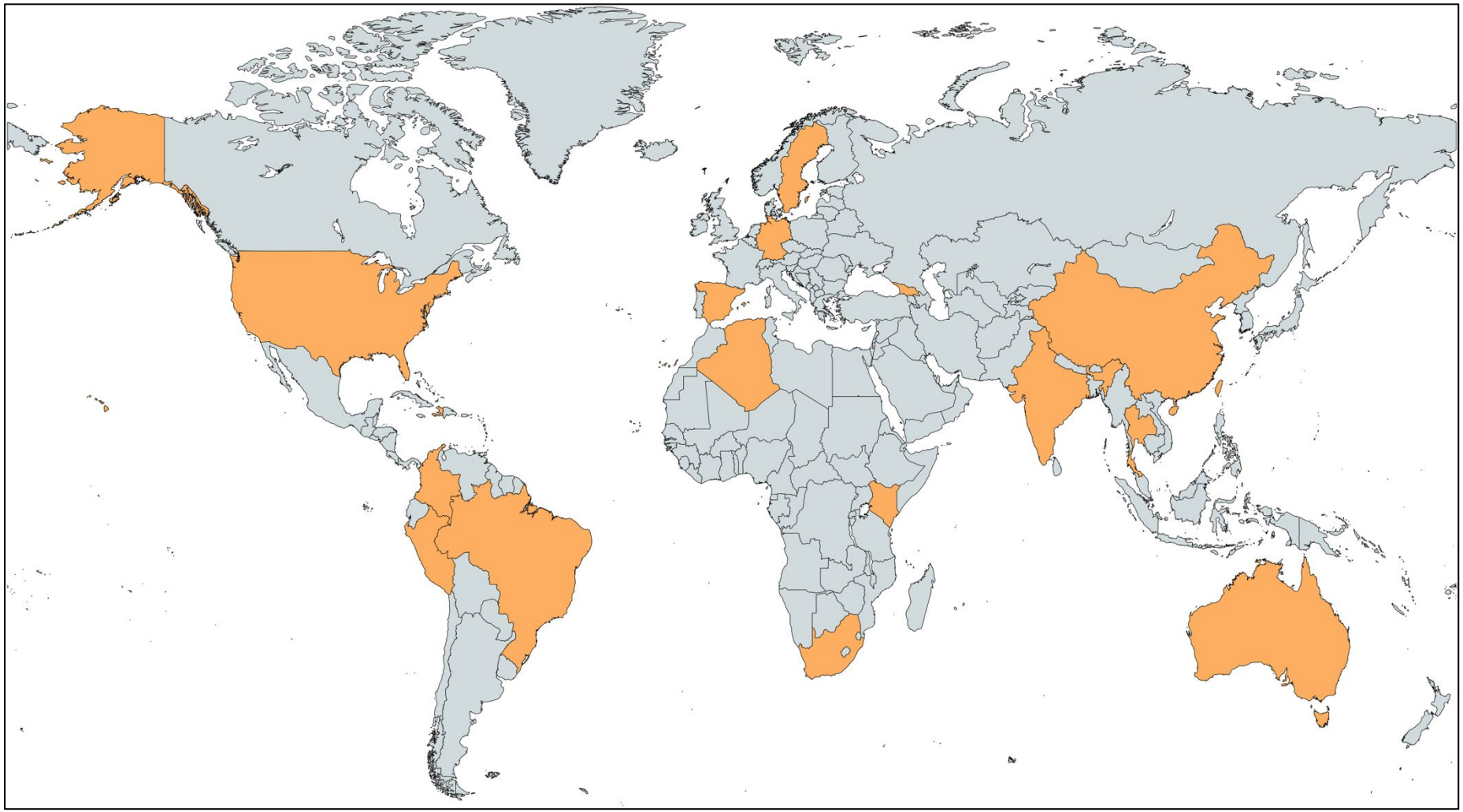
Figure S1. Map of Location of Included Studies.



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