Sex differences in the risk of *Mycobacterium tuberculosis* infection: a systematic review and meta-analysis of population-based immunoreactivity surveys

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Summary

Background Tuberculosis killed 1·25 million people globally in 2023. Men have a 1·7 times higher tuberculosis incidence than women, but it is not known to what extent this discrepancy is driven by greater exposure to *Mycobacterium tuberculosis*. We aimed to analyse the effect of age and sex on *M tuberculosis* immunoreactivity.

Methods In this systematic review and meta-analysis, we reviewed Embase, Global Health databases, Science Citation Index Expanded, and Global Index Medicus for population-based *M tuberculosis* immunoreactivity (with interferon-γ release assay or skin test) surveys done in high tuberculosis incidence settings from Jan 1, 1993, to Dec 31, 2022, with a sample size of at least 150 people. We included cross-sectional surveys, baseline surveys for interventional or cohort studies, and control groups of case–control studies with population-representative groups. We extracted data on *M tuberculosis* immunoreactivity prevalence, disaggregated by sex and age group. We constructed Bayesian hierarchical models, first of immunoreactivity prevalence by age and sex and second of the male-to-female (M:F) prevalence ratio by age. We analysed the effect of covariables including region, tuberculosis incidence, and study year. This study was registered on PROSPERO (CRD42022360483).

Findings We screened 26 517 studies, of which 167 met our inclusion criteria. Sex-disaggregated results were available from 80 studies (81 surveys), from 38 different countries, comprising data from 478 968 participants. We found little sex difference in *M tuberculosis* immunoreactivity in childhood (M:F prevalence ratio for children younger than 10 years was 0·95; 95% credible interval 0·90–1·01). However, from adolescence onwards, men experienced higher immunoreactivity conversion than women (1·4 times higher by age 30 years). This higher conversion rate cumulatively drove a higher immunoreactivity prevalence in men, with a prevalence ratio of 1·07 (95% credible interval 1·01–1·13) in those aged 10–19 years, 1·13 (1·06–1·20) in those aged 20–39 years, and 1·28 (1·19–1·37) for those aged 40 years and older. Adult men had consistently higher *M tuberculosis* prevalence across different settings, with low between-study heterogeneity in M:F prevalence ratio.

Interpretation Men have higher *M tuberculosis* immunoreactivity risk than women, which is likely to be a key driver of the sex differences in global tuberculosis morbidity and mortality. This difference could be due to higher exposure through social and behavioural differences in time spent in congregate indoor spaces where tuberculosis transmission occurs, further amplified by longer duration of infectiousness in men, and age-assortative and sex-assortative mixing. Public health interventions addressing men's determinants of *M tuberculosis* exposure will be crucial to ending the tuberculosis epidemic.

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Introduction

Tuberculosis killed 1·25 million people globally in 2023, including 646 000 adult men and 410 000 adult women.[1] Men have a 1·7 times higher tuberculosis incidence than women;[1] this higher incidence combines with a longer duration of disease (due to gendered barriers to accessing care) to cause a higher tuberculosis prevalence.[2–4] Men's higher prevalence of undiagnosed infectious disease is a major driver of community transmission, with the majority of tuberculosis transmission in high-burden settings believed to be from adult men;[5] age-assortative and sex-assortative mixing means that men are themselves more likely to be infected, further amplifying disparities.

Sex discrepancies in tuberculosis disease are age dependent. Little difference is seen in tuberculosis incidence or prevalence among children,[1,3,6] but WHO estimates a male-to-female (M:F) incidence ratio of 1·2 in people aged 15–24 years, 1·5 in those aged 25–34 years, and 1·7 in those aged 35–44 years,[1] with similar age dependence in prevalence ratios also observed.[3]

Research in context

Evidence before this study

Previous systematic reviews have found that globally men have a higher incidence and prevalence of tuberculosis, and experience higher tuberculosis mortality, than women. We searched MEDLINE, Embase, CAB Global Health database, Science Citation Index Expanded, and Global Index Medicus, using terms related to *Mycobacterium tuberculosis* immunoreactivity and epidemiological study type for surveys done between Jan 1, 1993, and Dec 31, 2022. Although we identified 167 individual *M tuberculosis* immunoreactivity surveys, just under half of which provided sex-disaggregated results, there were no systematic reviews or meta-analyses examining the prevalence of *M tuberculosis* immunoreactivity by age and sex in population-based surveys globally. A repeat search done on Dec 23, 2024, limited to only systematic reviews and meta-analyses, did not identify any new relevant analyses.

Added value of this study

This systematic review and meta-analysis included results from 81 surveys, 38 countries, and almost half a million participants. We found that from adolescence onwards, men have higher *M tuberculosis* infection, resulting in a higher prevalence of immunoreactivity.

Implications of all the available evidence

Men have higher *M tuberculosis* infection rates than women, with higher exposure likely to be an important driver of their higher incidence of tuberculosis disease, and to contribute to their higher mortality from tuberculosis. Gender-sensitive public health strategies are essential to address this disparity in tuberculosis transmission and end the global tuberculosis pandemic.

Infection with *Mycobacterium tuberculosis* is the initial step in the tuberculosis pathogenic pathway. Although sex differences in the incidence and prevalence of tuberculosis disease are well established, disparities in *M tuberculosis* infection are less researched. As current tests cannot directly detect *M tuberculosis* infection, immunoreactivity is measured with tuberculin skin tests (TSTs) or interferon-γ release assays (IGRAs).[7] Although immunoreactivity is an imperfect proxy for ongoing viable infection, and only a minority of people with *M tuberculosis* immunoreactivity go on to develop tuberculosis disease,[8,9] immunoreactivity serves as an epidemiological marker of *M tuberculosis* exposure.[7,10,11] Traditionally, immunoreactivity has been assumed to be lifelong, although the importance of reversion is increasingly understood.[12]

Since the 1940s, surveys in sentinel groups (eg, schoolchildren) have measured *M tuberculosis* immunoreactivity prevalence as a marker of cumulative lifetime exposure, to estimate an annual risk of tuberculosis infection, infer tuberculosis burden, monitor population-level trends, and identify groups at high risk.[10,11] Although previous systematic reviews have explored the overall burden of *M tuberculosis* immunoreactivity across populations,[13,14] and other studies have noted sex differences therein,[15–18] to our knowledge the M:F prevalence ratio of *M tuberculosis* immunoreactivity has not been systematically investigated across populations in the past few decades.

Fundamentally, men's higher incidence of tuberculosis disease could occur from any one, or a combination, of higher *M tuberculosis* exposure, greater propensity to develop *M tuberculosis* infection if exposed, or increased progression from infection to disease. Higher exposure might arise from time spent in high-transmission venues, such as workplaces, educational facilities, prisons, social venues, and public transport,[19,20] amplified by age-assortative and sex-assortative social mixing.[5] Lung damage due to smoking or air pollution could make *M tuberculosis* infection more probable in exposed individuals.[21,22] If differential *M tuberculosis* exposure or infection are primary drivers of sex differences in tuberculosis incidence, we would expect this to be reflected in a higher prevalence of *M tuberculosis* immunoreactivity in adult men than adult women. Alternatively, higher progression from infection to disease could occur due to sex-related immunological differences[23] or increased prevalence of risk factors for progression, such as cigarette smoking, alcohol consumption, diabetes, and untreated HIV.[1,22,24]

Understanding sex differences in *M tuberculosis* infection and their interaction with age is key to disentangling the complex causal mechanisms underlying the sex-specific epidemiology of tuberculosis. This knowledge will inform gender-sensitive public health responses and identify the groups at highest risk of infection who could benefit most from interventions such as screening, preventive treatment, and vaccination. We therefore sought to meta-analyse age-dependent differences in the prevalence of *M tuberculosis* immunoreactivity between males and females in high-burden settings.

Methods

Search strategy and inclusion criteria

In this systematic review and meta-analysis, we systematically reviewed the literature for population-representative surveys of *M tuberculosis* immunoreactivity. We included cross-sectional surveys, baseline surveys for interventional or cohort studies, and control groups of case–control studies if they were from a population-representative sample. Surveys were excluded if they only included populations at high risk or that had been specifically selected, such as household contacts of people with tuberculosis, health-care workers, incarcerated individuals, people living with HIV, inpatients, and symptomatic individuals. We included surveys that

recruited from primary or secondary education, but not tertiary education (as in most settings this would no longer represent a population-representative group). We excluded surveys that solely or predominantly included participants of one sex (eg, male military recruits or pregnant women).

We (HMR) searched MEDLINE, Embase, CAB Global Health database, Science Citation Index Expanded, and Global Index Medicus, with terms related to *M tuberculosis* immunoreactivity and epidemiological study type (appendix p 6). We additionally screened the reference list of two systematic reviews of national *M tuberculosis* surveys,[13,14] one systematic review of the performance of Diaskintest (a newer skin test widely used in Russia),[25] and an online document from the WHO Global Task Force on TB Impact Measurement.[26] There were no language restrictions. The search strategy was reviewed by an information specialist against *Peer Review of Electronic Search Strategies* guidelines.[27]

We included surveys done between Jan 1, 1993 (the year of the WHO Directly Observed Treatment, short-course strategy, considered a defining moment in investment in global tuberculosis management with expected effects on transmission dynamics) and Dec 31, 2022 that included a minimum of 150 participants tested for *M tuberculosis* immunoreactivity through TST, IGRA, or newer skin tests (eg, C-Tb [Serum Institute of India, Pune, India] and Diaskintest [Generium, Moscow, Russia]). As our focus was on community transmission, rather than settings in which tuberculosis epidemiology is dominated by migration or key populations, we included only surveys from high tuberculosis incidence settings, defined as having a WHO-estimated national tuberculosis incidence of at least 40 cases per 100 000 people per year,[28] or subnational surveys which reported a regional incidence, prevalence, or case notification rate of at least 40 cases per 100 000 people per year.

Deduplication was done in EndNote (version 20) and screening on the web-based rayyan platform (which facilitates masked screening between collaborating researchers). A single reviewer (HMR) initially pre-screened titles based on filter terms related to non-human studies, non-tuberculous mycobacteria, and case reports or series. A random 10% sample of pre-screened titles and abstracts were screened in duplicate by two masked reviewers (either HMR, MDP, or HRAF). Once concordance was checked and conflicts resolved, the remaining titles and abstracts were screened by a single reviewer (either HMR, MDP, HRAF, MK, or HS). All articles identified for full-text screening were independently reviewed by two reviewers (HMR, MDP, HRAF, MK, or HS), with conflicts resolved by consensus and discussion with a third reviewer (PM), if required. Non-English language articles were reviewed by at least one reader proficient in that language.

Data extraction was done by a single reviewer (HMR) through an Open Data Kit tool. When a study met inclusion criteria but age-disaggregated or sex-disaggregated results were not published, authors were contacted by email and asked to share data.

This study is reported in accordance with the PRISMA statement (appendix pp 1–5). Our protocol was registered before study commencement (PROSPERO reference CRD42022360483).

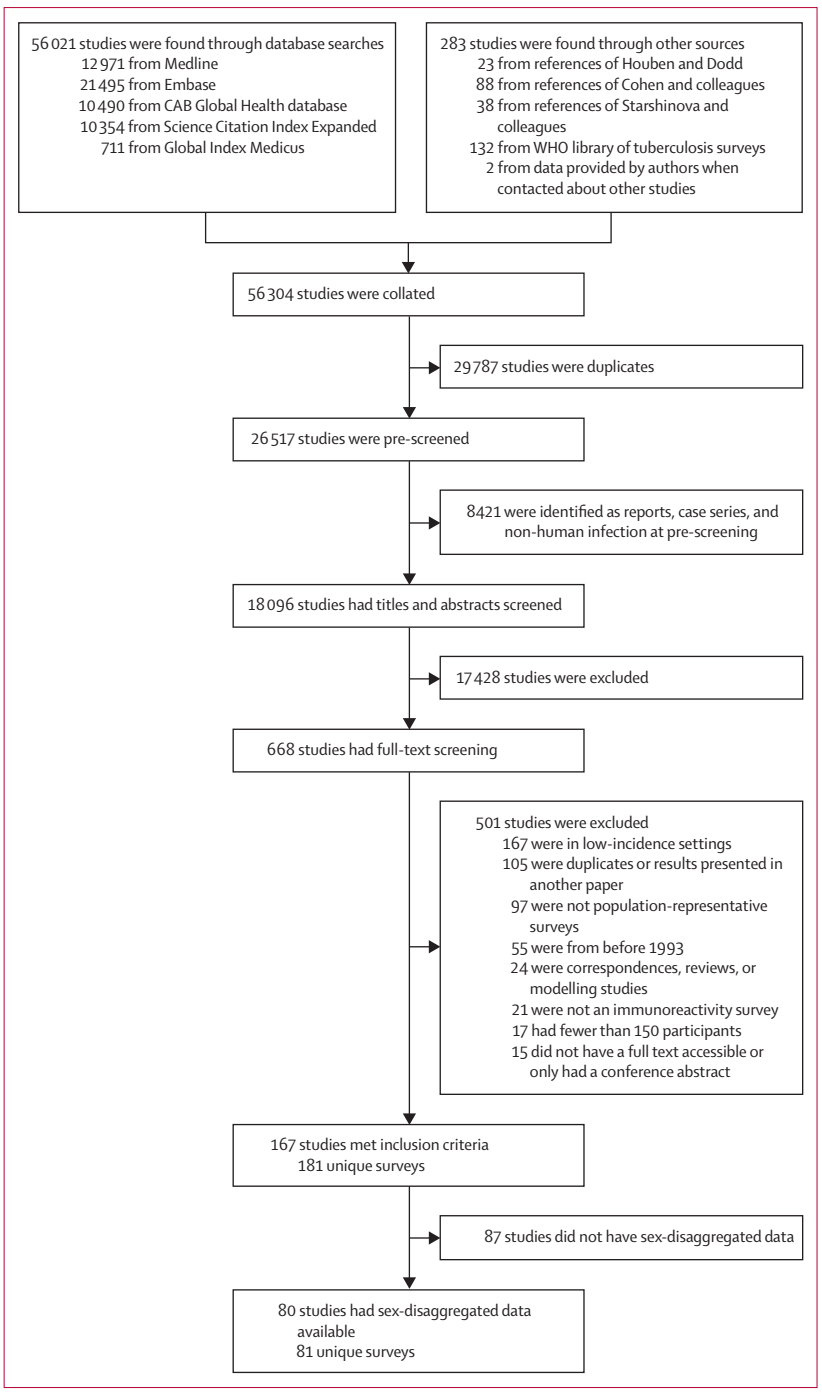

Figure 1: **Studies identified and included in the systematic review**
Additional references from Houben and Dodd,[13] Cohen and colleagues,[14] Starshinova and colleagues,[25] and an online WHO document of tuberculosis surveys.[26]

See **Online** for appendix

For the **rayyan software** see https://rayyan.ai

For **Open Data Kit** see https://getodk.org

	Surveys, n=81	Participants, n=478 968
Mycobacterium tuberculosis positive	..	90 833 (19·0%)
Sex		
Male	..	237 677 (49·6%)
Female	..	241 291 (50·4%)
Age <15 years	..	367 749 (76·8%)
Male	..	187 593/367 749 (51·0%)
Female		180 156/367 749 (49·0%)
Age ≥15 years	..	111 219 (23·2%)
Male	..	50 084/111 219 (45·0%)
Female	..	61 135/111 219 (55·0%)
Number of age groups per survey		
1	47 (58·0%)	..
2–5	19 (23·5%)	..
6–10	12 (14·8%)	..
≥11	3 (3·7%)	..
Number of participants per survey		
Mean (SD)	5910 (11 900)	..
Median (range)	2250 (174–96 200)	..
Survey year		
1993–99	10 (12·3%)	29 248 (6·1%)
2000–04	13 (16·0%)	165 008 (34·5%)
2005–09	22 (27·2%)	129 765 (27·1%)
2010–14	15 (18·5%)	87 253 (18·2%)
2015–19	19 (23·5%)	61 724 (12·9%)
2020–24	2 (2·5%)	5 970 (1·2%)
WHO region		
African	29 (35·8%)	164 988 (34·4%)
Western Pacific	23 (28·4%)	170 647 (35·6%)
South-East Asia	13 (16·0%)	58 638 (12·2%)
Eastern Mediterranean	7 (8·6%)	62 520 (13·1%)
Americas	5 (6·2%)	6 253 (1·3%)
European	4 (4·9%)	15 922 (3·3%)
Survey scope		
National	17 (21·0%)	263 187 (54·9%)
Subnational	64 (79·0%)	215 781 (45·1%)
M tuberculosis test		
TST	56 (69·1%)	416 911 (87·0%)*
IGRA	21 (25·9%)	89 600 (18·7%)*
Both IGRA and TST	4 (4·9%)	NA*
Rural or urban		
Both or national	37 (45·7%)	316 891 (66·2%)
Urban	25 (30·9%)	55 847 (11·7%)
Rural	19 (23·5%)	106 230 (22·2%)
Risk of bias		
Low	47 (58·0%)	332 020 (69·3%)
Moderate	13 (16·0%)	87 800 (18·3%)
High	21 (25·9%)	59 148 (12·3%)

Data are n (%) or n/N (%), unless otherwise specified. IGRA=interferon-γ release assay. NA=not applicable. TST=tuberculin skin test. *For the *M tuberculosis* test, participant-level data are given for the total number of test results available for TST and IGRA; this exceeds the total number of participants as some participants have both TST and IGRA but it is not possible at a study level to identify whether the same individuals had both. Participants with test results for both are not double-counted in other categories.

Table 1: **Surveys and participants included in the meta-analysis**

For the **plot-digitiser used in this study** see https://automeris.io/

Data analysis

The outcome of interest was the proportion of people in each reported age–sex group that had a positive *M tuberculosis* immunoreactivity test (eg, TST or IGRA). If the numerator and denominator were not published but could be back-calculated from the data presented, including from graphs via an online plot-digitiser, this was done. When indeterminate test results were reported, these were excluded from the denominator. The cutoff to define a positive test followed the authors' own definition; when multiple cutoffs were used in the same study, we extracted data according to standard cutoffs (eg, 0·35 IU/mL for QuantiFERON-TB or 10 mm for TST).[29] When surveys used both IGRA and TST, IGRA results were used; the exception was the analysis comparing assays, in which surveys could contribute both TST and IGRA data to the comparison. We extracted age-disaggregated results using the same age categories used by the authors of individual studies.

The central estimate of each age group was defined through the mean age, when available, or the midpoint when the mean was unavailable. Populations were defined as rural, urban, or mixed according to the original studies. We used WHO estimates of country-level tuberculosis incidence; as these are only published from 2000 onwards, we used linear extrapolation of post-2000 estimates for studies done between 1993 and 1999.[28]

Risk of bias was assessed by one reviewer (HMR) through Hoy and colleagues' Risk of Bias Tool for Prevalence Studies, with modified test-specific items for skin tests and IGRAs[30] (appendix p 8). We compared studies with and without sex-disaggregated data, constructed a funnel plot based on the study-level M:F prevalence ratio, and used Egger's test to assess for publication bias or small study effects.

We did a meta-analysis of age–sex-disaggregated prevalence by fitting a hierarchical Bayesian regression model (appendix p 9) with a binomial distribution, survey-level random intercepts, and covariables of sex, age-group mean or midpoint (natural cubic spline with one internal knot), and their interaction. In sensitivity analyses, model fits for linear and non-linear age trends with different numbers of knots were compared through

the leave one out cross-validation statistic; when no model was clearly preferred, the more parsimonious model was selected. We used weakly informative priors, and four chains with 5000 iterations for model fitting. All computations were done in R (version 4.2) with the R brms interface to Stan. Posterior predictive checks were done, including inspection of trace plots, effective sample sizes, and R^ values.

Predictions of prevalence were made by taking samples from the posterior distribution for each sex and year of age, summarised with means and quantile-based 95% credible intervals, and excluding random effects (as the intention was not to estimate a weighted average of absolute prevalence or conversion risk, but rather to visualise the underlying fixed effects of age and sex). We also predicted annual risk of immunoreactivity conversion by sex through the change in prevalence across each 1-year age bracket, under traditional assumptions of lifelong immunoreactivity and ignoring reversion (appendix pp 10–11).

We calculated an M:F prevalence ratio for each age-disaggregated datapoint and fitted hierarchical Bayesian models to estimate the precision-weighted, log-transformed prevalence ratio predicted by age. We first modelled age as a categorical variable (0–9, 10–19, 20–39, and ≥40 years), and subsequently as a continuous variable. Models were fitted and evaluated as previously described. Covariables included rural or urban status, WHO region, country-level tuberculosis incidence, and study test.

Role of the funding source

The funders had no role in the study design, data collection, data analysis, data interpretation, writing of the manuscript, or the decision to submit.

Results

We identified 26 517 unique studies (figure 1), with 668 included in full-text screening (appendix pp 12–32). Overall, 167 studies (which reported on 181 unique surveys) met our inclusion criteria. Of these, sex-disaggregated results were available for 80 studies (81 surveys), which are included in this analysis (appendix pp 33–38).[16–18,31–107] Sex-disaggregated data were more likely to be available for more recent studies (appendix p 39), but there was no evidence of publication bias by overall M:F prevalence ratio (appendix p 40).

In total, this analysis includes results from 478 968 participants, from 38 different countries in all six WHO regions (table 1). The African and Western Pacific regions contributed the most data: 29 (35·8%) of 81 surveys and 164 988 (34·4%) participants were from Africa, and 23 (28·4%) of 81 surveys and 170 647 (35·6%) participants were from the Western Pacific region. The most represented countries were China (12 surveys), India (10 surveys), and South Africa (8 surveys). 17 (21·0%) of 81 were national surveys. 56 (69·1%) of 81 surveys used TST alone, 21 (25·9%) IGRA alone, and 4 (4·9%) had results for both TST and IGRA. Most surveys using TST (39 of 60; 65·0%) either showed evidence of digit preference or did not evaluate for it.

In total, 367 749 (76·8%) of 478 968 participants were younger than 15 years. Overall, 237 677 (49·6%) participants were male, but men were under-represented in adults (aged ≥15 years; 50 084 of 111 219 adults; 45·0%). 90 833 (19·0%) participants had a positive test of *M tuberculosis* immunoreactivity.

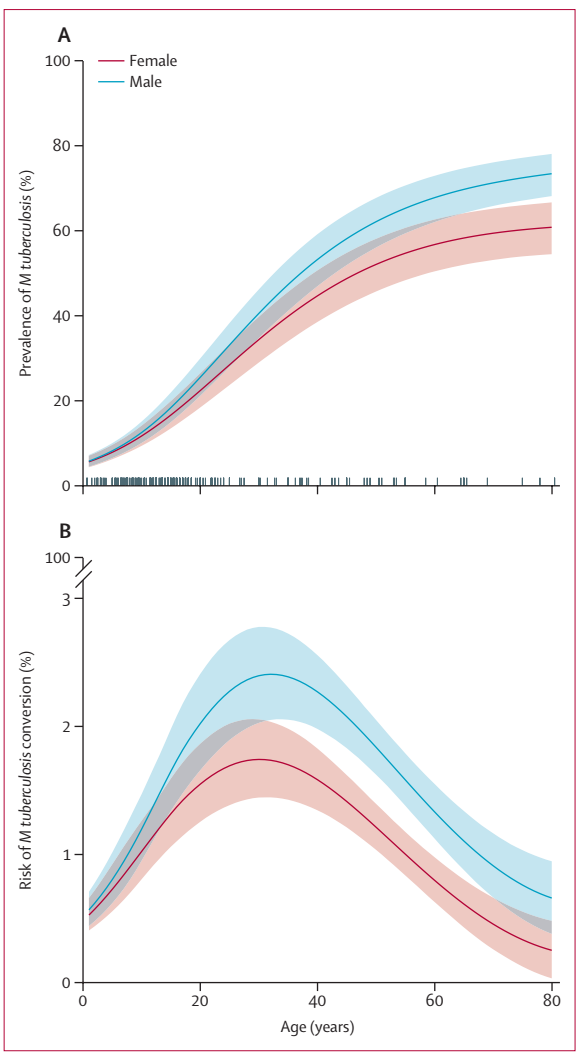

Figure 2: **Effect of sex and age on prevalence of *Mycobacterium tuberculosis* immunoreactivity and annual risk of conversion**
(A) Average prevalence of *M tuberculosis* immunoreactivity by age and sex: summary of posterior draws from Bayesian meta-regression model of prevalence, with associated 95% credible intervals, X-axis rug shows the age-group midpoints from individual studies that contributed data. (B) Annual risk of conversion from *M tuberculosis* negative to positive per year: summary of posterior draws from the prevalence model to show the estimated proportion of people converting from *M tuberculosis* negative to positive per year of age. Absolute prevalence and conversion risk varied markedly by study. Study-level random effects are ignored. Estimates represent an average across studies included in this meta-analysis. The intention is not to estimate a weighted average of absolute prevalence or conversion risk, but rather to focus on the fixed effects of age and sex.

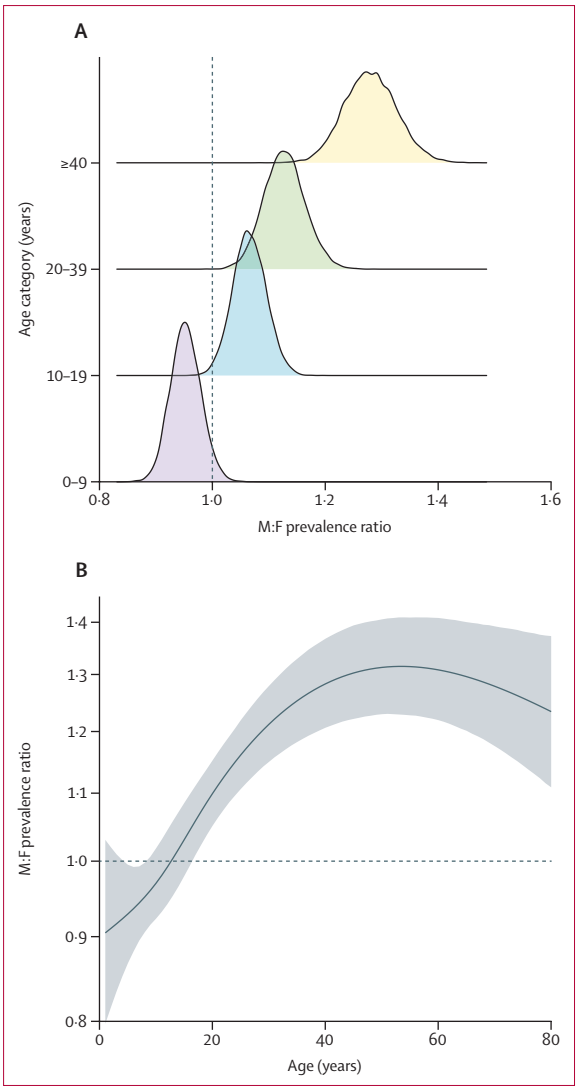

Figure 3: **M:F prevalence ratio of *Mycobacterium tuberculosis* immunoreactivity, by age**
(A) Average M:F prevalence ratio of *M tuberculosis* immunoreactivity by age category; summary of posterior draws from Bayesian meta-regression model of M:F prevalence ratio, ignoring random effects. (B) Average M:F prevalence ratio of *M tuberculosis* immunoreactivity by age, modelled continuously; summary of posterior draws from Bayesian meta-regression model of M:F prevalence ratio, ignoring random effects, with 95% credible intervals. M:F=male-to-female.

In our meta-regression model, the prevalence of *M tuberculosis* immunoreactivity varied markedly by study (τ 1·04). As expected, *M tuberculosis* prevalence increased with age (reflecting cumulative exposure; figure 2B). We found an interaction between age and sex: predicted prevalence diverged in men and women from adolescence. By age 30 years, predicted prevalences were 40·5% (95% credible interval 35·2–46·0) in men and 34·3% (29·5–39·6) in women, and the estimated prevalence in men remained higher than in women throughout adult life.

The higher prevalence corresponded to a higher annual rate of conversion to *M tuberculosis* immunoreactivity in men than women, which also varied by age (figure 2B). The rate of conversion increased for both sexes from childhood, peaking at age 32 years for men and age 30 years for women, and was higher in men than in women. By age 20 years, the estimated annual rate of conversion was 1·31 (95% credible interval 1·24–1·38) times higher in men than in women, at 2·02% (1·67–2·39) in men versus 1·55% (1·27–1·86) in women. At age 30 years, the annual rate of conversion was 1·38 (1·31–1·44) times higher in men than in women (2·39% [2·04–2·77] in men *vs* 1·74% [1·45–2·05] in women), and at age 50 years it was 1·52 (1·38–1·66) times higher in men (1·84% [1·63–2·05] in men *vs* 1·21% [1·04–1·40] in women).

When M:F prevalence ratios were modelled by age category, the ratio for children younger than 10 years was 0·95 (95% credible interval 0·90–1·01), with an estimated 95·2% posterior probability that prevalence was higher in girls than boys (figure 3A). For older age groups, male prevalence was higher than female prevalence, with a prevalence ratio of 1·07 (95% credible interval 1·01–1·13) in those aged 10–19 years, 1·13 (1·06–1·20) in those aged 20–39 years, and 1·28 (1·19–1·37) for those aged 40 years and older. When age was modelled continuously, we again observed a lower M:F ratio in young children—0·93 (0·87–1·00) at age 5 years—which increased to a peak at age 53 years at 1·32 (1·23–1·41; figure 3B). There was low between-study heterogeneity in M:F prevalence ratio (τ 0·14).

In a meta-regression investigating covariates, we found no effect of study test (TST *vs* IGRA multiplicative effect 1·04; 95% credible interval 0·95–1·13) on the age-adjusted M:F prevalence ratio (table 2). Overall, 47 (58·0%) of 81 surveys, which included 332 020 (69·3%) participants, had a low risk of bias; 13 (16·0%) had a moderate risk of bias; and 21 (25·9%) had a high risk of bias. The most common issues were non-response bias (24 surveys; 29·6%) and an unrepresentative target population (20 surveys; 24·7%). There was no difference in prevalence ratios in surveys with a moderate (1·08; 95% credible interval 0·97–1·19) or high (1·06; 0·96–1·17) risk of bias compared with those with a low risk of bias. We also found no difference between rural and urban settings, by WHO region, by tuberculosis incidence of the country, or by the year in which the study was done.

Discussion

This meta-analysis of 81 population-based surveys, including almost 500 000 participants from 38 countries, is to our knowledge the first to systematically review the effect of age and sex on *M tuberculosis* immunoreactivity. In keeping with trends in tuberculosis disease,[1] rates of *M tuberculosis* immunoreactivity conversion were higher in males than females from adolescence onwards; in people aged 30 years, immunoreactivity

conversion rates were around 1·4 times higher in men than women, and in people aged 50 years they were 1·5 times higher. This higher conversion rate cumulatively drives a higher immunoreactivity prevalence in men. As most tuberculosis is due to recently acquired infection,[9] men's more intense exposure to *M tuberculosis* is implicated as a key driver of the substantial sex differences in global tuberculosis morbidity and mortality. The age-adjusted M:F prevalence ratio was remarkably consistent across different WHO regions, settings, tuberculosis-incidence strata, and study year.

Our hypothesis is that higher rates of immunoreactivity conversion are due to differences in *M tuberculosis* exposure. Behaviour change around adolescence results in increased time spent in contact with infectious individuals, and consequently a rise in infection rate in both men and women. Men might have disproportionately higher exposure due to time spent in indoor congregate settings, such as educational facilities, workplaces, social venues, prisons, and public transportation.[19,20] Men who then develop tuberculosis disease have gendered barriers to accessing treatment, resulting in a longer average duration of infectiousness[2–4] and making them more likely to transmit *M tuberculosis* onwards—disproportionately to other men due to age-assortative and sex-assortative mixing,[5,108] which further amplifies men's higher exposure.

Our findings do not exclude additional contributions from sex differences in progression from *M tuberculosis* infection to disease. Previous meta-analyses[8,109] have not formally explored the effect of sex on the risk of progression in people with *M tuberculosis* immunoreactivity, but this could be an area for future research. Many important modifiable risk factors for tuberculosis progression, such as cigarette smoking, alcohol consumption, diabetes, and untreated HIV,[1] are globally more prevalent in men than in women;[24,110,111] addressing these risk factors is crucial to mitigating men's increased *M tuberculosis* exposure.

We unexpectedly found a higher risk of *M tuberculosis* immunoreactivity in girls than boys when they were younger than 10 years (M:F prevalence ratio 0·95; 95% credible interval 0·90–1·01). Sex differences in social contact patterns are less substantial in young children,[5] and globally both tuberculosis incidence and mortality for people younger than 5 years are slightly higher in boys than in girls.[6] Immunological differences could have contributed: male and female infants differ markedly in their response to BCG vaccination[112] and to *M tuberculosis* exposure;[113] TST in particular could be influenced by non-specific responses to environmental non-tuberculous mycobacteria or recent BCG vaccination.[114] Although higher BCG vaccination coverage in girls could theoretically explain this finding, studies in several settings show vaccination rates that are similar or higher in boys.[115,116] Unfortunately, few of our included studies reported sex-disaggregated BCG vaccination data.

	Multiplicative effect on age-adjusted M:F prevalence ratio
Study test	
IGRA	1·00 (ref)
TST	1·04 (0·95–1·13)
Risk of bias	
Low	1·00 (ref)
Moderate	1·08 (0·97–1·19)
High	1·06 (0·96–1·17)
WHO region	
Africa	1·00 (ref)
South-East Asia	0·96 (0·85–1·08)
Western Pacific	0·97 (0·87–1·07)
Other region	0·95 (0·86–1·06)
TB incidence*	1·01 (0·98–1·01)
Study year	1·01 (0·99–1·01)
Study setting	
Both or national	1·00 (ref)
Rural	1·09 (0·99–1·20)
Urban	1·04 (0·96–1·14)

M:F=male to female. IGRA=interferon-γ release assays. TST=tuberculin skin test. *For each 100 cases per 100 000 people per year change in incidence.

Table 2: **Effect of covariables on M:F prevalence ratio of *Mycobacterium tuberculosis* immunoreactivity**

This study has several important limitations. First, we interpret TST and IGRA as markers of *M tuberculosis* exposure, but it is theoretically possible that the sex differences reported here reflect differences in T-cell response to *M tuberculosis*, resulting in differential conversion risk at fixed intensity of exposure, or differences in reversion rates.[117] Studies examining IGRA conversion risk by sex after tuberculosis exposure have found mixed results.[118,119] A meta-analysis has reported a higher rate of IGRA reversion in men,[119] suggesting that the true relative rate of *M tuberculosis* infection in men could be even higher than our estimates. As *M tuberculosis* immunoreactivity prevalence reflects cumulative lifetime exposure and reversion, the prevalence in older individuals in particular incorporates historical and contemporary trends.[10,120] The modelled estimates of absolute prevalence and risk of immunoreactivity presented in figure 2 represent an average across heterogeneous studies and, as such, cannot be interpreted as a global estimate; rather, our intention is to estimate the effect of age and sex on prevalence, within settings.

42% of the surveys included were at moderate or high risk of bias. Overall, 55% of adult participants were female, suggesting under-recruitment of men who could have systematically differed in their *M tuberculosis* infection risk. Survival bias could also have influenced recruitment, particularly in older age groups and in the very young (who have a high rate of progression to

tuberculosis disease and high tuberculosis case-fatality rate).[121] We obtained sex-disaggregated results from just less than 50% of potentially eligible studies; although we observed no evidence of publication bias, surveys that showed a sex difference might have been more likely to present sex-disaggregated results, inflating the observed effect. Measurement error is possible: various different TST cutoffs were used, and most TST surveys either showed evidence of digit preference or did not assess for it. Surveys used different age groupings to present their data and, when the mean age was not available, we approximated using the midpoint. WHO regions were not evenly represented, limiting our ability to fully explore regional trends; for example, most data in the oldest age groups were from Asia. It is possible that between-study heterogeneity that could have been explained by regional factors was instead absorbed into the study-level random effect. Very few studies reported HIV prevalence.

Despite these limitations, our findings have important implications and support the need for gender-sensitive strategies to end tuberculosis. Our findings suggest that unequal *M tuberculosis* exposure is an important driver of tuberculosis disease disparities, supporting serious efforts to address transmission of respiratory pathogens in congregate settings.[122] Transmission can also be reduced by lowering the burden of infectious tuberculosis in the population; as the majority of transmission to men (and, indeed, to other groups) is from other men,[5] our findings further underscore the need to improve their access to timely diagnosis and treatment. Furthermore, as men have a higher burden of *M tuberculosis* infection than women, they are a key target population for infection-focused interventions, such as vaccination or expanded preventive treatment. Despite being central to the tuberculosis epidemic, men have historically been poorly served by both routine health-care services and by tuberculosis-specific public health interventions, which are frequently designed around the convenience of the health service rather than the needs and priorities of the people they intend to reach.[4,123] More accessible services and responsive strategies, such as peer-to-peer support and interventions in non-clinical spaces, could help to bridge this gap.[4,123]

In conclusion, this meta-analysis of population-based *M tuberculosis* immunoreactivity surveys found a higher risk of *M tuberculosis* infection in men than women from adolescence onwards, consistent across settings, suggesting that much of the excess burden of tuberculosis disease and deaths in men is driven by increased transmission. To meet WHO's End TB goals it is important to engage men with interventions that address the underlying social, behavioural, and structural determinants of transmission and disease.

Contributors

Conceptualisation: HMR, MDP, HRAF, DWD, PJD, ELC, and PM. Formal analysis: HMR, ESN, PJD, and PM. Funding acquisition: HMR, ELC, and PM. Investigation: HMR, MDP, HRAF, MK, and HS. Methods: HMR, KCH, DWD, ESN, PJD, ELC, and PM. Supervision: KCH, ESN, ELC, and PM. Visualisation: HMR, ESN, PJD, and PM. Writing of original draft: HMR, ELC, and PM. Writing review and editing: MDP, HRAF, MK, HS, KCH, DWD, ESN, and PJD. Data verification: HMR and PM. All authors had access to data and accept responsibility to submit for publication.

Declaration of interests

KCH receives consulting fees from the World Health Organization and is the Chair of the Working Group on Gender Equity in TB at the International Union Against TB and Lung Disease (unpaid). All other authors report no competing interests.

Data sharing

This study only uses secondary data. Some age-disaggregated and sex-disaggregated data that had not been previously published were shared by the original authors for the purposes of this analysis. We have deposited an open-access dataset of all data that were already in the public domain (ie, excluding those shared by authors) and the code required to reproduce the analysis at github.com/hannahrickman.

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References

1 WHO. Global tuberculosis report 2024. World Health Organization, 2024.
2 Horton KC, Sumner T, Houben RMGJ, Corbett EL, White RG. A Bayesian approach to understanding sex differences in tuberculosis disease burden. *Am J Epidemiol* 2018; **187:** 2431–38.
3 Horton KC, MacPherson P, Houben RMGJ, White RG, Corbett EL. Sex differences in tuberculosis burden and notifications in low- and middle-income countries: a systematic review and meta-analysis. *PLoS Med* 2016; **13:** e1002119.
4 Chikovore J, Pai M, Horton KC, et al. Missing men with tuberculosis: the need to address structural influences and implement targeted and multidimensional interventions. *BMJ Glob Health* 2020; **5:** e002255.
5 Dodd PJ, Looker C, Plumb ID, et al. Age- and sex-specific social contact patterns and incidence of *Mycobacterium tuberculosis* infection. *Am J Epidemiol* 2016; **183:** 156–66.
6 Dodd PJ, Sismanidis C, Glaziou P. Methods for estimating tuberculosis incidence and mortality by age and sex. *Int J Epidemiol* 2021; **50:** 570–77.
7 Coussens AK, Zaidi SMA, Allwood BW, et al. Classification of early tuberculosis states to guide research for improved care and prevention: an international Delphi consensus exercise. *Lancet Respir Med* 2024; **12:** 484–98.
8 Hamada Y, Gupta RK, Quartagno M, et al. Predictive performance of interferon-gamma release assays and the tuberculin skin test for incident tuberculosis: an individual participant data meta-analysis. *EClinicalMedicine* 2023; **56:** 101815.
9 Behr MA, Edelstein PH, Ramakrishnan L. Revisiting the timetable of tuberculosis. *BMJ* 2018; **362:** k2738.
10 Rickman HM, Kamchedzera W, Schwalb A, et al. Know your tuberculosis epidemic—is it time to add *Mycobacterium tuberculosis* immunoreactivity back into global surveillance? *PLoS Glob Public Health* 2022; **2:** e0001208.
11 van Leth F, van der Werf MJ, Borgdorff MW. Prevalence of tuberculous infection and incidence of tuberculosis: a re-assessment of the Styblo rule. *Bull World Health Organ* 2008; **86:** 20–26.

12 Schwalb A, Emery JC, Dale KD, Horton KC, Ugarte-Gil CA, Houben RMGJ. Impact of reversion of *Mycobacterium tuberculosis* immunoreactivity tests on the estimated annual risk of tuberculosis infection. *Am J Epidemiol* 2023; **192:** 1937–43.

13 Houben RMGJ, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. *PLoS Med* 2016; **13:** e1002152.

14 Cohen A, Mathiasen VD, Schön T, Wejse C. The global prevalence of latent tuberculosis: a systematic review and meta-analysis. *Eur Respir J* 2019; **54:** 1900655.

15 Nyboe J. Interpretation of tuberculosis infection age curves. *Bull World Health Organ* 1957; **17:** 319–39.

16 Gao L, Lu W, Bai L, et al. Latent tuberculosis infection in rural China: baseline results of a population-based, multicentre, prospective cohort study. *Lancet Infect Dis* 2015; **15:** 310–19.

17 Middelkoop K, Bekker L-GG, Liang H, et al. Force of tuberculosis infection among adolescents in a high HIV and TB prevalence community: a cross-sectional observation study. *BMC Infect Dis* 2011; **11:** 156.

18 Lienhardt C, Fielding K, Sillah J, et al. Risk factors for tuberculosis infection in sub-Saharan Africa: a contact study in The Gambia. *Am J Respir Crit Care Med* 2003; **168:** 448–55.

19 Churchyard G, Kim P, Shah NS, et al. What we know about tuberculosis transmission: an overview. *J Infect Dis* 2017; **216** (suppl 6): S629–35.

20 Auld SC, Shah NS, Cohen T, Martinson NA, Gandhi NR. Where is tuberculosis transmission happening? Insights from the literature, new tools to study transmission and implications for the elimination of tuberculosis. *Respirology* 2018; **23:** 807–17.

21 Blount RJ, Phan H, Trinh T, et al. Indoor air pollution and susceptibility to tuberculosis infection in urban Vietnamese children. *Am J Respir Crit Care Med* 2021; **204:** 1211–21.

22 Chiang CY, Slama K, Enarson DA. Associations between tobacco and tuberculosis. *Int J Tuberc Lung Dis* 2007; **11:** 258–62.

23 Gupta M, Srikrishna G, Klein SL, Bishai WR. Genetic and hormonal mechanisms underlying sex-specific immune responses in tuberculosis. *Trends Immunol* 2022; **43:** 640–56.

24 UNAIDS. 2024 global AIDS report—the urgency of now: AIDS at a crossroads. Joint United Nations Programme on HIV/AIDS, 2024.

28 WHO. Global tuberculosis programme data. https://www.who.int/teams/global-tuberculosis-programme/data (accessed Jan 1, 2022).

25 Starshinova A, Dovgalyk I, Malkova A, et al. Recombinant tuberculosis allergen (Diaskintest®) in tuberculosis diagnostic in Russia (meta-analysis). *Int J mycobacteriology* 2020; **9:** 335–46.

26 WHO Global Task Force on TB Impact Measurement. Appendix 4, table 2: list of TB infection prevalence surveys. 2005. https://cdn.who.int/media/docs/default-source/hq-tuberculosis/global-task-force-on-tb-impact-measurement/meetings/2006-06/tf1_background_04_surveys_tb_infection_disease_mortality.xls?sfvrsn=78c69e98_3 (accessed Sept 13, 2022).

27 McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. *J Clin Epidemiol* 2016; **75:** 40–46.

29 WHO. WHO consolidated guidelines on tuberculosis module 1: prevention—tuberculosis preventive treatment. World Health Organization, 2021.

30 Hoy D, Brooks P, Woolf A, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. *J Clin Epidemiol* 2012; **65:** 934–39.

31 Yorulmaz F, Cağlar T, Erel C, Ozaydin M. Prevalence and annual risk of tuberculosis infection in Edirne, Turkey. *Scand J Infect Dis* 2002; **34:** 654–56.

32 Gopi PG, Subramani R, Radhakrishna S, et al. A baseline survey of the prevalence of tuberculosis in a community in south India at the commencement of a DOTS programme. *Int J Tuberc Lung Dis* 2003; **7:** 1154–62.

33 Shastri ART, Serane VT, Mahadevan S, Nalini P. Qualitative tuberculin response in the diagnosis of tuberculosis in apparently healthy schoolchildren. *Int J Tuberc Lung Dis* 2003; **7:** 1092–96.

34 Dubuis M, Fiekert K, Johnston M, Neuenschwander BE, Rieder HL. A tuberculin skin test survey among Afghan children in Kabul. *Int J Tuberc Lung Dis* 2004; **8:** 1065–72.

35 Norval PY, Roustit C, San KK. From tuberculin to prevalence survey in Cambodia. *Int J Tuberc Lung Dis* 2004; **8:** 299–305.

36 Salaniponi FML, Kwanjana J, Veen J, Misljenovic O, Borgdorff MW. Risk of infection with *Mycobacterium tuberculosis* in Malawi: national tuberculin survey 1994. *Int J Tuberc Lung Dis* 2004; **8:** 718–23.

37 Shashidhara AN, Chadha VK, Jagannatha PS, Ray TK, Mania RN. The annual risk of tuberculous infection in Orissa State, India. *Int J Tuberc Lung Dis* 2004; **8:** 545–51.

38 Leung CC, Yew WW, Tam CM, et al. Tuberculin response in BCG vaccinated schoolchildren and the estimation of annual risk of infection in Hong Kong. *Thorax* 2005; **60:** 124–29.

39 Trébucq A, Guérin N, Ali Ismael H, Bernatas JJ, Sèvre JP, Rieder HL. Prevalence and trends of infection with *Mycobacterium tuberculosis* in Djibouti, testing an alternative method. *Int J Tuberc Lung Dis* 2005; **9:** 1097–104.

40 Yeh YP, Luh DL, Chang SH, Suo J, Chang HJ, Chen THH. Tuberculin reactivity in adults after 50 years of universal bacille Calmette–Guerin vaccination in Taiwan. *Trans R Soc Trop Med Hyg* 2005; **99:** 509–16.

41 den Boon S, van Lill SWP, Borgdorff MW, et al. Association between smoking and tuberculosis infection: a population survey in a high tuberculosis incidence area. *Thorax* 2005; **60:** 555–57.

42 Egwaga SM, Cobelens FG, Muwinge H, Verhage C, Kalisvaart N, Borgdorff MW. The impact of the HIV epidemic on tuberculosis transmission in Tanzania. *AIDS* 2006; **20:** 915–21.

43 Saito M, Pan WK, Gilman RH, et al. Comparison of altitude effect on *Mycobacterium tuberculosis* infection between rural and urban communities in Peru. *Am J Trop Med Hyg* 2006; **75:** 49–54.

44 Gustafson P, Lisse I, Gomes V, et al. Risk factors for positive tuberculin skin test in Guinea-Bissau. *Epidemiology* 2007; **18:** 340–47.

45 Doocy SC, Todd CS, Llainez YB, Ahmadzai A, Burnham GM. Population-based tuberculin skin testing and prevalence of tuberculosis infection in Afghanistan. *World Health Popul* 2008; **10:** 44–53.

46 Gopi PG, Prasad VV, Vasantha M, et al. Annual risk of tuberculosis infection in Chennai city. *Indian J Tuberc* 2008; **55:** 157–61.

47 Hee JK, Soo YO, Jin BL, Yun SP, Woo JL. Tuberculin survey to estimate the prevalence of tuberculosis infection of the elementary schoolchildren under high BCG vaccination coverage. *Tuberc Respir Dis* 2008; **65:** 268–76.

48 Munim A, Rajab Y, Barker A, Daniel M, Williams B. Risk of *Mycobacterium tuberculosis* infection in Somalia: national tuberculin survey 2006. *East Mediterr Health J* 2008; **14:** 518–30.

49 Rao VG, Gopi PG, Yadav R, et al. Annual risk of tuberculosis infection among tribal population of central India. *Trop Med Int Health* 2008; **13:** 1372–77.

50 Rao VG, Gopi PG, Yadav R, et al. Tuberculous infection in Saharia, a primitive tribal community of central India. *Trans R Soc Trop Med Hyg* 2008; **102:** 898–904.

51 Khamis AH, Alsuni A. Prevalence of tuberculosis in Khartoum State in Sudan: correlation of tuberculin reactivity with age. *Ahfad J* 1998; **15:** 15–24.

52 Al-Absi A, Bassili A, Abdul Bary H, et al. The decline of tuberculosis in Yemen: evaluation based on two nationwide tuberculin surveys. *Int J Tuberc Lung Dis* 2009; **13:** 1100–05.

53 Boccia D, Hargreaves J, Ayles H, Fielding K, Simwinga M, Godfrey-Faussett P. Tuberculosis infection in Zambia: the association with relative wealth. *Am J Trop Med Hyg* 2009; **80:** 1004–11.

54 Mustapha MG, Garba AM, Rabasa AI, Gimba MS. Prevalence of Mantoux test positivity among apparently healthy children in Maiduguri, Nigeria. *SAJCH* 2009; **3:** 80–82.

55 Basta PC, Coimbra CEAJ Jr, Welch JR, Corrêa Alves LC, Santos RV, Bastos Camacho LA. Tuberculosis among the Xavante Indians of the Brazilian Amazon: an epidemiological and ethnographic assessment. *Ann Hum Biol* 2010; **37:** 643–57.

56 Kabeer BSA, Perumal V, Paramasivam P, Raja A. Yield of QuantiFERON-TB gold in tube assay and tuberculin skin test in healthy persons from a tuberculosis endemic population. *J Pediatr Infect Dis* 2010; **5:** 125–29.

57 Legesse M, Ameni G, Mamo G, Medhin G, Bjune G, Abebe F. Community-based cross-sectional survey of latent tuberculosis infection in Afar pastoralists, Ethiopia, using QuantiFERON-TB Gold In-Tube and tuberculin skin test. *BMC Infect Dis* 2011; **11:** 89.

58 Mahomed H, Hawkridge T, Verver S, et al. Predictive factors for latent tuberculosis infection among adolescents in a high-burden area in South Africa. *Int J Tuberc Lung Dis* 2011; **15:** 331–36.

59 Nkurunungi G, Lutangira JE, Lule SA, et al. Determining *Mycobacterium tuberculosis* infection among BCG-immunised Ugandan children by T-SPOT.TB and tuberculin skin testing. *PLoS One* 2012; **7:** e47340.

60 Hoa NB, Cobelens FGJ, Sy DN, Nhung NV, Borgdorff MW, Tiemersma EW. First national tuberculin survey in Viet Nam: characteristics and association with tuberculosis prevalence. *Int J Tuberc Lung Dis* 2013; **17:** 738–44.

61 Hu Y, Zhao Q, Wu L, Wang W, Yuan Z, Xu B. Prevalence of latent tuberculosis infection and its risk factors in schoolchildren and adolescents in Shanghai, China. *Eur J Public Health* 2013; **23:** 1064–69.

62 Laniado-Laborin R, Cabrales-Vargas N, Lopez-Espinoza G, Lepe-Zuniga JL, Quinonez-Moreno S, Rico-Vargas CE. Prevalence of tuberculosis infection in students in the city of Tijuana, Mexico. *Salud Publica Mex* 1998; **40:** 47–52 (in Spanish).

63 Martinez L, Arman A, Haveman N, et al. Changes in tuberculin skin test positivity over 20 years in periurban shantytowns in Lima, Peru. *Am J Trop Med Hyg* 2013; **89:** 507–15.

64 Wijesinghe PR, Palihawadana P, De Alwis S, Samaraweera S. Annual risk of tuberculosis infection in Sri Lanka: a low prevalent country with a high BCG vaccination coverage in the South-East Asia region. *WHO South East Asia J Public Health* 2013; **2:** 34–40.

65 Michelsen SW, Soborg B, Koch A, et al. The effectiveness of BCG vaccination in preventing *Mycobacterium tuberculosis* infection and disease in Greenland. *Thorax* 2014; **69:** 851–56.

66 Uppada DR, Selvam S, Jesuraj N, et al. The tuberculin skin test in school going adolescents in South India: associations of socio-demographic and clinical characteristics with TST positivity and non-response. *BMC Infect Dis* 2014; **14:** 571.

67 Wang H-J, Li D, Dhondup T, Qujizhuoma, Xiaozhuoma, Ci N, Zhang R. Investigation on PPD test in primary and middle school students in Nyingchi, Tibet. *Chinese J Evidence-Based Med*. 2014; **14:** 671–73.

68 Adetifa IMO, Muhammad AK, Jeffries D, et al. A tuberculin skin test survey and the annual risk of *Mycobacterium tuberculosis* infection in Gambian school children. *PLoS One* 2015; **10:** e0139354.

69 Chen C, Zhu T, Wang Z, et al. High latent TB infection rate and associated risk factors in the eastern China of low TB incidence. *PLoS One* 2015; **10:** e0141511.

70 Kizza FN, List J, Nkwata AK, et al. Prevalence of latent tuberculosis infection and associated risk factors in an urban African setting. *BMC Infect Dis* 2015; **15:** 165.

71 Mumpe-Mwanja D, Verver S, Yeka A, et al. Prevalence and risk factors of latent tuberculosis among adolescents in rural eastern Uganda. *Afr Health Sci* 2015; **15:** 851–60.

72 Pang Y, Kang W, Zhao A, et al. The effect of bacille Calmette–Guérin vaccination at birth on immune response in China. *Vaccine* 2015; **33:** 209–13.

73 Lockman S, Tappero JW, Kenyon TA, Rumisha D, Huebner RE, Binkin NJ. Tuberculin reactivity in a pediatric population with high BCG vaccination coverage. *Int J Tuberc Lung Dis* 1999; **3:** 23–30.

74 Ranaivomanana P, Raharimanga V, Dubois PM, Richard V, Rasolofo Razanamparany V. Study of the BCG vaccine-induced cellular immune response in schoolchildren in Antananarivo, Madagascar. *PLoS One* 2015; **10:** e0127590.

75 Yuen CM, Krapivina TM, Kazennyy BY, et al. Annual risk of tuberculous infection measured using serial skin testing, Orel Oblast, Russia, 1991–2005. *Int J Tuberc Lung Dis* 2015; **19:** 39–43.

76 Elias D, Akuffo H, Abate E, Mekonnen Y, Aseffa A, Britton S. Risk of tuberculous infection in adolescents and adults in a rural community in Ethiopia. *Int J Tuberc Lung Dis* 2016; **20:** 218–22.

77 Khan PY, Glynn JR, Fielding KL, et al. Risk factors for *Mycobacterium tuberculosis* infection in 2–4 year olds in a rural HIV-prevalent setting. *Int J Tuberc Lung Dis* 2016; **20:** 342–49.

78 Liu Y, Huang S, Jiang H, et al. The prevalence of latent tuberculosis infection in rural Jiangsu, China. *Public Health* 2017; **146:** 39–45.

79 Marks GB, Nhung NV, Nguyen TA, et al. Prevalence of latent tuberculous infection among adults in the general population of Ca Mau, Viet Nam. *Int J Tuberc Lung Dis* 2018; **22:** 246–51.

80 Teklu T, Legesse M, Medhin G, et al. Latent tuberculosis infection and associated risk indicators in pastoral communities in southern Ethiopia: a community based cross-sectional study. *BMC Public Health* 2018; **18:** 266.

81 Yap P, Tan KHX, Lim WY, et al. Prevalence of and risk factors associated with latent tuberculosis in Singapore: a cross-sectional survey. *Int J Infect Dis* 2018; **72:** 55–62.

82 Albers AE, Pope K, Sijali TR, Subramanya SH, Verma SC, Bates MN. Household fuel use and latent tuberculosis infection in a Nepali population. *Environ Res* 2019; **173:** 69–76.

83 Bunyasi EW, Geldenhuys H, Mulenga H, et al. Temporal trends in the prevalence of *Mycobacterium tuberculosis* infection in South African adolescents. *Int J Tuberc Lung Dis* 2019; **23:** 571–78.

84 Neuenschwander BE, Zwahlen M, Kim SJ, Engel RR, Rieder HL. Trends in the prevalence of infection with *Mycobacterium tuberculosis* in Korea from 1965 to 1995: an analysis of seven surveys by mixture models. *Int J Tuberc Lung Dis* 2000; **4:** 719–29.

85 Dorjee K, Topgyal S, Dorjee C, et al. High prevalence of active and latent tuberculosis in children and adolescents in Tibetan schools in India: the Zero TB Kids initiative in Tibetan refugee children. *Clin Infect Dis* 2019; **69:** 760–68.

86 Ganmaa D, Khudyakov P, Buyanjargal U, et al. Prevalence and determinants of QuantiFERON-diagnosed tuberculosis infection in 9810 Mongolian schoolchildren. *Clin Infect Dis* 2019; **69:** 813–19.

87 Nduba V, Van't Hoog AH, de Bruijn A, Mitchell EMH, Laserson K, Borgdorff M. Estimating the annual risk of infection with *Mycobacterium tuberculosis* among adolescents in western Kenya in preparation for TB vaccine trials. *BMC Infect Dis* 2019; **19:** 682.

88 Socaci A, Arghir IA, Borgazi E, Ion I, Petcu LC. Prevalence and annual risk of tuberculous infection to children and adolescents in two high endemic TB counties from Romania. *Med-Surg J* 2019; **123:** 661–69.

89 Xin H, Zhang H, Liu J, et al. *Mycobacterium tuberculosis* infection among the elderly in 20 486 rural residents aged 50–70 years in Zhongmu County, China. *Clin Microbiol Infect* 2019; **25:** 1120–26.

90 Gatchalian SR, Agathis NT, Castillo-Carandang NT, Gunter SM, Murray KO, Mandalakas AM. Design and evaluation of risk assessment tools to identify pediatric tuberculosis infection in Bohol, the Philippines, a low-HIV- and high-TB-burden setting. *Am J Trop Med Hyg* 2020; **103:** 1818–26.

91 Mokti K, Ibrahim MY, Giloi N, et al. Factors contribute to tuberculin skin test (TST) positive among urban Islander, Malaysian Borneo. *Gazi Med J* 2020; **32:** 11–16.

92 Khalid FA, Eldirdery MM, El-Gasim ME-O, Mukhtar MM. Tuberculin reactivity in schoolchildren, Kassala State, Sudan. *Int J Mycobacteriol* 2020; **9:** 200–04.

93 Lwin TT, Apidechkul T, Saising J, et al. Prevalence and determinants of TB infection in a rural population in northeastern Myanmar. *BMC Infect Dis* 2020; **20:** 904.

94 Munseri P, Said J, Amour M, et al. DAR-901 vaccine for the prevention of infection with *Mycobacterium tuberculosis* among BCG-immunized adolescents in Tanzania: a randomized controlled, double-blind phase 2b trial. *Vaccine* 2020; **38:** 7239–45.

95 Tupasi TE, Radhakrishna S, Pascual ML, et al. BCG coverage and the annual risk of tuberculosis infection over a 14-year period in the Philippines assessed from the nationwide prevalence surveys. *Int J Tuberc Lung Dis* 2000; **4:** 216–22.

96 Jeremiah K, Lyimo E, Ritz C, et al. Prevalence of *Mycobacterium tuberculosis* infection as measured by the QuantiFERONTB Gold assay and ESAT-6 free IGRA among adolescents in Mwanza, Tanzania. *PLoS One* 2021; 16: 1–12.

97 Mzembe T, Lessells R, Karat AS, et al. Prevalence and risk factors for *Mycobacterium tuberculosis* infection among adolescents in rural South Africa. *Open Forum Infect Dis* 2020; **8:** ofaa520.

98 Jia J, Chen D, Liu L, et al. Prevalence of latent tuberculosis infection among healthy young children and adolescents and a two-step approach for the diagnosis of tuberculosis infection in Chengdu, China. *Pediatr Infect Dis J* 2022; **41:** 6–11.

99 Cai E, Zhang S. Screening results of tuberculin test of 1900 junior middle school students in a county of Cangzhou City. *Occup Health* 2011; **27:** 2007–08.

100 Lin T, Hu Y, Hou Y, Jiang W-L, Tao T, MA H, et al. Prevalence of latent tuberculosis infection and its risk factors among senior students from four primary schools in Shanghai. *Chinese J Infect Dis*. 2011; **29:** 148–53.

101 Yates TA, Cebekhulu S, Mthethwa M, et al. Tuberculin skin test surveys and the annual risk of tuberculous infection in school children in northern KwaZulu-Natal. *PLOS Glob Public Health* 2024; **4:** e0003263.

102 Bustamante-Rengifo JA, González-Salazar LÁ, Osorio-Certuche N, et al. Prevalence of and risk factors associated with latent tuberculosis infection in a Latin American region. *PeerJ* 2020; **8:** e9429.

103 Yin S-L, Xu Z, Xu H, et al. Prevalence of latent tuberculosis infection and its related risk factors in rural Xiangtan County. *Chinese J Zoonoses* 2020; **36:** 4–8.

104 Amofa-Sekyi M, Schaap A, Mureithi L, et al. Prevalence and risk factors of *M tuberculosis* infection in young people across 14 communities in Zambia and South Africa. *PLoS Glob Public Health* 2023; **3:** e0002077.

105 Middelkoop K, Micklesfield L, Stewart J, et al. Influence of vitamin D supplementation on growth, body composition, pubertal development and spirometry in South African schoolchildren: a randomised controlled trial (ViDiKids). *BMJ Paediatr Open* 2024; **8:** 1–12.

106 Black GF, Warndorff DK, Floyd S, et al, and the Fine PEM. Relationship between IFN-γ and skin test responsiveness to *Mycobacterium tuberculosis* PPD in healthy, non-BCG-vaccinated young adults in Northern Malawi. *Int J Tuberc Lung Dis* 2001; **5:** 664–72.

107 Serane VT, Nalini P. Tuberculin reactivity in healthy school children in Pondicherry. *Indian J Pediatr* 2001; **68:** 729–32.

108 Mousa A, Winskill P, Watson OJ, et al. Social contact patterns and implications for infectious disease transmission—a systematic review and meta-analysis of contact surveys. *eLife* 2021; **10:** 10.

109 Gupta RK, Calderwood CJ, Yavlinsky A, et al. Discovery and validation of a personalized risk predictor for incident tuberculosis in low transmission settings. *Nat Med* 2020; **26:** 1941–49.

110 GBD 2019 Tuberculosis Collaborators. Global, regional, and national sex differences in the global burden of tuberculosis by HIV status, 1990–2019: results from the Global Burden of Disease Study 2019. *Lancet Infect Dis* 2022; **22:** 222–41.

111 Reitsma MB, Kendrick PJ, Ababneh E, et al. Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990-2019: a systematic analysis from the Global Burden of Disease Study 2019. *Lancet* 2021; **397:** 2337–60.

112 Roth A, Sodemann M, Jensen H, et al. Tuberculin reaction, BCG scar, and lower female mortality. *Epidemiology* 2006; **17:** 562–68.

113 Fox GJ, Orlova M, Schurr E. Tuberculosis in newborns: the lessons of the "Lübeck disaster" (1929–1933). *PLoS Pathog* 2016; **12:** e1005271.

114 Rieder HL. Methodological issues in the estimation of the tuberculosis problem from tuberculin surveys. *Tuber Lung Dis* 1995; **76:** 114–21.

115 Osborne A, Wongnaah FG, Bangura C, Ahinkorah BO. Trends and inequalities in BCG immunisation coverage among one-year-olds in Sierra Leone, 2008–2019. *BMC Public Health* 2024; **24:** 3342.

116 Corsi DJ, Bassani DG, Kumar R, et al. Gender inequity and age-appropriate immunization coverage in India from 1992 to 2006. *BMC Int Health Hum Rights* 2009; **9** (suppl 1)**:** S3.

117 Bothamley GH. Male sex bias in immune biomarkers for tuberculosis. *Front Immunol* 2021; **12:** 640903.

118 Wada PY, Costa AG, Araújo-Pereira M, et al. Possible sex difference in latent tuberculosis infection risk among close tuberculosis contacts. *Int J Infect Dis* 2022; **122:** 685–92.

119 Wang M-S, Li-Hunnam J, Chen Y-L, et al. Conversion or reversion of interferon γ release assays for *Mycobacterium tuberculosis* infection: a systematic review and meta-analysis. *Clin Infect Dis* 2025; **80:** 168–79.

120 Dowdy DW, Behr MA. Are we underestimating the annual risk of infection with *Mycobacterium tuberculosis* in high-burden settings? *Lancet Infect Dis* 2022; **22:** e271–78.

121 Martinez L, Cords O, Horsburgh CR, Andrews JR. The risk of tuberculosis in children after close exposure: a systematic review and individual-participant meta-analysis. *Lancet* 2020; **395:** 973-984.

122 Yates TA, Tanser F, Abubakar I. Plan Beta for tuberculosis: it's time to think seriously about poorly ventilated congregate settings. *Int J Tuberc Lung Dis* 2016; **20:** 5-10.

123 Medina-Marino A, Bezuidenhout D, Ngcelwane N, et al. Qualitative identification of intervention preferences to support men's engagement and retention in TB care in South Africa. *Am J Mens Health* 2022; **16:** 15579883221129349.