Effectiveness of preventive therapy among persons with differing age and *Mycobacterium tuberculosis infection* status: A systematic review and individual-participant meta-analysis

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Abstract

Background

Tuberculosis is a preventable disease. However, there is debate regarding which individuals would benefit most from preventive therapy and whether these benefits are distinct in tuberculosis high- or low-burden settings. We aimed to compare the effectiveness of tuberculosis preventive therapy in individuals of differing ages, *Mycobacterium tuberculosis* infection status, and HIV status, while considering settings with a high- and low-burden of tuberculosis.

Methods

In this individual-participant meta-analysis, we investigated the development of tuberculosis in persons closely exposed to an individual with tuberculosis and followed for incident disease. We restricted our search to cohort studies published between Jan 1, 1998, and April 6, 2018. These included characteristics of the exposed person, the index case, and environmental characteristics. We estimated adjusted hazard ratios (aHRs) for incident tuberculosis with mixed-effects Poisson and Cox regression models. We also estimated the number needed to treat (NNT) to prevent one tuberculosis case. Propensity score matching procedures were used in all analyses.

Results

In total, 407,312 participants from 32 cohort studies were followed for 1.26 million person-years, during which 2,523 incident tuberculosis cases were diagnosed. Overall, effectiveness of preventive therapy was 58% (aHR, 0.42; 95% CI, 0.35–0.49). Participants with a positive TST or IGRA result at baseline benefitted from greater protection, regardless of age (aHR, 0.09 [95% CI, 0.05–0.17] in <5-years; 0.19 [95% CI, 0.13–0.26] in 5–17-years; 0.14 [95% CI, 0.10–0.18] in adults). The effectiveness of preventive therapy was greater in high- versus low-burden settings (aHR, 0.34 [95% CI, 0.27–0.43] versus 0.58 [95% CI, 0.47–0.72]). The NNT ranged from 10–40 among participants in both high and low-burden settings with a positive TST or IGRA; when unrestricted by test result, the NNT remained low (~30–40) in high-burden settings but rose steeply in low-burden settings (~200-400).

Discussion

Our findings suggest that a risk-targeted strategy prioritizing contacts with evidence of *M. tuberculosis* infection is indicated in low-burden settings while a broad approach including all contacts should be considered in high-burden settings. Regardless of background burden, preventive therapy should be expanded to include contacts of all ages.

Introduction

Tuberculosis is both preventable and treatable;[1-3] nevertheless, approximately 9.9 million people developed the disease in 2020 leading to 1.5 million annual deaths.[4] Achieving the World Health Organization's End TB Strategic goals is unlikely in the absence of a vaccine more effective than *M. bovis* Bacille-Calmette-Guérin (BCG)[5,6] and improvements in prevention of progression from *Mycobacterium tuberculosis* infection to tuberculosis disease.[3,7,8] Nevertheless, there remains considerable uncertainty regarding the effectiveness of preventive strategies and how to incorporate them into settings with distinct tuberculosis epidemics.[9-11]

Preventive therapy for tuberculosis reduces the risk of disease in people who are not sick.[2,8-10,12] However, there is debate about whom to target for preventive therapy interventions. National tuberculosis programs must decide whether to target distinct age groups (i.e., children, adolescents, adults), test for *Mycobacterium tuberculosis* infection, concentrate on specific groups at especially high-risk (e.g., persons living with HIV [PLHIV]), or use a combination of these approaches.[9-13] Whether these considerations are distinct in high- and low-burden settings is debated.[13] Large-scale cohort studies from a variety of settings are not available but are needed to understand differential protection of preventive therapy to at-risk groups in order to inform national and global guidelines.

To further understand the effectiveness of preventive therapy against tuberculosis among differing groups, we convened a large data consortium group with longitudinal cohort studies of exposed contacts of tuberculosis cases implemented over the past 20 years. We aimed to evaluate and compare the effectiveness of preventive therapy in individuals of differing ages, *Mycobacterium tuberculosis* infection status, HIV status, and distinct settings with a high- and low-burden of tuberculosis. To gain additional insights useful for policy formulation, we also aimed to estimate and compare the number needed to treat to prevent one tuberculosis case among these groups and settings.

Methods

Search Strategy and Data Collation

In this systematic review and meta-analysis, we investigated the development of tuberculosis in persons closely exposed to a tuberculosis case. The consortium included cohorts have been described previously.[3,5] 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"; articles were unrestricted by language. The 20-year timeframe was chosen on the basis of expected availability of individual-participant data.

Individual-participant data and a pre-specified list of variables were requested from authors of all eligible studies. These included characteristics of the exposed contact, the index case, and environmental characteristics. To be eligible for inclusion in the final analysis, a dataset needed to include: (1) follow-up for tuberculosis for a minimum of 6 months; (2) individuals with household or close exposure to an individual with tuberculosis; (3) information on the age and sex of the contact; (5) start and end follow-up dates; (6) information on whether or not the contact was given preventive therapy; and (7) the timing of preventive therapy.

We pooled individual-participant data from all included cohorts with available data on preventive therapy. Our primary study outcome was incident tuberculosis. We calculated follow-up time from the first baseline visit to development of tuberculosis, loss to follow-up, death, or study completion. Incident tuberculosis was defined as a new tuberculosis case diagnosed more than 90 days after the initial evaluation. Tuberculosis-exposed participants were defined as participants 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 definitions were defined by the investigators leading each cohort, and we accepted study-specific definitions employed by included studies. *M. 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 (≥10mm 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 contacts.

Statistical Analysis

Tuberculosis incidence was categorized by days following study enrolment (>90 days). We estimated tuberculosis incidence through mixed-effects, Cox regression models, with study-level random effects for all analyses. The likelihood ratio test was used to derive p values. To assess the protective effect of preventive therapy on tuberculosis risk, we conducted a propensity score analysis, with matching based on individual-level covariates of age, sex, study design, and prior tuberculosis. We then matched contact participants who began preventive therapy with contact participants who did not using a nearest neighbor matching algorithm. In this matched cohort, we conducted our Cox regression models to compare covariate-adjusted risk of incident tuberculosis between groups when examining the protective effectiveness of preventive therapy. We repeated this analysis for participants with and without tuberculosis infection and participants that were young children (<5 years of age), older children (5–17 years of age) and adults (≥18 years of age) and participants from high- and low-tuberculosis burden settings. We defined high- and low-tuberculosis burden by whether the study was implemented in a setting with a background incidence above or below 100 cases per 100 thousand population.

We estimated the number needed to treat to prevent one tuberculosis case under distinct situations and within groups of participants, as done previously.[14] For these analyses, we first assessed the total number of events by age groups, using Kaplan-Meier analysis, and calculated a pooled absolute risk difference through mixed-effects multivariable models and study-level random effects for each specific group of interest. The number needed to treat was estimated as the reciprocal of the absolute risk differences between the incidence of groups that were prescribed and not prescribed preventive therapy after adjustment through multivariable modeling. We calculated a number needed to treat for young children (<5 years of age), older children (5-17 years of age), adults (18 years and above) and all ages. We repeated these analyses among the entire population and in low- and high-burden settings separately.

Results

In total, 407,312 participants from 32 cohort studies were eligible (Figure 1a). These cohorts came from 26 distinct countries with representation across global regions (Figure 1b). The number of cohorts in the Western Pacific, Americas, European, South-East Asian, and African WHO regions were five, ten, six, three, and ten, respectively. Participants were followed for 1.26 million person-years (median of 2.7 years; IQR, 1.3–4.4), during which 2,523 incident tuberculosis cases were diagnosed (Table 1). Treatment adherence was not assessed in most studies. Preventive therapy regimens included isoniazid for 6 or 9 months, rifampicine for 3 months, and isoniazid and rifapentine for 3 months, among others. The most common regimen used was a 6-month regimen of isoniazid.

Overall, effectiveness of TPT to prevent tuberculosis disease was 58% (aHR, 0.42; 95% CI, 0.35–0.49) among all participants. The effect against tuberculosis was largely similar among contacts only exposed to drug-susceptible tuberculosis index cases (aHR, 0.45; 95% CI, 0.34–0.60). When restricting the outcome to pulmonary and extrapulmonary tuberculosis, effectiveness was 51% (aHR, 0.49; 95% CI, 0.26–0.92) and 58% (aHR, 0.42; 95% CI, 0.35–0.49), respectively. When restricting the outcome to death after baseline, the odds of subsequent death was 34% lower among participants who took preventive therapy compared to participants who did not (aOR, 0.66; 95% CI, 0.56–0.79).

Effectiveness of preventive therapy against incident tuberculosis was statistically similar in children <5-year-old participants (aHR, 0.33; 95% CI, 0.22–0.88) compared to participants 5–17 (aHR, 0.42; 95% CI, 0.32–0.54), or 18 years of age and older (aHR, 0.56; 95% CI, 0.44–0.72). Participants with a positive TST or IGRA were afforded much greater protection against incident tuberculosis, regardless of age. Among participants with a positive TST or IGRA, protection was generally similar among <5-year-old participants (aHR, 0.09; 95% CI, 0.05–0.17), 5–17-year-old participants (aHR, 0.19; 95% CI, 0.13 –0.26), and adults (aHR, 0.14; 95% CI, 0.10–0.18). Among participants with a negative baseline TST and/or IGRA result, preventive therapy afforded no protection; risk of incident tuberculosis (aHR, 0.84; 95% CI, 0.62–1.14) was similar in those who did and did not receive preventive therapy (Figure 2).

Results remained consistent regardless of the test or cutoff used to define *M. tuberculosis* infection (Figure S3). Effectiveness of preventive therapy against tuberculosis was similar among participants with a QuantiFERON test 0.35 IU/mL and above (aHR, 0.15; 95% CI, 0.07–0.31), a tuberculin skin test 5mm or above (aHR, 0.15; 95% CI, 0.11–0.21), 10mm or above (aHR, 0.14; 95% CI, 0.12–0.18). When stratifying these results by distinct ages, results remained generally consistent across these groups. When further

stratifying QuantiFERON results, effectiveness was similar among participants with an interferon-γ –nil 0.35–4.00 IU/mL (aHR, 0.02; 95% CI, 0.01–0.13) and >4.00 IU/mL (aHR, 0.09; 95% CI, 0.03–0.34).

The effectiveness of preventive therapy was greater in tuberculosis high- versus low-burden settings (aHR, 0.34 [95% CI, 0.27–0.43] versus 0.58 [95% CI, 0.47–0.74]) and in participants that were TST or IGRA positive at baseline (aHR, 0.12 [95% CI, -0.09–0.15] versus 0.31 [95% CI, 0.21–0.44] effectiveness). However, the effectiveness of preventive therapy was similar in most subgroups when considering tuberculosis burden of the study settings (Figure 3). For example, effectiveness of preventive therapy was statistically similar in high versus low burden settings among children <5 years old (aHR, 0.30 [95% CI, 0.18–48] versus 0.51 [95% CI, 0.25–1.04]), 5–17 years old (aHR, 0.38 [95% CI, 0.27–0.54] versus 0.50 [95% CI, 0.33–0.74]), and adults (aHR, 0.33 [95% CI, 0.18–0.60] versus 0.65 [95% CI, 0.49–0.86]). Effectiveness was also similar in both settings among participants with a negative TST or IGRA at baseline (aHR, 0.92 [95% CI, 0.45–1.90] versus 0.79 [95% CI, 0.50–1.25]).

Preventive therapy was 75% effective among PLHIV if they had a positive TST or IGRA result (aHR, 0.25; 95% CI, 0.09–0.74). This protection was not seen when restricting the analysis to PLHIV with a negative baseline TST and/or IGRA result (aHR, 0.62; 95% CI, 0.12–3.25); however, this analysis may have been underpowered. Among all PLHIV in whom TST/IGRA data was available, preventive therapy was protective in a regression model adjusting for TST/IGRA status (aHR, 0.40; 95% CI, 0.17–0.96). However, preventive therapy was not protective in a regression model that did not adjusting for TST/IGRA status (aHR, 0.67; 95% CI, 0.28–1.58).

To estimate the potential effect of preventive therapy in different age groups, we calculated the number needed to treat to prevent one future tuberculosis case. Among all participants regardless of TST or IGRA result, the number needed to treat to prevent one tuberculosis case was 145 (95% CI, 114–204) and lower in high- versus low-burden settings (45 [95% CI, 35–63] versus 303 [95% CI, 196–625]). The number needed to treat (regardless of TST or IGRA result) was 87 (95% CI, 61–152) for individuals <5 years (29 [95% CI, 35–63] versus 455 [95% CI, -455–149] in high- and low-burden settings), 125 (95% CI, 88–208) for those aged 5–17 years (43 [95% CI, 30–83] versus 345 [95% CI, 175–5,000] in high- and low-burden settings), and 149 (95% CI, 102–278) for adults (42 [95% CI, 27–94] versus 213 [95% CI, 139–476] in high- and low-burden settings) (Figure 4). In analysis restricted to TST or IGRA positive groups, the number needed to treat was substantially lower and increased with age in both low- and high-burden settings. In high-burden settings, the number needed to treat among this group increased with age ranging from 9 (95% CI, 7–12) among children <5 years of age to 30 (95% CI, 19–68) among adults. Among TST or IGRA positive participants in low-

burden settings, the number needed to treat was between 22 (95% CI, 16–37) in children <5 years of age to 34 (95% CI, 28–44) in adults (Figure 4).

Discussion

In this analysis, we used individual-level data from over 400 thousand persons exposed to tuberculosis and followed for over 1.2 million person-years. We demonstrate that preventive therapy reduced the risk of progressing to tuberculosis by 58% among all participants largely driven by high effectiveness (>80%) in persons with a positive IGRA or tuberculin skin test. Importantly, we found comparable effectiveness among adults and older children compared to young children below 5 years of age; however, the number needed to treat was significantly lower in young children in all analyses. The effectiveness of preventive therapy was greater in high- versus low-burden settings. In total, our findings support risk-targeted strategies prioritizing contacts with evidence of *M. tuberculosis* infection in low-burden settings; in areas where the background tuberculosis burden is high, all contacts, regardless of TST/IGRA status or age, can benefit from preventive therapy and should be prioritized if resources and cost-effectiveness can be ensured.

The results of this analysis provide robust and comprehensive estimates of the effectiveness of preventive therapy against the development of tuberculosis in all individuals exposed to tuberculosis and in important subgroups. Although several trials have convincingly demonstrated the efficacy of preventive therapy against tuberculosis,[1,14-16] there remains debate about preferentially providing preventive therapy to perceived risk-groups such as young children, individuals with a positive IGRA test or any positive test for *M. tuberculosis* infection, and PLHIV, to name a few.[11,17,18] Although children have a higher risk of tuberculosis after primary exposure compared to older age groups[3,12,19-21], our results suggest that the relative reduction afforded by preventive therapy was comparable across all age groups both when analysis included all participants and when analysis was restricted to only participants with either a positive TST or IGRA. These result support recently revised global guidelines recommending preventive therapy for tuberculosis contacts of all ages rather than child contacts only.[22] Despite preventive therapy providing similar effectiveness across age groups, the number needed to treat to prevent one case of tuberculosis was lower among children compared to adults in high-burden settings. This finding likely reflects the greater risk of progression to tuberculosis following primary exposure in young age groups.[19-21] Although beyond the scope of our analysis, it is likely that the association between number needed to treat and age has cost-implications that should be considered when developing local preventive therapy strategies.

Effectiveness was greater in high- compared to low-burden settings overall and among participants that tested TST or IGRA positive. Despite this, amongst participants testing TST or IGRA positive, the number needed to treat to prevent one tuberculosis case remained modest in low-burden settings (~20–30 depending on age), roughly equivalent to the same population in high-burden settings (~10–30). However, when including all

contacts regardless of TST or IGRA result, the number needed to treat rose steeply in low-burden settings (~200-400) but remained low in high-burden settings (~30–40). In low-burden settings, TST or IGRA testing likely provides substantial gains by reducing unnecessary use of preventive therapy. An important recent study in several low-burden settings found that by grouping individuals to reduce the number needed to treat to prevent one case.[19] Our findings suggest that testing contacts with TST or IGRAs in high-burden settings may provide minimal gains toward preventing future tuberculosis cases. As TST and IGRA testing is resource-intensive and often cost-prohibitive, this suggests providing preventive therapy more broadly to all contacts should be considered. However, several factors are relevant to mention with such a recommendation. First, cost-effectiveness should be ensured and may be distinct in different high burden settings. Second, reinfection associated with future risk of tuberculosis is an important concern in tuberculosis high-burden settings.[8,17,23,24] Third, if implementation for all contacts is not possible in certain high-burden settings than a localized strategy for tuberculosis prevention should be identified and may include prioritizing higher-risk contacts; a recent study using a predictive risk score in Peru is one potential solution.[9] Lastly, preventive treatment strategies in settings with a high-burden of multidrug-resistance are currently limited. Despite these important concerns, the low number needed to treat in high-burden settings found in our analysis provides support for robust use of preventive therapy targeting all contacts if disease has been excluded.

Evidence generated from this analysis has additional clinical and public health implications. First, our effectiveness results were similar when using distinct cutoffs of the TST and IGRA, suggesting that cutoffs used to interpret these diagnostic tests may not impact the effectiveness of preventive therapy even though they may relate to higher incident tuberculosis.[25,26] Second, PLHIV are at high-risk of developing tuberculosis after exposure[27]; in this analysis, preventive therapy provided substantial protection (75%) against tuberculosis among PLHIV who had a positive TST or IGRA. Notably, preventive therapy afforded no protection against progression to tuberculosis in PLHIV who had a negative TST and/or IGRA result. However, we interpret these results with caution recognizing the lower sensitivity of current diagnostic tests for *M tuberculosis* infection among PLHIV and low statistical power of this specific subgroup analysis.[28]

This study has several strengths. Participants were located in diverse settings and with widely varying characteristics, allowing stratification by specific subgroups of interest. Although clinical trials are a critical component of the evaluation of interventions and treatments, subgroup analyses are often difficult to interpret, underpowered, or do not include key groups of interest.[29,30] In contrast, observational studies with large sample sizes, sufficient follow-up, and key data on risk factors provide important opportunities to answer questions that may be difficult using only clinical trials.[29] Our multi-cohort consortium and large

sample size from 26 countries allowed us to focus on distinct characteristics of individuals that may most benefit from preventive therapy. Although almost all studies were observational, quality was judged as being high in most included studies.[3,5] The availability of information for many clinical characteristics allowed adjustment for potentially confounding differences using propensity score matching.

Our study has limitations. First, our data did not allow comparison of distinct preventive therapy regimens as the vast majority of studies provided six months of isoniazid. Nevertheless, novel, shorter regimens generally have similar effectiveness suggesting that our findings may be generalizable to these regimens. Second, although we found high effectiveness of preventive therapy, we were not able to identify specific reasons for development of tuberculosis. These may include non-adherence, re-exposure after completion of preventive therapy, rapid metabolization of certain drugs, amongst others.[31] Third, confounding by indication could occur if therapy was given to persons at higher 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 effectiveness estimates towards the null. Fourth, despite the large dataset, there was limited quantitative IGRA data. Although we found statistically significant effects of preventive therapy among participants with differing IGRA quantitative levels, we were underpowered to demonstrate effects after stratification by age, setting, and/or background tuberculosis burden. Fifth, few studies collected information on preventive therapy adherence which may lead to an underestimation of the effectiveness of preventive therapy. Lastly, mean follow-up was almost three years; therefore, we could not evaluate the impact of preventive therapy beyond three years. Nevertheless, the vast majority of individuals who progress to tuberculosis will do so within the first few years of exposure.[3,19,32]

In conclusion, our consortium of 32 cohort studies included over 400 thousand individuals and supported investigation of key age- and risk-specific groups that would benefit most from preventive therapy. Importantly, effectiveness was greater in high tuberculosis burden settings. Our findings suggest that a risk-targeted strategy prioritizing contacts with evidence of *M. tuberculosis* infection is indicated in low-burden settings; a low number needed to treat regardless of TST/IGRA testing in high-burden settings suggests a broad approach including all contacts should be considered. Regardless of background burden, preventive therapy should be expanded to include contacts of all ages.

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Table and Figures

Table 1. Demographic characteristics of included cohort studies

Study or participant characteristic	Studies (n=32)	Proportion
Prospective study design	19	59.4
World Health Organization high-burden country*	13	40.6
Background burden, >100 incident cases per 100 thousand people	15	70.0
Country-level tuberculosis incidence (per 100 000 people)†		
Below 50	13	40.6
50–100	5	15.6
>100–200	5	15.6
Above 200	10	31.3
World Health Organization region		
African	9	28.1
Americas	10	31.3
Eastern Mediterranean	0	0.0
European	5	15.6
South-East Asia	3	9.4
Western Pacific	5	15.6
HIV status of participant reported	18	56.3
Cohort size		
<1000	19	59.4
1000–5000	7	21.9
>5000	6	18.8
Exposed to drug-resistant index cases		
Only drug-resistant index cases	3	9.4
Both drug-resistant and drug-susceptible index cases	9	28.1
Only drug-susceptible index cases	2	6.3
Other	18	56.3
QuantiFERON or tuberculin skin testing	25	78.1
Total person-years follow-up	1,260,158	…
Total individuals evaluated for incidence	407,312	…

Age (years)		
Median (IQR)	33.4 (19-50)	…
Mean (SD)	35.2 (20.8)	…

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

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

†Country-level tuberculosis incidence data were collected from WHO databases for each study.

Table 2. Effectiveness of preventive therapy for distinct tuberculosis-related outcomes.

Outcome	N studies	N events	Person-years of follow-up	N total participants	Adjusted Relative Risk (95% CI)**
Incidence, pulmonary‡	17	1,726	965,283	356,244	0.70 (0.60-0.83)
Incidence, extrapulmonary‡	17	118	962,891	354,644	0.49 (0.26-0.92)
Incidence, all†	32	2,526	1,259,481	407,312	0.42 (0.35-0.49)
Death*	6	951	N/A	46,266	0.66 (0.56-0.79)

‡ In the pulmonary tuberculosis analysis, participants who developed extrapulmonary tuberculosis over follow-up were excluded from this analysis. Similarly, in the extrapulmonary tuberculosis analysis, participants who developed pulmonary tuberculosis over follow-up were excluded from this analysis.

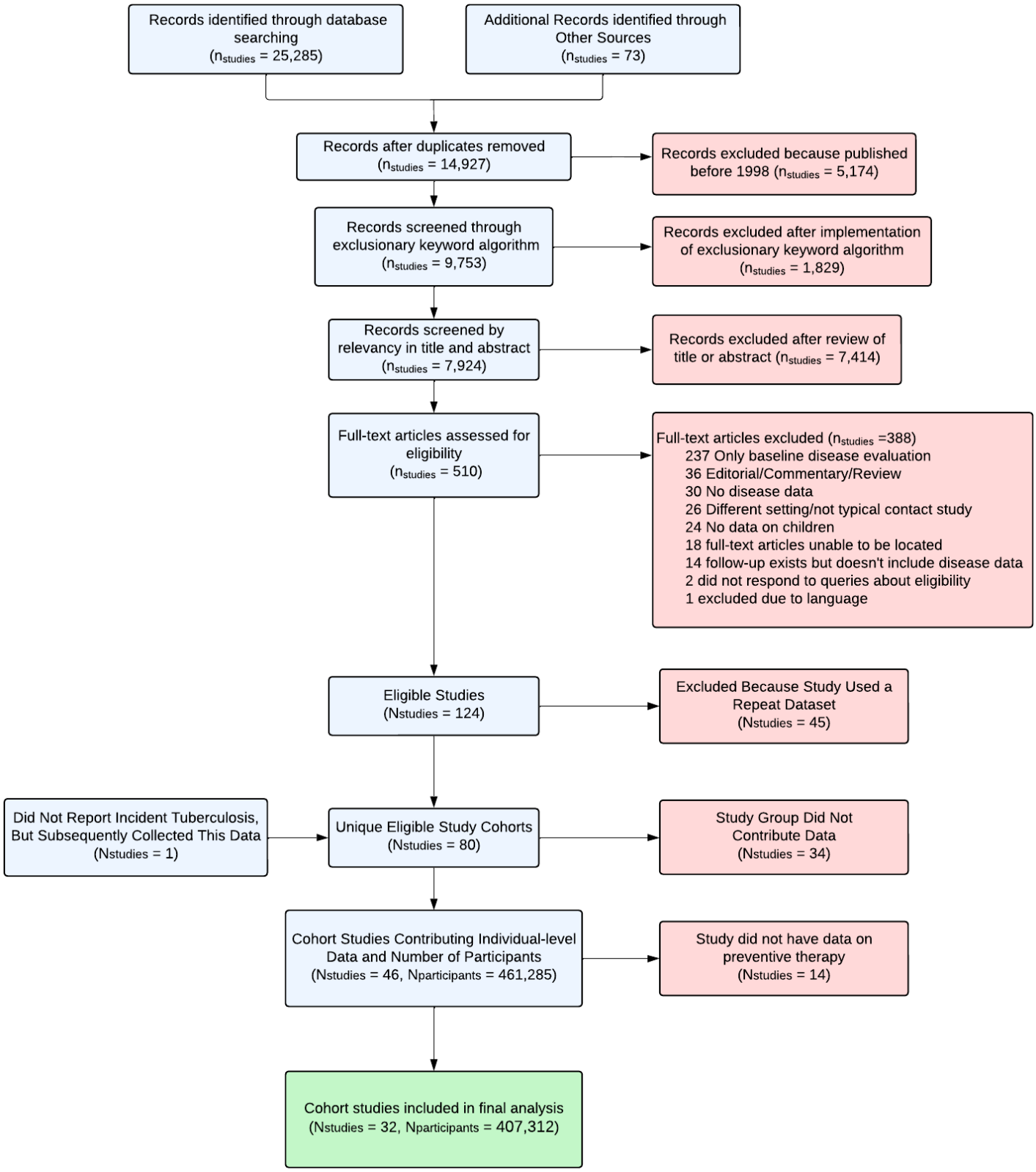
† Values for this outcome do not equal pulmonary and extrapulmonary rows as some studies did not group pulmonary and extrapulmonary outcomes. Therefore, there are more studies and participants in this row compared to the pulmonary and extrapulmonary rows.

*Follow-up was not available for all studies evaluating death and therefore an odds ratio was calculated rather than hazard ratio. For other outcomes listed (pulmonary tuberculosis, extrapulmonary incidence, and all incident outcomes), the relative risk listed is a hazard ratio calculated through a Cox regression model.

** Each individual row represents an independent mixed-effects model for the given row outcome. Each model uses a propensity score using a nearest neighbor matching algorithm with matching based on individual-level covariates of age, sex, study design, and prior tuberculosis. A preventive drug therapy regimen was defined as any preventive drug regimen given at the baseline visit of the contact tracing intervention. Preventive therapy was administered to contacts 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 most studies.

Figure 1. Flowchart of Systematic Search Process (a) and Location of Included Studies (b).

a)



b)

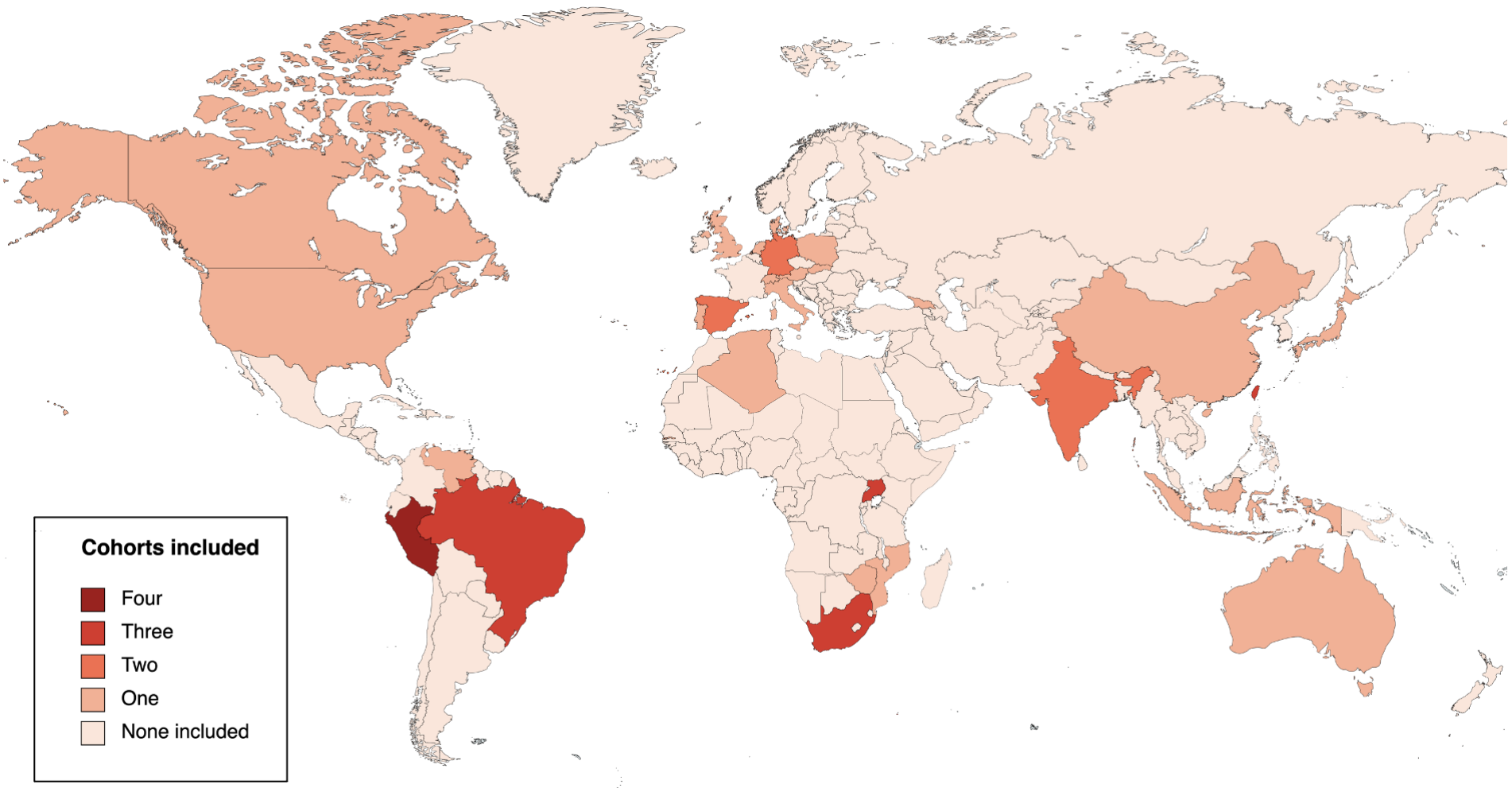
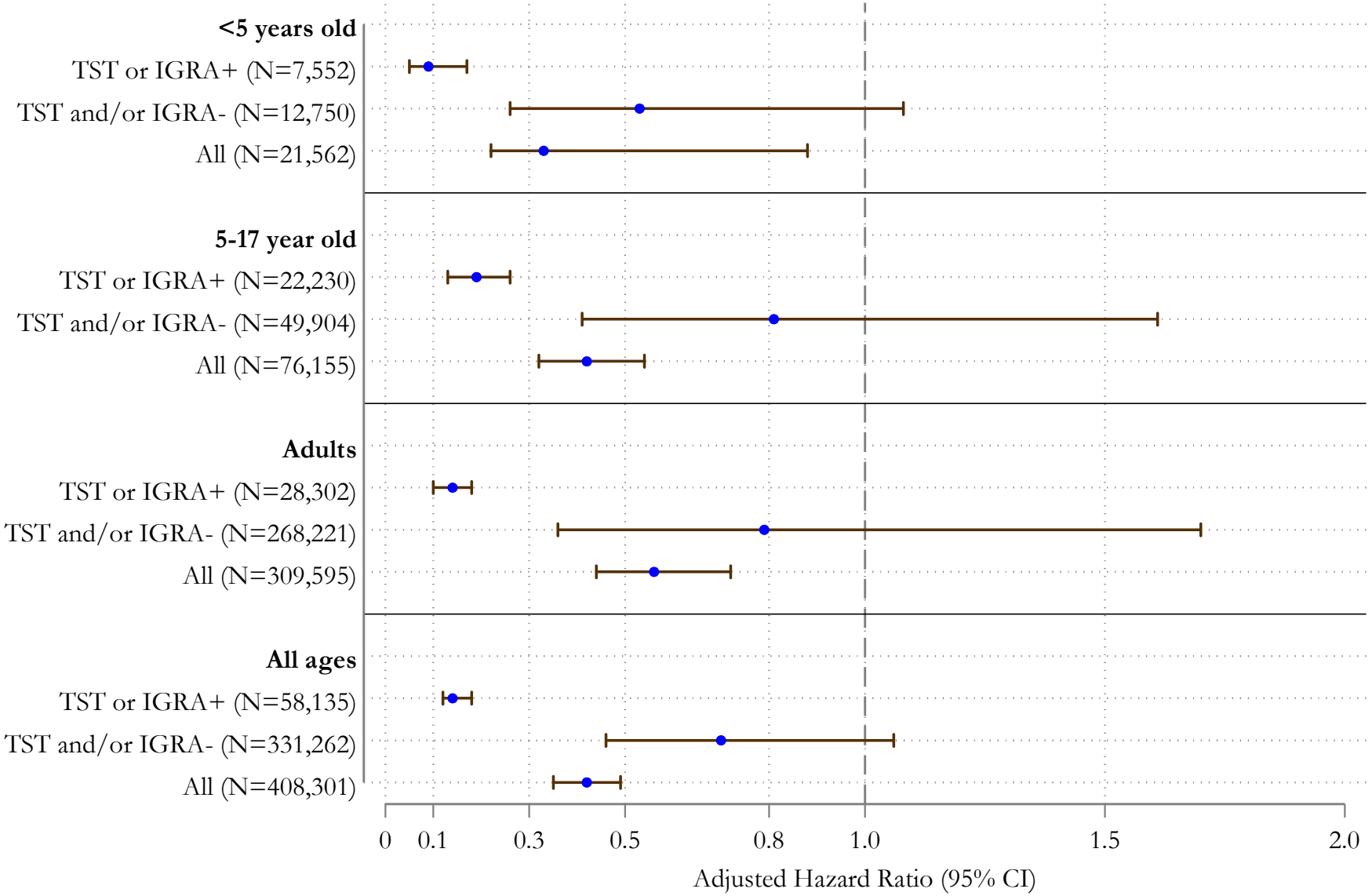


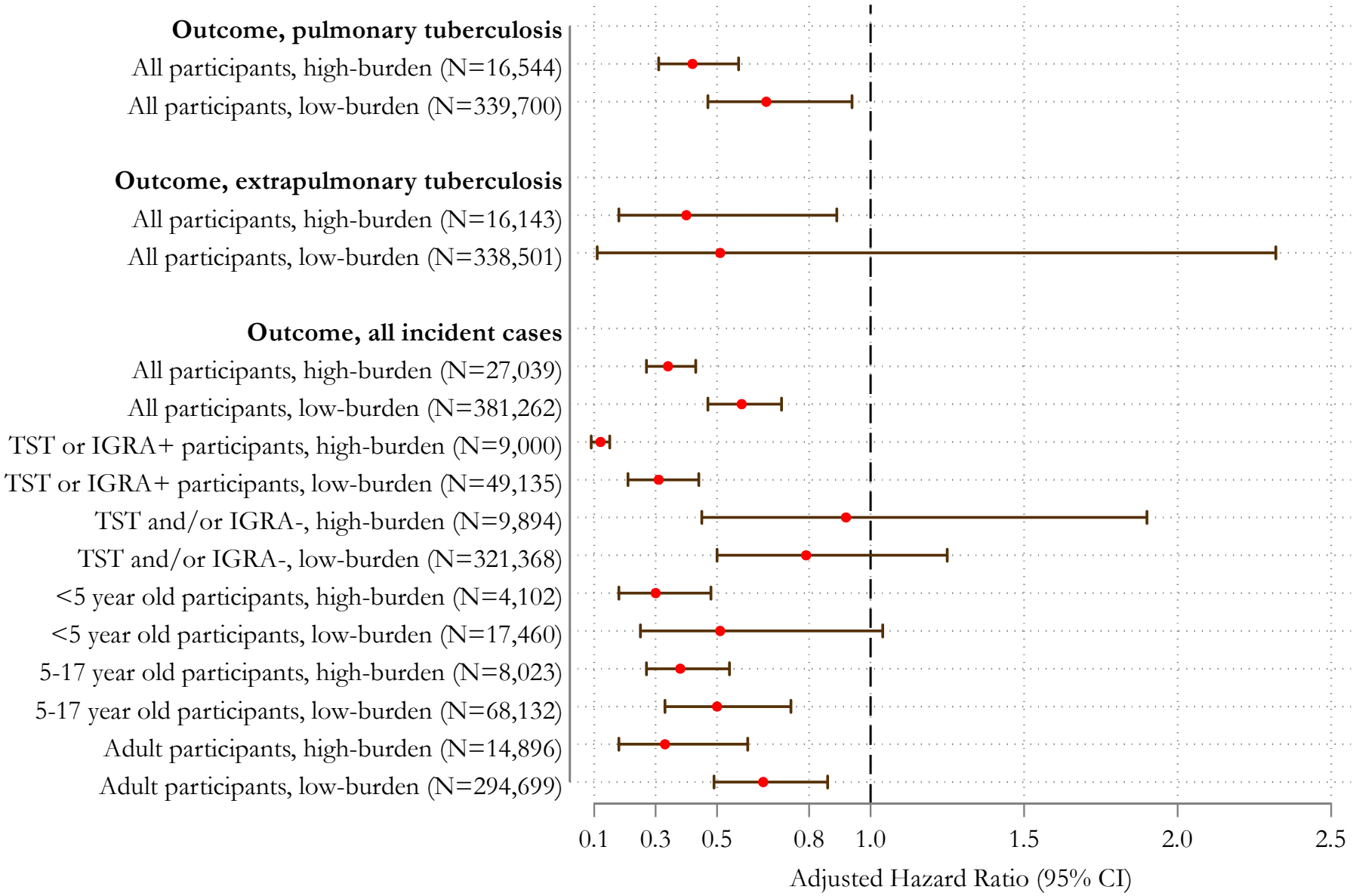
Figure 2. The effect of preventive therapy on the incidence of tuberculosis, stratified by age and *Mycobacterium tuberculosis* infection status.



The categorization of age groups is described in the manuscript and encompasses young children (<5 years of age), older children (5-17 years of age), adults (18 years and above), and all ages. Each individual row represents an independent mixed-effects model stratified by

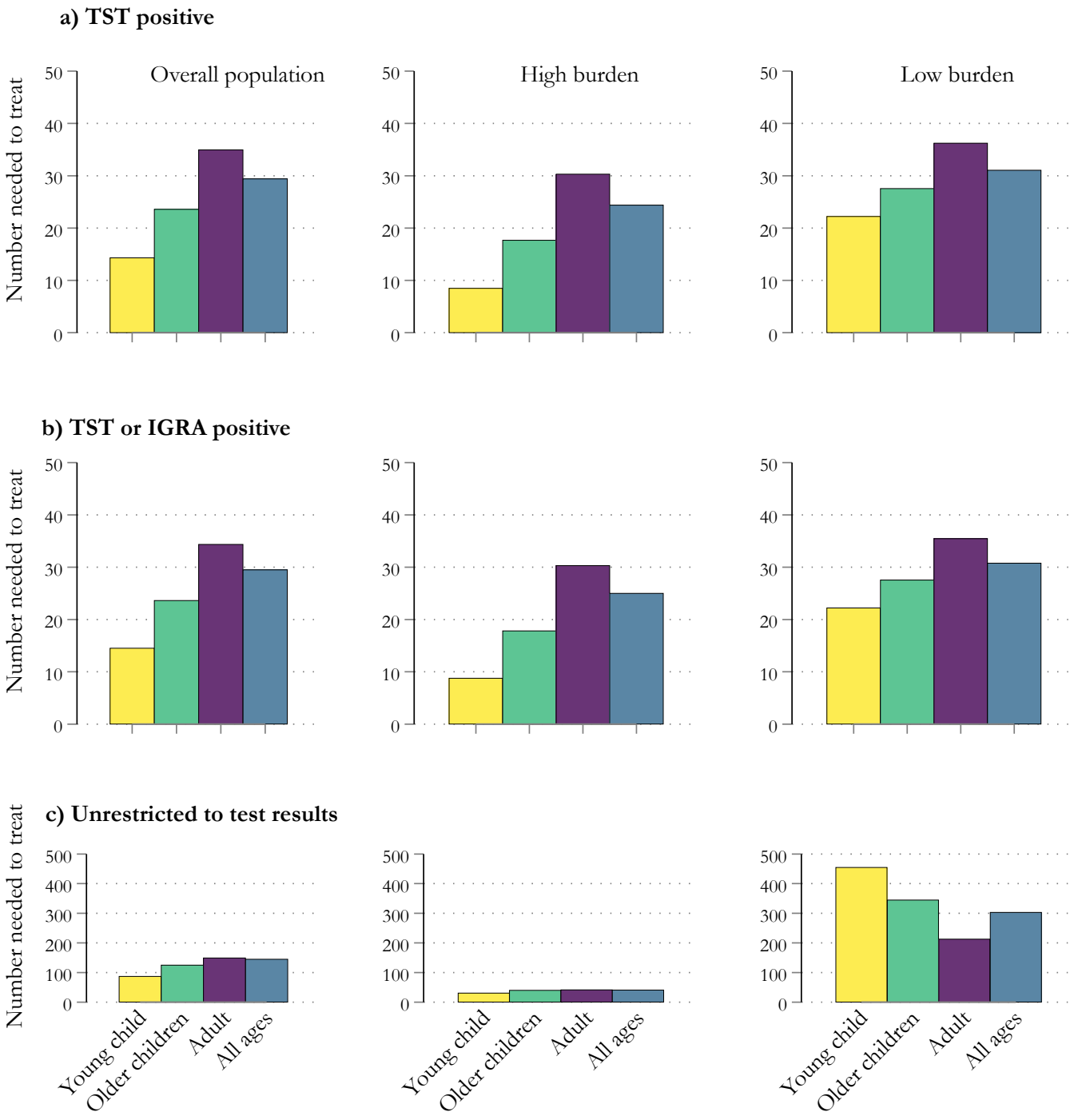
the given row characteristic. Each model uses a propensity score using a nearest neighbor matching algorithm with matching based on individual-level covariates of age, sex, study design, and prior tuberculosis. A preventive drug therapy regimen was defined as any preventive drug regimen given at the baseline visit of the contact tracing intervention. Preventive therapy was administered to contacts 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 most studies. A similar analysis was performed only for participants exposed to drug-susceptible tuberculosis cases with comparable results. This analysis can be found in the Supplementary Appendix.

Figure 3. Effectiveness of preventive therapy in settings with differing tuberculosis burden



We defined high- and low-tuberculosis burden by whether the study was done in a setting with a background incidence above or below 100 cases per 100 thousand persons. Each individual row represents an independent mixed-effects model stratified by the given row characteristic. Each model uses a propensity score with a nearest neighbor matching algorithm for matching based on individual-level covariates of age, sex, study design, and prior tuberculosis. A preventive drug therapy regimen was defined as any preventive drug regimen given at the baseline visit of the contact tracing intervention. Preventive therapy was administered to contacts 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 most studies.

Figure 4. Estimated number needed to treat to prevent one tuberculosis case among persons with differing *Mycobacterium tuberculosis* infection status and background tuberculosis burden.



We defined high- and low-tuberculosis burden by whether the study was done in a setting with a background incidence above or below 100 cases per 100 thousand persons. The categorization of age groups is described in the manuscript. We calculated a number needed to treat for young children (<5 years of age; yellow bars), older children (5-17 years of age; green bars), adults (18 years and above; purple bars), and all ages (blue bars). We estimated the number needed to treat to prevent one tuberculosis case under distinct situations and groups of participants by calculating a pooled absolute risk difference through mixed-effects multivariable models and study-level random effects for each

specific group of interest. The number needed to treat was estimated as the reciprocal of the absolute risk differences between the incidence of groups that were prescribed and not prescribed preventive therapy after adjustment through multivariable modeling. We repeated these analyses among participants that tested tuberculin skin test positive (panel a), interferon gamma release assay or tuberculin skin test positive (panel b), or unrestricted by test results (panel c). We further stratified these analyses by the entire population (left column) and in high- and low-burden settings (middle and right column). We did not include IGRA results alone in this figure due to limited sample size after stratification by age and background burden.