The risk of tuberculosis in children after close exposure: an individual-participant systematic review and 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 (4) 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 exposed children were evaluated at baseline and 130 512 children were followed for 429 538 child-years, during which 1299 prevalent and 999 incident tuberculosis cases were diagnosed. [A: OK as edited?] 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 85% (adjusted HR 0·15 [95% CI 0·11–0·20]) among those with a positive result for tuberculosis infection. [A: Would you like to add results of your first primary aim (estimating the risk of developing tuberculosis by time-period of follow-up, demographics, and clinical attributes)?] 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 earlier diagnosis of adult cases, or community-wide screening approaches.

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Introduction [A: Please add page numbers to all mentions of the appendix] Tens of millions of children are exposed to *Mycobacterium tuberculosis* every year,13 and tuberculosis remains a leading infectious cause of global childhood morbidity and mortality.1,2 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. 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. A reassessment 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 paediatric 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 [A: Please replace with “since 19XX”, to be more precise]. 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 XX–XX). 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 pp XX–XX), 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. We included data that were unpublished, deposited on data storage repositories, conference abstracts, and dissertations if eligible.

Because of the broad nature of our search terms, we developed a list of exclusionary words (appendix...
pp XX–XX) 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 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 pp XX–XX). To be eligible for inclusion in the final dataset, a study 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 (4) 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 [A: Correct?] 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. 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.

Individual-participant data [A: Title OK?]
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 XX–XX).

Tuberculosis infection was defined as a positive Quantiferon-TB Gold In-Tube test (QFT; IFN-γ nil ≥0.35 IU/mL), T-SPOT.TB 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.
We included any reported preventive therapy regimen in our analysis; a preventive therapy regimen was defined as any preventive drug regimen given to children [A: At the baseline visit? According to table 2 legend]. Treatment adherence was not assessed in most studies. Preventive therapy regimens included isoniazid for 6 months or 9 months, rifampin for 3 months, 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 definition" [A: perhaps you could name this definition?] (appendix pp XX–XX), 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. [A: OK as edited?] 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 XX–XX).

This study follows PRISMA-IPD guidelines for individual-participant data reporting (appendix pp XX–XX). [A: OK as edited?] The study protocol is registered with PROSPERO (CRD42018087022) and includes a prespecified 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 XX–XX). 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 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 (appendix pp XX–XX). 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 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. See appendix (pp XX–XX) 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.
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 results 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.

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

[A: We reserve the use of “significant” to statistical significance. Please check your Results with this in mind] From our multi-database search, we found 14,927 original titles and reviewed 7924 abstracts and titles published after Jan 1, 1998 (figure 1, [A: We have added the study selection figure to the Article. OK to cite it here?] appendix pp XX–XX). 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 XX–XX). 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 pp XX–XX).

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 child-years [A: is there a difference between “child-years”, used here, and “person-years”, used below? If not, could you use one term for consistency?] and 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 pp XX–XX).

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 results 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, XX (61%) of XX were diagnosed in the first 90 days of screening (figure 3A). This number increased to XX (82%) among children with a baseline positive TST or IGRA result. Among XX children below 5 years of age who developed tuberculosis, XX (83%) were diagnosed within 90 days; among these young children with a positive TST or IGRA result, XX (96%) 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, [A: Please add numbers alongside percentages]).
<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 or IGRA results had a similar U-shaped curve, but slightly lower rates [A: 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 or IGRA results, greatest among children below 5 years of age (19·0% [95% CI 8·4–37·4]; appendix pp XX–XX). 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 year 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]). There was substantial between-study heterogeneity in prevalent and incident tuberculosis, with differences by study design and region (figure 5).

Prevalent and incident tuberculosis rates changed substantially based on the cutoff threshold used (appendix pp XX–XX). 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 pp XX–XX). 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 4·6% (1·8–10·8; appendix pp XX–XX) 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 XX–XX). 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<0·001).

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

<table>
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<th>Male sex</th>
<th>Coprevalent [A1] tuberculosis adjusted OR (95% CI)</th>
<th>Incident tuberculosis adjusted HR (95% CI)</th>
<th>All tuberculosis* adjusted OR (95% CI)</th>
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<td>0·99 (0·88–1·13)</td>
<td>1·03 (0·94–1·12)</td>
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<td>Tuberculosis infection?</td>
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<tr>
<td>TST induration ≥10 mm</td>
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<td>3·34 (2·86–3·89)</td>
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<tr>
<td>QuantIFERON Gold In-Tube Test ≥0·35 IU/mL</td>
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<td>6·47 (2·11–18·90)</td>
<td>14·26 (6·94–29·28)</td>
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<td>1·91 (0·64–5·70)</td>
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<td>6·58 (4·40–9·84)</td>
<td>3·20 (2·22–4·51)</td>
<td>5·30 (3·99–7·06)</td>
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Table 2: Risk factors for tuberculosis among 137 647 children below 15 years of age

[A1: OK?]

[A: Please move this text to the Methods]

¶Propensity score matching is based on site and we accepted each study’s decision to administer preventive therapy. Completion of preventive therapy was not be understood as diagnostic ORs. ‡Administration of diagnostic tests, please check. **Includes both prevalent and incident tuberculosis. *Includes both prevalent and incident tuberculosis as one outcome. 

[A: T-SPOT.TB in the main text?]

[A: OK to reward you have not defined coprevalent anywhere else? 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 XX–XX). 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. OR=odds ratio. HR=hazard ratio. TST=tuberculin skin test. IGRA=interferon-γ release assay. 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. *Includes both prevalent and incident tuberculosis as one outcome. †All tests for tuberculosis infection (TST, QuantIFERON Gold In-Tube test, and ELISPOT [A: T-SPOT.TB in the main text?]) 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: Should they all be understood as diagnostic ORs?]. Administration of preventive therapy, including any type of preventive therapy regimen. [A: Unclear how this is related to the ELISPOT diagnostic tests, please check] A preventive drug therapy regimen was defined as any preventive drug regimen given to children at the baseline visit. 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. [A: Please move this text to the Methods] Propensity score matching is based on the age and sex of the contact and whether the study design is prospective or retrospective.
Figure 5: Study-specific prevalent (A) and incident (B) tuberculosis in all children, stratified by study design and region.
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]) in children 2–5 years of age,6,7 whereas non-affected regions had rates of tuberculosis in children below the age of 1 year of 30–50% in early infancy.8–11

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 region22 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.

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 child-years [A: OK?], and found that the 2-year cumulative risk of tuberculosis in children is 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 nearly two-thirds [A: Please change to a percentage, to match the rest] of all paediatric tuberculosis cases and more than 80% of cases among young children [A: Please could you define young children?] 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,2,3 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 prior to 1950 were recently synthesised.17 These historical studies suggested that the risk of tuberculosis after recent infection was between 30–50% in early infancy.18–21 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,22 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 also face an increasing risk following childhood [A: by adolescents, do you mean people aged 19-24 here? Please specify].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 or IGRA results, but there was a relation among all children. Among children with negative TST or IGRA results there was a 44% protective effect, however this association was not significant (95% CI –10 to 60%) [A: Please indicate where these data can be found]. 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 [A: Correct?] 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,26 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.27 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 IGRA results may perform poorly in young children; however, recent studies have found good performance in infants below 2 years of age.28–30 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,12,13 as available diagnostics lack sensitivity, particularly among young children. As a result, experts typically recommend using composite definitions for diagnosis.31 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 IGRA 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 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
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