The Risk of Tuberculosis in Children After Close Exposure: An Individual-Participant Meta-analysis Including 137,647 Children from 46 Cohort Studies

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Research in context

Evidence before this study

No contemporary studies have attempted to quantify the risk of developing paediatric tuberculosis after close exposure to a tuberculosis case or recently acquired tuberculosis infection. One narrative review of seven historical studies conducted prior to 1940 exists. This study synthesized results from these historical studies and found that approximately 50% of children <1 year of age with recent infection developed tuberculosis. This risk in children dropped to 10–15% in children 1–2 years of age, 5–6% in children 2–5 years of age, 2% in children 5–10 years of age, and rises to 10% among children >10 years old.

We searched MEDLINE and Google Scholar for articles published prior October 1, 2019. We used the search terms “child”, “tuberculosis”, “transmission”, “household”, “pediatric”, “paediatric”, “contact”, “close”, among others. We also reviewed reference lists, bibliographies, and other narrative reviews on incident tuberculosis for additional relevant articles. We found several contemporary household contact exposure studies that included children but none that focused on children or that included a large sample size. We did not identify estimates of longitudinal risk of tuberculosis in infants and young children with close exposure or recent infection. Due to this knowledge gap, the effectiveness of contact investigations and preventive therapy remains poorly understood.

Added value of this study

Using individual-level data from 46 cohort studies including 137,647 exposed children followed for 429,538 child-years, these results provide the first contemporary estimates of tuberculosis risk in children after close exposure. We found that exposed, TST/IGRA positive children <1

year of age who did not receive preventive therapy had 18% risk of developing disease within two years of enrollment. In contrast to previous estimates suggesting risk falls to 5% in 2–5-year-olds, we found that this age group had 19% two-year cumulative tuberculosis risk. In addition, the effectiveness of preventive therapy to prevent incident tuberculosis was high, 85% among children with tuberculosis infection. Despite this, the majority of children developed tuberculosis within weeks of the initial baseline contact investigation visit.

Implications of all the available evidence

Results from this multi-cohort collaboration indicate that greater focus should be placed on the first five years of life as a period of high risk of progression from tuberculosis infection to disease. The risk of developing tuberculosis among exposed infants and young children was very high, approaching 20% two years after exposure. Despite the effectiveness of preventive therapy, the majority of cases occurred within weeks of contact investigation initiation. While contact tracing is a high yield means for early case detection, many children are reached too late to prevent disease. Earlier diagnosis of adult cases or community-wide screening approaches in children may be needed to improve prevention of tuberculosis in children.

ABSTRACT.

Background.

Tens of millions of children are exposed to *Mycobacterium tuberculosis* globally every year; however, there are no contemporary estimates of the risk of developing tuberculosis in exposed children. The effectiveness of contact investigations and preventive therapy remains poorly understood.

Methods.

We conducted an individual participant data meta-analysis of cohort studies in which children (<19 years of age) with close tuberculosis exposure were investigated for tuberculosis and followed for incident disease. We estimated the odds of prevalent tuberculosis with mixed-effects logistic models, and estimated adjusted hazard ratios (AHR) for incident tuberculosis with mixed-effects Poisson regression models. The effectiveness of preventive therapy against incident tuberculosis was estimated through propensity score matching.

Findings.

We pooled participant-level data from 46 cohort studies in 34 countries. We included 137,647 exposed children followed for 429,538 child-years, during which 1,299 prevalent and 999 incident cases were diagnosed. The two-year risk of developing tuberculosis among infected children not receiving preventive therapy was 19.0% from 0 to 5 years of age. The effectiveness of preventive therapy was 63% (AHR, 0.37, 95% confidence intervals [CI], 0.30–0.47) among all exposed children, and 85% (AHR, 0.15, 95% CI, 0.11–0.20) among those with a positive test of

infection. Among all children <5 years of age who developed tuberculosis, 83% were diagnosed within 90 days of the baseline visit.

Interpretation.

The risk of developing tuberculosis among exposed infants and young children is very high. The majority of cases occurred within weeks of contact investigation initiation and may not be preventable through prophylaxis. This suggests that alternative strategies for prevention, such as earlier initiation of preventive therapy through earlier diagnosis of adult cases or community-wide screening approaches, are needed.

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INTRODUCTION

Tens of millions of children are exposed to *Mycobacterium tuberculosis* every year,[1,2] and tuberculosis remains a leading infectious cause of global childhood morbidity and mortality.[3-5] Historically, pediatric tuberculosis has been largely understudied, and its natural history in children remains poorly understood. Due to this, there is considerable uncertainty regarding the effectiveness of public health strategies for detection and prevention of tuberculosis among exposed children.

The majority of evidence concerning the natural history of tuberculosis in children relies upon studies performed prior to 1950.[6-11] Many changes have occurred in the control of tuberculosis and in the health of populations more broadly, including the introduction of tuberculosis drug chemotherapy, widespread administration of the BCG vaccination, substantial decline of the prevalence of undernutrition in children, and the HIV-epidemic.[12-16] A re-assessment of age-specific risks of tuberculosis and identifying risk factors for disease in exposed children is necessary to inform clinical and policy decision-making. Public health interventions targeting exposed children are urgently needed but remain poorly measured; the population-impact of pediatric case-finding and preventive interventions is currently unknown.

To address these knowledge gaps, we pooled data from longitudinal cohort studies conducted over the past 20 years. We estimated the risk of developing tuberculosis in children after close exposure, stratified by age and individual-level determinants of risk. We also examined how disease risk was impacted by preventive therapy, BCG vaccination, and time since tuberculosis exposure to better understand the role of various public health interventions.

METHODS

Search Strategy and Study Selection

We conducted a systematic review investigating development of tuberculosis in children closely exposed to a tuberculosis case. We registered a protocol with PROSPERO (CRD42018087022) that includes a prespecified analytical plan; this article follows PRISMA for Individual-Patient Data reporting guidelines (Supplementary Appendix).[17]

Our search entailed several steps which are detailed in the appendix. Briefly, we searched for cohort studies from January 1, 1998 to April 6, 2018 in MEDLINE, Web of Science, BIOSIS, and Embase electronic databases. Since incident tuberculosis was our primary study outcome, we restricted our search to cohort studies – case-control studies and outbreak reports were excluded. Search terms included “mycobacterium tuberculosis”, “TB”, “tuberculosis”, and “contact” (full search can be found in the appendix), and articles were unrestricted by language. The 20-year time-frame was chosen based on expected availability of individual-participant data. We additionally reviewed reference lists of other systematic reviews and selected primary or narrative review articles of contact investigations.[18-21] We included data that was unpublished, deposited on data storage repositories, conference abstracts, and dissertations if eligible.

Due to the broad nature of our search terms, we developed a list of exclusionary words (Supplementary Appendix) that ruled out articles if present in manuscript titles. In order to evaluate the accuracy of this process, we implemented the algorithm on a random list of 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. Two

reviewers (LM and OC) independently reviewed articles in two stages: evaluation of titles and abstracts followed by full-text review. At each stage, the two reviewers discussed discrepancies and re-evaluated articles until consensus was reached.

Individual-participant data and a pre-specified list of variables was requested from authors of all eligible studies. These included characteristics of the exposed child, the index case, and environmental characteristics (Supplementary Appendix). To be eligible for inclusion in the final analysis, a dataset needed to include: (1) individuals below 19 years of age; (2) follow-up for tuberculosis for a minimum of six months; (3) individuals with household or close exposure to an individual with tuberculosis; (4) information on the age and sex of the child; (4) provide start and end follow-up dates. Studies assessing incident tuberculosis but without dates or time of follow-up were excluded. All data was appropriately de-identified prior to sharing and, due to this, the project was deemed exempt from further review by Stanford University's institutional review board. Two reviewers (LM, OC) independently assessed quality of each study using a modified rubric of the Newcastle-Ottawa scale.[21] 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 <3 points. Discrepancies between the two reviewers were resolved by re-evaluating the study for consensus. To assess potential selection bias, we compared characteristics of studies that contributed participant-level data to studies that did not.

Study Definitions

Tuberculosis-exposed children were defined as participants <19 years of age with reported ‘close’ contact, either living in the same household or with substantial interaction outside the household, to a microbiologically or radiologically diagnosed tuberculosis case. Exposure and index case diagnoses were defined by the investigators leading each cohort, and we used study definitions among included studies (Supplementary Appendix).

Tuberculosis infection was defined as a positive QuantiFERON-TB Gold In-Tube (QFT) (interferon-γ-nil ≥0.35 IU/mL), T-SPOT.TB (>8 spot forming cells per well), or tuberculin skin test (TST) (≥10-millimeter induration) was used to indicate tuberculosis infection. Preventive therapy was assigned to participants according each study’s protocol or local guidelines and practices. We included any reported preventive therapy regimen in our analysis. A preventive therapy regimen was defined as initiation of any preventive drug regimen given and started to children. Treatment adherence was not assessed in most studies. These regimens included isoniazid for six months, isoniazid for nine months, rifampin for three months, and rifapentine for three months, among others.

Prevalent and incident tuberculosis were defined based on the time from the baseline enrollment of the participant in the contact investigation. Prevalent tuberculosis was defined as any diagnosis of tuberculosis at the initial visit or within 90 days of baseline evaluation based on a conventional definition[19] (further discussion in the Supplementary Appendix). Incident tuberculosis was defined as a new tuberculosis case diagnosed >90 days after the initial evaluation. We utilized each study’s classification of tuberculosis case. Definitions for tuberculosis diagnosis, diagnostic tests, and algorithms used for diagnosis at baseline and follow-up in each study are listed in the Supplementary Appendix.

Statistical Analyses

We pooled individual participant-level data from all included cohorts. Our primary study outcomes were prevalent and incident tuberculosis. We calculated follow-up time from the first baseline visit to development of tuberculosis, loss to follow-up, death, or study completion. Heterogeneity was assessed using the I^2 statistic.

Our analysis had two primary aims: (i) estimating the risk of developing tuberculosis by time-period of follow-up, demographic (age, region) and clinical attributes (HIV, tuberculosis infection status, prior tuberculosis); and (ii) estimating the effectiveness of preventive therapy and BCG vaccination on the risk of developing tuberculosis.

To estimate the 2-year cumulative incidence of tuberculosis, we included only prospective studies to avoid potential biases associated with case ascertainment from retrospective studies. Only children not given preventive therapy are included in this analysis. The cumulative incidence included both prevalent and incident tuberculosis in the first two years of follow-up in these studies. We stratified these results by age and baseline results of tuberculin skin test or interferon gamma release assay.

The analysis of tuberculosis risk factors was performed using separate outcomes measures: prevalent tuberculosis, incident tuberculosis, and cumulative incidence outcome (ie, including both prevalence and incidence together). For the prevalent and cumulative incidence outcomes, we used mixed-effects logistic regression analyses. For the incident tuberculosis outcome, we used mixed-effects Poisson and parametric survival-time models. In incident regression models,

variables were modelled with time fixed effects. For this analysis prospective and retrospective cohort studies were used, both separately and pooled (stratified analysis in the Supplementary Appendix). Each statistical model accounted for clustering at the study-level and was adjusted for the variable of interest, baseline child age and sex, and whether data was collected prospectively or retrospectively.

We estimated tuberculosis prevalence using a mixed-effects logistic regression and tuberculosis incidence through mixed-effects Poisson regression models, with study-level random effects for all analyses. Tuberculosis incidence was stratified by days following study enrollment: 91–365, 366–730, and >730 days. To assess the influence of demographic and clinical factors on tuberculosis risk, we used mixed-effects Poisson and parametric survival-time models with a Weibull distribution. The likelihood ratio test was used to derive *P* values. Because of the large sample size of one study relative to the other included cohort studies, we re-analyzed our risk factor analysis without this study to assess the influence of this study on our results.

When evaluating the protective impact of preventive therapy, we performed a propensity score analysis, matching based on individual-level covariates of age, sex, study design (see the Supplementary Appendix). We then matched children who began preventive therapy with children who did not start using a nearest neighbor matching algorithm. In this matched cohort, we repeated our parametric survival-time models to estimate covariate-adjusted risk of prevalent and incident tuberculosis between groups when examining the protective effectiveness of preventive therapy. We repeated this analysis for children with and without tuberculosis infection. We evaluated several alternative propensity scores using additional variables. The Supplementary Appendix provides additional details about the analytical methodologies used.

We conducted several sensitivity analyses of different thresholds for prevalent and incident tuberculosis. We compared prevalence using the primary analysis cutoff of 90 days from the baseline investigation to other cutoffs including 0, 30, and 60 days.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Description of study population

From our multi-database search, we found 14,927 original titles and reviewed 7,924 abstracts and titles published after January 1, 1998 (Supplementary Figure 1). After title, abstract, and full-text review, 80 study groups were contacted for individual-participant data. In all, study groups from 53 cohorts in 46 studies – 29 (63%) prospective studies and 17 (37%) retrospective – agreed to share their data and were included in the final analysis (Table 1; references listed in Supplementary Appendix). Studies were from geographically diverse settings in 34 countries, and the majority rated as high or moderate quality (Table 1). Microbiological testing was used to diagnose tuberculosis in child contacts in 32 studies (70%). Among studies with household clustering data, we found that the median number of children per household included in the study was 2 (Interquartile Range, 1-4). Characteristics of studies that contributed participant-level data were generally similar to those that were not included (Supplementary Appendix).

Tuberculosis prevalence and incidence among exposed children

Of 137,647 children evaluated at baseline, 1,299 (1%) were diagnosed with prevalent tuberculosis. For the cohort analysis, 130,512 children were followed for 429.538 child-years, including 395,531 years after the 90 day initial evaluation window, leading to 999 incident tuberculosis cases. Baseline TST or interferon gamma release assay (IGRA) results were available for 117,712 children, among whom 34,692 (random-effects prevalence estimate: 34.7%, 95% confidence intervals [CI], 29.6%-40.1%) had positive tests, with prevalence increasing with age (Supplemental Figure 2).

We calculated the risk of prevalent tuberculosis (cases diagnosed within 90 days of enrollment) and incident tuberculosis, among individuals not receiving preventive therapy, over two years of follow up (Figure 1). The risk of tuberculosis over follow-up was highest within 90 days of enrollment (2.9%, 95% CI: 1.7-4.9%). Prevalence was much higher among children with a baseline positive TST/IGRA (6.5% versus 0.8% among children with a negative TST/IGRA at baseline). Incident tuberculosis consistently decreased over time (2.1, 0.7, and 0.3 cases per 100 person-years during follow-up days 91–365, 365–730, and >730, respectively). Among children with a baseline positive TST/IGRA, incidence per 100 person-years was 3.9 at 91–365 days, 1.2 at 366–730 days, and 1.1 at >730 days from baseline. Among children with a baseline negative TST/IGRA, incidence over these same intervals was 1.1, 0.5, and <0.1 cases per 100 person-years (Figure 2).

Among all children who developed tuberculosis, 61% were diagnosed in the first 90 days of screening (Figure 2a). This number increased to 82% among children with a baseline positive TST/IGRA. Among children <5 years of age that developed tuberculosis, 83% were diagnosed within 90 days; among these young children with a positive TST/IGRA, 96% were diagnosed within 90 days (Figure 2b). The proportion of children that developed tuberculosis in the first 90 days of screening was much higher for children <5 years of age compared to children 5–18 years of age (Figure 2b and 2c).

The two-year cumulative risk of developing tuberculosis among children not receiving preventive therapy varied substantially by age and infection status. Among all children not on preventive therapy, the 2-year cumulative risk was U-shaped by age (Figure 3c), ranging from 7.6% in children under 5 years of age, decreasing to 5.2% in children 5-9 (P=0.0027 compared to <5

year old children), 5.6% in children 10-14 years old (*P*=0.0145 compared to <5 year old children), followed by a subsequent increase in risk to 6.7% among children >15 years old *P*=0.3491 compared to <5 year old children). Children with a negative baseline TST/IGRA had a similar U-shaped curve, but slightly lower rates (Figure 3b). Children with positive baseline TST/IGRAs had significantly higher 2-year cumulative tuberculosis incidence (Figure 3a), greatest among children <5 years of age (19.0%; 95% CI, 8.4-37.4%) (Supplementary Table 2). The cumulative risk among children <5 years old with positive baseline TST/IGRAs was statistically higher when compared to 5–9 year old TST/IGRA positive children (*P*<0.0001), 10–14 year old TST/IGRA positive children (*P*<0.0001), and 15–18 year old TST/IGRA positive children (*P*=0.0006). Among children <5 years of age with a positive baseline TST/IGRA, the 2-year cumulative tuberculosis incidence was relatively consistent in one-year age bins ranging from 16% to 22%.

Children living with HIV had higher risk of prevalent (Adjusted Odds Ratio [AOR], 2.80, 95% CI, 1.62–4.85) and incident (Adjusted Hazard Ratio [AHR], 5.31, 95% CI, 2.39–11.81) disease (Table 2). Children with a previous tuberculosis episode were more likely to be diagnosed with tuberculosis at baseline (AOR, 6.58, 95% CI, 4.40–9.84) and during follow up (AHR, 3.20, 95% CI, 2.22–4.51). There was substantial between-study heterogeneity in prevalent and incident tuberculosis, with differences by study design and region (Figure 4).

Prevalent and incident tuberculosis rates changed substantially based on the cutoff threshold used (Supplementary Appendix). Among all children, for cutoff thresholds from baseline of 0, 30, and 60 days from baseline, prevalence rates were 0.4% (95% CI, 0.2–1.2%), 1.2% (95% CI, 0.4–3.5%), and 1.7% (95% CI, 0.7–4.3) (Supplementary Table S5). Among children with a

positive TST/IGRA, for cutoff thresholds from baseline of 0, 30, and 60 days from baseline, prevalence rates were 0.9% (95% CI, 0.2–3.7%), 3.8% (95% CI, 1.6–9.1%), and 4.6% (95% CI, 1.8–10.8) (Supplementary Table S5).

Protective Effectiveness of Preventive Therapy and BCG Vaccination

Children given preventive therapy were at substantially lower risk of developing tuberculosis compared to those who were not, and this effect was modified by infection status. The effectiveness of preventive therapy was 63% (AHR, 0.37, 95% CI, 0.30–0.47) among all exposed children. The effectiveness was greater in children with baseline infection (AHR, 0.09, 95% CI, 0.05–0.15), and a strong but nonsignificant relation in children without baseline infection (AHR, 0.66, 95% CI, 0.40–1.10). This analysis was reasonably robust to alternative statistical models without use of propensity score matching and alternative propensity scores (Supplementary Appendix). Additionally, the effect of preventive therapy in drug for incident tuberculosis was present in contacts of drug-susceptible (AHR, 0.33, 95% CI, 0.20–0.54) and drug-resistant (AHR, 0.44, 95% CI, 0.21–0.93) tuberculosis index cases ($P_{interaction}$=0.454).

In children <5 years old, BCG vaccination was protective against all forms of tuberculosis (AOR, 0.64, 95% CI, 0.50, 0.84). However, among children five years and above, those receiving a BCG vaccination had similar risk of tuberculosis compared to those that did not (Table 2).

Study Heterogeneity

There was between-study heterogeneity in prevalent and incident tuberculosis. Prevalent tuberculosis ranged from 0–15% (Figure 4a). The rate of incident tuberculosis per 100 person-years ranged from 0–3.3% (Figure 4b). Much of the heterogeneity for both prevalent and incident tuberculosis was due to the global region of the study and the prospective/retrospective nature of data collection (Figure 4a and Figure 4b).

Compared to studies in the African region, studies demonstrated substantially lower rates of prevalent tuberculosis in the Americas Region (AOR, 0.48, 95% CI, 0.21–1.12) and the Western Pacific Region (AOR, O.10, 95% CI, 0.04–0.23). Incident tuberculosis was also lower in the Western Pacific Region versus the African Region (AHR, 0.16, 95% CI, 0.07–0.35). Prospective studies identified more prevalent (AOR 3.26, 95% CI, 1.49–7.12) and incident tuberculosis (AHR 3.12, 95% CI, 1.65–5.90) (Table 2).

The region and design of studies were correlated; all studies from the African Region were prospective and all but one study in the Western Pacific Region[22] were retrospective. Therefore, we were unable to evaluate whether between-study heterogeneity was due to regional epidemiological differences, prospective or retrospective study design, or a combination of both.

DISCUSSION

Using individual-level data from 137,647 exposed children followed for 429,538 child-years, we found that the two-year cumulative risk of tuberculosis in children is very high, approaching 20% in tuberculosis-infected children under the age of 5. Preventive therapy was 63% effective among all children, and 91% effective among those with a positive TST/IGRA. However, we also found that nearly two-thirds of all pediatric tuberculosis cases, and >80% of cases among young children, were diagnosed within 90 days of contact investigation initiation, suggesting a large proportion of cases may not be avoided by preventive therapy. As over 15 million children are exposed to tuberculosis globally every year,[1-2] these estimates indicate that many exposed children, especially those with recent infection, are at substantial risk of developing tuberculosis and must be prioritized by development of new prevention and early case finding strategies.

These results provide the first contemporary estimates of tuberculosis risk in children after close exposure. Historical studies on children performed prior to 1950 were recently synthesized.[6,7] These historical studies suggested that the risk of tuberculosis after recent infection was between 30–50% in early infancy.[8-11] We found that exposed, TST/IGRA positive children <1 year of age who did not receive preventive therapy had 18% risk of developing disease within two years of enrollment. In contrast to previous estimates suggesting risk falls to 5% in 2–5-year-olds,[6,7] we found that this age group had 19% two-year cumulative tuberculosis risk. Additionally, although our results indicate that young children have the highest risk of developing tuberculosis, adolescents also face an increasing risk following childhood.[23,24]

We believe these findings have several important clinical and public health implications. First, we found marked protection of preventive therapy against incident tuberculosis. Protection was greatest among children with a positive TST/IGRA (91%), but there was a relationship among all children. Among children with a negative TST/IGRA, there was a 44% protective effect however this association was not statistically significant (95% CI, -10–60%). A meta-analysis of seven trials including 10,320 children (8,537 recruited prior to 1975) found that efficacy was 59% among children over 4 months of age, comparable to our overall estimate of 63%, but lacked analyses stratified by infection status.[25] Second, we found that 61% of all tuberculosis cases in children were diagnosed within 90 days of initial screening, and thus are not targetable by preventive therapy. This number increased to 82% and 83% in children with tuberculosis infection and below 5 years of age, suggesting the importance of early case-finding. While preventive therapy and contact tracing are effective and have value in averting disease among children,[3] most children are reached too late to prevent disease. Although cost-effectiveness analyses and implementation barriers should be assessed, earlier diagnosis of adult cases or community-wide screening approaches in children may be needed to improve prevention of tuberculosis in children.[26] Third, we provide robust estimates of tuberculosis risk in children living with HIV infection or with a prior tuberculosis diagnosis. These children should be prioritized for prevention interventions and monitoring for development of disease. Fourth, there has been concern that IGRAs may perform poorly in young children; however, recent studies have found good performance in infants <2 years of age.[27,28] Our study confirms these results in all children, finding that a child <19 years of age with a positive IGRA test has 6–7 times higher risk of incident tuberculosis than a child with a negative IGRA test.

The results of our analyses should be understood within the context of the limitations of the observational data from the multiple cohorts included in this study. First, there was heterogeneity in the definition of close exposure and tuberculosis diagnosis across studies. Diagnosis of tuberculosis in children is inherently challenging,[3,27,29] as available diagnostics lack sensitivity, particularly among young children. As a result, experts typically recommend using composite definitions for diagnosis.[29] Most studies included in this analysis used composite definitions that included microbiological testing as part of the diagnostic criteria. Due to poor ascertainment of pediatric tuberculosis during passive case finding, we limited our analysis of the tuberculosis incidence to prospective cohort studies. When assessing the effectiveness of preventive therapy, confounding by indication may occur if therapy was given to the children at higher or lower tuberculosis risk. We used propensity score matching to account for covariates predicting receipt of preventive therapy. However, residual confounding is possible and could bias these efficacy estimates in either direction. We also did not have dates of preventive therapy initiation. Additionally, TST/IGRAs may be used in the case definition for tuberculosis, potentially leading to diagnostic bias. These factors may partially explain the high proportion of tuberculosis cases diagnosed within 90 days. We defined prevalent tuberculosis as cases diagnosed within 90 days of enrollment, to account for diagnostic delays inherent in establishing a tuberculosis diagnosis in children; we examined multiple other thresholds (0, 30, 60 days) in sensitivity analyses and found an increased prevalence between 0 and 90 days of age which may reflect rapid development of incident cases.

In summary, this study represents a combined analysis of data from 46 cohort studies in 34 countries, representing diverse sociodemographic and epidemiological settings. These results identify key age and risk-factor specific groups of children that can be prioritized by tuberculosis

control programs and find that while preventive therapy is highly effective for the individual child, this strategy can only be targeted to a minority of children and must be used as a supplementary intervention with intensified case-finding efforts to address the global burden of pediatric tuberculosis.

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All authors contributed to the acquisition of the work. Leonardo Martinez and Olivia Cords conducted the systematic search, screened and identified studies, and made final decisions regarding study inclusion. Leonardo Martinez, Olivia Cords, Sanjay Basu, and Jason Andrews designed the analyses. Leonardo Martinez received and checked data, conducted analyses, and had full access to all materials and results. Jason Andrews conducted analyses and created figures. Olivia conducted analyses and helped create tables and figures. Leonardo Martinez, Olivia Cords, Jason R. Andrews wrote the first draft of the report. All writing committee members helped revise the drafted version before and after circulation to collaborators. All 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.

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Tables and Figures.

Table 1. Demographic Descriptions of Included Cohort Studies.

Table 2. Risk Factors for Tuberculosis Amongst Children Less Than 19 Years of Age.

Figure 1. Risk of Tuberculosis Over Time Among Exposed Children Not Receiving Preventive Therapy.

Figure 2. Proportion of All Tuberculosis Cases Found Over Follow-up Time.

Figure 3. Two-year Cumulative Incidence of Tuberculosis in Children Not on Preventive Therapy, Stratified by Infected, Uninfected, and All Children.

Figure 4. Study-specific Prevalent (a) and Incident (b) Tuberculosis in Children, Stratified by the Study Design and Region.

892 Table 1. Demographic Descriptions of Included Cohort Studies.

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Characteristic	Number of Studies (N=46)	Percentage
Prospective Study Design	28	61
World Health Organization High-burden†	18	39
Tuberculosis Incidence Burden of Country, per 100 thousand persons‡		
<50	16	36
50–100	9	19
>100–200	9	19
>200	12	23
World Health Organization Region		
African	9	20
Americas	16	33
Eastern Mediterranean	1	2
European	7	15
Southeast Asia	4	9
Western Pacific	9	20
Income Group§		
High	14	30
Upper-middle	18	39
Lower-middle	8	17
Low	6	13

HIV Status of Child Reported	23	49
Study Quality Assessment		
High	33	72
Moderate	11	24
Low	2	4
Mean Duration of Study Follow-up		
<2 years	24	56
2–4 years	13	28
5–7 years	3	11
>7 years	3	7
Cohort size		
<1000	20	43
1000-5000	14	30
>5000	12	26
Exposed to Drug Resistant Index Cases		
Only Drug-Resistant Index Cases	3	6
Both Drug-Resistant and Susceptible Index Cases	12	26
Only Drug-Susceptible Index Cases	2	4
Preventive Therapy included*	32	70
QuantiFERON or Tuberculin Skin Testing	38	78
Total		
Persons-years	429,538	…
Total Individuals Evaluated for Prevalence	137,647	…
Total Individuals Evaluated for Incidence	130,512	…

Median age (IQR)	10.5 (5.7, 15.2)	…
Mean age (SD)	10.3 (5.4)	…

Abbreviations: HIV, human immunodeficiency virus. BCG, bacillus Calmette–Guérin.

Percentages may not total 100% because within-column percentages were rounded to the nearest integer.

† Studies were designated as being located in a “high-burden” country as classified by the World Health Organization.

‡ Country-level tuberculosis incidence data was collected from World Health Organization databases for each study.

§ Studies were 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.

* This refers to preventive therapy being given to some participants and includes any type of preventive therapy regimen.

907 Table 2. Risk Factors for Tuberculosis Amongst Children Less than 19 Years of Age.

Characteristic	Coprevalent Tuberculosis, Adjusted Odds Ratio (95% CI)	Incident Tuberculosis, Adjusted Hazard Ratio (95% CI)	All Tuberculosis, Adjusted Odds Ratio (95% CI)
All Studies (N = 137,647)			
Male Sex	1.05 (0.96, 1.13)	0.99 (0.88, 1.13)	1.03 (0.94, 1.12)
Tuberculosis Infection‡			
Tuberculin Skin Test Induration ≥10 mm	18.30 (14.87, 22.52)	3.34 (2.86, 3.89)	7.05 (6.27, 7.94)
QuantiFERON Gold In-Tube Test, ≥0.35 IU/mL	21.90 (8.41, 57.06)	6.47 (2.21, 18.90)	14.26 (6.94, 29.28)
ELISPOT, >8 spot-forming cells*	7.77 (1.69, 35.63)	1.91 (0.64, 5.70)	3.06 (6.94, 29.28)
HIV infection	2.80 (1.62, 4.85)	5.31 (2.39, 11.81)	3.55 (2.20, 5.74)
Prior Tuberculosis Event	6.58 (4.40, 9.84)	3.20 (2.22, 4.51)	5.30 (3.99, 7.06)
Preventive Drug Therapy Regimen†			
All children	…	0.37 (0.30, 0.47)	…
TST+ or IGRA+	…	0.15 (0.11, 0.20)	…
TST+ or IGRA+, Propensity-Score Matched	…	0.09 (0.05, 0.15)	…
TST- or IGRA-	…	0.65 (0.40, 1.06)	…

TST- or IGRA-, Propensity-Score Matched	…	0.66 (0.40, 1.10)	…
BCG vaccination			
5–18 years of age	0.96 (0.70, 1.31)	0.91 (0.70, 1.18)	0.90 (0.73, 1.10)
<5 years of age	0.62 (0.45, 0.85)	0.71 (0.46, 1.08)	0.64 (0.50, 0.84)
Prospective (versus Retrospective) Data Collection	3.00 (1.45, 6.21)	3.42 (1.83, 6.42)	2.38 (1.38, 4.13)

908 Abbreviations: TST, Tuberculin Skin Test. IGRA, Interferon Gamma Release Assay. CI, confidence interval. HIV, human
909 immunodeficiency virus. BCG, bacillus Calmette–Guérin.
910 Both prospective and retrospective studies are included in this analysis. This analysis was repeated with stratification of the
911 prospective/retrospective nature of the data collection; this stratified analysis can be seen in the Supplementary Appendix.
912 Each row represents a distinct statistical model. Each statistical model is adjusted for the variable of interest, baseline child age
913 and sex, whether data was collected prospectively or retrospectively, and the study. The referent group for each row is the
914 opposing value of the listed characteristic. For example, for HIV infection the reference group is children living without HIV. This
915 includes sub-characteristics of variables. For example, the referent group for the sub-characteristic ‘Tuberculin Skin Test
916 Induration ≥10 mm’ under the variable ‘Tuberculosis Infection’ is participants with a ‘Tuberculin Skin Test Induration <10 mm’.
917 Measures of association are reported with 95% confidence intervals for all outcomes. Odds ratios are reported for “All
918 Tuberculosis” which includes both prevalent and incident tuberculosis as one outcome. Prevalent tuberculosis was defined as any
919 diagnosed disease before 90 days from the baseline evaluation. Incident tuberculosis was defined as diagnosed tuberculosis at or

after 90 days from the initial contact investigation visit. In this case, contacts with prevalent tuberculosis are not given or protected by preventive therapy.

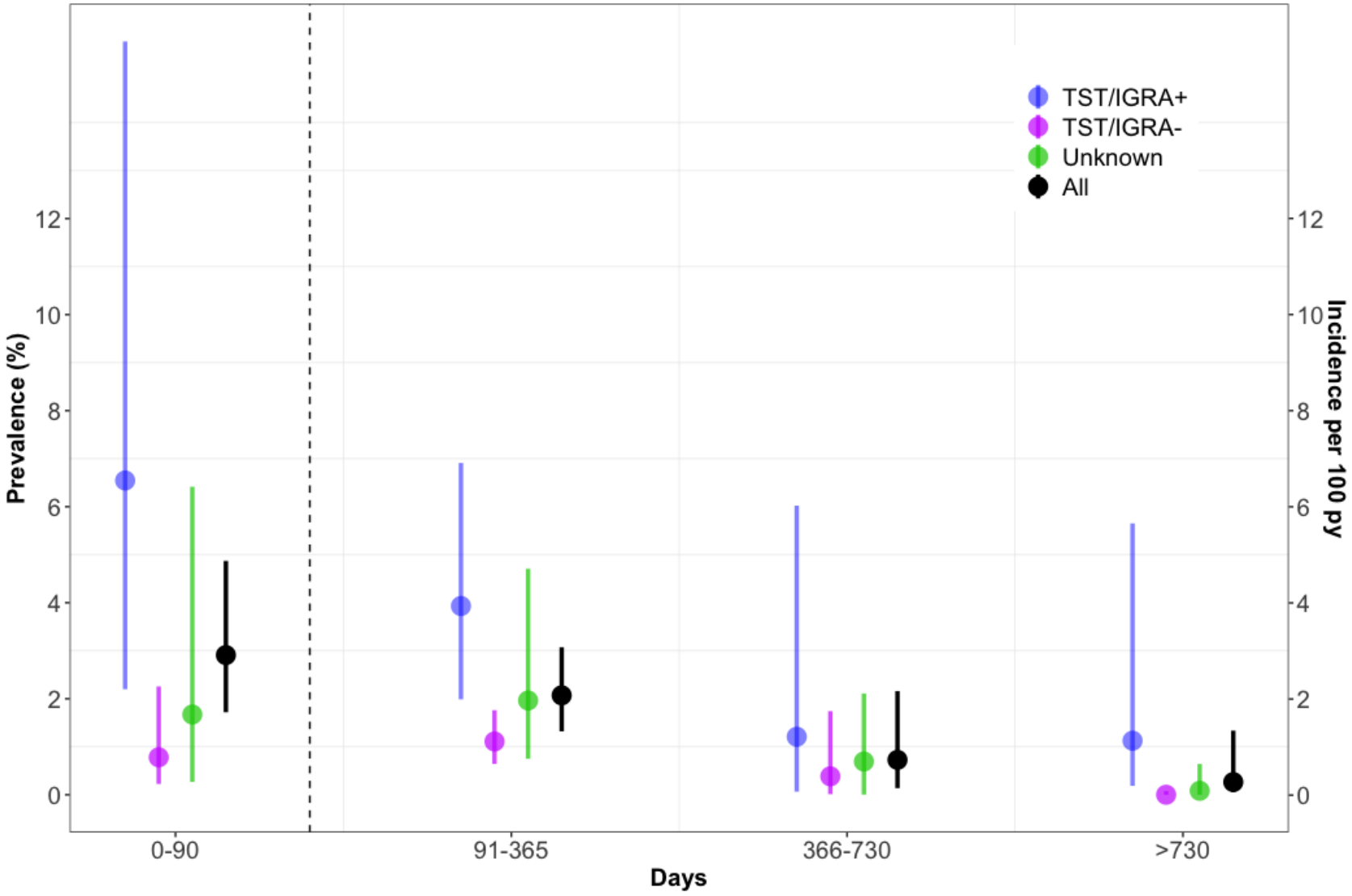
‡ All tests for tuberculosis infection (tuberculin skin test, QuantiFERON Gold In-Tube test, and ELISpot tests) were administered at baseline. TST/IGRAs may be used in the case definition for tuberculosis, potentially leading to diagnostic bias. Odds Ratios for tests of tuberculosis infection may be understood as “Diagnostic Odds Ratios”.

*Administration of preventive therapy, including any type of preventive therapy regimen.

** Propensity score matching is based on the age and sex of the contact and whether the study design is prospective or retrospective.

† A preventive drug therapy regimen was defined as iniitation of any regimen given and started to children at the baseline visit. These included isoniazid for six months, isoniazid for nine months, rifampin for three months, and rifapentine for three months. Preventive therapy was administered to children at the discretion of each study site and we accepted each study’s decision to administer preventive therapy. Completion of preventive therapy was not reported for almost all studies.

Figure 1. Risk of Developing Tuberculosis Over Time Among Exposed Children Not Receiving Preventive Therapy.

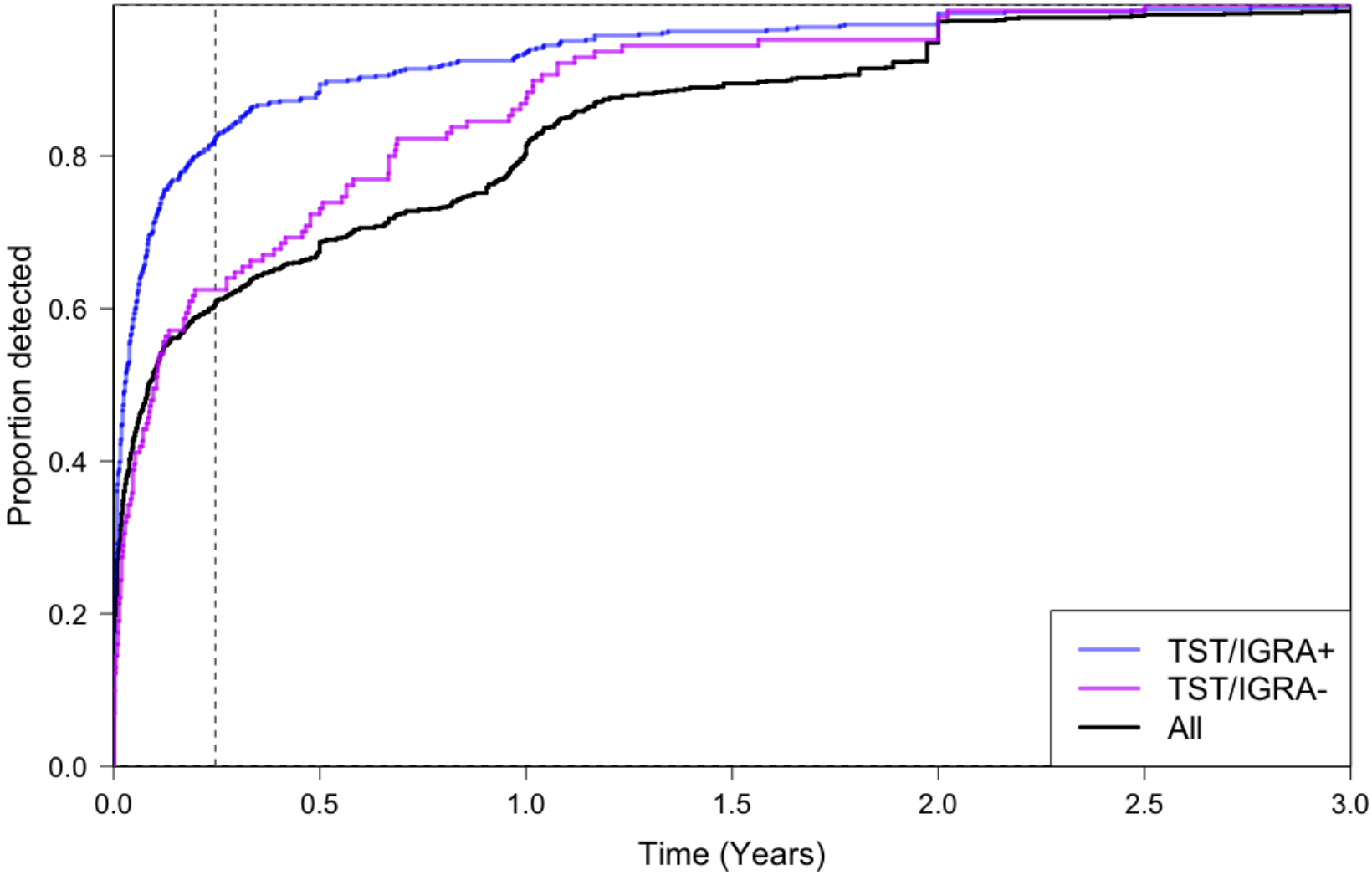


Abbreviations. py, person-years. TST, Tuberculin Skin Test. IGRA, Interferon Gamma Release Assay.

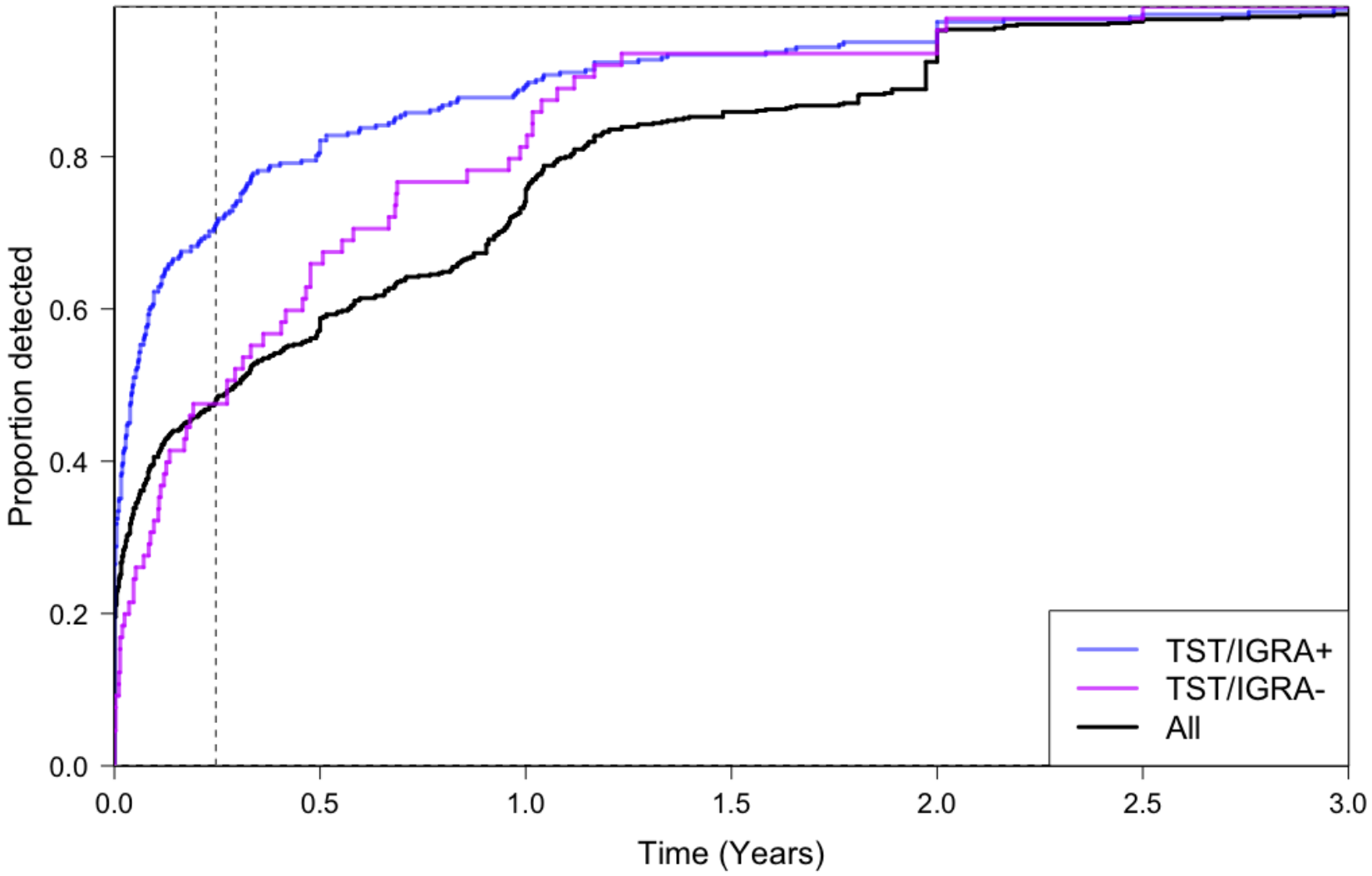
Only prospective studies are included in this analysis. Only children who did not receive preventive chemotherapy were included. The dotted vertical line represents 90 days. Circles represent mean estimates and bars represent 95% confidence intervals for each estimate. Bars may not be visible for some estimates at '>730 days' because the confidence intervals are narrow. Tuberculosis prevalence and incidence are measured on distinct left and right y-axes on the left and right of the Figure. Shown are tuberculosis prevalence within 90 days of enrollment (left y-axis) and subsequent tuberculosis incidence over various intervals (right y-axis), stratified by baseline tuberculin skin test (TST) or interferon gamma release assay (IGRA) status. A positive tuberculin skin test was defined as an induration ≥10 mm, and a positive IGRA result was defined as a positive QuantiFERON-TB Gold In-Tube (QFT) (interferon-γ - nil ≥0.35 IU/mL), or TB-Spot (>8 spot forming cells per well).

Figure 2. Proportion of All Tuberculosis Cases Diagnosed Over Follow-up Time.

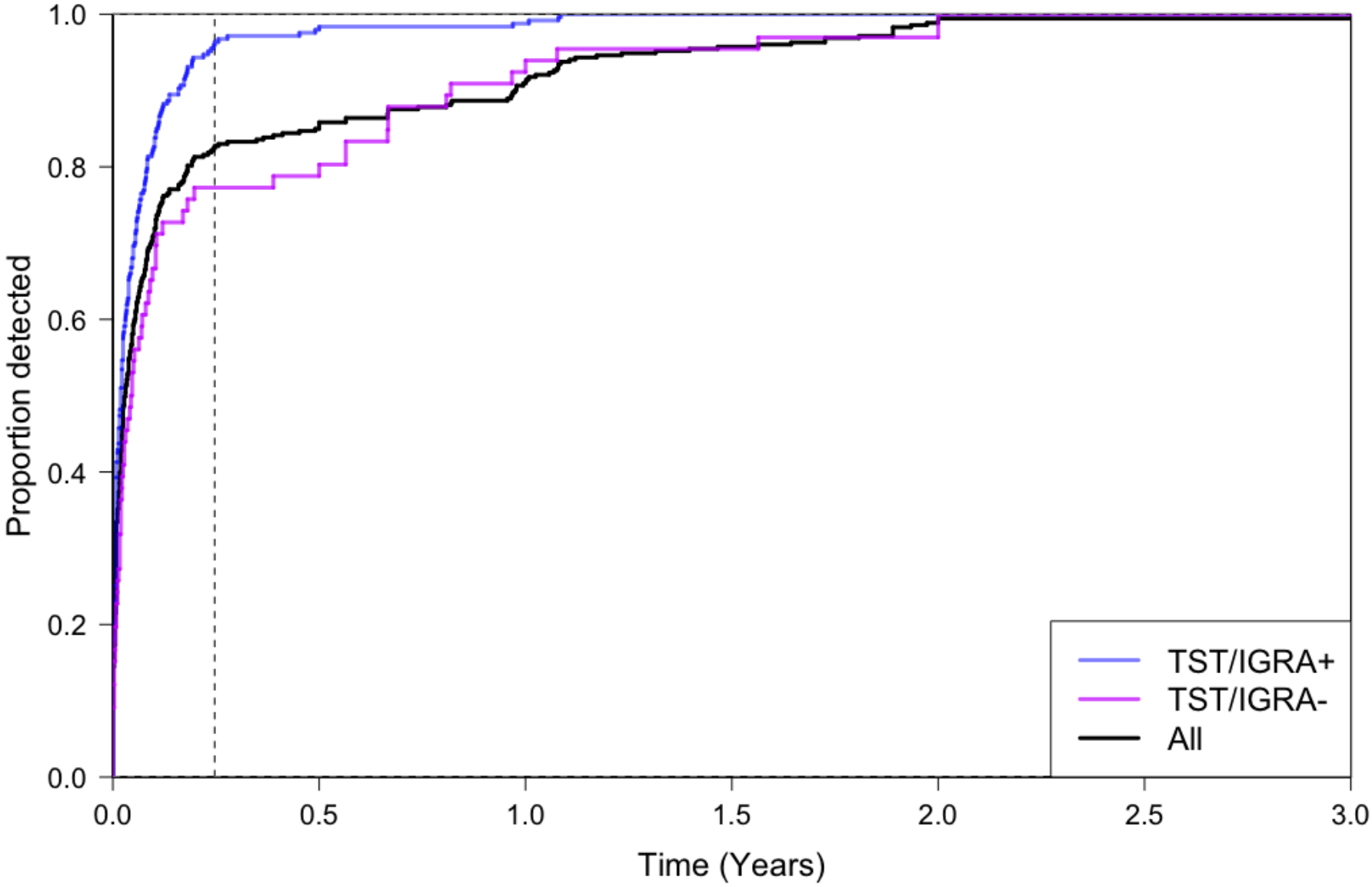
(a) All Children



(b) Children 5–18 Years of Age.

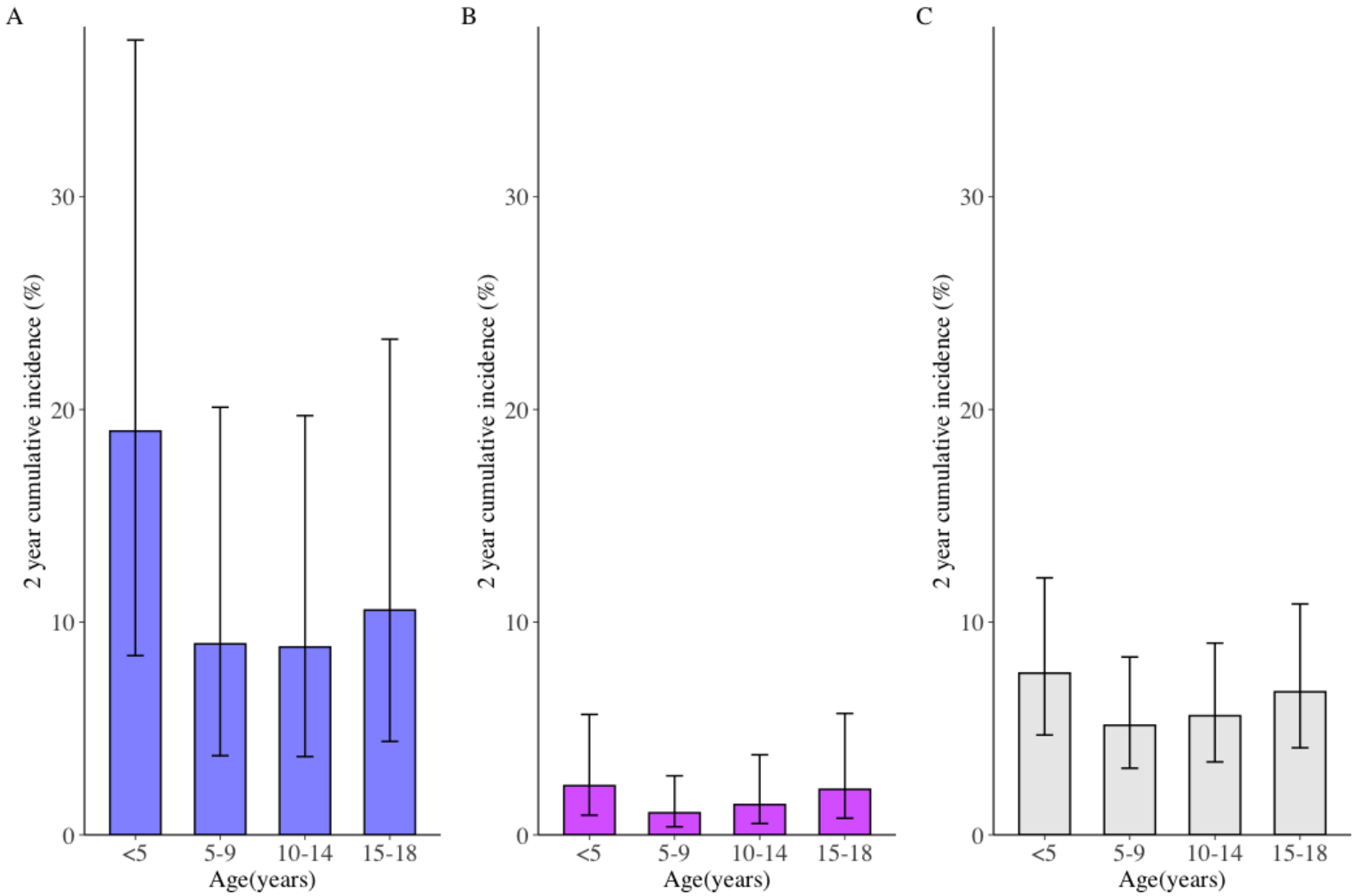


(c) Children <5 Years of Age.



Abbreviations. py, person-years. TST, Tuberculin Skin Test. IGRA, Interferon Gamma Release Assay.
Only prospective studies are included in this analysis. Only children who did not receive preventive chemotherapy were included. The ‘All’ group represents all participants regardless of TST and/or IGRA testing, which is a much larger group of children than those with TST/IGRA+ or TST/IGRA-; the detection proportion for ‘all children’ therefore does not appear as a weighted average between those two groups.
A positive tuberculin skin test was defined as an induration ≥10 mm, and a positive IGRA result was defined as a positive QuantiFERON-TB Gold In-Tube (QFT) (interferon-γ - nil ≥0.35 IU/mL), or TB-Spot (>8 spot forming cells per well). Dotted vertical line represents 90 days in both Figure 2a, 2b, and 2c.

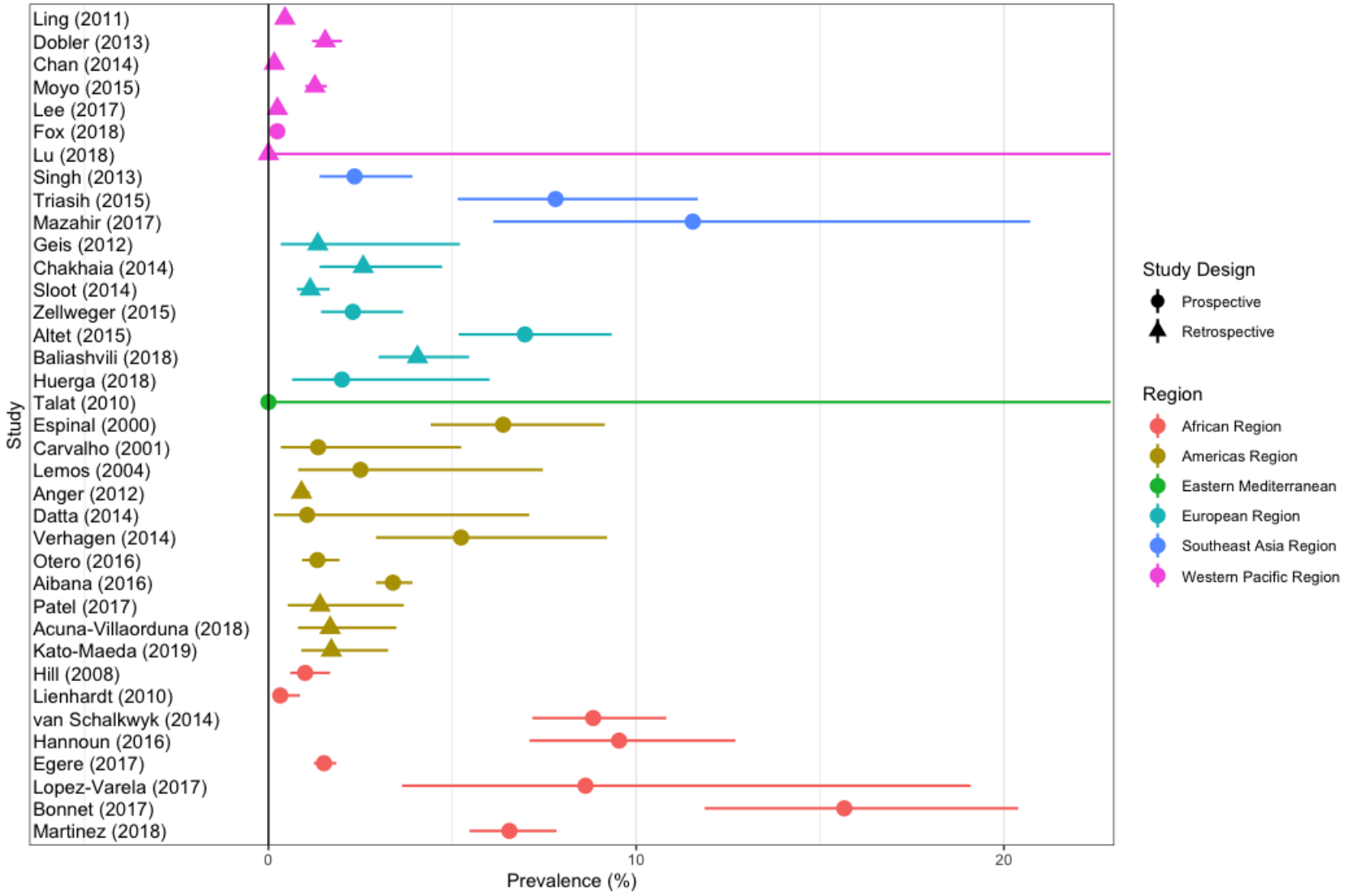
Figure 3. Two-year Cumulative Incidence of Tuberculosis Development in Children Not on Preventive Therapy, Stratified by Age and Infected (left), Uninfected (middle), and All (right) Children.



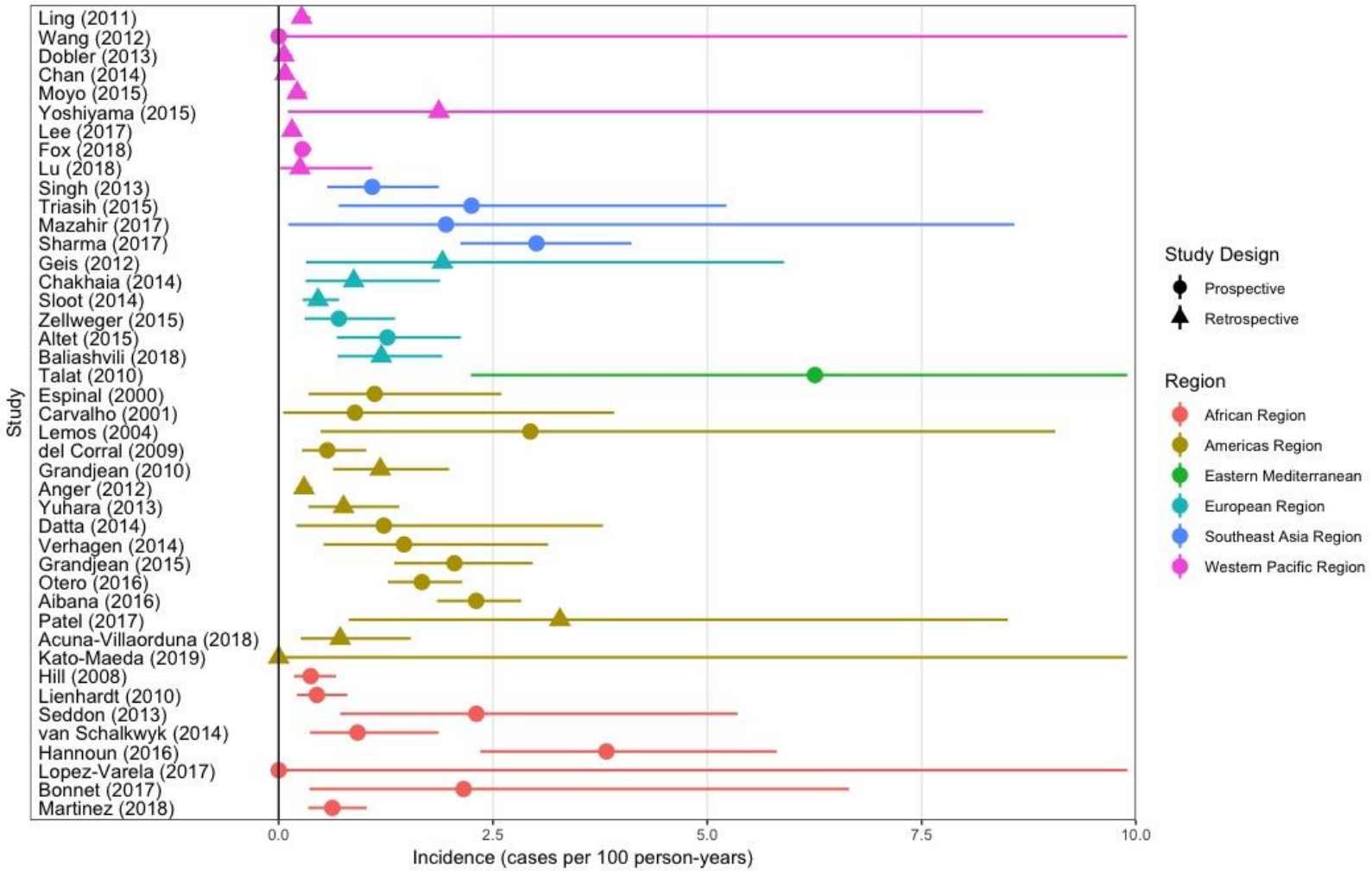
Abbreviations. py, person-years. TST, Tuberculin Skin Test. IGRA, Interferon Gamma Release Assay.
The two-year cumulative incidence of tuberculosis includes prevalent and incident tuberculosis in the first two years of follow-up from prospective cohort studies, stratified by age and baseline results of tuberculin skin test or interferon gamma release assay. Only children not given preventive therapy are included in this analysis. Panel A includes only children with tuberculosis infection. Panel B includes only children without tuberculosis infection. Panel C includes all children, including those not tested for tuberculosis infection. A positive infection was determined by one of the following criteria: a tuberculin skin test induration ≥10 mm, a QuantiFERON-TB Gold In-Tube (QFT) (interferon-γ - nil ≥0.35 IU/mL), or a positive TB-Spot (>8 spot forming cells per well). Bars represent mean estimates and lines represent 95% confidence intervals. The two-year cumulative incidence of tuberculosis for children with tuberculosis infection was consistent within each age group bin. For example, the two-year cumulative incidence of tuberculosis was 19% for infected children <5 years of age and ranged from 17% to 21%. Risk of tuberculosis for one-age year bins can be seen in the Supplementary Appendix. In Panel A, the cumulative risk among children <5 years old with positive baseline TST/IGRAs was statistically higher when compared to 5–9 year old TST/IGRA positive children (P<0.0001), 10–14 year old TST/IGRA positive children (P<0.0001), and 15–18 year old TST/IGRA positive children (P=0.0006). In Panel B, the cumulative risk among children <5 years old with negative baseline TST/IGRAs was statistically higher when compared to 5–9 year old TST/IGRA negative children (P=0.0189), but not compared to 10–14 year old TST/IGRA negative children (P=0.1576) or 15–18 year old TST/IGRA positive children (P=0.8335). In Panel C, the cumulative risk among all children <5 years old with positive baseline TST/IGRAs was statistically higher when compared to 5–9 year old TST/IGRA positive children (P=0.0027) and 10–14 year old TST/IGRA positive children (P=0.0145), but not compared to 15–18 year old TST/IGRA positive children (P=0.3491).

Figure 4. Study-specific Prevalent (a) and Incident (b) Tuberculosis in Children, Stratified by the Study Design and Region.

(a) Tuberculosis Prevalence



(b) Tuberculosis Incidence



All children were included in Figure 4a and 4b

Supplementary Appendix.

Supplement to: The Risk of Tuberculosis in Children After Close Exposure: The Risk of Tuberculosis in Children After Close Exposure: An Individual-Participant Meta-analysis Including 137,647 Children from 46 Cohort Studies

Table of Contents.

1. Additional Methodological Information.

Event Ascertainment

Events were ascertained using several strategies selected by each cohort's investigator group. For tuberculosis diagnosis events, cohorts either diagnosed children 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. The full diagnostic algorithms and tests used for each study can be seen in the supplementary appendix. 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.

Definition

Children were defined as included participants <19 years of age.

Systematic Search.

Case-control studies and outbreak reports were excluded, as were reviews, editorials, letters, or studies for which individual outcomes were not reported. Our search did not include child-specific terminology because many studies do not focus on children but include them as a sub-sample within their cohort. 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 (LM and OC) 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. One study was found through an online database (Aibana, 2016).

Reviewers.

LM is a postdoctoral researcher with experience conducting meta-analyses. OC is a graduate research assistant at Stanford University with research experience and training on meta-analytic methodology.

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.

Individual- and Study-level characteristics.
We collected individual-level characteristics of the contact such as age, sex and follow-up time from all studies. We also collected other characteristics if available including HIV status, diabetes status, body mass index, preventive therapy, BCG vaccination status, past active tuberculosis and others (fully detailed in Supplementary Table S13). Initially, we requested data on children <18 years of age however we changed this age range to <19 years of age post-hoc of the protocol.

We also requested index case characteristics if available including age, sex, HIV status, smoking status, education level and others (fully detailed in Supplementary Table S13). We included radiologically diagnosed index cases to allow for investigators to decide how they diagnosed tuberculosis index cases. Although less infectious than smear-positive tuberculosis, smear-negative tuberculosis cases do transmit disease (Behr et al, The Lancet, 1999; Tostmann, Clinical Infectious Diseases, 2008).

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.

Cutoff Used for Prevalent and Incident Tuberculosis.
We chose a 3-month cutoff to distinguish prevalent and incident tuberculosis. This cutoff is considered the standard cutoff used by most researchers, including in a meta-analysis of contact tracing studies (Fox, European Respiratory Journal, 2013). Participants with early, subclinical tuberculosis may not be immediately picked up by certain diagnostic algorithms (e.g., sputum tests for contacts with tuberculosis-related signs or symptoms). A 3-month cutoff has been used in most contact tracing studies (Martinez, *Lanc Resp Med*, 2018; Martinez, *Am J Resp Care Med*, 2018; Guwatudde, *American Journal of Epidemiology*, 2002). This 3-month cutoff from the baseline visit has also been used in population-based studies (Winje et al, *Thorax*, 2018; Hermanson, *Thorax*, 2016)

Despite this, other cutoffs have been used including at baseline (Aibana, *PloS One*, 2016). Due to this, we have varied the cutoff used to distinguish prevalent and incident tuberculosis and assessed the prevalence of tuberculosis in each cutoff used (0, 30, 60, and 90 days from baseline). This can be seen in the Supplementary Tables.

Analytical code
All statistical analyses were conducted using Stata, version 14.0 (StataCorp LP, College Station, Texas) and R statistical software (R Foundation for Statistical Computing). The analytical code and data requests can be made to the corresponding author.

Statistical Analysis
We chose a Weibull distribution because a restriction made by the Exponential distribution is that the hazard (ie, tuberculosis in our case) is not constant over time. For tuberculosis, hazard rates are changing over time (likely decreasing in a case-contact study). If the hazard is changing steadily over time, the exponential model would not be ideal.

There were three deviations from the initial PROSPERO protocol. These included: (i) a change of ages included from <18 to <19 years of age; (ii) including a comparison of traditional meta-analyses and a one-stage individual participant meta-analyses; and (iii) conducting an exclusionary word algorithm to inspect eligibility of articles.

2. Additional Results.

Risk Factors for Prevalent and Incident Tuberculosis

Children with positive tests for tuberculosis infection were much more likely to be diagnosed with prevalent tuberculosis at baseline. Children were more than 15 times as likely to have prevalent tuberculosis if they were TST positive (AOR, 18.89, 95% CI, 15.29–23.33) or QuantiFERON positive (AOR, 22.82, 95% CI, 8.76–59.43). Among children with a positive ELISpot test, the odds of prevalent tuberculosis were lower but still statistically significant (AOR, 5.39, 95% CI, 1.14–25.54). The risk of incident tuberculosis was also statistically elevated for children with positive QuantiFERON, ELISPOT, and TSTs. The hazard of incident tuberculosis was 3.36 (95% CI, 2.88, 3.93), 6.05 (95% CI, 2.11–17.35), and 2.31 (95% CI, 0.73–7.29) for children with a positive TST, QuantiFERON, or ELISpot, respectively.

Most young children (<6 years of age) who developed pediatric tuberculosis <90 days from baseline were TST+/IGRA+ (78% in <2 years old children; 83% in children 2-5 year old) and did not take preventive therapy (91% in <2 years old children; 92% in children 2-5 year old). A majority of these young children were BCG vaccinated (65% in <2 years old children; 68% in children 2-5 year old).

Children Living with HIV.

Of the 23 studies that reported HIV status in children, only one reported ART coverage. In this study, 89% (8 of 9) of children living with HIV were on antiretroviral therapy.

Study Heterogeneity

There was between-study heterogeneity in prevalent and incident tuberculosis. Prevalent tuberculosis ranged from 0–15% (Figure 3a). The rate of incident tuberculosis over 100 person-years ranged from 0–3.3% (Figure 3b). Much of the heterogeneity for both prevalent and incident tuberculosis was due to the global region of the study and the prospective/retrospective nature of data collection (Figure 3a and Figure 3b).

The I^2 for the prevalence model is 99.8%. For prevalence, the I^2 = 99.2% among prospective studies. For prevalence, the I^2 = 98.9% among retrospective studies.

The I^2 for the incidence model is 98.8%. For incidence, the I^2 = 90.1% among prospective studies. For prevalence, the I^2 = 97.1% among retrospective studies.

We also report heterogeneity estimates for each output of our mixed-effects logistic and survival-time models reported in the main manuscript. These I^2 heterogeneity estimates are reported in the Supplementary Appendix and are generally low (all can be seen below).

Compared to studies in the African region, studies demonstrated substantially lower rates of prevalent tuberculosis in the Americas Region (AOR, 0.48, 95% CI, 0.21–1.12) and the Western

Pacific Region (AOR, O.10, 95% CI, 0.04–0.23). Incident tuberculosis was also statistically lower in the Western Pacific Region versus the African Region (AHR, 0.16, 95% CI, 0.07–0.35). Prospective studies identified more prevalent (AOR 3.26, 95% CI, 1.49–7.12) and incident tuberculosis (AHR 3.12, 95% CI, 1.65–5.90) (Table 2).

The region and design of studies were correlated; all studies from the African Region were prospective and all but one study in the Western Pacific Region[22] were retrospective. Therefore, we were unable to evaluate whether between-study heterogeneity was due to regional epidemiological differences, prospective or retrospective study design, or a combination of both.

3. Sensitivity Analyses.

We conducted several sensitivity analyses. When looking at predictive factors for prevalent and incident tuberculosis, we stratified our results by whether participants were recruited prospectively or retrospectively. Generally, we found similar results. To assess whether the prospective/retrospective nature of data collection impacted risk factors for disease we evaluated statistical interaction. For prevalent tuberculosis, we found no statistically significant interaction for the study design and BCG vaccination for children <5 years of age ($P_{interaction}$=0.951) or children 5 to 18 years of age ($P_{interaction}$=0.093). There were few children living with HIV or with a previous tuberculosis diagnosis in retrospective studies and therefore we were unable to test for an interaction in these variables. For incident tuberculosis, there was no statistically significant interaction between the prospective/retrospective nature of data collection and HIV infection ($P_{interaction}$=0.768) and BCG vaccination (for children <5 years of age, $P_{interaction}$=0.892; for children 5 to 18 years of age, $P_{interaction}$=0.944). There was a statistically significant interaction for a previous tuberculosis diagnosis ($P_{interaction}$=0.011).

Because of the large sample size of one study (Lee, 2017) relative to the other included cohort studies, we re-analyzed our risk factor analysis without this study and found that our results remained consistent and largely unchanged.

We performed several other propensity scores adding BCG vaccination, HIV infection, or past tuberculosis, for which missing data precluded simultaneously in primary propensity score analyses. There were minimal changes to the effectiveness of preventive therapy when comparing the original propensity score and these alternative propensity scores among all children or among TST- or IGRA- children. Among TST+ or IGRA+ children, the new propensity scores showed less effectiveness of preventive therapy compared to the older propensity score, however, the general effectiveness was still very high (ie, >79% protection in all models).

We also assessed adding survival follow-up time to the propensity score to evaluate whether differential follow-up may be an influential modifier of disease risk. Among all children, TST+/IGRA+ children, and TST-/IGRA- children, hazard ratios assessing protection from preventive therapy were similar when including and not including survival follow-up time as a variable in propensity scores. The hazard ratios for all children, TST+/IGRA+ children, and TST-/IGRA- children were 0.39 (95% CI, 0.32–0.49), 0.23 (95% CI, 0.17–0.32), and 0.66 (95% CI, 0.40–1.07), respectively.

4. References.

Aibana, O., Acharya, X., Huang, C.C., Becerra, M.C., Galea, J.T., Chiang, S.S., Contreras, C., Calderon, R., Yataco, R., Velásquez, G.E. and Tintaya, K., 2016. Nutritional status and tuberculosis risk in adult and pediatric household contacts. *PloS One*, 11(11), p.e0166333.

Behr, M.A., Warren, S.A., Salamon, H., Hopewell, P.C., De Leon, A.P., Daley, C.L. and Small, P.M., 1999. Transmission of Mycobacterium tuberculosis from patients smear-negative for acid-fast bacilli. The Lancet, 353(9151), pp.444-449.

Fox, G.J., Barry, S.E., Britton, W.J. and Marks, G.B., 2013. Contact investigation for tuberculosis: a systematic review and meta-analysis. *European Respiratory Journal*, 41(1), pp.140-156

Guwatudde, D., Nakakeeto, M., Jones-Lopez, E.C., Maganda, A., Chiunda, A., Mugerwa, R.D., Ellner, J.J., Bukenya, G. and Whalen, C.C., 2003. Tuberculosis in household contacts of infectious cases in Kampala, Uganda. *American Journal of Epidemiology*, 158(9), pp.887-898.

Hermansen, T.S., Lillebaek, T., Kristensen, K.L., Andersen, P.H. and Ravn, P., 2016. Prognostic value of interferon-γ release assays, a population-based study from a TB low-incidence country. *Thorax*, 71(7), pp.652-658.

Martinez, L., Shen, Y., Handel, A., Chakraburty, S., Stein, C.M., Malone, L.L., Boom, W.H., Quinn, F.D., Joloba, M.L., Whalen, C.C. and Zalwango, S., 2018. Effectiveness of WHO's pragmatic screening algorithm for child contacts of tuberculosis cases in resource-constrained settings: a prospective cohort study in Uganda. *The Lancet Respiratory Medicine*, 6(4), pp.276-286.

Martinez, L., Handel, A., Shen, Y., Chakraburty, S., Quinn, F.D., Stein, C.M., Malone, L.L., Zalwango, S. and Whalen, C.C., 2018. A prospective validation of a clinical algorithm to detect tuberculosis in child contacts. *American Journal of Respiratory and Critical Care Medicine*, 197(9), pp.1214-1216.

Tostmann, A., Kik, S.V., Kalisvaart, N.A., Sebek, M.M., Verver, S., Boeree, M.J. and van Soolingen, D., 2008. Tuberculosis transmission by patients with smear-negative pulmonary tuberculosis in a large cohort in the Netherlands. Clinical Infectious Diseases, 47(9), pp.1135-1142.

Winje, B.A., White, R., Syre, H., Skutlaberg, D.H., Oftung, F., Mengshoel, A.T., Blix, H.S., Brantsæter, A.B., Holter, E.K., Handal, N. and Simonsen, G.S., 2018. Stratification by interferon-γ release assay level predicts risk of incident TB. *Thorax*, 73(7), pp.652-661.

5. Search Strategy.

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

6. 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

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 =
(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
    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, 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, sarcoidoisis, 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., 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

7. Author Contributions.

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Leonardo Martinez, Olivia Cords, and Jason R. Andrews formed the primary writing group. C. Robert Horsburgh, Sanjay Basu, Nathan C. Lo, Ted Cohen, Heather J. Zar, and Mark Hatherill gave advisement on various portions of the project as needed.

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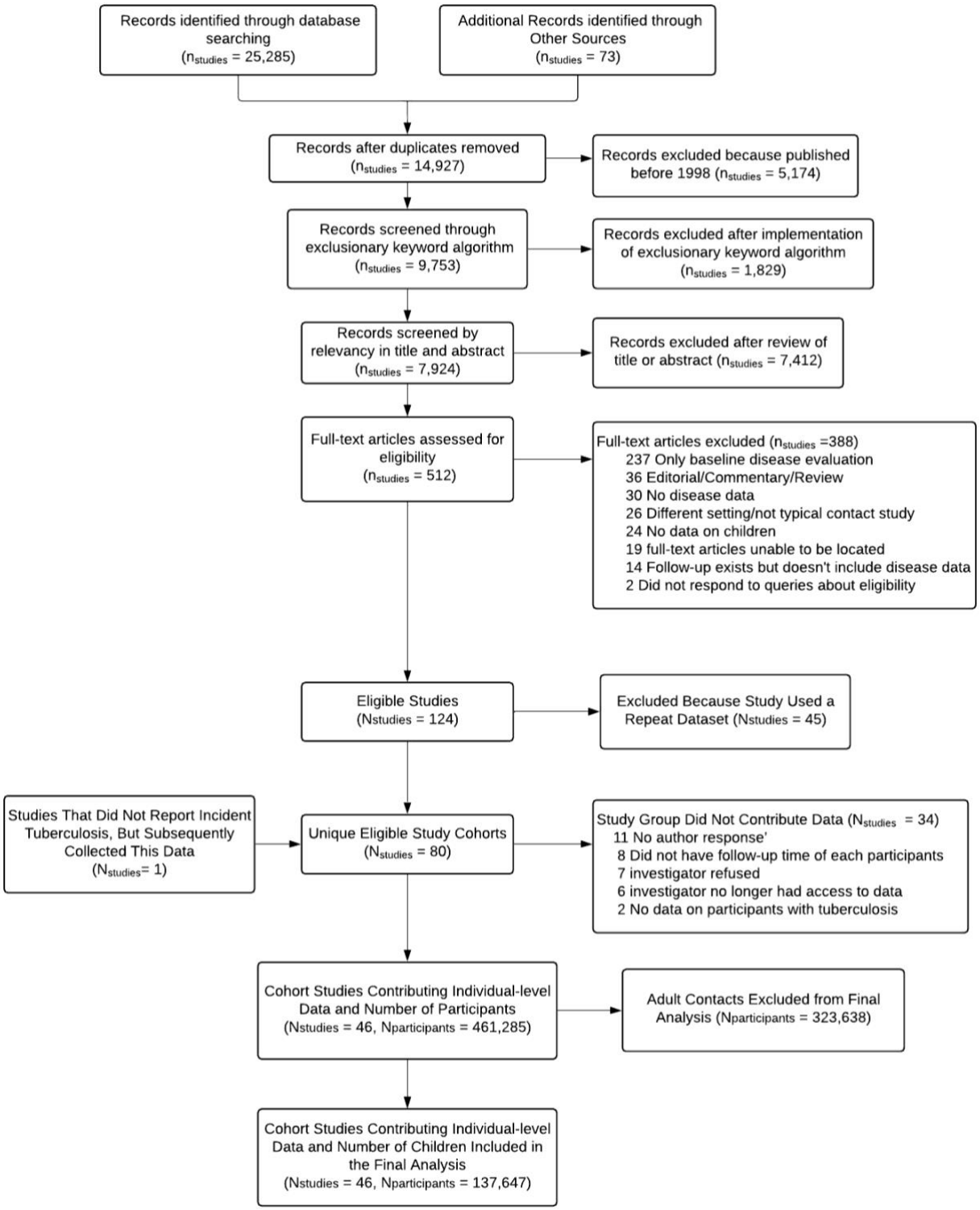
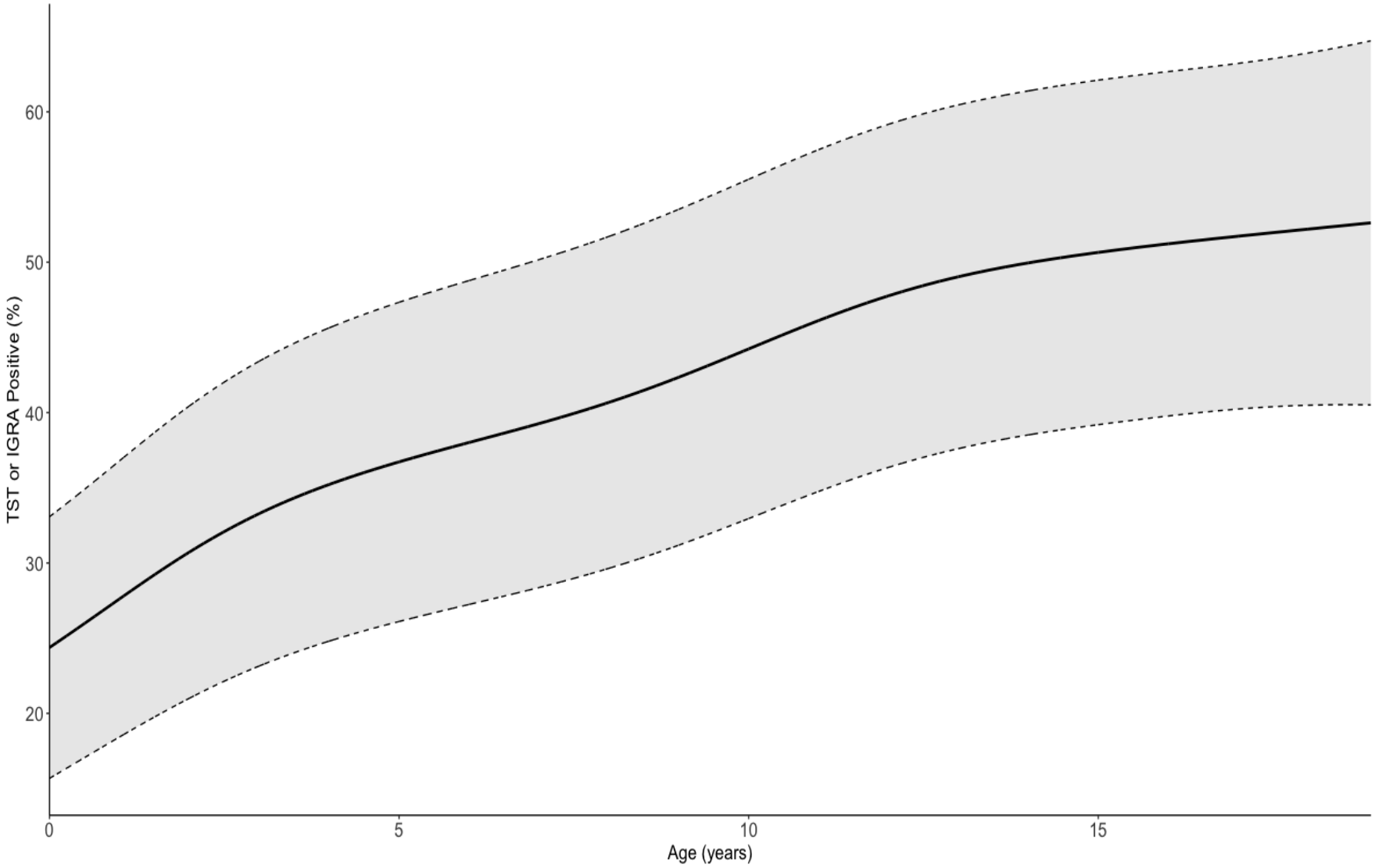
9. Supplementary Figure S1. Flowchart of Systematic Search Process and Study Selection.†



† In the "Full-text articles excluded" box, excluded articles may have more than one reason for exclusion. Only one reason for exclusion was listed for each excluded manuscript. In addition, one study is added to the 'Unique Eligible Study Cohorts' box because we later found out that a study collected incident data (although this was not published).

10. Supplementary Figure S2. Tuberculin Skin Test or Interferon-Gamma Assay Positivity by Age.



11. Supplementary Table S1. All Included Individual Studies and Demographic Information.

First Author, Year [Ref]	Country	Median Age (IQR)	Years, Data Collection	Study Design	N Children Included	Child-Years of Follow-up
Aibana, 2016	Peru	8 (4–13)	2009–2012	Prospective	5170	4927
Grandjean, 2011	Peru	10 (5–15)	2005–2008	Retrospective	1313	1552
Grandjean, 2015	Peru	9 (4–14)	2010–2013	Prospective	724	1565
Otero, 2016	Peru	9 (4–14)	2010–2011	Retrospective	2030	3907
Hill, 2008	The Gambia	8 (4–13)	2002–2006	Prospective	1403	5333
Acuna-Villaorduna, 2017	Brazil	9 (5–14)	2008–2013	Retrospective	417	1982
Lee, 2017	Taiwan	12 (7–16)	2007–2013	Retrospective	64573	183902
Chan, 2014	Taiwan	8 (5–10)	2008–2009	Retrospective	9411	26256
Ling, 2011	Taiwan	12 (7–16)	2005–2007	Retrospective	6469	35299
Triasih, 2015	Indonesia	6 (3–11)	2010–2012	Prospective	269	239
Seddon, 2013	South Africa	3 (1–4)	2010–2011	Prospective	186	219
Chakhaia, 2014	Georgia	7 (3–12)	2010–2013	Retrospective	388	664
Yoshiyama 2015	Japan	10 (9–10)	2010–2013	Retrospective	38	68
Singh, 2013	India	12 (7–16)	2007–2009	Prospective	598	1331
Altet, 2015	Spain	10 (6–14)	2007–2009	Prospective	588	2151
Yuhara, 2013	Brazil	7 (4–12)	2006–2011	Retrospective	894	1784
Zellweger, 2015	10 European Countries	13 (7–15)	2009–2013	Prospective	741	1715
Wang, 2012	Taiwan	15 (13–17)	2007–2009	Prospective	41	86
Mazahir, 2017	India	8 (4–11)	2014–2015	Prospective	79	68
Moyo, 2015	Australia	14 (7–17)	2005–2013	Retrospective	5696	29532
Lu, 2015	China	7 (4–11)	2015–2016	Retrospective	232	966
Martinez, 2018	Uganda	7 (3–12)	1995–2008	Prospective	1694	2564
del Corral, 2009	Colombia	9 (4–14)	2005–2008	Prospective	919	2427
Sloot, 2014	The Netherlands	11 (5–16)	2002–2012	Retrospective	2289	14611
Verhagen, 2014	Venezuela	9 (5–12)	2010–2011	Prospective	210	413
Datta, 2014	Peru	9 (3–13)	2006–2013	Retrospective	95	720
Sharma, 2017	India	12 (8–15)	2008–2012	Prospective	679	1331
Lemos, 2004	Brazil	12 (7–16)	1997–1999	Prospective	117	94
Fox, 2018	Vietnam	11 (6–15)	2010–2015	Prospective	6236	12454
Lienhardt, 2010	Senegal	10 (4–14)	2004–2006	Prospective	1397	2987
Dobler, 2013	Australia	11 (5–16)	2000–2009	Retrospective	3582	14337

Van Schalwayk, 2014	South Africa	9 (4–13)	2009–2010	Prospective	859	863
Lopez-Varela, 2017	Mozambique	2 (1–2)	2011–2012	Prospective	58	39
Hannoun, 2016	Algeria	6 (3–10)	2014–2016	Prospective	430	674
Talat, 2010	Pakistan	14 (11–17)	2001-2008	Prospective	49	168
Anger, 2012/Gounder, 2015	United States	10 (5–15)	1997–2007	Retrospective	8924	68642
Egere, 2017	The Gambia	6 (3–10)	2012–2014	Prospective	6222	N/A
Espinal, 2000	Dominican Republic	7 (4–12)	1994–1995	Prospective	396	454
Geis, 2012	Germany	13 (8–17)	2008–2012	Prospective	135	143
Bonnet, 2017	Uganda	3 (2–4)	2012–2014	Prospective	281	149
Baliashvili, 2018	Georgia	10 (4–15)	2012–2014	Retrospective	1013	1497
Huerga, 2018	Armenia	6 (3–10)	2012–2016	Prospective	138	N/A
Carvalho, 2001	Brazil	9 (5–13)	1995–1997	Prospective	148	148
Kato-Maeda, 2019	United States	15 (9–17)	2008–2012	Retrospective	527	1230

† Anger (2012) and Gounder (2015) were part of the same cohort but were published in separate manuscripts. The total numbers of the single cohort are included here.

12. Supplementary Table S2. Risk Factors for Tuberculosis Amongst Children Less than 19 Years of Age, Stratified by the Study Design.

Characteristic	Coprevalent Tuberculosis, Adjusted Odds Ratio (95% CI)	Incident Tuberculosis, Adjusted Hazard Ratio (95% CI)	All Tuberculosis, Adjusted Odds Ratio (95% CI)
Prospective Studies (N = 28,506)			
Male Sex	1.12 (0.95, 1.31)	0.93 (0.78, 1.11)	1.04 (0.92, 1.17)
Tuberculosis Infection			
Tuberculin Skin Test Induration ≥10 mm	13.30 (10.10, 17.52)	3.90 (3.04, 4.99)	7.97 (6.45, 9.85)
QuantiFERON Gold In-Tube Test, ≥0.35 IU/mL	21.43 (8.20, 56.04)	4.20 (1.38, 12.73)	13.18 (6.32, 27.48)
HIV infection	3.06 (1.76, 5.30)	5.42 (2.32, 12.66)	3.45 (2.07, 5.74)
Prior Tuberculosis Event	8.02 (5.29, 12.15)	2.54 (1.59, 4.07)	5.17 (3.68, 7.26)
Preventive Therapy			
All children	…	0.28 (0.21, 0.38)	…
TST+ or IGRA+	…	0.21 (0.14, 0.31)	…
TST- or IGRA-	…	0.62 (0.37, 1.04)	…
BCG vaccination			
5–18 years of age	1.07 (0.75, 1.53)	0.91 (0.67, 1.23)	0.88 (0.69, 1.12)
<5 years of age	0.63 (0.45, 0.88)	0.72 (0.45, 1.15)	0.65 (0.48, 0.89)
Retrospective Studies (N = 109,141)			
Tuberculosis Infection			
Tuberculin Skin Test Induration ≥10 mm	32.64 (23.13, 46.06)	3.32 (2.70, 4.08)	7.52 (6.40, 8.84)
QuantiFERON Gold In-Tube Test, ≥0.35 IU/mL	Undefined	6.34 (0.83, 48.57)	11.79 (1.59, 87.28)
ELISPOT, >8 spot-forming cells*	N/A	6.34 (0.83, 48.57)	N/A
HIV infection	Undefined	2.51 (0.19, 33.24)	N/A
Prior Tuberculosis Event	Undefined	6.07 (3.56, 10.36)	7.79 (4.34, 13.99)
Preventive Therapy			
All children	…	0.56 (0.41, 0.77)	…
TST+ or IGRA+	…	0.13 (0.08, 0.19)	…
TST- or IGRA-	…	0.83 (0.19, 3.55)	…
BCG vaccination			
5–18 years of age	0.44 (0.21, 0.94)	0.82 (0.47, 1.42)	0.62 (0.40, 0.98)
<5 years of age	0.55 (0.15, 2.02)	0.63 (0.23, 1.74)	0.64 (0.28, 1.50)

All Studies (N = 137,647)			
Tuberculosis Infection			
Tuberculin Skin Test Induration ≥10 mm	21.10 (16.38, 27.19)	3.36 (2.88, 3.93)	6.86 (6.03, 7.81)
QuantiFERON Gold In-Tube Test, ≥0.35 IU/mL	22.22 (9.39, 52.56)	6.13 (2.57, 14.61)	14.00 (7.54, 25.85)
HIV infection	2.83 (1.63, 4.90)	5.19 (2.32, 11.63)	3.34 (2.02, 5.53)
Prior Tuberculosis Event	6.86 (4.59, 10.25)	3.20 (2.25, 4.55)	5.06 (3.70, 6.94)
Preventive Therapy			
All children	…	0.37 (0.30, 0.47)	…
TST+ or IGRA+	…	0.15 (0.11, 0.20)	…
TST+ or IGRA+, Propensity-Score Matched	…	0.09 (0.05, 0.15)	…
TST- or IGRA-	…	0.65 (0.40, 1.06)	…
TST- or IGRA-, Propensity-Score Matched	…	0.66 (0.40, 1.10)	…
BCG vaccination			
5–18 years of age	0.97 (0.70, 1.32)	0.90 (0.69, 1.18)	0.82 (0.67, 1.02)
<5 years of age	0.62 (0.44, 0.89)	0.69 (0.45, 1.05)	0.65 (0.49, 0.87)
Prospective (versus Retrospective) Data Collection	3.26 (1.49, 7.12)	3.12 (1.65, 5.90)	2.60 (1.47, 4.63)

Abbreviations: TST, tuberculin skin test. CI, confidence interval. IGRA, interferon gamma release assay.

13. Supplementary Table S3: Two-year cumulative tuberculosis incidence (%) by age and infection status.

Infection Status	Age (years)			
	<5	5-9	10-14	15-18
QFT/TST Positive	19.0 (8.4-37.4)	9.0 (3.7-20.1)	8.8 (3.7-19.7)	10.6 (4.4-23.3)
QFT/TST Negative	2.3 (0.9-5.7)	1.0 (0.4-2.8)	1.4 (0.5-3.8)	2.1 (0.8-5.7)
All	7.6 (4.7-12.1)	5.2 (3.1-8.4)	5.6 (3.4-9.0)	6.7 (4.1-10.9)

All children were included in this table.

14. Supplementary Table S4. Two-year cumulative tuberculosis incidence (%) by age and infection status for every year of life.

Age	2-year Cumulative Risk Among Children with Tuberculosis Infection	2-year Cumulative Risk Among Children without Tuberculosis Infection	2-year Cumulative Risk Among All Children
0-1 years old	17.93 (5.73, 43.07)	2.03 (0.44, 6.49)	6.76 (3.32, 12.70)
1-2 years old	15.81 (2.11, 60.21)	1.43 (0.08, 14.04)	6.11 (1.62, 19.91)
2-3 years old	21.45 (3.09, 68.93)	2.49 (0.19, 19.52)	9.21 (2.72, 26.93)
3-4 years old	14.86 (1.95, 59.05)	2.10 (0.14, 17.77)	6.96 (1.91, 21.88)
4-5 years old	19.55 (2.91, 65.37)	1.59 (0.10, 14.75)	7.90 (2.19, 23.98)
5-6 years old	5.42 (0.56, 33.95)	0.67 (0.03, 8.29)	3.27 (0.75, 12.10)
6-7 years old	12.29 (1.54, 53.16)	1.53 (0.09, 15.21)	6.54 (1.74, 20.70)
7-8 years old	7.65 (0.90, 40.11)	0.41 (0.01, 6.68)	4.48 (1.09, 15.64)
8-9 years old	10.60 (1.24, 50.02)	0.12 (0.01, 3.54)	4.84 (1.23, 16.60)
9-10 years old	8.66 (1.03, 42.81)	2.00 (0.12, 17.16)	6.34 (1.71, 19.78)
10-11 years old	7.04 (0.83, 39.79)	1.87 (0.11, 17.52)	4.91 (1.31, 16.54)
11-12 years old	9.98 (1.28, 47.14)	0.48 (0.01, 7.84)	5.55 (1.49, 18.38)
12-13 years old	10.25 (1.38, 47.73)	1.21 (0.04, 14.29)	5.85 (1.57, 19.22)
13-14 years old	5.13 (0.57, 31.52)	0.57 (0.01, 9.56)	4.36 (1.10, 14.94)
14-15 years old	11.15 (1.46, 50.46)	2.25 (0.13, 20.72)	7.09 (1.95, 21.68)
15-16 years old	12.95 (1.68, 55.13)	0.60 (0.01, 9.56)	6.80 (1.87, 21.32)
16-17 years old	10.97 (1.41, 49.30)	0.76 (0.02, 12.14)	7.79 (2.20, 23.68)
17-18 years old	8.86 (1.05, 44.84)	2.51 (0.12, 24.25)	5.43 (1.39, 18.40)
18-19 years old	9.43 (1.22, 44.06)	3.62 (0.25, 27.88)	6.77 (1.88, 21.05)

All children were included in this table.

15. Supplementary Table S5: Prevalence of Pediatric Tuberculosis by Definition of Prevalent Tuberculosis and Baseline Infection Status.

Infection Status	Prevalence by Diagnosis from Days from Enrollment			
	0	≤30	≤60	≤90
IGRA/TST Positive	0.9% (0.2-3.7%)	3.8% (1.6-9.1%)	4.5% (1.8-10.8%)	6.2% (2.5-14.5%)
IGRA/TST Negative	<0.1% (0.0-0.6%)	0.2% (0.0-1.6%)	0.4% (0.1-1.9%)	0.5% (0.1-2.7%)
All	0.4% (0.2-1.2%)	1.2% (0.4-3.5%)	1.7% (0.7-4.3%)	2.8% (1.1-6.9%)

Abbreviations: TST, tuberculin skin test. IGRA, interferon gamma release assay.
This table estimates the risk of prevalent tuberculosis based on defining prevalent tuberculosis as only at baseline, ≤30 days from baseline, ≤60 days from baseline, or ≤90 days from baseline. All children were included in this table.

16. Supplementary Table S6: Effectiveness of Preventive Therapy by Baseline Tuberculosis Infection Status and Definition of Incident Tuberculosis.

	Defined at >30 days from baseline	Defined at >60 days from baseline
QFT/TST Positive	0.16 (0.12, 0.22)	0.15 (0.11, 0.21)
QFT/TST Negative	0.77 (0.46, 1.27)	0.69 (0.42, 1.12)
All Children	0.44 (0.35, 0.55)	0.38 (0.30, 0.47)

All children were included in this table.

17. Supplementary Table S7. Adjusted Hazard Ratios for the Effectiveness of Preventive Therapy by the Background Burden of the Study.

Characteristic	WHO 'Low-Burden'	WHO 'High-Burden'
All Studies (N = 137,647)		
Preventive Drug Therapy Regimen		
All children	0.38 (0.30, 0.47)	0.39 (0.18, 0.86)
TST+ or IGRA+	0.16 (0.12, 0.22)	0.17 (0.07, 0.37)
TST+ or IGRA+, Propensity-Score Matched	0.16 (0.12, 0.22)	0.15 (0.07, 0.36)
TST- or IGRA-	0.64 (0.38, 1.07)	0.97 (0.23, 4.11)
TST- or IGRA-, Propensity-Score Matched	0.61 (0.37, 1.02)	0.88 (0.20, 3.99)

Characteristic	Incidence Burden <100 cases per 100,000 persons	Incidence Burden ≥100 cases per 100,000 persons
Preventive Drug Therapy Regimen		
All children	0.47 (0.34, 0.66)	0.32 (0.25, 0.43)
TST+ or IGRA+	0.12 (0.08, 0.17)	0.24 (0.16, 0.37)
TST+ or IGRA+, Propensity-Score Matched	0.11 (0.08, 0.18)	0.24 (0.16, 0.37)
TST- or IGRA-	0.66 (0.15, 2.91)	0.65 (0.38, 1.10)
TST- or IGRA-, Propensity-Score Matched	0.61 (0.14, 2.72)	0.65 (0.38, 1.10)

18. Supplementary Table S8. Characteristics of studies that shared and did not share individual-level data

Characteristic	Shared Individual Data		Did Not Share Individual Data	
	Number of Studies (N=46)	Percentage	Number of Studies (N=34)	Percentage
Prospective Study Design	28	61	20	57
World Health Organization High-burden†	18	39	16	45
Tuberculosis Incidence Burden of Country, per 100 thousand persons‡				
<50	16	36	11	35
50–100	9	19	3	10
>100–200	9	19	8	26
>200	12	23	8	26
World Health Organization Region				
African	9	20	12	34
Americas	16	33	9	26
Eastern Mediterranean	1	2	1	3
European	7	15	3	9
Southeast Asia	4	9	5	14
Western Pacific	9	20	2	6
Income Group				
High	14	30	5	16
Upper-middle	18	39	13	41
Lower-middle	8	17	6	19
Low	6	13	8	25
Preventive Therapy included	32	70	21	60
QuantiFERON or Tuberculin Skin Testing	38	78	26	74

† For the group of studies that did not share individual-level data the numbers may not add up to 100% of the 34 studies because of missing data. Some manuscripts did not detail details listed in the table.

19. Supplementary Table S9. Heterogeneity estimates in multivariable models of pediatric tuberculosis risk.

Characteristic	Outcome, Prevalent Tuberculosis	Outcome, Incident Tuberculosis	Outcome, All Tuberculosis
	I_2	I_2	I_2
Male Sex	0	0	0
Tuberculosis Infection‡			
Tuberculin Skin Test Induration ≥10 mm	83	79	88
QuantiFERON Gold In-Tube Test, ≥0.35 IU/mL	0	46	0
ELISPOT, >8 spot-forming cells*	…	0	0
HIV infection	0	0	2
Prior Tuberculosis Event	0	0	32
Preventive Drug Therapy Regimen			
All children	…	22	…
TST+ or IGRA+	…	33	…
TST- or IGRA-	…	39	…
BCG vaccination			
5–18 years of age	46	0	5
<5 years of age	15	0	8

We have rounded all numbers to the nearest percentage.

20. Supplementary Table S10. Missingness of Age, Sex, HIV Infection, Prior Tuberculosis, and Study Design.

Characteristics	$N_{participants}$, Data Available (%)	$N_{participants}$, Missing data (%)
Age	137,647 (100)	0 (0)
Sex	137,647 (100)	0 (0)
HIV infection	91,218 (66.3)	46,429 (33.7)
Prior tuberculosis	99,524 (72.3)	38,123 (27.7)
BCG Vaccination	42,153 (30.6)	95,494 (69.4)
Study Design (ie, Prospective/Retrospective)	137,647 (100)	0 (0)

21. Supplementary Table S11: Univariable Regression Analyses to Identify Factors for Tuberculosis Amongst Children Less than 19 Years of Age.

Characteristic	Coprevalent Tuberculosis, Univariable Odds Ratio (95% CI)	Incident Tuberculosis, Univariable Hazard Ratio (95% CI)	All Tuberculosis, Univariable Odds Ratio (95% CI)
All Studies (N = 137,647)			
Male Sex	1.05 (0.93, 1.19)	0.99 (0.87, 1.12)	1.03 (0.94, 1.12)
Tuberculosis Infection			
Tuberculin Skin Test Induration ≥10 mm	17.27 (14.09, 21.16)	3.35 (2.87, 3.90)	7.02 (6.23, 7.90)
QuantiFERON Gold In-Tube Test, ≥0.35 IU/mL	18.62 (7.85, 44.12)	6.96 (2.64, 18.39)	13.83 (7.21, 26.55)
ELISPOT, >8 spot-forming cells*	7.93 (1.73, 36.32)	1.99 (0.67, 5.91)	3.18 (1.29, 7.85)
HIV infection	2.82 (1.63, 4.88)	5.08 (2.28, 11.33)	3.45 (2.14, 5.56)
Prior Tuberculosis Event	6.37 (4.28, 9.49)	3.68 (2.60, 5.21)	5.80 (4.37, 7.70)
Preventive Drug Therapy Regimen†			
All children	…	0.35 (0.28, 0.43)	…
TST+ or IGRA+	…	0.16 (0.12, 0.21)	…
TST+ or IGRA+, Propensity-Score Matched	…		…

TST- or IGRA-	…	0.64 (0.40, 1.05)	…
TST- or IGRA-, Propensity-Score Matched	…		…
BCG vaccination			
5–18 years of age	0.92 (0.68, 1.25)	0.90 (0.69, 1.17)	0.88 (0.72, 1.07)
<5 years of age	0.60 (0.44, 0.82)	0.71 (0.47, 1.09)	0.64 (0.49, 0.83)
Prospective (versus Retrospective) Data Collection	3.41 (1.62, 7.17)	2.93 (1.57, 5.48)	2.34 (1.36, 4.05)

‘All children were included in this table.

22. Supplementary Table S12: Performance of the Propensity Score Matching Algorithm‡

	Unmatched, % bias	Matched, % bias	% reduction in bias	P Value, t-test†
Age	-54.5	-0.2	99.6	0.788
Sex	-3.3	0	99.2	0.973
Prospective/Retrospective Design	24.1	-0.6	97.7	0.550

† This is a t-test on the hypothesis that the mean value of each variable is the same in the treatment group and the non-treatment group. It is done after matching.
‡A bias before and after matching is calculated for each variable and the change in this bias is stated. This “bias” is defined as the difference of the mean values of the treatment group and the (not matched/matched) non treatment group, divided by the square root of the average sample variance in the treatment group and the not matched non treatment group.

The performance of the matching algorithm was strong. Please see a table below detailing the % bias before and after matching.

As one can see, after propensity score matching, there was a large reduction in bias in the matching variables. Therefore, we believe our choice of matching was likely correct.

23. Supplementary Table S13: Household definition for included studies on proportion of tuberculosis infections acquired in the household.

First Author, Year	Household and/or Close Contact Definition
Martinez, 2018	'Household contacts were identified through household contact tracing performed within 4 weeks of the initial diagnosis of tuberculosis in the index case.'
Aibana, 2016	Household exposure; no specific definition found
Grandjean, 2015	'any person living in the same house as the index case for more than one day a week'
Grandjean, 2011	'A household contact was defined as any individual who lived with the index case for >1 day each week in the period during which the index case was symptomatic with TB disease. This definition was chosen to include those lodging or intermittently working away from home.'
Otero, 2016	'A HHC was defined as a person sleeping under the same roof and sharing cooking facilities with the index case for at least three months before the case's diagnosis'
Hill, 2008	'Household contacts were defined as individuals at least 6 months of age living the majority of the time on the same compound as the respective index TB case, sharing meals and identifying a common household head.'
Acuna-Villaorduna, 2017	'Household contacts were defined as an individual of any age fulfilling at least one of the following criteria of close contact with the index TB case for ⩾3 months before enrolment: 1) sleeping under the same roof ⩾5 days per week, 2) sharing meals ⩾5 days per week, 3) watching TV together on week nights or weekends and 4) other significant contact (85% of these visited the household ⩾18 days per month)'
Lee, 2017	Household and community exposure; no specific definition found
Chan, 2014	'In Taiwan, enhanced surveillance criteria of either an 8-hour exposure to index cases within 1 day or a 40-hour cumulative exposure is used to define the contacts. The household family members are the main targets. The contact investigations are also routinely conducted in the congregate settings, such as schools, healthcare facilities, and prisons.'
Ling, 2011	'household family members and office co-workers of TB cases were targeted for contact investigations, which are regularly conducted in congregate settings such as schools, health care facilities and prisons'
Triasih, 2015	'Close contact was defined as living in the same house with the index case within the last 3 months, or having had frequent contact with the index case for a minimum of 8 hours per day, within the last 3 months if not living in the same house.'

Seddon, 2013	‘Significant exposure was defined as living with or having regular daily interaction with the MDR tuberculosis source patient’
Chakhaia, 2014	‘Contacts were defined as any persons who were exposed to an index case, according to WHO criteria. Eligible contacts for this study included any contacts referred to the NCTBLD by an enrolled index patient including HH (defined as person who shared the same enclosed living space for one or more nights or for frequent or extended periods during the day with the index case during the 3 months before commencement of the current treatment episode) and other non-HH, close contacts (defined as a person who is not in the household but shared an enclosed space, such as a social gathering place, workplace or facility, for extended periods during the day with the index case during the 3 months before commencement of the current treatment episode)’
Yoshiyama 2015	‘The target contacts included household contacts and workplace contacts, as well as hospital contacts that shared a room with patients diagnosed with TB’
Singh, 2013	‘A household was defined as a group of people living within one residence that lives and eats together and identified a head of family who makes decisions for the household’ AND ‘A household contact was defined as an individual who had resided in the household for at least seven consecutive days during the three months prior to the diagnosis of tuberculosis with the index case. Household contacts included their family members, close friends, workplace contacts.’
Altet, 2015	‘All contacts included were from the first circle of exposure: individuals with daily exposure, or with a minimum exposure of 6 hours/week’
Yuhara, 2013	‘A contact was defined as any person living in the same environment as an index case at the time of TB diagnosis. Contact interactions took place at home, at work, in long-term stay institutions, at school, or at preschool’
Zellweger, 2015	‘Contacts living in the same household as the index patient were defined as “close contacts/relatives.” Contacts with short but intensive contact not living in the same household were defined as “close contacts/not relatives.” Those not belonging to these categories but having contact to an index patient during work, school activities, leisure, or travel for more than 8 hours were defined as “prolonged contacts.” When contact investigation was considered to be necessary by the responsible public health authorities, although the intensity and duration of exposure could not be verified, contacts were defined as “other contacts.”’
Wang, 2012	Household exposure; no specific definition found

Mazahir, 2017	Household exposure; no specific definition found
Moyo, 2015	‘Close contact is defined as people who have had frequent, prolonged and close contact in an enclosed environment with an infectious case, such as all people living in the same dwelling; relatives and friends who have frequent, prolonged and close contact; and work colleagues who share the same indoor work area on a daily basis, following an individual risk assessment’
Lu, 2015	‘Household contacts were defined as any individual spending at least seven consecutive days in the same household as the index case £ 3 months before diagnosis and £ 14 days after initiating therapy’
del Corral, 2009	Household and community exposure; no specific definition found
Sloot, 2014	‘The PHS staff investigates recent contacts of PTB index patients and evaluates duration and frequency of exposure to the index patient during the infectious period. Accordingly, contacts are listed as first ring, second ring, third ring, and so forth (contacts in rings beyond the second ring are categorized as casual contacts) based on national guidelines for contact investigation’
Verhagen, 2014	‘household contacts of culture-confirmed TB patients who registered for TB treatment in the Venezuelan National TB Control Program were included’
Datta, 2017	‘Patients’’ contacts were invited to participate if they spent ≥6hours/week in the patient’s household in the 2 weeks prior to the patient’s diagnosis’
Sharma, 2017	‘household contacts of pulmonary TB patients were defined as extended group of family members residing together with the pulmonary TB index case in the same household >3 months and having a common cooking arrangement’
Lemos, 2004	Household exposure; no specific definition found
Fox, 2018	‘Contacts of all ages were eligible for enrollment if they had lived in the household occupied by the index patient during the 2 months before the diagnosis of tuberculosis’
Lienhardt, 2010	‘The household of each index case was visited by trained field assistants within a week of their recruitment. We defined household as the extended family living together in the same area, eating from the same pot. A written informed consent was obtained from each household member or child care-taker prior to enrolment. Demographic information was collected from all individuals (adults and children) living in the household for more than 3 months’
Dobler, 2013	Household and community exposure; no specific definition found
Van Schalwayk, 2014	Household exposure; no specific definition found
Lopez-Varela, 2017	Household exposure; no specific definition found

Hannoun, 2016	‘living in contact with a PTM+ patient’
Talat, 2010	‘Household contacts (n = 109) of 20 patients with recently diagnosed sputum-positive pulmonary TB (index case-patients)’
Anger, 2012/Gounder, 2015†	‘In NYC, as in many other TB control programs, the concentric circle approach is applied to contact investigation]. Contacts considered to have the most exposure are prioritized for evaluation (in most cases, household contacts are considered those with most exposure). Depending on evaluation results of the household contacts, a determination is then made whether or not to proceed to test contacts in the workplace or other congregate settings. Testing is not typically performed in congregate settings within the window period during which the test for TB infection is not considered accurate; thus, non-household contacts often do not receive a test for TB infection until at least 8 weeks after the last date of exposure to the case. In addition to this program policy, additional constraints are often encountered when conducting contact tracing and testing in the field, especially for hard-to-reach populations which may not readily consent to being tested, and if tested with positive results, persuading these contacts to go to a clinic for clinical evaluation of active TB can also a challenging process’
Egere, 2017	‘Child contacts aged ,15 years living in the same compound with sputum smear positive adult TB cases were recruited. A compound was defined as a cluster of homes or buildings often owned by members of the same family,10 and a household as a group of individuals living in the same building and eating from the same pot’
Espinal, 2000	‘Household exposure; no specific definition found’
Geis, 2012	‘Household and community exposure; no specific definition found’
Bonnet, 2017	‘Contacts were children aged<5 years who had lived in the same household with newly diagnosed smear-positive and/or culture-positive index cases (age>=15 years) continuously for >=2 weeks within the 3-month period immediately preceding the diagnosis of TB in the index case’
Baliashvili, 2018	‘A household contact was defined as a contact living in the same household as the index TB case, and a close contact was defined as a contact of an active TB case who did not live in the same household as the index case (e.g., friend, work colleague, neighbor, classmate)’
Huerga, 2018	‘A paediatric contact was defined as a child <15 years old living in the household of the index case or who had more than 7 days of contact for at least 4 hours per day during the 6 months prior to the index case registration’
Carvalho, 2001	‘We defined a close contact as someone who lived and slept in the same household as an

	index case or someone who lived elsewhere but who reported contact with the index case at the case's household for at least 20 h per week during the previous 3 mo.'
Kato-Maeda, 2019	'Household exposures were those in which the contact and index resided in the same dwelling (house, apartment, shelter or single-room occupancy (SRO) hotel). Other exposures were defined as 'nonhousehold'.'

† Information found in the Supplementary Appendix

24. Supplementary Table S14. 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%. 32/45 (71.1%) of studies were high quality, 11/45 (24.4%) of studies were moderate quality, and 2/45 (4.4%) of studies were low quality.

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 children was not present at baseline. [c]	Comparability of cohorts (2 points)[d]	Assessment of pediatric tuberculosis (2 points)[e]	Was follow up long enough for outcomes to occur?[f]	Adequacy of follow up of exposed childrn [g]	Rating	PERCENT SCORE (X/9)	
Aibana, 2016	A*	A*	A*	A*/B*	A*/B*	A*	E	8	0.89	high
Grandjean, 2011	A*	A*	C	B*/C	A*/C	A*	E	5	0.56	moderate
Grandjean, 2015	C	A*	A*	A*/B*	A*/B*	A*	E	7	0.78	high
Otero, 2016	A*	A*	C	B*/C	B*	A*	D	5	0.56	moderate
Hill, 2008	A*	A*	A*	A*/B*	A*/B*	A*	C*	9	1.00	high
Acuna-Villaorduna, 2017	B*	A*	A*	B*/C	A*/B*	*A	E	7	0.78	high
Lee, 2017	A*	C	C	B*/C	D	A*	E	3	0.33	moderate
Chan, 2014	A*	A*	A*	B*/C	A*/B*	A*	E	7	0.78	high
Ling, 2011	A*	A*	A*	B*/C	A*/B*	A*	E	7	0.78	high

Triasih, 2015	C	A*	A*	A*/D	A*/B*	A*	B*	7	0.78	high
Seddon, 2013	B*	A*	B*	A*/D	A*/B*	A*	B*	8	0.89	high
Chakhaia, 2014	C	A*	A*	C/D	A*/B*	A*	E	5	0.56	moderate
Yoshiyama 2015	C	A*	B*	B*/C	A*/C	A*	D	5	0.56	moderate
Singh, 2013	A*	A*	A*	A*/B*	A*	A*	D	7	0.78	high
Altet, 2015	A*	A*	A*	A*/B*	A*/B*	A*	B*	9	1.00	high
Yuhara, 2013	A*	A*	B*	B*/C	A*/B*	A*	E	7	0.78	high
Zellweger, 2015	A*	B	A*	A*/D	D	A*	B*	5	0.56	moderate
Wang, 2012	B*	A*	B*	A*/B*	A*/B*	A*	E	8	0.89	high
Mazahir, 2017	A*	A*	A*	A*/D	A*/B*	A*	A*	8	0.89	high
Moyo, 2015	A*	A*	C	B*/C	A*	A*	C*	6	0.67	moderate
Lu, 2015	B*	A*	B*	B*	D	A*	C*	6	0.67	moderate
Martinez, 2018	A*	A*	A*	A*/C	A*/B*	A*	A*	8	0.89	high
del Corral, 2009	A*	A*	A*	A*/B*	A*/B*	A*	B*	9	1.00	high
Sloot, 2014	C	A*	A*	B*/C	A*/B*	A*	C*	7	0.78	high

Verhagen, 2014	A*	A*	A*	A*/B*	A*/B*	A*	D	8	0.89	high
Datta, 2014	A*	A*	C	A*/B*	A*	A*	B*	7	0.78	high
Sharma, 2017	B*	A*	B*	A*/B*	A*/B*	A*	E	8	0.89	high
Lemos, 2004	B*	A*	A*	A*/D	A*/B*	A*	B*	8	0.89	high
Fox, 2018	A*	A*	A*	A*/B*	A*/B*	A*	B*	9	1.00	high
Lienhardt, 2010	A*	A*	A*	A*/B*	A*/B*	A*	D	8	0.89	high
Dobler, 2013	A*	C	A*	C/D	D	A*	E	3	0.33	low
Van Schalwayk, 2014	B*	B	A*	A*/D	A*/C	A*	D	5	0.56	moderate
Lopez-Varela, 2017	A*	A*	A*	A*/D	A*/B*	A*	B*	8	0.89	high
Talat, 2010	A*	A*	A*	A*/B*	A*/B*	A*	B*	9	1.00	high
Anger, 2012	B*	A*	A*	C/B*	B*	A*	C*	7	0.78	high
Gounder, 2015	A*	A*	A*	C/B*	B*	A*	C*	7	0.78	high
Egere, 2017	A*	A*	A*	A*/D	A*/B*	A*	E	7	0.78	high
Espinal, 2000	B*	A*	B*	A*/D	A*/B*	A*	D	7	0.78	high
Macintyre, 1998	A*	C	A*	C/D	B*	A*	E	4	0.44	moderate

Haldar, 2013	B*	A*	A*	A*/D	A*/B*	A*	E	7	0.78	high
Geis, 2012	B*	A*	C	A*/D	B*	A*	B*	6	0.67	moderate
Bonnet, 2017	B*	A*	A*	A*/B*	A*/B*	A*	D	8	0.89	high
Huerga, 2018	A*	A*	A*	A*/B*	A*/B*	A*	C	8	0.89	high
Carvalho, 2001	B*	A*	A*	A*/D	B*	A*	E	6	0.67	high
Patel, 2017	A*	A*	C	A*/B*	A*/B*	A*	E	7	.77	high
Kato Maeda, 2019	A*	A*	C	A*/B*	A*/B*	A*	D	7	.77	high

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

[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.

25. Supplementary Table S15. Tuberculosis Case Definition for Each Study

First Author, Publication Year	Definition
Aibana, 2015	Defined TB disease according to the consensus guidelines[1] for classifying TB disease in children
Grandjean, 2011	Diagnosed via Peruvian Ministry of Health Database
Grandjean, 2015	Definition not clearly specified: TB disease is defined as any patient with evidence of TB disease from sputum smear, culture, chest X-ray or clinical diagnosis that led to initiation of TB treatment
Otero, 2016	Diagnosed via TB registers
Hill, 2008	Not specified
Acuna-Villaorduna, 2017	Diagnosed via the Information System for Disease Notification database.
Lee, 2017	Diagnosed via the National Health Insurance Research Database
Chan, 2014	Diagnosed determined via the Taiwan National Surveillance Network of Communicable Disease
Ling, 2011	Diagnosed via the Taiwan National Surveillance Network of Communicable Disease, and defined by the following criteria: 1) smear microscopy for acid-fast bacilli or culture positive for *Mycobacterium tuberculosis*, 2) histopathological diagnosis of TB or 3) clinical TB in the absence of microbiological diagnosis.
Triasih, 2015	TB disease was diagnosed if the child met the criteria for certain, probable, or possible TB. These definitions are listed below: 1. Certain TB: culture confirmation for *Mycobacterium TB.* 2. Probable TB: had at least 1 well-defined symptom; AND CXR was consistent with intrathoracic TB OR there was supportive evidence of extrapulmonary TB; AND there was a positive clinical response to antituberculosis treatment. 3. Possible TB: had at least 1 well-defined symptom; AND either of the following: a positive clinical response to anti-tuberculosis treatment OR CXR was consistent with intrathoracic TB.

	Well-defined symptoms: Persistent cough: an unremitting cough that is not improving and has been present for >21 days; fever: body temperature of >38°C for 14 days, after common causes such as malaria or pneumonia have been excluded; weight loss or failure to thrive: in addition to asking about weight loss or failure to thrive, evidence from the child's growth chart is also necessary
Seddon, 2013	TB disease was diagnosed if the child met the criteria for certain or probable TB. These definitions are listed below: 1. Confirmed TB: at least 1 suggestive sign/symptom; microbiological confirmation 2. Probable TB: at least 1 suggestive sign/symptom; chest radiograph is consistent; at least 1 of the following: (a) A positive clinical response to anti-tuberculosis treatment; (b) Documented exposure to *Mycobacterium TB*; (c) Immunological evidence of *Mycobacterium TB* infection
Chakhaia, 2014	Disease confirmed by a positive acid-fast bacilli culture for *Mycobacterium tuberculosis* or a clinical diagnosis of TB by a National Center for TB and Lung Diseases clinician based on compatible symptoms and radiographic findings.
Yoshiyama 2015	Bacillary cases diagnosed based on either culture or polymerase chain reaction for *Mycobacterium tuberculosis* with sputum or gastric juice specimens or with specimens from fiberoptic bronchoscopy. Non-bacillary TB cases were diagnosed by radiologists and pulmonologists based on chest computed tomography scan findings and slow improvement after TB treatment.
Singh, 2013	Not specified
Altet, 2015	Not specified
Yuhara, 2013	Diagnosed via the Information System for Disease Notification database
Zellweger, 2015	Not specified
Wang, 2012	Active TB disease was diagnosed if: 1) the mycobacterial cultures for sputum samples yielded *Mycobacterium tuberculosis*; and/or 2) chest radiography performed revealed new patch(es) of consolidation, collapse, lymphadenopathy, mass or nodule, cavitary lesion or infiltrate without other proven etiology, which was improved after standard anti-tuberculous treatment; and/or 3) information on the national TB reporting website showing that the contact had been reported and confirmed as a new case of TB.
Mazahir, 2017	Children were labeled diseased if symptomatic in addition to one of the following: sputum positive for acid-fast bacilli; chest X-ray finding consistent with TB; not responding to 7-day course of antibiotics; extra-pulmonary involvement consistent with the diagnosis of TB.
Moyo, 2015	Notified TB Cases were classified according to a standard case definition, based on either laboratory definitive evidence requiring isolation of *Mycobacterium TB* complex by culture or nucleic acid testing, or clinical diagnosis accompanied by treatment. Diagnosed via the Public Health Events Surveillance System.
Lu, 2018	Diagnosed via TB registers from the Center for Disease Control and Prevention of Jiangsu Province.

Martinez, 2018	Diagnosis based on positive *Mycobacterium TB* culture from at least 1 site, or at least 2 of the following in the context of a positive response to TB therapy: 1) symptoms of TB including fever, cough for >2 weeks, and weight loss; 2) a positive TST; 3) chest radiography consistent with active TB; or 4) failure to respond to empiric antibiotics in 2 weeks.
del Corral, 2009	Extrapulmonary and pediatric TB cases were diagnosed following American Thoracic Society's[2] and the Stop TB Partnership Childhood TB subgroup's guidelines[3]
Sloot, 2014	Diagnosis based on symptoms, chest radiograph, sputum smear and culture results, and/or by clinical response to treatment, based on national guidelines[4]
Villalba, 2018	Diagnosed TB included confirmed, possible, and probable cases. 1. Confirmed: isolation of *Mycobacterium TB* on culture. Polymerase chain reaction restriction analysis of the hsp65 gene was performed to differentiate *Mycobacterium TB* from nontuberculous mycobacteria. 2. Probable: clinical signs and symptoms of TB and radiographic findings consistent with intrathoracic TB as defined by Marais et al[5], and either 1) a positive TST or QFT-GIT or 2) histopathologic findings compatible with TB, without positive mycobacterial culture results. 3. Possible: clinical signs and symptoms of TB and abnormal CXR findings not consistent with but possibly related to active TB (eg, nonspecific shadows) and either 1) a positive TST or QFT-GIT or 2) histopathologic findings compatible with TB, without positive mycobacterial culture results. In children <3 years of age, a diagnosis of probable or possible TB was also made when clinical signs and symptoms of TB were present together with radiographic findings but without a positive TST or QFT-GIT, because in this age group these T-cell based tests have low sensitivity for TB disease. When clinically indicated, additional examinations to diagnose extrapulmonary forms of TB were performed.
Datta, 2014	Definition for diagnoses in actively screened contacts not specified. Self-reported TB episodes were confirmed by checking national TB program records.
Sharma, 2017	Diagnosed cases were classified as definitive and probable. 1. Definitive: *Mycobacterium TB* demonstrated in smear and/or culture or *Mycobacterium TB*-PCR was positive in various body fluids (sputum, BAL, pleural fluid, ascitic fluid, pericardial fluid, CSF, bone marrow aspirates, pus specimens from cold abscesses). 2. Probable: Specimen for smear and/or culture or *Mycobacterium TB*-PCR was negative or cannot be obtained due to technical difficulties. The diagnosis of TB was made primarily on the basis of imaging or presence of exudative effusion or other body fluids with elevated adenosine deaminase activity (>35 U/L).
Lemos, 2004	Diagnosed if contact had a positive acid-fast bacilli smear or TB culture and/or a clinical picture of TB, a suggestive thorax X-ray plus clinical improvement with TB treatment within 30 days.
Fox, 2018	The diagnosis of TB among contacts was made by routine clinical staff members working within the National TB Program, according to a combination of standard clinical, microbiologic, and radiologic criteria based on WHO guidelines[6]

Lienhardt, 2010	Diagnosed cases were classified as possible, probable, or definite. 1. Definite: 1 positive acid-fast bacilli result - smear or gastric aspirate, excluding single scanty acid-fast bacilli result; Or 1 positive culture from any body tissue, fluids, or secretion 2. Probable: any child with possible TB who had, in addition to the above: Chest X-ray with features of pulmonary TB, single scant acid-fast bacilli result. 3. Possible: chest X-ray, TST >15 mm or TST 10 mm if BCG scar absent, or proven recent TST conversion and suggestive clinical signs and symptoms.
Dobler, 2013	Diagnosed via the New South Wales notifiable disease database.
van Schalkwyk, 2014	TB case definition based on Shapiro et al[7]. and defined as follows: confirmed, culture-positive specimen in which M. tuberculosis was identified; or probable, smear-positive sample without culture confirmation, or a culture-positive specimen without definitive speciation. If participants reported diagnosis in between visits, diagnosis was verified by treatment card. Deaths reported by relatives attributable to TB were counted as cases.
Lopez-Varela, 2017	A standardized clinical case definition of intrathoracic TB disease and included confirmed plus probable cases. 1. Confirmed: those with compatible symptoms plus a positive culture with *Mycobacterium TB* 2. Probable TB: 1) compatible symptoms unresolved at last clinical follow-up visit (before any TB treatment initiation) plus 2) compatible CXR (for children with ≥1 CXR, the latter was used given the likelihood of seeing resolving pneumonias) plus 3) at least one of the following: TB exposure, positive TST or positive response to TB treatment. Extrapulmonary TB cases followed the same definition except for the requirement of having an abnormal CXR. Compatible TB symptoms: cough for ≥ 14 days not responding to appropriate course of antibiotics; fever greater than 38°C ≥14 days, after common causes like malaria or pneumonia were excluded; malnutrition defined as under 60% weight for height, failure to gain weight for more than 2 months or any loss of weight and not responded to nutritional interventional; unexplained wheeze ≥14 days not responding to standard treatments; lower respiratory tract infection ≥14 days not responding to antibiotics after 72 hours; TB exposure in the last 12 months; symptoms compatible with Extrapulmonary TB, such as painless enlarged lymph nodes with or without fistula formation ≥14 days, arthritis, gibbus, meningitis, effusion or unexplained hematuria, dysuria or polaquiuria for ≥21 days.
Hannoun, 2016	Not specified
Talat, 2010	Not specified
Anger, 2012	Diagnosed via New York City TB registry, based on Center for Disease Control criteria[8]
Gounder, 2015	Diagnosed via New York City TB registry, based on Center for Disease Control criteria[8]

Egere, 2017	Case definitions based on revised World Health Organization case definitions[9]. Specifically: 1. Confirmed: detection of acid-fast bacilli using microscopy or secretions, or identification of *Mycobacterium TB* on culture, or identification of *Mycobacterium TB* using Xpert. 2. Clinically diagnosed: does not fulfil criteria for bacteriological confirmation, but appearance on chest X-ray suggestive of TB, and favourable response to specific anti-tuberculosis treatment, ± positive tuberculin skin test, ± histological appearance on biopsy material suggestive of TB
Espinal, 2000	Not specified
Geis, 2012	Diagnosed TB case is defined as clinically apparent disease requiring anti-tuberculous treatment
Bonnet, 2017	A TB case had clinical, microbiological, or chest X-ray features judged by the on-site clinician to warrant anti-tuberculous treatment.
Huerga, 2018	Children with TB disease were classified according to consensus guidelines[1]: 1. Confirmed: at least one positive culture/Xpert for *Mycobacterium TB* 2. Probable: suggestive symptoms and chest X-ray consistent with intrathoracic TB disease 3. Possible: suggestive symptoms or chest X-ray consistent with intrathoracic TB disease
Kato-Maeda, 2019	Diagnosed via TB registry, based on Center for Disease Control criteria[8]
Carvalho, 2001	Not specified
Patel, 2017	Diagnosed via provincial TB registries
Baliashvili, 2018	Diagnosed via National Center for Disease Control and Public Health of Georgia database

Abbreviations: TB, tuberculosis. TST, tuberculin skin test. CXR, chest X-ray. BCG, Bacillus Calmette–Guérin. QFT-GIT, QuantiFERON®-TB Gold In-tube. WHO, World Health Organization.

[1] Graham SM, Ahmed T, Amanullah F, Browning R, Cardenas V, Casenghi M, et al. Evaluation of tuberculosis diagnostics in children: 1. Proposed clinical case definitions for classification of intrathoracic tuberculosis disease. Consensus from an expert panel. J Infect Dis. 2012; 205 Suppl 2: S199–208.
[2] American Thoracic Society, CDC (1990) Diagnostic standards and classification of tuberculosis. Am Rev Res Dis 142: 725–735.
[3] Stop TB Partnership Childhood TB Subgroup World Health Organization (2006) Introduction and Diagnosis of tuberculosis in children. In: Guidance for National Tuberculosis Programmes on the Management of tuberculosis in children WHO.

[4] KNCV Tuberculosis Foundation. Landelijke Coordinatie Infectieziektebestrijding. Richtlijn Tuberculosecontactonderzoek. The Hague: KNCV; 2007.
[5] Marais BJ, Gie RP, Schaaf HS, Starke JR, Hesseling AC, Donald PR, Beyers N: A proposed radiological classification of childhood intra-thoracic tuberculosis. Pediatr Radiol 2004, 34:886–894.
[6] Treatment of tuberculosis: guidelines. 4th ed. Geneva: World Health Organization, 2010)
[7] Shapiro, A.E., Variava, E., Rakgokong, M.H., Moodley, N., Luke, B., Salimi, S., Chaisson, R.E., Golub, J.E. and Martinson, N.A., 2012. Community-based targeted case finding for tuberculosis and HIV in household contacts of patients with tuberculosis in South Africa. American journal of respiratory and critical care medicine, 185(10), pp.1110-1116.
[8] Centers for Disease Control and Prevention. Case definitions for infectious conditions under public health surveillance. MMWR Recomm Rep 1997; 46:1–55.
[9] Eurosurveillance Editorial Team. WHO revised definitions and reporting framework for tuberculosis. Euro Surveill 2013; 18: 20455.

26. Supplementary Table S16. All included individual studies and demographic information on the year of data collection, the country, the study design, WHO 'High Burden' status, and whether the country has an incidence ≥100 cases per 100 thousand persons.

First Author, Year	Years, Data Collection	Country	WHO High Burden Country	≥100 cases per 100K	Study Design
Aibana, 2016	2009–2012	Peru	Yes	Yes	Prospective
Grandjean, 2011	2005–2008	Peru	Yes	Yes	Retrospective
Grandjean, 2015	2010–2013	Peru	Yes	Yes	Prospective
Otero, 2016	2010–2011	Peru	Yes	Yes	Retrospective
Hill, 2008	2002–2006	The Gambia	No	Yes	Prospective
Acuna-Villaorduna, 2017	2008–2013	Brazil	Yes	No	Retrospective
Lee, 2017	2007–2013	Taiwan	No	No	Retrospective
Chan, 2014	2008–2009	Taiwan	No	No	Retrospective
Ling, 2011	2005–2007	Taiwan	No	No	Retrospective
Triasih, 2015	2010–2012	Indonesia	Yes	Yes	Prospective
Seddon, 2013	2010–2011	South Africa	Yes	Yes	Prospective
Chakhaia, 2014	2010–2013	Georgia	No	No	Retrospective
Yoshiyama 2015	2010–2013	Japan	No	No	Retrospective
Singh, 2013	2007–2009	India	Yes	Yes	Prospective
Altet, 2015	2007–2009	Spain	No	No	Prospective
Yuhara, 2013	2006–2011	Brazil	Yes	No	Retrospective
Zellweger, 2015	2009–2013	10 European Countries	No	No	Prospective
Wang, 2012	2007–2009	Taiwan	No	No	Prospective
Mazahir, 2017	2014–2015	India	Yes	Yes	Prospective
Moyo, 2015	2005–2013	Australia	No	No	Retrospective
Lu, 2015	2015–2016	China	Yes	No	Retrospective
Martinez, 2018	1995–2008	Uganda	Yes	Yes	Prospective
del Corral, 2009	2005–2008	Colombia	No	No	Prospective
Sloot, 2014	2002–2012	The Netherlands	No	No	Retrospective
Verhagen, 2014	2010–2011	Venezuela	No	No	Prospective
Datta, 2014	2006–2013	Peru	Yes	Yes	Retrospective
Sharma, 2017	2008–2012	India	Yes	Yes	Prospective

Lemos, 2004	1997–1999	Brazil	Yes	No	Prospective
Fox, 2018	2010–2015	Vietnam	Yes	Yes	Prospective
Lienhardt, 2010	2004–2006	Senegal	No	Yes	Prospective
Dobler, 2013	2000–2009	Australia	No	No	Retrospective
Van Schalwayk, 2014	2009–2010	South Africa	Yes	Yes	Prospective
Lopez-Varela, 2017	2011–2012	Mozambique	Yes	Yes	Prospective
Hannoun, 2016	2014–2016	Algeria	No	No	Prospective
Talat, 2010	2001-2008	Pakistan	Yes	Yes	Prospective
Anger, 2012/Gounder, 2015	1997–2007	United States	No	No	Retrospective
Egere, 2017	2012–2014	The Gambia	No	Yes	Prospective
Espinal, 2000	1994–1995	Dominican Republic	No	No	Prospective
Geis, 2012	2008–2012	Germany	No	No	Prospective
Bonnet, 2017	2012–2014	Uganda	Yes	Yes	Prospective
Baliashvili, 2018	2012–2014	Georgia	No	No	Retrospective
Huerga, 2018	2012–2016	Armenia	No	No	Prospective
Carvalho, 2001	1995–1997	Brazil	Yes	No	Prospective
Kato-Maeda, 2019	2008–2012	United States	No	No	Retrospective

We provide a table below detailing the prospective and retrospective nature of the data collection of each study with the corresponding national tuberculosis incidence of the country in which the study was conducted (Table 2). We also provide a table below detailing the prospective and retrospective nature of the data collection of each study with whether the country of the study was classified as ‘High Burden’ by the World Health Organization (Table 2).

27. Supplementary Table S17. Correlation between the Prospective/Retrospective data collection of studies included with the incidence burden of the study's country as classified by the World Health Organization.

Incidence Burden ≥100 cases per 100,000 persons	Prospective Study Design	Retrospective Study Design	Total
Yes	18 (94.7)	1 (5.3)	19 (100)
No	10 (38.5)	16 (61.5)	26 (100)

28. Supplementary Table S18. Correlation between the Prospective/Retrospective data collection of studies included with the 'High Burden' status of the study's country as classified by the World Health Organization.

WHO classified 'High Burden' Country	Prospective Study Design	Retrospective Study Design	Total
Yes	14 (87.5)	2 (12.5)	16 (100)
No	14 (48.2)	15 (51.8)	29 (100)

29. Supplementary Table S19. Diagnostic Criteria or Algorithms Used in Baseline Evaluations for Included Studies.
We summarize the baseline diagnostic algorithm used by each study by reading a representative manuscript. (See 'References for All Individual Studies'.) Not all diagnostic approaches were readily accessible from these published manuscripts. Baseline diagnostic evaluations were divided into those that were given to all participants, those that were given to a subset of participants, and those for which it was not specified whether they were given to the entirety or a subset of the cohort.

First Author, Publication Year	Baseline Evaluations, All Participants	Baseline Evaluations, Subset of Participants	Baseline Evaluations, Participants Not Specified
Aibana, 2016	TST, symptom screen	clinical assessment, culture, smear	
Grandjean, 2011	case notification		clinical assessment, culture, smear
Grandjean, 2015			clinical assessment, CXR, culture, smear
Otero, 2016	case notification		CXR, TST
Hill, 2008	symptom screen, TST	CXR, culture, smear, response to treatment-	
Acuna-Villaorduna, 2017	case notification, TST, IGRA	culture, smear	
Lee, 2017	case notification		
Chan, 2014	case notification, clinical assessment, CXR, TST		
Ling, 2011	clinical assessment, TST	CXR	culture, smear
Triasih, 2015	clinical assessment, CXR, symptom screen, TST	culture, smear	
Seddon, 2013	clinical assessment, CXR	culture	
Chakhaia, 2014	clinical assessment, CXR, TST	smear, culture	
Yoshiyama 2015	case notification, IGRA	CT scan, CXR, PCR, response to treatment, sputum culture,	
Singh, 2013			
Altet, 2015	culture, smear, symptom screen, TST		
Yuhara, 2013	clinical assessment, CXR, IGRA, TST		culture, smear
	case notification, TST		biopsy, cerebrospinal fluid analysis, CT scan, CXR, symptom screen, culture, smear
Zellweger, 2015	case notification, IGRA		QFT, T-SPOT, CXR, culture, smear
Wang, 2012	CXR, culture, smear, T-SPOT	response to treatment	

Mazahir, 2017	CXR, gastric aspirate, symptom screen, TST, smear	fine needle cytology, response to treatment, culture, histology, neuroimaging	
Moyo, 2015	case notification, TST		clinical assessment, response to treatment, culture
Lu, 2015	case notification, TST		
Martinez, 2018	symptom screen, TST, clinical assessment	cerebrospinal fluid, CXR, gastric aspirates, lymph node aspirates, pleural fluid, culture, smear	
del Corral, 2009	clinical assessment, IGRA, TST	CXR, gastric aspirate	
Sloot, 2014	case notification, CXR, TST	IGRA, response to treatment	clinical assessment, culture, smear
Villalba, 2018	CXR, TST, IGRA, gastric aspirate, culture, smear		
Datta, 2014	symptom screen, TST (≥15 years)	culture, smear	
Sharma, 2017	IGRA, TST, symptom screen	CXR, PCR, imaging for extrapulmonary TB, culture, smear,	
Lemos, 2004	clinical assessment, CXR, TST	culture, smear, response to treatment	
Fox, 2018	clinical assessment, CXR, symptom screen	culture, smear	
Fox, 2018	case notifications, symptom screen	clinical assessment, culture, smear	
Lienhardt, 2010	clinical assessment, IGRA, symptom screen, TST	CXR, gastric aspirate, culture, smear	
Dobler, 2013	case notification, TST		
Van Schalwayk, 2014	culture, smear, clinical assessment		
Lopez-Varela, 2017			
Hannoun, 2016	IGRA, TST		
Talat, 2010			clinical assessment, CXR, smear, TST
Anger, 2012	case notification, symptom screen, TST	CXR, culture, smear	
Gounder, 2015	case notification, TST		
Egere, 2017	symptom screen, TST	clinical assessment, CXR, histology, smear, response to treatment,	
Espinal, 2000	symptom screen, TST	clinical assessment, CXR, smear	
Macintyre, 1998	case notification		TST, CXR

Geis, 2012	IGRA, TST	clinical assessment, CXR, culture, smear	
Bonnet, 2017	CXR, TST	clinical assessment, culture, smear, Xpert	
Huerga, 2018	clinical assessment, CXR, IGRA, TST	culture, smear, laryngopharyngeal or gastric aspiration, stool samples	
Carvalho, 2001	CXR, symptom screen, TST		
Patel, 2017	case notification, TST		Culture
Kato-Maeda, 2019	case notification		

30. Supplementary Table 20. Diagnostic Criteria or Algorithms Used in Follow-up Evaluations for Included Studies.

In the below table, we summarize the baseline diagnostic algorithm used by each study by reading a representative manuscript. (See 'References for All Individual Studies'.) Not all diagnostic approaches were readily accessible from these published manuscripts. Baseline diagnostic evaluations were divided into those that were given to all participants, those that were given to a subset of participants, and those for which it was not specified whether they were given to the entirety or a subset of the cohort.

First Author, Publication Year	Follow-up Evaluations, All Participants	Follow-up Evaluations, Subset of Participants	Follow-up Evaluations, Participants Not Specified
Aibana, 2015	TST, symptom screen	clinical assessment, culture, smear	
Grandjean, 2011	case notification		clinical assessment, culture, smear
Grandjean, 2015			clinical assessment, CXR, culture, smear
Otero, 2016	case notification		CXR, TST
Hill, 2008	TST	CXR, culture, smear, response to treatment	
Acuna-Villaorduna, 2017	case notification		culture, smear
Lee, 2017	case notification		
Chan, 2014	case notification, CXR		
Ling, 2011			culture, smear
Triasih, 2015	symptom screen	culture, smear	
Seddon, 2013	clinical assessment, CXR	culture	
Chakhaia, 2014	case notification		
Yoshiyama 2015	case notification, CXR	CT scan, culture, PCR, response to treatment	
Singh, 2013	not specified		
Altet, 2015	case notification		sputum culture, sputum smear
Yuhara, 2013	case notification		biopsy, cerebrospinal fluid analysis, CT scan, CXR, TST,

			symptom screen, culture, smear
	case notification		
Zellweger, 2015	CXR, culture, smear, TSPOT	response to treatment	
Wang, 2012			CXR, response to treatment, symptom screen, culture, smear
Mazahir, 2017	case notification		clinical assessment, response to treatment, culture
Lu, 2015			
Martinez, 2018		clinical assessment, cerebrospinal fluid, CXR, gastric aspirates, lymph node aspirates, pleural fluid, culture, smear	
del Corral, 2009	symptom screen, TST	clinical assessment, CXR, gastric aspirate	
Sloot, 2014	case notification		clinical assessment, CXR, response to treatment, culture, smear
Villalba, 2018	clinical assessment, TST, CXR, IGRA	CXR, IGRA	gastric aspirate, culture, smear
Datta, 2014	case notifications, symptom screen	culture, smear	
Sharma, 2017	symptom screen	clinical assessment, CXR, PCR, imaging for extrapulmonary TB, culture, smear	
Lemos, 2004	clinical assessment, CXR, TST		
Fox, 2018	clinical assessment, CXR, symptom screen,	culture, smear	

Fox, 2018	symptom screen	clinical assessment, culture, smear	
Lienhardt, Senegal	symptom screen	clinical assessment, CXR, gastric lavage, culture, smear	
Dobler, Australia	case notification		
Van Schalwayk, South Africa	case notification, symptom screen, culture, smear		
Maunank (Shah), South Africa	IGRA, TST	clinical assessment	
Hannoun, Algeria			
Talat, Pakistan	case notification		clinical assessment, CXR, smear
Anger, US	case notification	CXR, culture, smear	
Gounder, US	case notification		
Egere, The Gambia	symptom screen	clinical assessment, CXR, histology, smear, response to treatment	
Espinal, Dominican Republic	symptom screen, TST	clinical assessment, CXR, smear	
Macintyre, Canada	case notification		
Geis, Germany	symptom screen	clinical assessment, CXR, culture, smear	
Bonnet, Uganda	symptom screen	clinical assessment, CXR, culture, smear, Xpert	
Huerga, Armenia	clinical assessment, CXR, IGRA, TST	culture, smear, laryngopharyngeal or gastric aspiration, stool samples	
Carvalho, 2001			smear, response to treatment, tests for hilar adenopathy
Patel, 2017	case notification		culture
Kato-Maeda, 2019	case notification		

31. Supplementary Table S21. Requested variables from externally contacted authors with individual-patient data.

Contact Requested Variables	Index Case Requested Variables	Environmental Characteristics
Age	Age	Number of Persons in Household
Sex	Sex	Number of Siblings
HIV Status	HIV status	Charcoal use in household
Body Mass Index	Smoking Status (yes/no, # per day, etc.)	Household Ventilation
Relationship to the Index Case	Education Level	Type of housing
Administered Preventive Therapy	Duration of cough (or diagnostic delay)	
BCG Vaccination status	Sputum Smear Status	
Education Level	Cavitary disease status	
Past Active Tuberculosis	Culture status	
Household or community exposure	Multidrug-resistant status (if available)	
Closeness to Index Case	Alcohol use (yes/no, # per day, etc)	
Fever (any of >14 days)	Sputum smear grade	
Cough (any or of a certain length)	History of incarceration	
Hemoptysis	Diabetes status	
Weight loss or failure to thrive		
Night sweats		
Poor appetite		
Coprevalent (baseline) tuberculosis		
Incident tuberculosis		
Time from baseline of TB diagnosis		
Alcohol use (yes/no, # per day, etc)		
Diabetes status		
Smoking Status (yes/no, # per day, etc)		

32. Supplementary Table S22. PRISMA-IPD Checklist of items to include when reporting a systematic review and meta-analysis of individual participant data (IPD)

A1 – A3 denote new items that are additional to standard PRISMA items. A4 has been created as a result of re-arranging content of the standard PRISMA statement to suit the way that systematic review IPD meta-analyses are reported.

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data.	1
Abstract			
Structured summary	2	Provide a structured summary including as applicable:	2
		Background: state research question and main objectives, with information on participants, interventions, comparators and outcomes.	
		Methods: report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias.	
		Results: provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice.	
		Discussion: state main strengths and limitations of the evidence, general interpretation of the results and any important implications.	
		Other: report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis.	
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups.	3
Methods			
Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	4
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e.	4

		whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated.	
Identifying studies - information sources	7	Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation.	4
Identifying studies - search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection processes	9	State the process for determining which studies were eligible for inclusion.	4
Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study).	4
		If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators.	
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of standardising or translating variables within the IPD datasets to ensure common scales or measurements across studies.	4
IPD integrity	A1	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	4-5
Risk of bias assessment in individual studies.	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis.	5

Study characteristics	18	For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD.	7-8
IPD integrity	A3	Report any important issues identified in checking IPD or state that there were none.	7
Risk of bias within studies	19	Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions.	7-8
Results of individual studies	20	For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest plot.	7
Results of syntheses	21	Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based.	7-9
		When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials.	
		Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice.	
Risk of bias across studies	22	Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables.	7
Additional analyses	23	Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarise the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available.	8-9

Discussion			
Summary of evidence	24	Summarise the main findings, including the strength of evidence for each main outcome.	9-10
Strengths and limitations	25	Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available.	10-11
Conclusions	26	Provide a general interpretation of the findings in the context of other evidence.	9-11
Implications	A4	Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research.	9-11
Funding			
Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	15

Specification of outcomes and effect measures	13	State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome.	5
Synthesis methods	14	Describe the meta-analysis methods used to synthesise IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to): • Use of a one-stage or two-stage approach. • How effect estimates were generated separately within each study and combined across studies (where applicable). • Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for. • Use of fixed or random effects models and any other model assumptions, such as proportional hazards. • How (summary) survival curves were generated (where applicable). • Methods for quantifying statistical heterogeneity (such as I^2 and τ^2). • How studies providing IPD and not providing IPD were analysed together (where applicable). • How missing data within the IPD were dealt with (where applicable).	5-6
Exploration of variation in effects	A2	If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analysed as potential effect modifiers, and whether these were pre-specified.	5-6
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	5
Additional analyses	16	Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified.	5-6
Results			
Study selection and IPD obtained	17	Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram.	7

33. Supplementary Table S23. Characteristics of young children diagnosed <90 days from baseline.*

Characteristic	Tuberculosis Cases <90 days from Baseline		
	N	%	Prevalence
0-2 year old children			
All	181	100	0.67
TST and IGRA status			
TST+/IGRA+	131	78.4	2.83
TST-/IGRA-	36	21.6	0.14
Missing	14	…	…
BCG vaccination			
Vaccinated	75	65.2	1.14
Not Vaccinated	40	34.8	1.93
Missing	66	…	…
Preventive Therapy			
Administered	10	8.9	0.68
Not Administered	102	91.1	0.11
Missing	69	…	…
2-5 year old children			
All	339	100	0.61
TST and IGRA status			
TST+/IGRA+	260	83.1	2.71
TST-/IGRA-	53	16.9	0.15
Missing	26	…	…
BCG vaccination			
Vaccinated	158	67.8	1.22
Not Vaccinated	75	32.2	1.55
Not recorded	106	…	…
Preventive Therapy			
Administered	17	8.4	0.12
Not Administered	185	91.6	0.67
Not recorded	137	…	…

* All cohorts are included regardless of study design.

34. Supplementary Table S24. Positive and Negative Predictive Values between Prevalent Pediatric Tuberculosis and the Tuberculin Skin test, QuantiFERON Gold In-Tube Test, and ELISPOT Test

	Tuberculin Skin Test Induration ≥10 mm	QuantiFERON Gold In-Tube Test, ≥0.35 IU/mL	ELISPOT, >8 spot-forming cells*
Positive Predictive Value	2.2	5.7	1.7
Negative Predictive Value	99.9	99.5	99.8

We did not use a mixed-effects model but a crude analysis of each diagnostic test in relation to prevalent tuberculosis.