The risk of tuberculosis in children after close exposure: a systematic review and individual-participant meta-analysis

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Summary

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 In this systematic review and meta-analysis, we investigated the development of tuberculosis in children closely exposed to a tuberculosis case and followed for incident disease. We restricted our search to cohort studies published between Jan 1, 1998, and April 6, 2018, in MEDLINE, Web of Science, BIOSIS, and Embase electronic databases. Individual-participant data and a pre-specified list of variables were requested from authors of all eligible studies. These included characteristics of the exposed child, the index case, and environmental characteristics. 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 6 months; (3) individuals with household or close exposure to an individual with tuberculosis; (4) information on the age and sex of the child; and (5) start and end follow-up dates. Studies assessing incident tuberculosis but without dates or time of follow-up were excluded. Our analysis had two primary aims: (1) estimating the risk of developing tuberculosis by time-period of follow-up, demographics (age, region), and clinical attributes (HIV, tuberculosis infection status, previous tuberculosis); and (2) estimating the effectiveness of preventive therapy and BCG vaccination on the risk of developing tuberculosis. We estimated the odds of prevalent tuberculosis with mixed-effects logistic models and estimated adjusted hazard ratios (HRs) for incident tuberculosis with mixed-effects Poisson regression models. The effectiveness of preventive therapy against incident tuberculosis was estimated through propensity score matching. The study protocol is registered with PROSPERO (CRD42018087022).

Findings In total, study groups from 46 cohort studies in 34 countries—29 (63%) prospective studies and 17 (37%) retrospective—agreed to share their data and were included in the final analysis. 137 647 tuberculosis-exposed children were evaluated at baseline and 130 512 children were followed for 429 538 person-years, during which 1299 prevalent and 999 incident tuberculosis cases were diagnosed. Children not receiving preventive therapy with a positive result for tuberculosis infection had significantly higher 2-year cumulative tuberculosis incidence than children with a negative result for tuberculosis infection, and this incidence was greatest among children below 5 years of age (19·0% [95% CI 8·4–37·4]). The effectiveness of preventive therapy was 63% (adjusted HR 0·37 [95% CI 0·30–0·47]) among all exposed children, and 91% (adjusted HR 0·09 [0·05–0·15]) among those with a positive result for tuberculosis 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. Most cases occurred within weeks of contact investigation initiation and might not be preventable through prophylaxis. This suggests that alternative strategies for prevention are needed, such as earlier initiation of preventive therapy through rapid diagnosis of adult cases or community-wide screening approaches.

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See **Comment** page 924

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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, paediatric tuberculosis has been largely understudied, and its natural history in children remains poorly understood. Because of 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 on studies which took place before 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 reassessment of age-specific risks of tuberculosis and identifying risk factors for disease in exposed children is

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 from before 1940 synthesised results from these studies, and found that approximately 50% of children below the age of 1 year with recent infection developed tuberculosis. This risk 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 rose to 10% among children above 10 years of age. We searched MEDLINE and Google Scholar for articles published before April 6, 2018. We used the search terms "child", "tuberculosis", "transmission", "household", "pediatric", "paediatric", "contact", and "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. Because of this knowledge gap, the effectiveness of contact investigations and preventive therapy remains poorly understood.

Added value of this study

In this systematic review and meta-analysis, we used individual-level data from 46 cohort studies in 34 countries to provide the first contemporary estimates of tuberculosis risk in children after close exposure. 137 647 exposed children were evaluated at baseline and 130 512 children were followed for 429 538 person-years, during which 1299 prevalent and 999 incident tuberculosis cases were diagnosed. We found that exposed children below the age of 1 year, who were positive for tuberculosis infection and did not receive preventive therapy had an 18% risk of developing disease within 2 years of enrolment. In contrast to previous estimates suggesting risk falls to 5% in children aged 2–5-years, we found that this age group had a 2-year cumulative tuberculosis risk of 19%. Additionally, the effectiveness of preventive therapy to prevent incident tuberculosis was high—91% among children with tuberculosis infection. Despite this, the majority of children (82% of children with tuberculosis infection and 83% of all children below 5 years of age) 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 5 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% 2 years after exposure. Despite the effectiveness of preventive therapy, most cases occurred within weeks of initiation of the contact investigation. Although 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 might be needed to improve prevention of tuberculosis in children.

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 paediatric case finding and preventive interventions is currently unknown.

To address these knowledge gaps, we pooled data from longitudinal cohort studies conducted since 1998. 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 affected by preventive therapy, BCG vaccination, and time since tuberculosis exposure to better understand the role of various public health interventions.

Methods

Search strategy and selection criteria

In this systematic review and meta-analysis, we investigated the development of tuberculosis in children closely exposed to a tuberculosis case. The steps of our search are detailed in the appendix (pp 9–15). Briefly, we searched for cohort studies published between Jan 1, 1998, and 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 p 9), and articles were unrestricted by language. The 20-year timeframe was chosen on the basis of 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.[17–20] We included data that were unpublished, deposited on data storage repositories, conference abstracts, and dissertations if eligible.

See Online for appendix

Because of the broad nature of our search terms, we developed a list of exclusionary words (appendix pp 10–15) that ruled out articles if present in manuscript titles. To measure 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 remaining articles in two stages: the first stage was evaluation of titles and abstracts, followed by full-text review as the second stage. The

two reviewers discussed discrepancies and re-evaluated articles until consensus was reached.

Individual-participant data and a pre-specified list of variables were requested from authors of all eligible studies. These included characteristics of the exposed child, the index case, and environmental characteristics (appendix p 64). 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 6 months; (3) individuals with household or close exposure to an individual with tuberculosis; (4) information on the age and sex of the child; and (5) start and end follow-up dates. Studies assessing incident tuberculosis but without dates or time of follow-up were excluded. All data were appropriately de-identified by authors of eligible studies before sharing, so the project was deemed exempt from further review by Stanford University's institutional review board. Two reviewers (LM and OC) independently assessed the quality of each study using a modified rubric of the Newcastle-Ottawa scale.[20] Each study was judged on the basis of a 9-point scale using three broad criteria: selection of participants (4 points), comparability of studies (2 points), and ascertainment of outcome of interest (3 points). High study quality was defined as a score of 6 or greater, moderate quality as 3 to 6 points, and low quality as below 3 points. Discrepancies 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 below 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 (appendix pp 39–43 and 48–53).

Tuberculosis infection was defined as a positive QuantiFERON-TB Gold In-Tube test (interferon-γ–nil ≥0·35 IU/mL), ELISpot test (>8 spot-forming cells per well), or tuberculin skin test (TST; ≥10 mm induration). Preventive therapy was assigned to participants according to each study's protocol or local guidelines and practices. A preventive therapy regimen was defined as any preventive drug regimen given to children. Treatment adherence was not assessed in most studies. Preventive therapy regimens included isoniazid for 6 or 9 months, rifampin for 3 months, and isoniazid and rifapentine for 3 months, among others.

Prevalent and incident tuberculosis were defined on the basis of time from baseline enrolment of the participant in the contact investigation. Prevalent tuberculosis was defined on the basis of a conventional

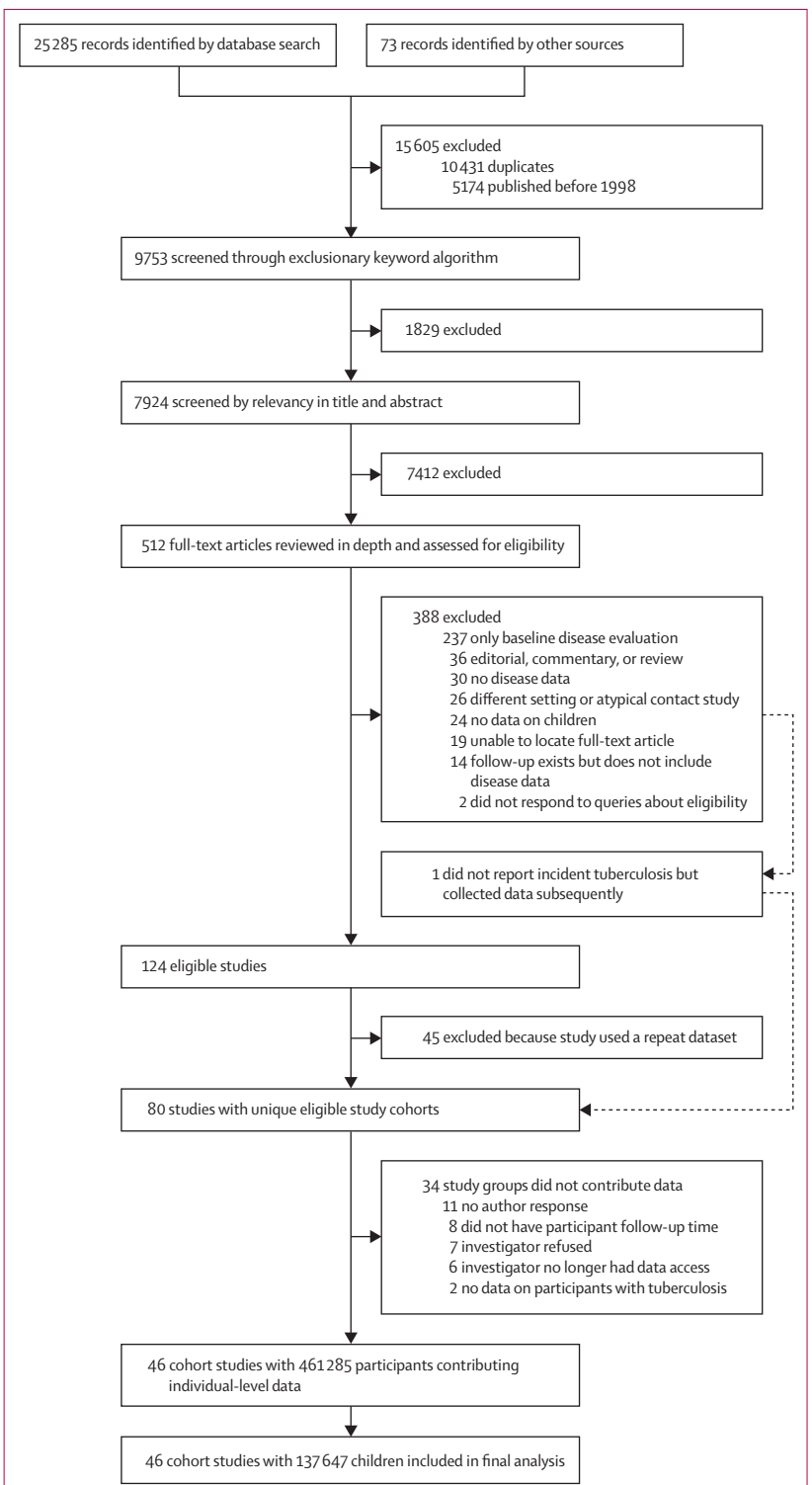

Figure 1: **Study selection**
Excluded full-text articles may have had more than one reason for exclusion, but only one reason for exclusion was listed for each excluded manuscript.

	Studies (n=46)
Prospective study design	28 (61%)
WHO high-burden country*	18 (39%)
Country-level tuberculosis incidence (per 100 000 people)†	
<50	16 (36%)
50–100	9 (19%)
>100–200	9 (19%)
>200	12 (23%)
WHO region	
African	9 (20%)
Americas	16 (33%)
Eastern Mediterranean	1 (2%)
European	7 (15%)
South-East 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	34 (72%)
Moderate	10 (24%)
Low	2 (4%)
Mean duration of study follow-up (years)	
<2	24 (56%)
2–4	13 (28%)
5–7	3 (11%)
>7	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 drug-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 person-years	429 538
Total individuals evaluated for prevalence	137 647
Total individuals evaluated for incidence	130 512
Age (years)	
Median (IQR)	10·5 (5·7–15·2)
Mean (SD)	10·3 (5·4)

Data are n or n (%) unless otherwise specified. *Studies were designated as being located in a high-burden country as classified by WHO. †Country-level tuberculosis incidence data were collected from WHO databases for each study. ‡Studies were grouped into WHO global regions and World Bank country-level economies (high income, upper-middle income, lower-middle income, and low income) as of October, 2018. §By use of a modified rubric of the Newcastle-Ottawa scale. ¶This refers to preventive therapy that was given to some participants and includes any type of preventive therapy regimen.

Table 1: **Demographic characteristics of included cohort studies**

definition[18] (appendix p 5), as any diagnosis of tuberculosis at the initial visit or within 90 days of baseline evaluation. Incident tuberculosis was defined as a new tuberculosis case diagnosed more than 90 days after the initial evaluation. To define a tuberculosis case, we used the classification provided by each study. Definitions for tuberculosis diagnosis, diagnostic tests, and algorithms used for diagnosis at baseline and follow-up in each study are listed in the appendix (pp 48–53 and 58–63).

This study follows PRISMA-IPD guidelines for individual-participant data reporting (appendix pp 65–69).[21] The study protocol is registered with PROSPERO (CRD42018087022) and includes a pre-specified analytical plan.

Data analysis

We pooled individual-participant 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: (1) estimating the risk of developing tuberculosis by time-period of follow-up, demographics (age, region), and clinical attributes (HIV, tuberculosis infection status, previous tuberculosis); and (2) 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 were included in this analysis. The cumulative incidence included both prevalent and incident tuberculosis in the first 2 years of follow-up in these studies. We stratified these results by age and baseline results of TST or interferon-γ release assay (IGRA).

The analysis of tuberculosis risk factors was done 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 appendix pp 36–37). 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

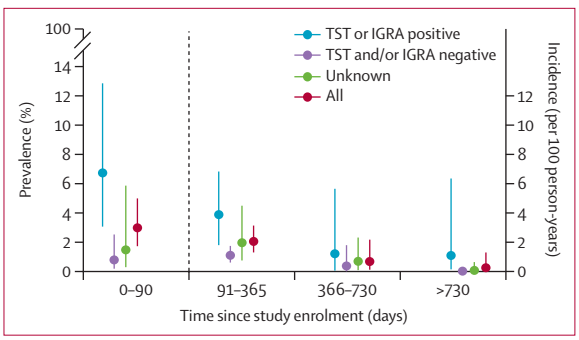

Figure 2: **Risk of tuberculosis over time among exposed children not receiving preventive therapy**
Only children from prospective studies who did not receive preventive chemotherapy were included in this analysis. Shown are tuberculosis prevalence within 90 days of enrolment (left y-axis) and subsequent tuberculosis incidence over various intervals (right y-axis), stratified by baseline TST or IGRA status. The bars represent 95% CIs of each mean estimate. Bars might not be visible for some estimates at more than 730 days since study enrolment because the CIs are narrow. The dotted vertical line represents 90 days. If both a TST and IGRA was used in the study then this was categorised as TST and IGRA negative (ie, both tests were negative). If only one test was used in a study, representing the vast majority of studies, then this was categorised as TST or IGRA negative. TST=tuberculin skin test. IGRA=interferon-γ release assay.

study-level random effects for all analyses. Tuberculosis incidence was stratified by days following study enrolment (91–365, 366–730, and >730 days). To assess the effect 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-analysed our risk factor analysis without this study to assess the effect of this study on our results.

When evaluating the protective effect of preventive therapy, we did a propensity score analysis, with matching based on individual-level covariates of age, sex, and study design. We then matched children who began preventive therapy with children who did not using a nearest-neighbor matching algorithm. In this matched cohort, we repeated our parametric survival-time models to estimate covariate-adjusted risk of 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. See appendix (pp 7, 32, and 38) for additional details of the analytical methodologies used.

We did 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.

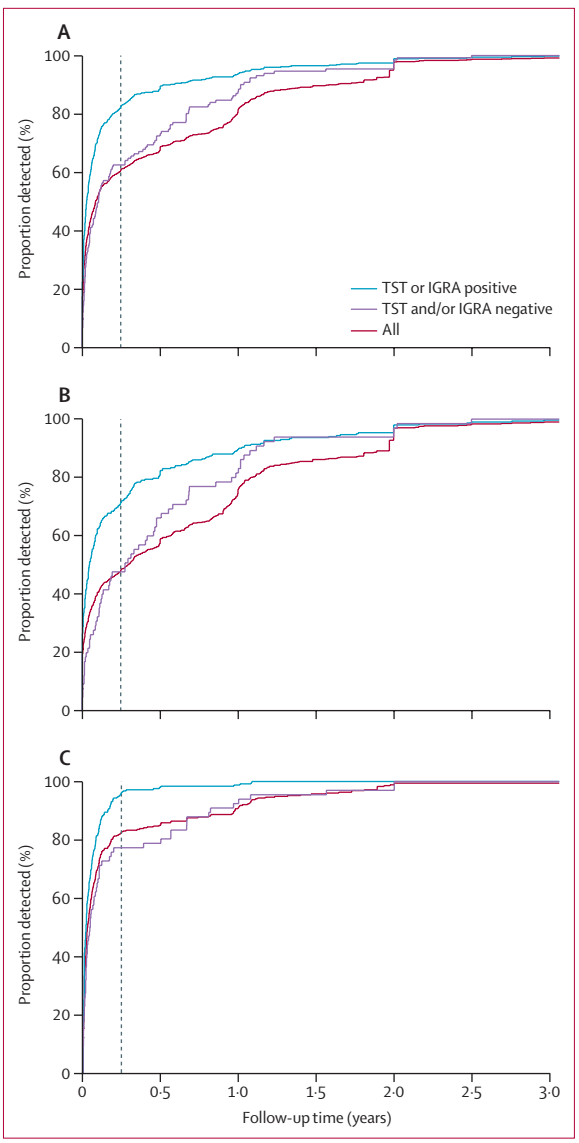

Figure 3: **Tuberculosis cases diagnosed over follow-up time**
(A) All children. (B) Children 5–18 years of age. (C) Children below 5 years of age. Only children from prospective studies who did not receive preventive chemotherapy were included in this analysis. All children represent all participants, regardless of TST or IGRA testing, which is a larger group of children than those with positive or negative results for TST or IGRA. The detection proportion for all children therefore does not appear as a weighted average between those two groups. The dotted vertical line represents 90 days. If both a TST and IGRA was used in the study then this was categorised as TST and IGRA negative (ie, both tests were negative). If only one test was used in a study, representing the vast majority of studies, then this was categorised as TST or IGRA negative. TST=tuberculin skin test. IGRA=interferon-γ release assay.

Results

From our multi-database search, we found 14 927 original titles and reviewed 7924 abstracts and titles published

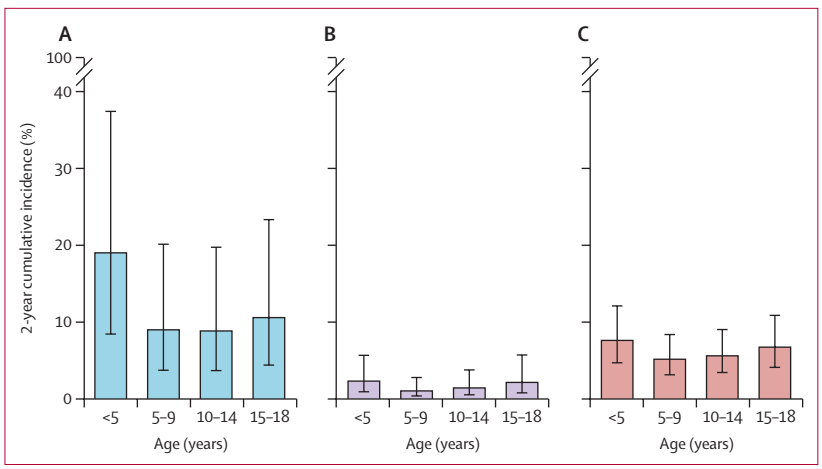

Figure 4: **2-year cumulative incidence of tuberculosis among children not receiving preventive therapy, with positive baseline TST or IGRA results (A), negative baseline TST and/or IGRA results (B), and in all children, including those not tested for tuberculosis infection (C)**

The 2-year cumulative incidence of tuberculosis includes prevalent and incident tuberculosis in the first 2 years of follow-up from prospective cohort studies, stratified by age and baseline results of TST or IGRA. Bars represent mean estimates and lines represent 95% CIs. Risk of tuberculosis for 1-year age bins can be seen in the appendix (p 29). In panel A, the 2-year cumulative incidence of tuberculosis for children with positive baseline TST or IGRA results was consistent within each age group bin; for example the 2-year cumulative incidence of tuberculosis was 19% (range 17–21) for children below 5 years of age. Additionally, the 2-year cumulative incidence of tuberculosis for children with positive baseline TST or IGRA results below 5 years of age was significantly higher compared with children aged 5–9 years (p<0·0001), 10–14 years (p<0·0001), and 15–18 years (p=0·0006). In panel B, the 2-year cumulative incidence of tuberculosis for children with negative baseline TST and/or IGRA results below 5 years of age was significantly higher compared with children aged 5–9 years (p=0·0189), but not compared with children aged 10–14 years (p=0·1576) or children with positive baseline TST or IGRA results who were 15–18 years of age (p=0·8335). In panel C, the cumulative risk among all children below 5 years of age, was higher compared with children aged 5–9 years (p=0·0027) and 10–14 years (p=0·0145), but not compared with children aged 15–18 years with positive baseline TST or IGRA results (p=0·3491). If both a TST and IGRA was used in the study then this was categorised as TST and IGRA negative (ie, both tests were negative). If only one test was used in a study, representing the vast majority of studies, then this was categorised as TST or IGRA negative. TST=tuberculin skin test. IGRA=interferon-γ release assay.

after Jan 1, 1998 (figure 1). After title, abstract, and full-text review, 80 study groups were contacted for individual-participant data. In total, 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; appendix pp 24–25). 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 (70%) studies. Among studies with household clustering data, we found that the median number of children per household included in the study was two (IQR 1–4). Characteristics of studies that contributed participant-level data were generally similar to those that were not included (appendix p 33).

Of 137 647 children evaluated at baseline, 1299 (1%) were diagnosed with prevalent tuberculosis. For the cohort analysis, 130 512 children were followed for 429 538 person-years, including 395 531 years after the 90-day initial evaluation window, leading to 999 incident tuberculosis cases. Baseline TST or IGRA results were available for 117 712 children, among whom 34 692 (random-effects prevalence estimate 34·7% [95% CI 29·6–40·1]) had positive tests, with prevalence increasing with age (appendix p 23).

We calculated the risk of prevalent tuberculosis (cases diagnosed within 90 days of enrolment) and incident tuberculosis, among individuals not receiving preventive therapy, over 2 years of follow-up (figure 2). The risk of tuberculosis over follow-up was highest within 90 days of enrolment (2·9% [95% CI 1·7–4·9]). Prevalence of tuberculosis was much higher among children with baseline positive TST or IGRA results (6·5% *vs* 0·8% among children with a negative TST or IGRA result 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). Among children with a baseline positive TST or IGRA result, 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 or IGRA result, incidence over these same intervals was 1·1, 0·5, and <0·1 cases per 100 person-years (figure 3).

Among all children who developed tuberculosis, 586 (61%) of 962 were diagnosed in the first 90 days of screening (figure 3A). This number increased to 453 (82%) of 550 among children with a baseline positive TST or IGRA result. Among 353 children below 5 years of age who developed tuberculosis, 292 (83%) were diagnosed within 90 days; among these young children with a positive TST or IGRA result, 238 (96%) of 247 were diagnosed within 90 days (figure 3B). The proportion of children who developed tuberculosis in the first 90 days of screening was much higher for children below 5 years of age compared with children 5–18 years of age (figure 3B, 3C).

The 2-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 4C), ranging from 7·6% in children below 5 years of age to 5·2% in children 5–9 years of age (p=0·0027 compared with children <5 years of age) and 5·6% in children 10–14 years of age (p=0·0145 compared with children <5 years of age), followed by a subsequent increase in risk to 6·7% among children above 15 years of age (p=0·3491 compared with children <5 years of age). Children with negative baseline TST and/or IGRA results had a similar U-shaped curve, but slightly lower cumulative risks (figure 4B). Children with positive baseline TST or IGRA results had significantly higher 2-year cumulative tuberculosis incidence (figure 4A) than children with negative baseline TST and/or IGRA results, and this incidence was greatest among children below 5 years of age (19·0% [95% CI 8·4–37·4]; figure 4). The cumulative risk among children below 5 years of age with positive baseline TST or IGRA results was significantly higher than in children 5–9 years of age (p<0·0001), 10–14 years of age (p<0·0001), and 15–18 years of age (p=0·0006) who had positive baseline

TST or IGRA results. Among children below 5 years of age with positive baseline TST or IGRA results, the 2-year cumulative tuberculosis incidence was relatively consistent in 1-year age bins, ranging from 16% to 22%.

Children living with HIV had a higher risk of prevalent (adjusted odds ratio [OR] 2·80 [95% CI 1·62–4·85]) and incident (adjusted hazard ratio [HR] 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 (adjusted OR 6·58 [4·40–9·84]) and during follow-up (adjusted HR 3·20 [2·22–4·51]).

Prevalent and incident tuberculosis rates changed substantially based on the cutoff threshold used (appendix p 30). Among all children, for cutoff thresholds from baseline of 0, 30, and 60 days, prevalence of tuberculosis was 0·4% (95% CI 0·2–1·2), 1·2% (0·4–3·5), and 1·7% (0·7–4·3; appendix p 30). Among children with positive TST or IGRA results, prevalence of tuberculosis was 0·9% (0·2–3·7), 3·8% (1·6–9·1), and 4·5% (1·8–10·8; appendix p 30) for cutoff thresholds from baseline of 0, 30, and 60 days.

Children who received preventive therapy were at substantially lower risk of developing tuberculosis compared with those who did not, and this effect was modified by infection status. The effectiveness of preventive therapy was 63% (adjusted HR 0·37 [95% CI 0·30–0·47]) among all exposed children. The effectiveness was greater in children with baseline infection (adjusted HR 0·09 [0·05–0·15]), and had a non-significant relation in children without baseline infection (adjusted HR 0·66 [0·40–1·10]). This analysis was reasonably robust to alternative statistical models without use of propensity score matching and alternative propensity scores (appendix pp 7, 26–27, 32, and 36–37). Additionally, the effect of preventive therapy for incident tuberculosis was present in contacts of drug-susceptible (adjusted HR 0·33 [0·20–0·54]) and drug-resistant (adjusted HR 0·44 [0·21–0·93]) tuberculosis index cases ($p_{interaction}$=0·454).

In children below 5 years of age, BCG vaccination was protective against all forms of tuberculosis (adjusted OR 0·64 [95% CI 0·50–0·84]). However, among children aged five years or above, those receiving a BCG vaccination had similar risk of tuberculosis compared with those who did not (table 2).

There was between-study heterogeneity in prevalent and incident tuberculosis. Prevalent tuberculosis ranged from 0–15% (figure 5A). The rate of incident tuberculosis per 100 person-years ranged from 0–3·3% (figure 5B). Much of the heterogeneity for both prevalent and incident tuberculosis was due to the global region the study took place in, and the prospective or retrospective nature of data collection (figure 4A, 5B).

Compared with studies in the WHO African region, studies showed substantially lower rates of prevalent tuberculosis in the Americas region (adjusted OR 0·48 [95% CI 0·21–1·12]) and the Western Pacific region (adjusted OR 0·10 [0·04–0·23]). Incident tuberculosis was also lower in the Western Pacific region versus the African region (adjusted HR 0·16 [95% CI 0·07–0·35]). Prospective studies identified more prevalent (adjusted OR 3·26 [1·49–7·12]) and incident tuberculosis (adjusted HR 3·12 [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 establish whether between-study heterogeneity was due to regional epidemiological differences, prospective or retrospective study design, or a combination of both.

	Prevalent tuberculosis adjusted OR (95% CI)	Incident tuberculosis adjusted HR (95% CI)	All tuberculosis* adjusted OR (95% CI)
Male sex	1·05 (0·96–1·13)	0·99 (0·88–1·13)	1·03 (0·94–1·12)
Tuberculosis infection†			
TST 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)
Previous 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 positive or IGRA positive	..	0·15 (0·11–0·20)	..
TST positive or IGRA positive, propensity score matched§	..	0·09 (0·05–0·15)	..
TST negative and/or IGRA negative ¶	..	0·65 (0·40–1·06)	..
TST negative and/or IGRA negative, 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 (*vs* retrospective) data collection	3·00 (1·45–6·21)	3·42 (1·83–6·42)	2·38 (1·38–4·13)

Both prospective and retrospective studies are included in this analysis. The analysis was repeated with stratification of the prospective or retrospective nature of the data collection (appendix pp 26–27). Each row represents a distinct statistical model. Each statistical model is adjusted for the variable of interest, baseline child age and sex, whether data was collected prospectively or retrospectively, and the study. The referent group for each row (including rows of sub-characteristics) is the opposing value of the listed characteristic. For example, for HIV infection the reference group is children living without HIV. Prevalent tuberculosis was defined as any 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 were not given or protected by preventive therapy. OR=odds ratio. HR=hazard ratio. TST=tuberculin skin test. IGRA=interferon-γ release assay. *Includes both prevalent and incident tuberculosis as one outcome. †All tests for tuberculosis infection (TST, QuantiFERON Gold In-Tube test, and ELISpot tests) were administered at baseline. TSTs or IGRAs may have been used in the case definition for tuberculosis, potentially leading to diagnostic bias. ORs for tests of tuberculosis infection may be understood as diagnostic ORs. ‡A preventive drug therapy regimen was defined as any preventive drug regimen given to children. 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. §Propensity score matching is based on the age and sex of the contact and whether the study design is prospective or retrospective. ¶If both a TST and IGRA was used in the study then this was categorised as TST and IGRA negative (ie, both tests were negative). If only one test was used in a study, representing the vast majority of studies, then this was categorised as TST or IGRA negative.

Table 2: **Risk factors for tuberculosis among 137 647 children below 19 years of age**

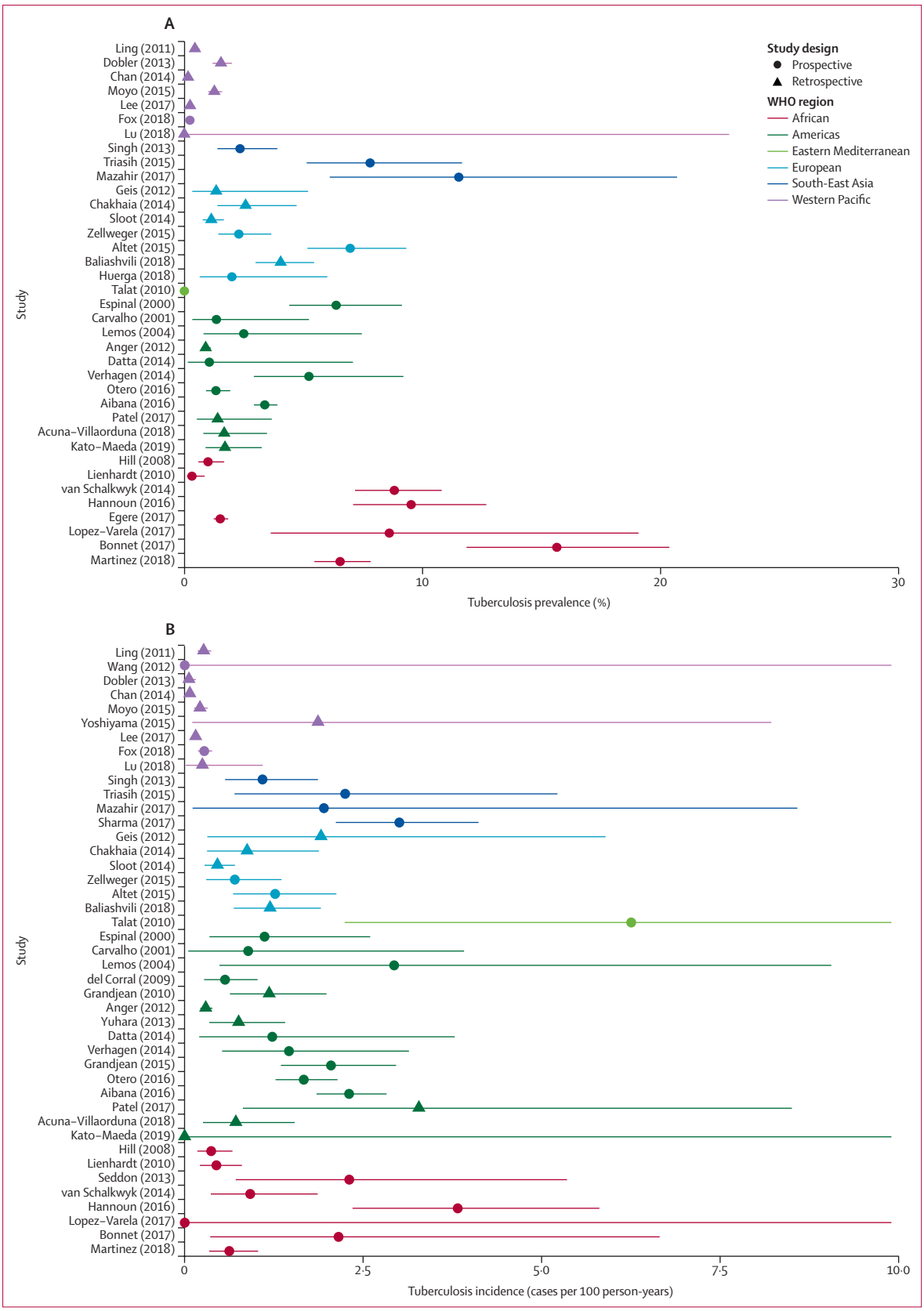

Figure 5: **Study-specific prevalent (A) and incident (B) tuberculosis in all children, stratified by study design and region**

Discussion

In this systematic review and meta-analysis we used individual-level data from 137 647 exposed children, 130 512 of which were followed for 429 538 person-years, and found that the 2-year cumulative risk of tuberculosis in children is very high, approaching 20% in children positive for tuberculosis infection who are below 5 years of age. The effectiveness of preventive therapy was 63% among all children, and 91% among those with positive TST or IGRA results. However, we also found that 61% of all paediatric tuberculosis cases and 83% of cases among children below 5 years of age were diagnosed within 90 days of initiation of contact investigation, suggesting a large proportion of cases might not be avoided by preventive therapy. As over 15 million children are exposed to tuberculosis globally every year,[1,2] our estimates indicate that many exposed children, especially those with recent infection, are at substantial risk of developing tuberculosis and must be prioritised by development of new prevention and early case finding strategies.

The results of this study provide the first contemporary estimates of tuberculosis risk in children after close exposure. Historical studies on children performed before 1950 were recently synthesised.[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 children below the age of 1 year who had positive TST or IGRA results and did not receive preventive therapy had an 18% risk of developing disease within 2 years of enrolment. In contrast to previous estimates suggesting risk falls to 5% in children 2–5 years of age,[6,7] we found that this age group had a 2-year cumulative tuberculosis risk of 19%. Additionally, although our results indicate that young children have the highest risk of developing tuberculosis, adolescents (aged 10–18 years) face a greater risk following lower risks between the ages of 5–9 years.[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 positive TST or IGRA results, but there was also protection among all children. Among children with negative TST and/or IGRA results there was a 44% protective effect; however this association was not significant (95% CI –10 to 60; table 2). A meta-analysis of seven trials including 10 320 children (8537 recruited before 1975) found that efficacy of preventive therapy was 59% among children over 4 months of age,[25] comparable with our overall estimate of 63%, but this meta-analysis did not include analyses stratified by infection status. 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 proportion increased to 82% in children with tuberculosis infection and to 83% in children below 5 years of age, suggesting the importance of early case finding. Although 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 might 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 previous tuberculosis diagnosis. These children should be prioritised for preventive 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 below 2 years of age.[27,28] Our study confirms these results in all children, finding that a child below 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 observational data from 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. Because of poor ascertainment of paediatric tuberculosis during passive case finding, we limited our analysis of tuberculosis incidence to prospective cohort studies. When assessing the effectiveness of preventive therapy, confounding by indication could 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 or IGRAs may be used in the case definition for tuberculosis, potentially leading to diagnostic bias. These factors might partially explain the high proportion of tuberculosis cases diagnosed within 90 days. We defined prevalent tuberculosis as cases diagnosed within 90 days of enrolment, to account for diagnostic delays inherent in establishing a tuberculosis diagnosis in children; we examined multiple other thresholds (0, 30, and 60 days) in sensitivity analyses and found an increased prevalence between 0 and 90 days of age which might reflect rapid development of incident cases.

In summary, our study represents a combined analysis of data from 46 cohort studies in 34 countries, representing diverse sociodemographic and epidemiological settings. The results identify key age-specific and risk-factor specific

groups of children that can be prioritised by tuberculosis control programmes, and find that although 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 paediatric tuberculosis.

Contributors

All authors contributed to the acquisition of the work. Sanjay Basu, Nathan C Lo, Ted Cohen, Mark Hatherill, Heather J Zar, and CRH were members of the advisory committee. LM, OC, CRH, and JRA were members of the primary analysis and writing group. LM and OC did the systematic search, screened and identified studies, and made final decisions regarding study inclusion. LM, OC, and JRA designed the analyses. LM received and checked data, conducted analyses, and had full access to all materials and results. JRA conducted analyses and created figures. OC conducted analyses and helped create tables and figures. LM, OC, and JRA wrote the first draft of the report. All writing committee members (LM, JRA, and OC) 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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Declaration of interests
We declare no competing interests.

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