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# The global prevalence of latent tuberculosis: a systematic review and meta-analysis

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**Summary of messages:**

Using a novel strategy, global estimates of latent tuberculosis were updated to 24.8% for IGRAs and 21.2% for TSTs using prevalence surveys of 351.811 individuals. Regional estimates varied between 11-27% and 12-33% for IGRAs and TSTs respectively.

**Key words:**

Latent Tuberculosis; Prevalence; Global Health; Interferon-Gamma Release Assay (IGRA); Tuberculin Skin Test (TST)

# Abstract

In 1999, the WHO estimated that one-third of the world's population had latent tuberculosis infection (LTBI) which was recently updated to one-fourth. However, this is still based on controversial assumptions in combination with tuberculin skin test (TST) surveys. Interferon-gamma release assays (IGRAs) with a higher specificity than TST have since been widely implemented, but never used to estimate the global LTBI prevalence.

We conducted a systematic review and meta-analysis of LTBI estimates based on both IGRA and TST results published between 2005 and 2018. Regional and global estimates of LTBI prevalence were calculated. Stratification was performed for low, intermediate and high TB incidence countries and a pooled estimate for each area was calculated using a random effects model.

Among 3280 studies screened, we included 88 studies from 36 countries with 41 IGRA (n=67 167) and 67 TST estimates (n=284 644). The global prevalence of LTBI was 24.8% (95% CI: 19.7-30.0%) and 21.2% (95% CI: 17.9-24.4%) based on IGRA and a 10 mm TST cut-off respectively. The prevalence estimates correlated well to WHO incidence rates (Rs=0.70, $p<0.001$).

In the first study of the global prevalence of LTBI derived from both IGRA and TST surveys, we found that one-fourth of the world's population is infected. This is of relevance as both tests, although imperfect, are used to identify individuals eligible for preventive therapy. Enhanced efforts are needed targeting the large pool of latently infected as these individuals continuously constitutes an enormous source of potential active TB.

# Introduction

The World Health Organization (WHO) estimated in 1999 that 1.8 billion people, or one-third of the world's population, were infected with *Mycobacterium tuberculosis* (Mtb) but without clinical symptoms of active tuberculosis (TB) which is the definition of latent TB infection (LTBI) [1]. Since, this estimate has been referred to frequently, but has not been updated until recently. In 2016, a WHO endorsed estimate updated the global prevalence of LTBI to 23% corresponding to 1.7 billion people infected worldwide [2,3].

The reactivation rate of LTBI into active disease is controversial, partly as reinfection may occur, but mainly because there are no methods to identify LTBI subjects at highest risk of developing active TB. Nevertheless, the current estimate of the LTBI burden clearly indicates a large reservoir of individuals at risk of developing active TB. Global incidence and mortality rates of active TB have declined since 1990, and the global incidence rate has been decreasing since the WHO goals were appointed in the beginning of the new milliennium [3]. Improved attention to LTBI screening and preventive therapy has been pointed out as crucial for The End TB Strategy for 2050 to be achieved [4,5]. It is hardly possible to eliminate TB unless progression to active TB is prevented underlining the need to determine the actual prevalence of LTBI and define hot spot areas [6].

The previous WHO estimate was only based on tuberculin skin test (TST) to a small extent (13%) [1], but mainly on annual risk of infection (ARI) calculated from the incidence of smear positive cases using the Styblo rule [7], derived from empirical data and assumptions on duration of infectiousness and transmissions per year. The ratio assumes that each smear positive case transmits ten infections per year; whereas a newer estimate suggested that this number could be as low as 2-6 [8]. The Stylbo rule also assumes that the duration of infectiousness is in general two years, which is now debated and likely to have decreased due to intensified case finding and treatment of active TB. Even in resource poor settings, treatment delay is reduced to an average of 3 months which enables a more rapid sputum conversion and reduction in infectiousness than when the rule was defined [9,10]. Additionally, transmission rates and infectiousness are highly dependent on age distributions, geographical location, drug availability, living conditions and population density [8]. Therefore, the assumption that the Styblo rule – even in its revised form used for the recent

update – still applies in the global TB settings of today could lead to an overestimation of the LTBI prevalence. Hence, basing LTBI prevalence on a rule of thumb, involving assumptions which may not be valid today, is likely to be more imprecise than using real data collected on populations in a large number of countries which does not involve assumptions on transmission rates or infectiousness but incorporates local conditions.

TST has traditionally been used as a screening tool for LTBI due to low direct costs and ease of use. In the last decades, commercial interferon-gamma release assays (IGRAs) have been introduced which solely contain antigens that are absent in Bacillie Calmette-Guérin (BCG)-vaccine strains and require no follow-up test [11]. Thus, IGRAs have superior specificity to TST in BCG-vaccinated populations and in regions with frequent non-tuberculous mycobacteria exposure [12].

So far, no global estimation of LTBI prevalence has been based on IGRAs, and it has been suggested that the prevalence of LTBI might be overestimated by TST compared with IGRA due to the improved specificity [13]. In this study, we aimed to investigate the global prevalence of LTBI based on TB incidence stratified estimates directly derived from both IGRA and TST as these are the tests currently applied to identify individuals for preventive therapy.

# Methods

## Search strategy and selection criteria

We performed a systematic review and meta-analysis using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Supplementary F) [14]. The protocol was registered on PROSPERO (CRD42019125380).

Studies that reported on the prevalence of LTBI diagnosed with IGRA and/or TST were eligible. Two investigators (A.C. and V.D.M.) searched the databases MEDLINE, Embase, Scopus, and Web of Science for articles published between 1$^{st}$ of January 2005 and the 30$^{th}$ of July 2018 using the following terms in different combinations and constructions depending on the applied database: “Latent tuberculosis” and (“Tuberculosis” AND “Prevalence” AND “Latent”) combined with “Tuberculin test”, “Tuberculin tests”, “Tuberculin skin test”, “Tuberculin skin tests” ,”TST*”, “Mantoux*”, “Interferon-gamma”, “Interferon-gamma

release assay", "Interferon-gamma release assays", "Interferon-gamma release test", "Interferon-gamma release tests", "IGRA*", "Quantiferon*", "QFT*", "T-SPOT.TB*", "Enzyme-Linked Immunospot Assay" and "Enzyme-linked Immunospot Assays" (Detailed electronic search strategy availiable in supplementary A). All search terms were searched in both title, abstract and field keywords. Our search combined free text and subject identifiers as medical subject heading (MeSH) terms. Additionally, we examined several reference lists of relevant articles. We did not set any language restrictions. The search was initiated in 2005 reflecting the widespread availability of stable, quality controlled and commercial IGRAs on the market, and in order to provide an updated analysis with recent surveys. The QuantiFERON-TB (QFT) test introduced in 2001 measured response to the same antigen mixture (purified protein derivate) as TST, while the QFT Gold (QFT-G) introduced in 2005 omitted antigens present in the BCG vaccine and in the ubiquitous non-tuberculous mycobacteria.

Full-texts were obtained for all studies identified by either A.C. or V.D.M. as potentially relevant.

## Study eligibility and quality assessment

Following deletion of duplicates, A.C. and V.D.M. screened titles, abstracts or entire articles for exclusion criteria and determined which studies met the eligibility criteria (Supplementary B). Only studies with a sample size of at least 200 were included to avoid selection bias from small studies. Meta-analyses, reviews, cost-effectiveness analyses and non-human studies were excluded. Studies on patients with presumed or active TB were excluded as well as if they did not report on prevalence of LTBI using IGRA-tests (any versions of QFT and/or T-SPOT.TB) or TST. Further, studies targeting risk-groups (i.e. not population-based) such as healthcare workers, drug-users, prison inmates, human immunodeficiency virus (HIV) positive, patients with inflammatory mediated disease among others were excluded to avoid overestimation of LTBI prevalence during targeted screening. Additionally, studies that applied interventions that could affect IGRA and TST results, and studies that selected their population based on specific test results, were excluded. In studies of risk groups along with control groups, control subgroups were included if no exclusion criteria were found (e.g. healthy controls). The most comprehensive paper, i.e. largest sample size or most detailed IGRA/TST results, was included when the same data were reported in more than one publication. Authors were contacted for clarification when the methodology was unclear.

We established criteria for assessment of the quality of the included studies, adopted from the Cochrane collaboration for analytical studies [15], on the STROBE guidelines for reporting observational studies [16] and according to a global prevalence review [17]. All included studies were assessed for quality on four criteria: Quality of sampling method, quality of selection method, response rate, and quality of prevalence assessment. These four criteria were evaluated on a three-point numerical scale (0, 1, or 2) and involved assessment of internal and external validity and attrition bias (Supplementary C).

## Data extraction

The following information was extracted: First author, year of publication, study design, study date, study population description, age, exclusion criteria, eligible and invited study population, participants and finally included participants. Enrolment data was used for the full study enrolment when data for selected subgroups were missing. Further, we extracted measures of TB verification, number of individuals with TB at the time of screening, and whether they were excluded from the final results, sample size, type of test (i.e. version of QFT, T-SPOT.TB and TST), and IGRA and TST test-positive as well as TST cut-offs. We only used baseline results from studies employing two-step TST to avoid a boosting phenomenon [18]. Indeterminate QFT results were registered, and whether they were excluded or not, and similarly for indeterminate T-SPOT.TB. When IGRA results for more than one cut-off point were presented, we used the manufactures' instructions for interpretation [19,20]. Due to the availability of LTBI survey data, which varied between years and areas, the latest country-specific incidence rates of active TB (including people living with HIV) and country population sizes were gathered July 2018 from WHO's global TB database [21].

## Definition of incidence intervals and evaluation of IGRA and TST results

In order to enable extrapolation of LTBI prevalence to countries with no data, we divided countries into three intervals of TB incidence: Low (0-10 cases / 100 000 person years$^{-1}$), intermediate (11-120 cases / 100 000 person years$^{-1}$) and high (>120 cases / 100 000 person years$^{-1}$). To our knowledge, there is no consensus on defining the upper limit of the intermediate TB incidence interval, and we based our definition on a combination of published data and visual inspection of the latest WHO estimates of TB incidence [3]. To accommodate this unscertainty, we sequentially performed statistical analysis on a upper

limit defined as all numbers between 20 and 150 and included the resulting range of final global IGRA and TST estimates. The upper limit of the low interval was based on WHO's Framework towards Tuberculosis Elimination in Low-Incidence Countries [22].

We calculated individual prevalence estimates for both IGRA and TST used in all studies and the primary estimate was based on a TST 10 mm cut-off and IGRA-tests without considering indeterminate results. However, other ways of calculating estimates were considered as described below. In studies including both QFT and T-SPOT.TB, we calculated a sample size weighted mean prevalence and used the QFT sample size as denominator. When both QFT-G, QFT Gold In-Tube (QFT-GIT) and/or QFT Gold Plus (QFT-Plus) results were presented, we prioritized data from the newest test version (i.e. QFT-GIT or QFT-Plus). The reported estimate was based on excluding indeterminate IGRA results, as it cannot be ascertained whether these are truly positive or negative. In order to compare different strategies for calculating IGRA results, we included the following strategies as a sensitivity analysis: (1) excluding indeterminate results when possible, (2) including indeterminate results in the denominator and regarding them as negative in the numerator, and in worst case scenario (3) including indeterminate results in the denominator and regarding them as positive in the numerator. We did not have access to quantitative IGRA data and thus, the proposed grey zone for QFT results (0.20-0.70 IU/ml) could not be evaluated [23]. We calculated TST results in three different ways: (1) cut-off at 5 mm or as close as possible, (2) cut-off at 10 mm or as close as possible and (3) cut-off at 15 mm or as close as possible. Exact 95% confidence intervals (CI) were calculated for all studies and estimates.

## Meta-analysis and statistical analysis

Study prevalence proportions of LTBI based on IGRA and TST were divided into three groups according to the aforementioned TB incidence intervals using WHO TB incidence rates. Firstly, proportions were transformed using the Freeman-Tukey double arcsine method [24]. We assessed a great variation within the study populations, possibly affecting study estimates, and therefore chose to employ a random effects model as also used in similar studies [25]. In the random effects analysis, increased sample size increases the weight of a study, but the more the study result varies from the other studies in the analysis, the more the weight decreases. This prevents very large studies in one country from affecting the overall result, but provides very small studies with a relatively high weight considering their small

population sizes [26]. A pooled inverse variance weighted random effects analysis was performed on each TB incidence group using the DerSimonian and Laird method [27]. Clopper-Pearson 95% CI were calculated for each study and for the TB incidence interval pooled estimates. We calculated weights of each TB incidence interval estimate by dividing the pooled country population size of each TB incidence interval with the global population size. Followingly, we calculated a global prevalence of LTBI by weighting the TB incidence interval prevalence estimates according to the population size represented. Study estimate heterogeneity was evaluated using $I^2$ statistics for each incidence interval. Further, we assessed the impact on difference between IGRA and TST global estimates by excluding single test studies. Using the TB incidence interval estimates for LTBI, we calculated LTBI prevalence estimates for each WHO region by weighting the three incidence interval estimates according to pooled population sizes of the same TB incidence intervals of each WHO region and compared them with WHO estimates. Finally, a Spearman's rank correlation coefficient was calculated to evaluate the relationship between IGRA- and TST-based LTBI prevalences and WHO incidence rates. Statistical analyses were performed using the meta 4.9-2 package in R (version 3.5.1).

# Results

In total, 8328 search results were identified through MEDLINE (n=2024), Embase (n=1936), Scopus (n=2394), and Web of Science (n=1974). After removal of duplicates, 3280 studies remained of which 770 full-text were assessed for eligibility, and 682 were excluded. Eighty-eight quantitative studies fulfilled the criteria for inclusion (Figure 1; studies listed in supplementary D) [13,28–113]. Among 36 countries represented, 41 IGRA (n=67 167) and 67 TST (n=284 644) estimates were available. Annual TB incidence rates ranged from 0.8/100 000 in the United Arab Emirates [28] to 781/100 000 in South Africa [106]. The mean age reported ranged from approximately 51 months [41] to 82.3 years [66].

Among the included studies, 36 used one or more variants of the QFT assay including individuals sampled with QFT Gold (n=8262) [29,36,48,58,59,70,78,83,94], QFT Gold In-Tube (n=56 327) [13,28,39,42,45,49,51,57,60,67,71,72,79–81,83,86–88,93,96,104–107,110,113] and a single study using QFT-Plus (n=829) [89]. Seven studies used TB.SPOT-TB (n=5547) [31,62,65,72,90,104,114] and two of these simultaneous QFT Gold In-Tube [72,104]. In total, 41 studies used one or more IGRA tools (n=67 167 individuals)

[13,28,29,31,36,39,42,45,48,49,51,57–60,62,65,67,70–72,78–81,83,86–90,93,94,96,104–107,110,113,114]. Sixty-seven studies had TST results (n=284 644 individuals) [13,30–38,40–47,49–56,61,63,65,66,68,69,72–77,80,82–87,91–93,95–109,112,113,115]. Twenty studies used both IGRA and TST [13,31,36,42,45,49,51,65,72,80,83,86,87,93,96,104–107,113]. The pooled sample sizes of studies using TST were larger than studies using IGRA in all intervals and largest in the high-incidence interval (Table 1).

The studies included country estimates (n=36) covering all incidence intervals and WHO regions (Supplementary E). A world map was compiled showing all countries with original LTBI prevalence data coloured in darker variants of blue, orange and red, depending on which of the three TB incidence intervals they were within (i.e. low, intermediate or high) (Figure 2). For the remaining countries without any current data (n=159), we used the weighted LTBI prevalence estimate of their respective TB incidence interval, and colored the countries in a lighter version of aforementioned colors.

The global prevalence of LTBI was 24.8% (95% CI: 19.7-29.9%) and 21.2% (95% CI: 17.9-24.4%) according to IGRA and TST (10 mm) results respectively. Prevalence of LTBI by TB incidence intervals for TSTs and IGRAs are shown in the forest plots in figure 3-4. There was a strong monotonic relationship between WHO TB incidence rates and LTBI prevalence based on both IGRAs ($r_s$=0.706, p<0.0001) and TSTs ($r_s$=0.697, p<0.0001). The between study estimate heterogenecity of the low, intermediate and high TB incidence interval, calculated with $I^2$ statistics, was 97%, 99% and 99% for IGRA respectively and 100% for all three incidence intervals with TST.

If including indeterminate results in the denominator, and regarding indeterminate results as negative, global prevalence based on IGRA was 24.2% (95% CI: 19.2-29.2%). In a worst-case scenario, regarding indeterminate as positive results, global prevalence was estimated to 26.3% (95% CI: 21.0-31.6%). Based on TST results, we calculated a global prevalence of 24.1% (95% CI: 20.2-28.0%), 21.2% (95% CI: 17.9-24.4%) and 17.4% (95% CI: 14.4-20.4%) using 5, 10 and 15-mm cut-offs. If only considering studies that used IGRA and TST tests concurrently, 20 studies remained with a pooled population of 43 861 (IGRA) and 44 238 (TST) [13,31,36,45,49,51,65,72,80,83,86,87,93,96,104–107,113]. The global IGRA estimate was then 25.2% (95% CI: 19.8-30.7%) (indeterminate results excluded) and the global TST estimate (10 mm) was 27.1% (95% CI: 18.9-35.3%). When calculations were performed sequentially with the upper limit of the intermediate TB prevalence interval

defined as all numbers between 20 and 150, the global estimate ranged between 22.6-25.0% (IGRA) and 20.6-22.3% (TST).

These new estimates based on both IGRA and TST (10 mm cut-off) were lower than WHO estimates in all WHO regions (Table 1). Most notably, new TST estimates of Southeast Asia and Western Pacific were more than one-third lower than the 1999 estimates. IGRA estimates were slightly higher in all WHO regions compared with new TST estimates.

The quality of the studies included varied ranging from 0-8 points out of eight possible (References available in supplementary C). Most studies employed convenience sampling (n=60/88). Information on response rate was presented in 42 out of 88 (47.7%) studies. Indeterminate results were reported in 30 of 41 (73.2%) studies on IGRA of which four had indeterminate results constituting more than 5% of all results [31,60,65,96]. Twenty-seven of 67 (40.3%) studies reported a 15 mm TST cut-off, fifthy-six (83.6%) a 10 mm cut-off and 26 (38.8%) a 5 mm cut-off.

# Discussion

In this study, we present an update of the global LTBI prevalence estimate, for the first time based directly on both IGRA and TST results, the tests currently being used to diagnose and select LTBI subjects eligible for preventive therapy. Data were gathered from more than 350 000 IGRA and TST results covering all WHO regions. New IGRA and TST estimates were comparable in most regions but systematically slightly higher for IGRAs. Our global estimate of the LTBI prevalence is an update of the WHO estimate from 1999 and very much in line with a similar ARI-based modelling study from 2016 suggesting a global prevalence of LTBI at 23% [2]. Our findings support that the global prevalence of LTBI is no longer a third of the world population, but closer to one-fourth, with large regional differences, which in this test-based study is similar to the old and new modelled estimates and the reductions are in many aspects, although not completely, aligned with the new modelled prevalences by Houben et al.

In accordance with the previous WHO estimates from 1999 as well as with the new estimates by Houben et al, we found that Southeast Asia is the region with the highest LTBI prevalence [1,2]. In contrast to both previous estimates, we observed that Africa had the second highest prevalence with 26.6% (IGRA) and 33.6% (TST) whereas Houben et al interestingly reported

a regional prevalence of only 22% considerably lower than the previous WHO estimate of 35%. According to WHO, the TB incidence rates in Africa have been decreasing since 2005 [3]. However, before 2005, while end-targets for TB fell in other regions, Africa saw a rise since monitoring began in the early 1990's. This could partly explain the slower pace in reducing LTBI prevalence in Africa, as is indicated by our estimates. Especially sub-Saharan Africa is a high-endemic region, and active TB is prioritized due to the high burden of disease and limited resources while LTBI is mainly a concern for close contacts to smear positive TB patients and people living with HIV [116]. Of further interest, we found considerably lower estimates for the Western Pacific Region (WPR) with 20.7% (IGRA) and 20.3% (TST) whereas Houben et al report 27.9% closer to the previous WHO estimate of 36%. Our estimates are more in line with specific estimates for China of 19% [13] which makes the estimate plausible since China constitutes 73% of the WPR population.

Estimating the true rate of LTBI is highly challenging due to the absence of a gold standard for LTBI. As both IGRA and TST detect memory T-cell response to previous Mtb antigen exposure, a positive test is not necessarily associated with infection of viable bacteria [117]. Of note, the tests are insufficient in detecting progression into active TB with very low positive predictive values of 2.7% (95% CI: 2.3-3.2) for IGRAs and 1.5% (95% CI:1.2-1.7) for TSTs in one systematic review [118]. Recently, a new version of IGRA, QFT-Plus, has been introduced containing additional TB antigens stimulating both CD4 and CD8 T-cells [119] which according to the manufacturer could result in an enhanced sensitivity; however, so far there is a high agreement (>95%) between the QFT-Plus and older versions of the QFT [120,121].

IGRA and TST are currently used to diagnose candidates for preventive LTBI therapy, and consequently, we applied these as surrogate markers for ongoing TB exposure [122]. We chose to present the estimate based on the TST 10 mm cut-offs and based on exclusion of indeterminate IGRA results from the numerator and denominator as a compromise between sensitivity and specificity. The variability for using other strategies was low. It was unexpected that despite a higher specificity of the blood test, almost all LTBI estimates using IGRA were higher than the senescent skin test. However, this may be dependent on the cut-off applied which is not clearly established for any of the tests with regards to LTBI. We speculate that one reason for the systematically higher IGRA estimates, compared to TST, may be that IGRAs are slightly more sensitive to detect LTBI than TST when using the 10

mm cut-off. When a 5 mm cut-off was applied, the tests were more comparable at 24.8% and 24.1% for IGRA and TST respectively. Further, the tests suffer from variability, and the most optimal cut-off levels are under discussion, in particular for the IGRAs where a grey zone for QFT in the range of 0.20-0.70 IU/ml has been suggested [23,123]. We chose to use the established cut-offs suggested by manufacturers and international guidelines as quantitative IGRA results were very rarely available. However, false positive QFT-results in the grey zone do exist and may have overestimated IGRA results marginally [23,124]. Another possible explanation could be a baseline difference in sampling, and we did find a slightly higher estimate from TST when limiting results to studies with both tests. This finding may indicate that IGRAs are not only more specific, but also more sensitive, although this is difficult to assess in the lack of a gold standard test for LTBI. But even though it has previously been perceived that TST is more frequently positive, as it also captures BCG vaccination and other mycobacteria, we may actually here see a display of the fact that in populations where BCG is given at infancy, it has limited impact on the test result [125]. On the other hand, impaired immunity such as HIV may have higher impact on TST results than IGRAs.

Our study has several limitations. Firstly, crude estimates were based on small study population sizes, especially for IGRAs, in studies of varying sampling technique and quality. We performed vast extrapolation with several assumptions; most notably that our pooled estimates of each incidence interval represented the mean prevalence among the large populations represented by each interval. Secondly, the exclusion of patients with inflammatory disease was based on the assumption that this group may show inferior sensitivity to IGRA and TST due to the underlying disease and/or concurrent immunosuppressive therapy. Thirdly, age was assumed representative of the global age prevalence in the study populations included, and was not accounted for in our extrapolation. Age could act as a surrogate marker for accumulated TB exposure and thus be a risk factor as several studies indicate [13,108]. As outlined in supplementary D, the LTBI prevalence data illustrates a consistent effect of age when comparing populations of younger and older surveyed study participants (i.e. South Africa 16% to 56%, Mexico 12% to 36.9%, Singapore 12.6% to 43.4%, Spain 0.9% to 9.3% and USA 1.5% to 8%) but that does not neccesarily imply that the studies are not representative. In a meta-analysis based on published prevalence surveys, it is not possible to adjust reliably for age, and we acknowledge that this

may introduce bias. Yet, we have no indications that the surveyed populations are skewed towards being particularly young or old individuals, which would force the prevalence estimate up or down. Moreover, children and adults were represented in all incidence intervals. Our estimate has the strength of being based on individual measurements in populations across a large number of countries across the world instead of being based on mathematical models. Fourthly, the relatively wide confidence intervals around specific prevalence estimates, which makes monitoring of incremental statistical changes in LTBI prevalence difficult, is another limitation. This is a reflection of the data available with low sample sizes in some of the surveys and large total populations in the surveyed countries, including populations with extrapolated prevalences. This variability of study estimates due to large and diverse populations is also reflected in the high heterogeneity (≥97%) calculated with $I^2$ statistics. We believe that although this represents uncertainty in our estimates, all studies not excluded represent important parts of the total background population which is undoubtly diverse.Yet an indication that the prevalences should be interpreted with caution. Fifthly, the included studies spanned 15 years and we assumed no development in TB prevalence during this period of years. Although these parameters were accounted for in the modelling study by Houben et al, we found remarkably comparable estimates [2]. Finally, we have excluded data on high-risk populations, and their contribution to the global burden of LTBI may therefore not be sufficiently represented. Studies with a focus on migrant populations were excluded, and migrants may not have been well-represented in population survey, which may also have led to an underestimation of the LTBI prevalence; in low-incidence countries, they may constitute the majority of LTBI cases, e.g. in Australia where Australian-born are stipulated to contribute with only 6.8% of all with LTBI [126].

As always in meta-analyses, the selection of studies may lead to bias, and extrapolations to countries with no data will most certainly introduce bias. Yet, it is important to keep in mind that models and estimations are also not free of bias, in particular if based on data of active TB and assumptions on infectiousness, which we hold is more uncertain than published survey data on IGRA/TST results. Models using the Styblo rule will also face difficulties in taking the age factor into consideration in case of changing epidemiology and population structures; hence, modelling may not lead to a better estimate, if the estimate is based on assumptions that are difficult to adequately predict. Children for instance are less likely to transmit than adults but perhaps that is controlled for, as they are less likely to be smear positive. However, this depends on the age and may not apply to children >15 years. With no

golden standard for diagnosing LTBI, and no method available to measure viable Mtb and to distinguish between 'true' LTBI and cleared infection, we believe that assessment of global prevalences of LTBI must be based on the measurements currently available and those used in clinical practice. The decision to initiate preventive therapy will not be based on assumptions but on individual testing, and although age is important in the assessment of the probability of infection, in the end, it will be the test outcome that determines who is eligible for therapy and who is not.

In conclusion, we estimate one-fourth of the world's population to be latently infected with TB, in the first study applying both IGRA and TST surveys. LTBI still represents an enormous reservoir of potential reactivated TB and this must be recognized as a considerable obstacle, and as a point of intervention, in reaching The End TB Strategy goals of 2050.

# Support statement

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# Contributors

CW and AC conceived and designed the study. All data were collected by AC and VDM. AC and VDM had access to all obtained data and conducted statistical analyses. AC drafted the first manuscript with contributions from VDM, TS and CW. All authors interpreted data as well as contributed with intellectual content to the final manuscript. CW and TS were study supervisors. All authors agree with the results and conclusions of this article.

# Declaration of interests

We declare no competing interests.

# References


1. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. JAMA. 1999 Aug 18;**282**(7):677–86.
2. Houben RMGJ, Dodd PJ. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. PLoS Med. 2016 Oct 25;**13**(10):e1002152.
3. WHO | Global tuberculosis report 2018. Accessed 2019 Feb 28. Available from: http://www.who.int/tb/publications/global_report/en/
4. Wejse C. Tuberculosis elimination in the post Millennium Development Goals era. Int J Infect Dis. 2015 Mar;**32**:152–5.
5. Churchyard GJ, Swindells S. Controlling latent TB tuberculosis infection in high-burden countries: A neglected strategy to end TB. PLoS Med. 2019 Apr;**16**(4):e1002787.
6. Esmail H, Barry CE, Young DB, Wilkinson RJ. The ongoing challenge of latent tuberculosis. Philos Trans R Soc B Biol Sci. 2014 May;**369**(1645):20130437–20130437.
7. Styblo K. The relationship between the risk of tuberculous infection and the risk of developing infectious tuberculosis. Bull Int Union Tuberc Lung Dis. 1985;**60**:117–9.
8. 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 Jan;**86**(1):20–6.
9. Virenfeldt J, Rudolf F, Camara C, Furtado A, Gomes V, Aaby P, Petersen E, Wejse C. Treatment delay affects clinical severity of tuberculosis: a longitudinal cohort study. BMJ Open. 2014 Jun 10;**4**(6):e004818.
10. Petersen E, Khamis F, Migliori GB, Bay JG, Marais B, Wejse C, Zumla A. De-isolation of patients with pulmonary tuberculosis after start of treatment - clear, unequivocal guidelines are missing. Int J Infect Dis. 2017 Mar;**56**:34–8.
11. Getahun H, Matteelli A, Chaisson RE, Raviglione M. Latent Mycobacterium tuberculosis Infection. N Engl J Med. 2015 May 28;**372**(22):2127–35.
12. Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. Ann Intern Med. 2008 Aug 5;**149**(3):177–84.
13. Gao L, Lu W, Bai L, Wang X, Xu J, Catanzaro A, Cárdenas V, Li X, Yang Y, Du J, Sui H, Xia Y, Li M, Feng B, Li Z, Xin H, Zhao R, Liu J, Pan S, Shen F, He J, Yang S, Si H, Wang Y, Xu Z, Tan Y, Chen T, Xu W, Peng H, Wang Z, Zhu T, Zhou F, Liu H, Zhao Y, Cheng S, Jin Q, LATENTTB-NSTM study team. Latent tuberculosis infection in rural China: baseline results of a population-based, multicentre, prospective cohort study. Lancet Infect Dis. 2015 Mar;**15**(3):310–9.
14. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009 Oct;**62**(10):e1–34.
15. Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JAC. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011 Oct;**343**:d5928.
16. Elm E von, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ. 2007 Oct 20;**335**(7624):806–8.

17. Romani L, Steer AC, Whitfeld MJ, Kaldor JM. Prevalence of scabies and impetigo worldwide: a systematic review. Lancet Infect Dis. 2015 Aug;**15**(8):960–7.

18. Murthy M, Selvam S, Jesuraj N, Bennett S, Doherty M, Grewal HMS, Vaz M. Two-Step Tuberculin Skin Testing in School-Going Adolescents with Initial 0-4 Millimeter Responses in a High Tuberculosis Prevalence Setting in South India. Caylà JA, editor. PLoS One. 2013 Sep 6;**8**(9):e71470.

19. QuantiFERON-TB gold (QFT) ELISA Package Insert - UK.pdf. Accessed 2019 Feb 28. Available from: http://www.quantiferon.com/wp-content/uploads/2017/04/English_QFT_ELISA_R04_082016.pdf

20. Package Insert - T-SPOT-PI-TB-US-v4.pdf. Accessed 2019 Feb 28. Available from: http://www.tspot.com/wp-content/uploads/2012/01/PI-TB-US-v4.pdf

21. WHO | WHO's global tuberculosis database. Accessed 2019 Feb 28. Available from: http://www.who.int/tb/data/en/

22. WHO | Framework towards tuberculosis elimination in low-incidence countries. Accessed 2019 Feb 28. Available from: http://www.who.int/tb/publications/elimination_framework/en/

23. Nemes E, Rozot V, Geldenhuys H, Bilek N, Mabwe S, Abrahams D, Makhethe L, Erasmus M, Keyser A, Toefy A, Cloete Y, Ratangee F, Blauenfeldt T, Ruhwald M, Walzl G, Smith B, Loxton AG, Hanekom WA, Andrews JR, Lempicki MD, Ellis R, Ginsberg AM, Hatherill M, Scriba TJ, C-040-404 Study Team and the Adolescent Cohort Study Team. Optimization and Interpretation of Serial QuantiFERON Testing to Measure Acquisition of Mycobacterium tuberculosis Infection. Am J Respir Crit Care Med. 2017;**196**(5):638–48.

24. Miller JJ. The Inverse of the Freeman – Tukey Double Arcsine Transformation. Am Stat. 1978 Nov;**32**(4):138–138.

25. Apriani L, McAllister S, Sharples K, Alisjahbana B, Ruslami R, Hill PC, Menzies D. Latent tuberculosis infection in health care workers in low and middle-income countries: an updated systematic review. Eur Respir J. 2019 Feb 20;

26. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, Hobbs FDR. Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. PLoS One. 2016;**11**(7):e0158765.

27. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 Sep;**7**(3):177–88.

28. Al Mekaini LA, Al Jabri ON, Narchi H, Kamal SM, Mabrook A, Al Kuwaiti MM, Sheek-Hussein MM, Souid A-K, Alsuwaidi AR. The use of an interferon-gamma release assay to screen for pediatric latent tuberculosis infection in the eastern region of the Emirate of Abu Dhabi. Int J Infect Dis. 2014 Jun;**23**:4–7.

29. Gaensbauer J, Gonzales B, Belknap R, Wilson ML, O'Connor ME. Interferon-Gamma Release Assay-Based Screening for Pediatric Latent Tuberculosis Infection in an Urban Primary Care Network. J Pediatr. 2018 Sep;**200**:202–9.

30. Birch SJ, Golbeck AL. The Effectiveness of Screening With Interferon-Gamma Release Assays in a University Health Care Setting With a Diverse Global Population. J Am Coll Heal. 2015 Apr 3;**63**(3):180–5.

31. Bienek DR, Chang CK. Evaluation of an interferon-gamma release assay, T-SPOT®.TB, in a population with a low prevalence of tuberculosis. Int J Tuberc Lung Dis. 2009;**13**(11):1416–21.

32. Katsenos S, Nikolopoulou M, Konstantinidis AK, Gartzonika C, Gogali A, Margelis I, Tatsioni A, Mavridis A, Constantopoulos SH, Daskalopoulos G. Interferon-gamma release assay clarifies the effect of bacille Calmette-Guérin vaccination in Greek army recruits. Int J Tuberc Lung Dis. 2010 May;**14**(5):545–50.

33. Dandoulakis M, Roussos N, Karageorgopoulos DE, Yatromanolakis N, Falagas ME. Trends of tuberculin skin test positivity rate among schoolchildren in Attica, Greece. Scand J Infect Dis. 2009 Jan 8;**41**(3):195–200.

34. German V, Giannakos G, Kopterides P, Falagas ME. Prevalence and predictors of tuberculin skin positivity in Hellenic Army recruits. BMC Infect Dis. 2006 Jun 23;**6**(1):102.

35. Berkel GM, Cobelens FG, de Vries G, Draayer-Jansen IW, Borgdorff MW. Tuberculin skin test: estimation of positive and negative predictive values from routine data. Int J Tuberc Lung Dis. 2005;**9**(3):310–6.

36. Elfrink F, van den Hoek A, Mensen ME, Sonder GJ. Screening travellers to high-endemic countries for infection with Mycobacterium tuberculosis using interferon gamma release assay; a prospective study. BMC Infect Dis. 2014 Dec 23;**14**(1):515.

37. Winje BA, Oftung F, Korsvold GE, Mannsåker T, Ly IN, Harstad I, Dyrhol-Riise AM, Heldal E. School based screening for tuberculosis infection in Norway: comparison of positive tuberculin skin test with interferon-gamma release assay. BMC Infect Dis. 2008 Oct 17;**8**:140.

38. Sancasciani S, Santori D, Bellugi A, Abdiaziz MA, Manzi F, Bennati D, Trezzi M, Zilianti E, Braito A. Prevalence of tuberculosis infection among teen-agers in Tuscany. J Prev Med Hyg. 2006 Dec;**47**(4):151–4.

39. Almarzooqi F, Alkhemeiri A, Aljaberi A, Hashmey R, Zoubeidi T, Souid A-K. Prospective cross-sectional study of tuberculosis screening in United Arab Emirates. Int J Infect Dis. 2018 May;**70**:81–5.

40. Villate JI, Ibanez B, Cabriada V, Pijoan JI, Taboada J, Urkaregi A. Analysis of latent tuberculosis and mycobacterium avium infection data using mixture models. BMC Public Health. 2006;**6**:240.

41. Espinosa Arévalo M, Vázquez Gallardo R, Gayoso Diz P. [The tuberculin skin test in a healthy child program: should we change our practice]. An Pediatr (Barc). 2006 Sep;**65**(3):225–8.

42. Balkhy HH, El Beltagy K, El-Saed A, Aljasir B, Althaqafi A, Alothman AF, Alshalaan M, Al-Jahdali H. Prevalence of Latent Mycobacterium Tuberculosis Infection (LTBI) in Saudi Arabia; Population based survey. Int J Infect Dis. 2017 Jul;**60**:11–6.

43. Sleiman R, Al-Tannir M, Dakdouki G, Ziade F, Assi NA, Rajab M. Interpretation of the tuberculin skin test in bacille Calmette-Guérin vaccinated and nonvaccinated school children. Pediatr Infect Dis J. 2007 Feb;**26**(2):134–8.

44. Alavi SM, Sefidgaran GH. Tuberculin survey among school-aged children in Ahvaz, Iran, 2006. Int J Infect Dis. 2008 Jul;**12**(4):406–9.

45. Asl HM, Alborzi A, Pourabbas B, Kalani M. QuantiFERON-TB Gold and Tuberculin Skin Test for the Diagnosis of Latent Tuberculosis Infection in Children. Iran J Med Sci. 2015 Sep;**40**(5):411–7.

46. Haghdoost AA, Afshari M, Baneshi MR, Gouya MM, Nasehi M, Movahednia M. Estimating the Annual Risk of Tuberculosis Infection and Disease in Southeast of Iran Using the Bayesian Mixture Method. Iran Red Crescent Med J. 2014 Sep 5;**16**(9).

47. Hafizi H, Aliko A, Sharra E, Fico A, Migliori GB, Castiglia P, Sotgiu G. Results of a tuberculin skin testing survey in Albania. J Infect Dev Ctries. 2014 Mar 13;**8**(03):310-314\.

48. Mori T, Harada N, Higuchi K, Sekiya Y, Uchimura K, Shimao T. Waning of the specific interferon-gamma response after years of tuberculosis infection. Int J Tuberc Lung Dis. 2007;**11**(9):1021–5.

49. Kruczak K, Duplaga M, Sanak M, Cmiel A, Mastalerz L, Sladek K, Nizankowska-Mogilnicka E. Comparison of IGRA tests and TST in the diagnosis of latent tuberculosis infection and predicting tuberculosis in risk groups in Krakow, Poland. Scand J Infect Dis. 2014 Sep 30;**46**(9):649–55.

50. Bennett DE, Courval JM, Onorato I, Agerton T, Gibson JD, Lambert L, McQuillan GM, Lewis B, Navin TR, Castro KG. Prevalence of Tuberculosis Infection in the United States Population. Am J Respir Crit Care Med. 2008 Feb;**177**(3):348–55.

51. Kuś J, Demkow U, Lewandowska K, Korzeniewska-Kosełа M, Rabczenko D, Siemion-Szcześniak I, Białas-Chromiec B,

Bychawska M, Sapigórski P, Maciejewski J. Prevalence of latent infection with Mycobacterium tuberculosis in Mazovia Region using interferon gamma release assay after stimulation with specific antigens ESAT-6 and CFP-10. Pneumonol Alergol Pol. 2011;**79**(6):407–18.

52. García-Sancho F MC, García-García L, Jiménez-Corona ME, Palacios-Martínez M, Ferreyra-Reyes LD, Canizales-Quintero S, Cano-Arellano B, Ponce-de-León A, Sifuentes-Osornio J, Small P, DeRiemer K. Is tuberculin skin testing useful to diagnose latent tuberculosis in BCG-vaccinated children? Int J Epidemiol. 2006 Dec;**35**(6):1447–54.
53. Hernández-Hernández E, Alberú J, González-Michaca L, Bobadilla-del Valle M, Quiroz-Mejía RA, Baizabal-Olarte R, Correa-Rotter R, Sifuentes-Osornio J. Screening for tuberculosis in the study of the living renal donor in a developing country. Transplantation. 2006 Jan 27;**81**(2):290–2.
54. Al-Khal AL, Bener A, Enarson DA. Tuberculosis Among Garment Workers in an Arabian Developing Country: State of Qatar. Arch Environ Occup Health. 2005 Nov 7;**60**(6):295–8.
55. Teixeira EG, Menzies D, Comstock GW, Cunha AJ, Kritski AL, Soares LC, Bethlem E, Zanetti G, Ruffino-Netto A, Belo MT, Selig L, Branco MM, Cherri D, Maia S, Marandino R, Luiz RR, Chaisson RE, Trajman A. Latent tuberculosis infection among undergraduate medical students in Rio de Janeiro State, Brazil. Int J Tuberc Lung Dis. 2005;**9**(8):841–7.
56. Gomes CMF, Terreri MT, Moraes-Pinto MI de, Barbosa C, Machado NP, Melo MR, Pinheiro MM. Incidence of active mycobacterial infections in Brazilian patients with chronic inflammatory arthritis and negative evaluation for latent tuberculosis infection at baseline - A longitudinal analysis after using TNFa blockers. Mem Inst Oswaldo Cruz. 2015 Nov;**110**(7):921–8.
57. Yap P, Tan KHX, Lim WY, Barkham T, Tan LWL, Chen MI-C, Wang YT, Chee CBE. Prevalence of and risk factors associated with latent tuberculosis in Singapore: A cross-sectional survey. Int J Infect Dis. 2018 Jul;**72**(3):55–62.
58. Wilder-Smith A, Foo W, Earnest A, Paton NI. High risk of Mycobacterium tuberculosis infection during the Hajj pilgrimage. Trop Med Int Heal. 2005 Apr;**10**(4):336–9.
59. Wong SH, Ip M, Tang W, Lin Z, Kee C, Hung E, Lui G, Lee N, Chan FKL, Wu JC, Sung JJY, Ng SC. Performance of Interferon-gamma Release Assay for Tuberculosis Screening in Inflammatory Bowel Disease Patients. Inflamm Bowel Dis. 2014 Nov;**20**(11):2067–72.
60. Fan W-C, Ting W-Y, Lee M-C, Huang S-F, Chiu C-H, Lai S-L, Chen Y-M, Shih J-F, Lin C-H, Kao S-J, Wu M-F, Tsao TCY, Wu C-H, Yang K-Y, Lee Y-C, Feng J-Y, Su W-J. Latent TB infection in newly diagnosed lung cancer patients – A multicenter prospective observational study. Lung Cancer. 2014 Sep;**85**(3):472–8.
61. Cain KP, Garman KN, Laserson KF, Ferrousier-Davis OP, Miranda AG, Wells CD, Haley CA. Moving toward tuberculosis elimination: implementation of statewide targeted tuberculin testing in Tennessee. Am J Respir Crit Care Med. 2012 Aug 1;**186**(3):273–9.
62. 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 Dec 1;**23**(6):1064–9.
63. Chan PC, Chang LY, Wu YC, Lu CY, Kuo HS, Lee CY, Huang LM, Chen CJ. Age-specific cut-offs for the tuberculin skin test to detect latent tuberculosis in BCG-vaccinated children. Int J Tuberc Lung Dis. 2008;**12**(12):1401–6.
64. Wu X, Hou Y, Liang Y, Zhang J, Yang Y, Wang L, Zhang C. Evaluation of a tuberculosis whole-blood interferon-gamma chemiluminescent immunoassay among Chinese military recruits. Mol Diagn Ther. 2011;**15**(6):341–6.
65. Zhao J, Wang Y, Wang H, Jiang C, Liu Z, Meng X, Song G, Cheng N, Graviss EA, Ma X. Low agreement between the T-

SPOT®.TB assay and the tuberculin skin test among college students in China. Int J Tuberc Lung Dis. 2011 Jan;**15**(1):134–6.

66. Chan-Yeung M, Cheung AHK, Dai DLK, Chan FHW, Kam KM, Tam CM, Leung CC. Prevalence and determinants of positive tuberculin reactions of residents in old age homes in Hong Kong. Int J Tuberc Lung Dis. 2006 Aug;**10**(8):892–8.

67. Chen C, Zhu T, Wang Z, Peng H, Kong W, Zhou Y, Shao Y, Zhu L, Lu W. High Latent TB Infection Rate and Associated Risk Factors in the Eastern China of Low TB Incidence. PLoS One. 2015 Oct 27;**10**(10):e0141511.

68. Bai X, Liang Y, Yang Y, Zhang J, Wu X. A new method of screening for latent tuberculosis infection: Results from army recruits in Beijing in 2014. Immunol Lett. 2017 Jun;**186**:28–32.

69. Choi CM, Kang CI, Kim DH, Kim CH, Kim HJ, Lee CH, Yim JJ. The role of TST in the diagnosis of latent tuberculosis infection among military personnel in South Korea. Int J Tuberc Lung Dis. 2006;**10**(12):1342–6.

70. Jambaldorj E, Han M, Jeong JC, Koo TY, Min S Il, Song EY, Ha J, Ahn C, Yang J. Poor predictability of QuantiFERON-TB assay in recipients and donors for tuberculosis development after kidney transplantation in an intermediate-TB-burden country. BMC Nephrol. 2017 Dec 14;**18**(1):88.

71. Chung W, Lee K, Jung Y, Kim Y, Park J, Sheen S, Lee J, Kang D, Park K. Serum CXCR3 ligands as biomarkers for the diagnosis and treatment monitoring of tuberculosis. Int J Tuberc Lung Dis. 2015 Dec 1;**19**(12):1476–84.

72. Mancuso JD, Mazurek GH, Tribble D, Olsen C, Aronson NE, Geiter L, Goodwin D, Keep LW. Discordance among Commercially Available Diagnostics for Latent Tuberculosis Infection. Am J Respir Crit Care Med. 2012 Feb 15;**185**(4):427–34.

73. Lee H, Cho SN, Kim HJ, Anh YM, Choi JE, Kim CH, Ock PJ, Oh SH, Kim DR, Floyd S, Dockrell HM. Evaluation of cell-mediated immune responses to two BCG vaccination regimes in young children in South Korea. Vaccine. 2011 Sep;**29**(38):6564–71.

74. Lee SW, Oh SY, Lee JB, Choi CM, Kim HJ. Tuberculin Skin Test Distribution following a Change in BCG Vaccination Policy. PLoS One. 2014 Jan 23;**9**(1):e86419.

75. Nantha YS, Puri A, Mohamad Ali SZ, Suppiah P, Che Ali SA, Ramasamy B, Ibrahim IM. Epidemiology of latent tuberculosis infection among patients with and without diabetes mellitus. Fam Pract. 2017 Sep;**34**(5):532–8.

76. Martinez L, Arman A, Haveman N, Lundgren A, Cabrera L, Evans CA, Pelly TF, Saito M, Callacondo D, Oberhelman R, Collazo G, Carnero AM, Gilman RH. Changes in tuberculin skin test positivity over 20 years in periurban shantytowns in Lima, Peru. Am J Trop Med Hyg. 2013 Sep 4;**89**(3):507–15.

77. Hohmuth BA, Yamanija JC, Dayal AS, Nardell E, Salazar JJ, Smith Fawzi MC. Latent tuberculosis infection: risks to health care students at a hospital in Lima, Peru. Int J Tuberc Lung Dis. 2006;**10**(10):1146–51.

78. Huaman MA, Ticona E, Miranda G, Kryscio RJ, Mugruza R, Aranda E, Rondan PL, Henson D, Ticona C, Sterling TR, Fichtenbaum CJ, Garvy BA. The Relationship Between Latent Tuberculosis Infection and Acute Myocardial Infarction. Clin Infect Dis. 2018 Mar 5;**66**(6):886–92.

79. Michelsen SW, Soborg B, Koch A, Carstensen L, Hoff ST, Agger EM, Lillebaek T., Sorensen HCF, Wohlfahrt J, Melbye M. The effectiveness of BCG vaccination in preventing Mycobacterium tuberculosis infection and disease in Greenland. Thorax. 2014 Sep;**69**(9):851–6.

80. Soborg B, Koch A, Thomsen VO, Ladefoged K, Andersson M, Wohlfahrt J, Melbye M, Andersen AB. Ongoing tuberculosis transmission to children in Greenland. Eur Respir J. 2010 Oct 1;**36**(4):878–84.

81. Marks GB, Nhung N V, Nguyen TA, Hoa NB, Khoa TH, Son N V, Phuong NTB, Tin DM, Ho J, Fox GJ. Prevalence of latent

tuberculous infection among adults in the general population of Ca Mau, Viet Nam. Int J Tuberc Lung Dis. 2018 Mar 1;**22**(3):246–51.

82. Hoa NB, Cobelens FGJ, Sy DN, Nhung N V, Borgdorff MW, Tiemersma EW. First national tuberculin survey in Viet Nam: characteristics and association with tuberculosis prevalence. Int J Tuberc Lung Dis. 2013 Jun;**17**(6):738–44.
83. Lempp JM, Zajdowicz MJ, Hankinson AL, Toney SR, Keep LW, Mancuso JD, Mazurek GH. Assessment of the QuantiFERON-TB Gold In-Tube test for the detection of Mycobacterium tuberculosis infection in United States Navy recruits. PLoS One. 2017 May 17;**12**(5):e0177752.
84. Shrestha KB, Malla P, Jha KK, Shakya TM, Akhtar M, Gunneberg C, van der Werf MJ. First national tuberculin survey in Nepal. Int J Tuberc Lung Dis. 2008 Aug;**12**(8):909–15.
85. Adetifa IMO, Muhammad AK, Jeffries D, Donkor S, Borgdorff MW., Corrah T, D'Alessandro U. A Tuberculin Skin Test Survey and the Annual Risk of Mycobacterium tuberculosis Infection in Gambian School Children. PLoS One. 2015 Oct;**10**(10):e0139354.
86. Wassie L, Aseffa A, Abebe M, Gebeyehu MZ, Zewdie M, Mihret A, Erenso G, Chanyalew M, Tilahun H, Yamuah LK, Andersen P, Doherty MT. Parasitic infection may be associated with discordant responses to QuantiFERON and tuberculin skin test in apparently healthy children and adolescents in a tuberculosis endemic setting, Ethiopia. BMC Infect Dis. 2013 Dec 5;**13**(1):265.
87. 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 Dec 9;**11**(1):89.
88. Teklu T, Legesse M, Medhin G, Zewude A, Chanyalew M, Zewdie M, Wondale B, Haile-Mariam M, Pieper R, Ameni G. Latent tuberculosis infection and associated risk indicators in pastoral communities in southern Ethiopia: a community based cross-sectional study. BMC Public Health. 2018 Dec 17;**18**(1):266.
89. König Walles J, Tesfaye F, Jansson M, Tolera Balcha T, Winqvist N, Kefeni M, Garoma Abeya S, Belachew F, Sturegård E, Björkman P. Performance of QuantiFERON-TB Gold Plus for detection of latent tuberculosis infection in pregnant women living in a tuberculosis- and HIV-endemic setting. PLoS One. 2018 Apr 4;**13**(4):e0193589.
90. Lule SA, Mawa PA, Nkurunungi G, Nampijja M, Kizito D, Akello F, Muhangi L, Elliott AM, Webb EL. Factors associated with tuberculosis infection, and with anti-mycobacterial immune responses, among five year olds BCG-immunised at birth in Entebbe, Uganda. Vaccine. 2015 Feb;**33**(6):796–804.
91. Kizza FN, List J, Nkwata AK, Okwera A, Ezeamama AE, Whalen CC, Sekandi JN. Prevalence of latent tuberculosis infection and associated risk factors in an urban African setting. BMC Infect Dis. 2015 Dec 29;**15**(1):165.
92. Mumpe-Mwanja D, Verver S, Yeka A, Etwom A, Waako J, Ssengooba W, Matovu J, Wanyenze R, Musoke P, Mayanja-Kizza H. Prevalence and risk factors of latent Tuberculosis among adolescents in rural Eastern Uganda. Afr Health Sci. 2015 Sep 9;**15**(3):851.
93. Mathad JS, Bhosale R, Sangar V, Mave V, Gupte N, Kanade S, Nangude A, Chopade K, Suryavanshi N, Deshpande P, Kulkarni V, Glesby MJ, Fitzgerald D, Bharadwaj R, Sambarey P, Gupta A. Pregnancy Differentially Impacts Performance of Latent Tuberculosis Diagnostics in a High-Burden Setting. PLoS One. 2014 Mar 21;**9**(3):e92308.
94. Gamsky TE, Lum T, Hung-Fan M, Green JA. Cumulative False-Positive QuantiFERON-TB Interferon-γ Release Assay Results. Ann Am Thorac Soc. 2016 May;**13**(5):660–5.

95. Uppada DR, Selvam S, Jesuraj N, Bennett S, Verver S, Grewal HM, Vaz M. 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 Dec 18;**14**(1):571.

96. Thomas TA, Mondal D, Noor Z, Liu L, Alam M, Haque R, Banu S, Sun H, Peterson KM. Malnutrition and Helminth Infection Affect Performance of an Interferon -Release Assay. Pediatrics. 2010 Dec 1;**126**(6):e1522–9.

97. Hossain S, Zaman K, Banu S, Quaiyum MA, Husain MA, Islam MA, Cooreman E, Borgdorff M, van Leth F. Tuberculin survey in Bangladesh, 2007-2009: prevalence of tuberculous infection and implications for TB control. Int J Tuberc Lung Dis. 2013 Oct;**17**(10):1267–72.

98. Raharimanga V, Ratovoson R, Ratsitorahina M, Ramarokoto H, Rasolofo V, Talarmin A, Richard V. Tuberculin reactivity in first-year schoolchildren in Madagascar. Trop Med Int Heal. 2012 Jul;**17**(7):871–6.

99. 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 Jul 27;**10**(7):e0127590.

100. Sheriff FG, Manji KP, Manji MP, Chagani MM, Mpembeni RM, Jusabani AM, Alwani ZR, Karimjee TS. Latent tuberculosis among pregnant mothers in a resource poor setting in Northern Tanzania: a cross-sectional study. BMC Infect Dis. 2010 Dec 7;**10**(1):52.

101. Agaya J, Nnadi CD, Odhiambo J, Obonyo C, Obiero V, Lipke V, Okeyo E, Cain K, Oeltmann JE. Tuberculosis and latent tuberculosis infection among healthcare workers in Kisumu, Kenya. Trop Med Int Heal. 2015 Dec;**20**(12):1797–804.

102. Gustafson P, Lisse I, Gomes V, Vieira CS, Lienhardt C, Nauclér A, Jensen H, Aaby P. Risk factors for positive tuberculin skin test in Guinea-Bissau. Epidemiology. 2007 May;**18**(3):340–7.

103. Minime-Lingoupou F, Ouambita-Mabo R, Komangoya-Nzozo A-D, Senekian D, Bate L, Yango F, Nambea B, Manirakiza A. Current tuberculin reactivity of schoolchildren in the Central African Republic. BMC Public Health. 2015 Dec 17;**15**(1):496.

104. Mandalakas AM, Kirchner HL, Walzl G, Gie RP, Schaaf HS, Cotton MF, Grewal HMS, Hesseling AC. Optimizing the Detection of Recent Tuberculosis Infection in Children in a High Tuberculosis–HIV Burden Setting. Am J Respir Crit Care Med. 2015 Apr;**191**(7):820–30.

105. Mancuso JD, Diffenderfer JM, Ghassemieh BJ, Horne DJ, Kao T-C. The Prevalence of Latent Tuberculosis Infection in the United States. Am J Respir Crit Care Med. 2016 Aug 15;**194**(4):501–9.

106. Mahomed H, Hawkridge T, Verver S, Geiter L, Hatherill M, Abrahams DA, Ehrlich R, Hanekom WA, Hussey GD, Team SAS. Predictive factors for latent tuberculosis infection among adolescents in a high-burden area in South Africa. Int J Tuberc Lung Dis. 2011;**15**(3):331–6.

107. Mahomed H, Hughes EJ, Hawkridge T, Minnies D, Simon E, Little F, Hanekom WA, Geiter L, Hussey GD. Comparison of mantoux skin test with three generations of a whole blood IFN-gamma assay for tuberculosis infection. Int J Tuberc Lung Dis. 2006;**10**(3):310–6.

108. Wood R, Liang H, Wu H, Middelkoop K, Oni T, Rangaka MX, Wilkinson RJ, Bekker LG, Lawn SD. Changing prevalence of tuberculosis infection with increasing age in high-burden townships in South Africa. Int J Tuberc Lung Dis. 2010;**14**(4):406–12.

109. Gallant CJ, Cobat A, Simkin L, Black GF, Stanley K, Hughes J, Doherty TM, Hanekom WA, Eley B, Beyers N, Jaïs J-P, van Helden P, Abel L, Alcaïs A, Hoal EG, Schurr E. Tuberculin Skin Test and In Vitro Assays Provide Complementary Measures of Antimycobacterial Immunity in Children and Adolescents. Chest. 2010 May;**137**(5):1071–7.

110. Lebina L, Abraham PM, Milovanovic M, Motlhaoleng K, Chaisson RE, Rakgokong M, Golub J, Variava E, Martinson NA. Latent tuberculous infection in schoolchildren and contact tracing in Matlosana, North West Province, South Africa. Int J Tuberc Lung Dis. 2015 Nov 1;**19**(11):1290–2.

111. Ncayiyana JR, Bassett J, West N, Westreich D, Musenge E, Emch M, Pettifor A, Hanrahan CF, Schwartz SR, Sanne I, van Rie A. Prevalence of latent tuberculosis infection and predictive factors in an urban informal settlement in Johannesburg, South Africa: a cross-sectional study. BMC Infect Dis. 2016 Dec;**16**(1):661.

112. Shanaube K, Sismanidis C, Ayles H, Beyers N, Schaap A, Lawrence K-A, Barker A, Godfrey-Faussett P. Annual risk of tuberculous infection using different methods in communities with a high prevalence of TB and HIV in Zambia and South Africa. PLoS One. 2009 Nov 13;**4**(11):e7749.

113. Simpson T, Fox J, Crouse K, Field K. Quantitative and qualitative QuantiFERON®-TB Gold In-Tube results among groups with varying risks of exposure to tuberculosis. Hear Lung J Acute Crit Care. 2012 Nov;**41**(6):553–61.

114. Yang X, Wu J-B, Liu Y, Xiong Y, Ji P, Wang S-J, Chen Y, Zhao G-P, Lu S-H, Wang Y. Identification of mycobacterial bacterioferritin B for immune screening of tuberculosis and latent tuberculosis infection. Tuberculosis (Edinb). 2017 Dec;**107**:119–25.

115. Wu X, Liang Y, Wang L, Wang Z, Zhang C, Yang Y, Zhang J. Latent tuberculosis infection among new recruits to the army in Beijing, China in 2009. APMIS. 2011;**119**(6):377–84.

116. Dheda K. Getting bang for buck in the latent tuberculosis care cascade. Lancet Infect Dis. 2016 Nov;**16**(11):1209–10.

117. O'Garra A, Redford PS, McNab FW, Bloom CI, Wilkinson RJ, Berry MPR. The immune response in tuberculosis. Annu Rev Immunol. 2013;**31**:475–527.

118. Diel R, Loddenkemper R, Meywald-Walter K, Niemann S, Nienhaus A. Predictive value of a whole blood IFN-gamma assay for the development of active tuberculosis disease after recent infection with Mycobacterium tuberculosis. Am J Respir Crit Care Med. 2008;**177**(10):1164–70.

119. Petruccioli E, Chiacchio T, Pepponi I, Vanini V, Urso R, Cuzzi G, Barcellini L, Cirillo DM, Palmieri F, Ippolito G, Goletti D. First characterization of the CD4 and CD8 T-cell responses to QuantiFERON-TB Plus. J Infect. 2016 Dec;**73**(6):588–97.

120. Theel ES, Hilgart H, Breen-Lyles M, McCoy K, Flury R, Breeher LE, Wilson J, Sia IG, Whitaker JA, Clain J, Aksamit TR, Escalantec P. Comparison of the QuantiFERON-TB gold plus and QuantiFERON-TB gold in-tube interferon gamma release assays in patients at risk for tuberculosis and in health care workers. J Clin Microbiol. 2018;**56**(7).

121. Pieterman ED, Liqui Lung FG, Verbon A, Bax HI, Ang CW, Berkhout J, Blaauw G, Brandenburg A, van Burgel ND, Claessen A, van Dijk K, Heron M, Hooghiemstra M, Leussenkamp-Hummelink R, van Lochem E, van Loo IHM, Mulder B, Ott A, Pontesilli O, Reuwer A, Rombouts P, Saegeman V, Scholing M, Vainio S, de Steenwinkel JEM. A multicentre verification study of the QuantiFERON®-TB Gold Plus assay. Tuberculosis (Edinb). 2018;**108**:136–42.

122. Lewinsohn DM, Leonard MK, LoBue PA, Cohn DL, Daley CL, Desmond E, Keane J, Lewinsohn DA, Loeffler AM, Mazurek GH, O'Brien RJ, Pai M, Richeldi L, Salfinger M, Shinnick TM, Sterling TR, Warshauer DM, Woods GL. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. Clin Infect Dis. 2017 Jan;**64**(2):e1–33.

123. Pai M, Denkinger CM, Kik S V, Rangaka MX, Zwerling A, Oxlade O, Metcalfe JZ, Cattamanchi A, Dowdy DW, Dheda K, Banaei N. Gamma interferon release assays for detection of Mycobacterium tuberculosis infection. Clin Microbiol Rev. 2014

Jan;**27**(1):3–20.

124. Jonsson J, Westman A, Bruchfeld J, Sturegård E, Gaines H, Schön T. A borderline range for Quantiferon Gold In-Tube results. PLoS One. 2017;**12**(11):e0187313.

125. Farhat M, Greenaway C, Pai M, Menzies D. False-positive tuberculin skin tests: what is the absolute effect of BCG and non-tuberculous mycobacteria? Int J Tuberc Lung Dis. 2006 Nov;**10**(11):1192–204.

126. Dale KD, Trauer JM, Dodd PJ, Houben RMGJ, Denholm JT. Estimating the prevalence of latent tuberculosis in a low-incidence setting: Australia. Eur Respir J. 2018 Dec;**52**(6).

# Tables

**Table 1: A) Pooled sample sizes of included studies and B) new and old estimates of latent tuberculosis infection prevalence by WHO region**

**Panel A.** Pooled sample sizes by interferon-gamma release assay (IGRA), tuberculin skin test (TST) (10 mm cut-off) and in total. Categorization of countries in TB incidence intervals are listed in the supplementary E. **Panel B.** Global and regional prevalences of latent tuberculosis infection displaying 1999 WHO estimates [1], new modelling estimates from 2016 by Houben et al [2], and our current estimates, including IGRA survey data.

| **A** | **Pooled sample sizes of included studies** | | |
|---|---|---|---|
| **TB incidence intervals** | **IGRA sample size (%)** | **TST sample size (%)** | **Total sample size (%)** |
| Low | 16 628 (24.8) | 104 379 (36.7) | 121 007 (34.4) |
| Intermediate | 37 392 (55.7) | 63 432 (22.3) | 100 824 (28.7) |
| High | 13 147 (19.6) | 116 833 (41.0) | 129 980 (36.9) |
| **Total sample size (%)** | 67 167 (19.1) | 284 644 (80.9) | 351 811 (100.0) |

| **B** | **Prevalence of latent tuberculosis infection** | | | |
|---|---|---|---|---|
| | **1999 WHO estimates** [1]**, %** | **2016 Houben et al estimates** [2]**, % (CI)** | **New estimates including IGRA data, % (CI)** | |
| **WHO region** | **TST*** | **ARI based on TST surveys and WHO TB prevalence data** | **TST**** | **IGRA** |
| Africa | 35 | 22.4 (20.6-24.6) | 26.6 (23.0-30.2) | 33.6 (24.4-42.9) |
| The Americas | 18 | 11.0 (7.0-20.0) | 13.5 (9.7-17.2) | 13.7 (11.0-16.3) |
| Eastern Mediterranean | 29 | 16.3 (13.4-20.5) | 21.1 (17.4-24.8) | 24.0 (19.4-28.5) |
| Europe | 15 | 13.7 (9.8-19.8) | 11.8 (8.6-15.0) | 12.2 (9.8-14.5) |
| Southeast Asia | 44 | 30.8 (28.3-34.8) | 27.7 (23.6-31.8) | 36.0 (25.3-46.7) |
| Western Pacific | 36 | 27.9 (19.3-40.1) | 20.3 (15.0-25.7) | 20.7 (16.8-24.5) |
| **Total** | 32 | 23.0 (20.4-26.4) | 21.2 (18.0-24.4) | 24.0 (18.8-29.3) |

TB, tuberculosis. IGRA, interferon-gamma release assay. TST, tuberculin skin test. WHO, The World Health Organization. CI, 95% confidence interval.

*Partly based on annual risk of infection and Styblo's rule. **10 mm cut-off for TST.

# Figure legends

**Figure 1**: **Study selection.**
Flow chart of study inclusion. Studies are listed in supplementary D. TB, tuberculosis. HIV, human immunodeficiency virus. LTBI, latent tuberculosis infection.

**Figure 2: World map of countries by TB incidence**

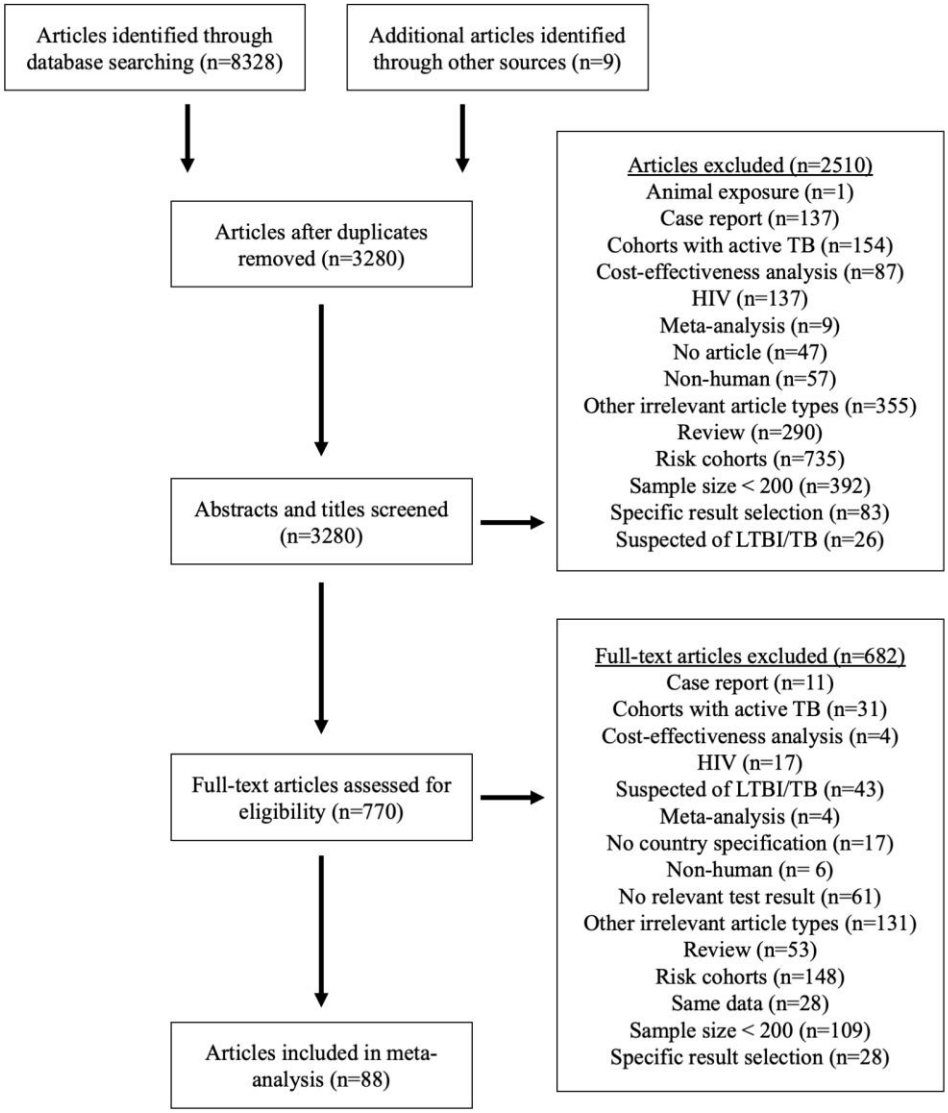
High, intermediate and low active tuberculosis (TB) incidence countries are coloured red, orange and blue respectively. The color red corresponds to an average LTBI prevalence of 28-36%, orange indicates 19-20% and blue 3-5% (from fig. 3 & 4). Darker shades of the colours indicate areas with original latent tuberculosis infection (LTBI) prevalence data, lighter shaded colours indicate countries where the weighted estimate of the countries TB incidence interval has been used.

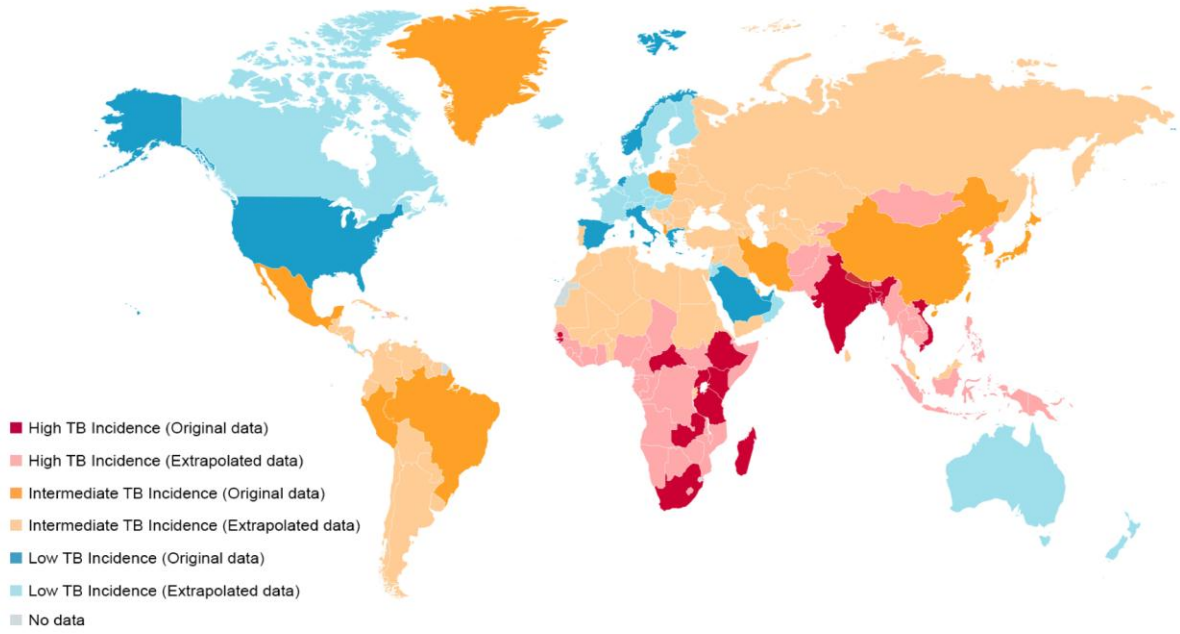
**Figure 3: Forest plot of tuberculin skin test data**

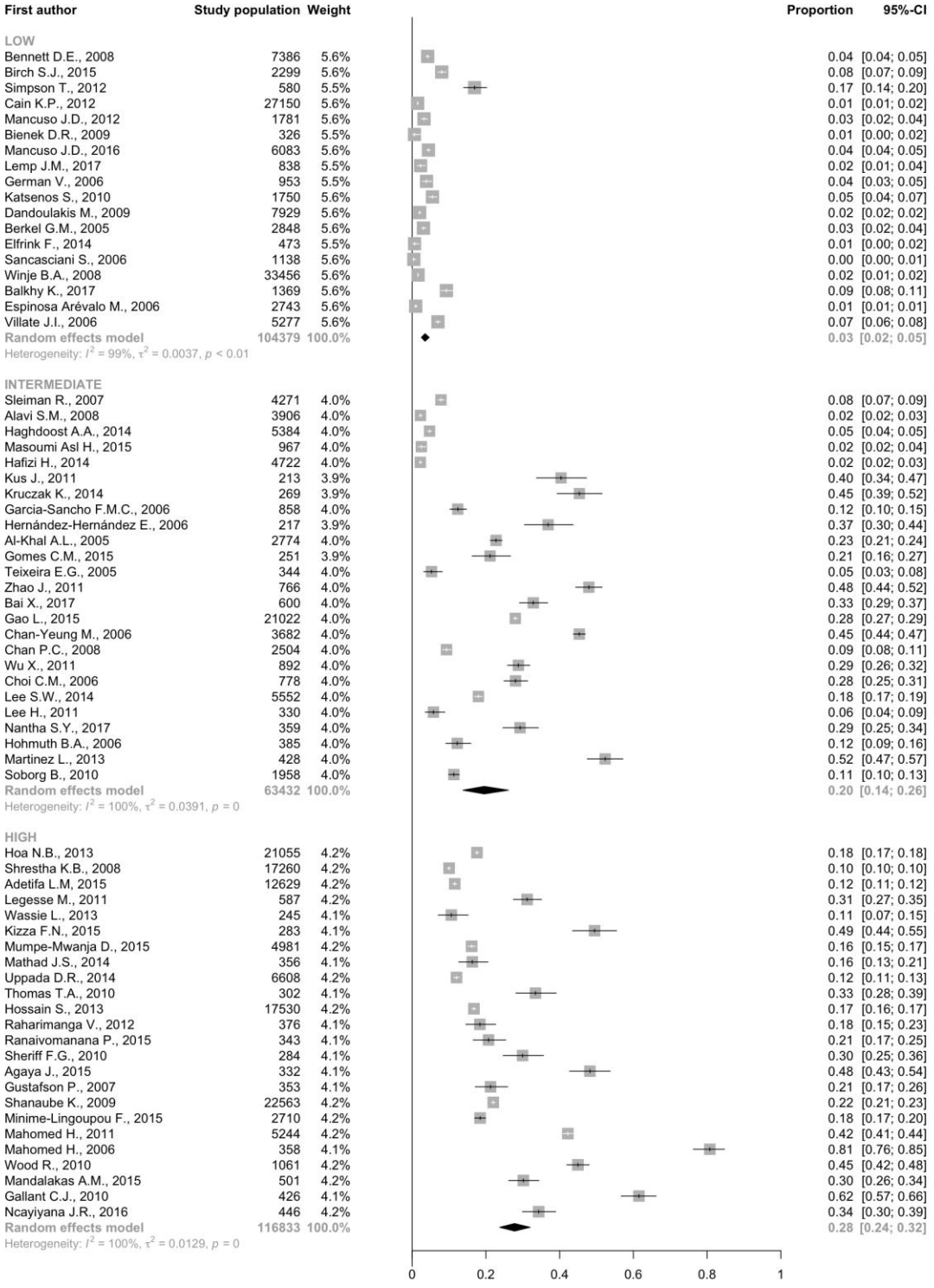
Prevalence of latent tuberculosis infection by tuberculosis incidence intervals using random effects model, weighted by standard error of the mean estimates. Latent infection based on tuberculin skin tests with a 10 mm cut-off. CI, confidence interval.

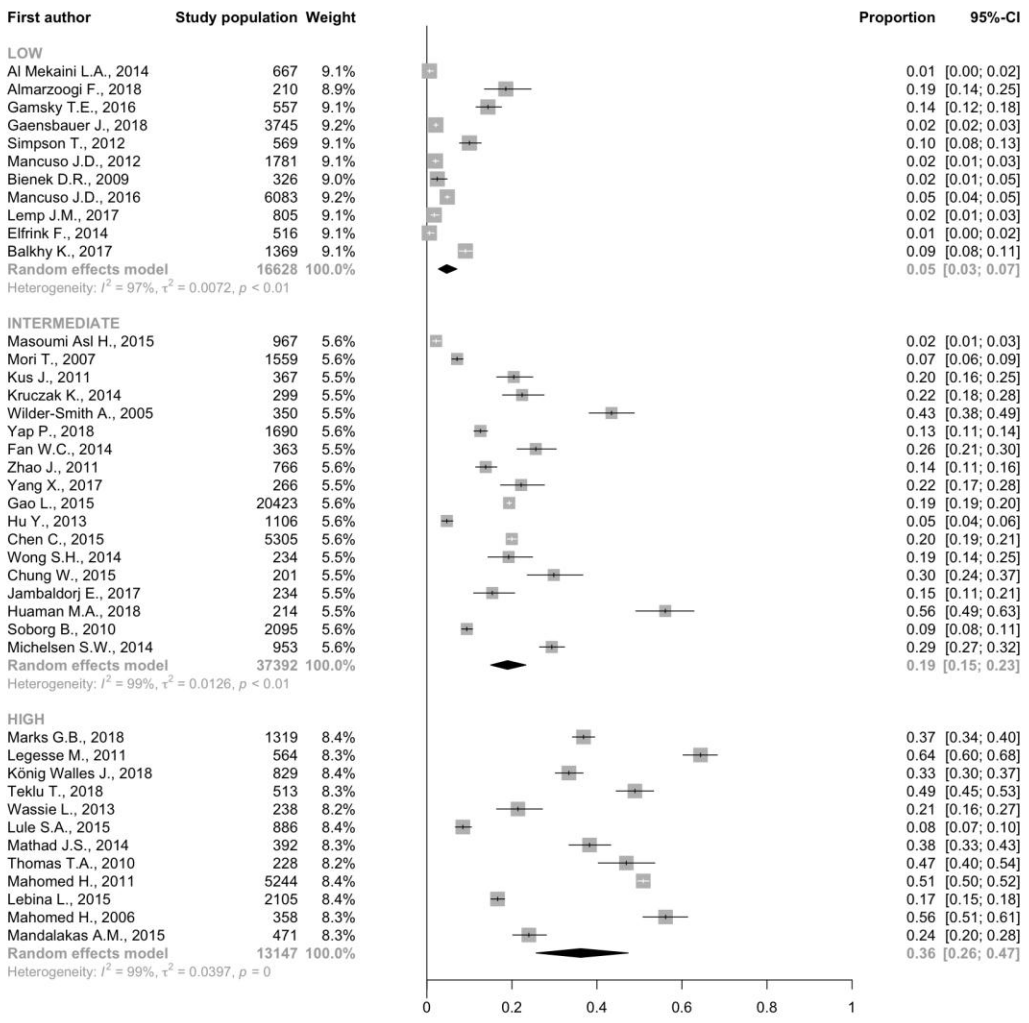
**Figure 4: Forest plot of interferon-gamma release assay data**

Prevalence of latent tuberculosis infection by tuberculosis incidence intervals using random effects model, weighted by standard error of the mean estimates. Latent infection based on interferon-gamma release assays with indeterminate excluded. CI, confidence interval.


Articles identified through database searching (n=8328)
Additional articles identified through other sources (n=9)
Articles after duplicates removed (n=3280)
Articles excluded (n=2510)
Animal exposure (n=1)
Case report (n=137)
Cohorts with active TB (n=154)
Cost-effectiveness analysis (n=87)
HIV (n=137)
Meta-analysis (n=9)
No article (n=47)
Non-human (n=57)
Other irrelevant article types (n=355)
Review (n=290)
Risk cohorts (n=735)
Sample size < 200 (n=392)
Specific result selection (n=83)
Suspected of LTBI/TB (n=26)
Abstracts and titles screened (n=3280)
Full-text articles excluded (n=682)
Case report (n=11)
Cohorts with active TB (n=31)
Cost-effectiveness analysis (n=4)
HIV (n=17)
Suspected of LTBI/TB (n=43)
Meta-analysis (n=4)
No country specification (n=17)
Non-human (n= 6)
No relevant test result (n=61)
Other irrelevant article types (n=131)
Review (n=53)
Risk cohorts (n=148)
Same data (n=28)
Sample size < 200 (n=109)
Specific result selection (n=28)
Full-text articles assessed for eligibility (n=770)
Articles included in meta-analysis (n=88)


High TB Incidence (Original data)
High TB Incidence (Extrapolated data)
Intermediate TB Incidence (Original data)
Intermediate TB Incidence (Extrapolated data)
Low TB Incidence (Original data)
Low TB Incidence (Extrapolated data)
No data


First author
Study population
Weight
Proportion
95%-CI
LOW
Bennett D.E., 2008 7386 5.6% 0.04 [0.04; 0.05]
Birch S.J., 2015 2299 5.6% 0.08 [0.07; 0.09]
Simpson T., 2012 580 5.5% 0.17 [0.14; 0.20]
Cain K.P., 2012 27150 5.6% 0.01 [0.01; 0.02]
Mancuso J.D., 2012 1781 5.6% 0.03 [0.02; 0.04]
Bienek D.R., 2009 326 5.5% 0.01 [0.00; 0.02]
Mancuso J.D., 2016 6083 5.6% 0.04 [0.04; 0.05]
Lemp J.M., 2017 838 5.5% 0.02 [0.01; 0.04]
German V., 2006 953 5.5% 0.04 [0.03; 0.05]
Katsenos S., 2010 1750 5.6% 0.05 [0.04; 0.07]
Dandoulakis M., 2009 7929 5.6% 0.02 [0.02; 0.02]
Berkel G.M., 2005 2848 5.6% 0.03 [0.02; 0.04]
Elfrink F., 2014 473 5.5% 0.01 [0.00; 0.02]
Sancasciani S., 2006 1138 5.6% 0.00 [0.00; 0.01]
Winje B.A., 2008 33456 5.6% 0.02 [0.01; 0.02]
Balkhy K., 2017 1369 5.6% 0.09 [0.08; 0.11]
Espinosa Arévalo M., 2006 2743 5.6% 0.01 [0.01; 0.01]
Villate J.I., 2006 5277 5.6% 0.07 [0.06; 0.08]
Random effects model 104379 100.0% 0.03 [0.02; 0.05]
Heterogeneity: $I^2$ = 99%, $\tau^2$ = 0.0037, $p$ < 0.01
INTERMEDIATE
Sleiman R., 2007 4271 4.0% 0.08 [0.07; 0.09]
Alavi S.M., 2008 3906 4.0% 0.02 [0.02; 0.03]
Haghdoost A.A., 2014 5384 4.0% 0.05 [0.04; 0.05]
Masoumi Asl H., 2015 967 4.0% 0.02 [0.02; 0.04]
Hafizi H., 2014 4722 4.0% 0.02 [0.02; 0.03]
Kus J., 2011 213 3.9% 0.40 [0.34; 0.47]
Kruczak K., 2014 269 3.9% 0.45 [0.39; 0.52]
Garcia-Sancho F.M.C., 2006 858 4.0% 0.12 [0.10; 0.15]
Hernández-Hernández E., 2006 217 3.9% 0.37 [0.30; 0.44]
Al-Khal A.L., 2005 2774 4.0% 0.23 [0.21; 0.24]
Gomes C.M., 2015 251 3.9% 0.21 [0.16; 0.27]
Teixeira E.G., 2005 344 4.0% 0.05 [0.03; 0.08]
Zhao J., 2011 766 4.0% 0.48 [0.44; 0.52]
Bai X., 2017 600 4.0% 0.33 [0.29; 0.37]
Gao L., 2015 21022 4.0% 0.28 [0.27; 0.29]
Chan-Yeung M., 2006 3682 4.0% 0.45 [0.44; 0.47]
Chan P.C., 2008 2504 4.0% 0.09 [0.08; 0.11]
Wu X., 2011 892 4.0% 0.29 [0.26; 0.32]
Choi C.M., 2006 778 4.0% 0.28 [0.25; 0.31]
Lee S.W., 2014 5552 4.0% 0.18 [0.17; 0.19]
Lee H., 2011 330 4.0% 0.06 [0.04; 0.09]
Nantha S.Y., 2017 359 4.0% 0.29 [0.25; 0.34]
Hohmuth B.A., 2006 385 4.0% 0.12 [0.09; 0.16]
Martinez L., 2013 428 4.0% 0.52 [0.47; 0.57]
Soborg B., 2010 1958 4.0% 0.11 [0.10; 0.13]
Random effects model 63432 100.0% 0.20 [0.14; 0.26]
Heterogeneity: $I^2$ = 100%, $\tau^2$ = 0.0391, $p$ = 0
HIGH
Hoa N.B., 2013 21055 4.2% 0.18 [0.17; 0.18]
Shrestha K.B., 2008 17260 4.2% 0.10 [0.10; 0.10]
Adetifa L.M, 2015 12629 4.2% 0.12 [0.11; 0.12]
Legesse M., 2011 587 4.2% 0.31 [0.27; 0.35]
Wassie L., 2013 245 4.1% 0.11 [0.07; 0.15]
Kizza F.N., 2015 283 4.1% 0.49 [0.44; 0.55]
Mumpe-Mwanja D., 2015 4981 4.2% 0.16 [0.15; 0.17]
Mathad J.S., 2014 356 4.1% 0.16 [0.13; 0.21]
Uppada D.R., 2014 6608 4.2% 0.12 [0.11; 0.13]
Thomas T.A., 2010 302 4.1% 0.33 [0.28; 0.39]
Hossain S., 2013 17530 4.2% 0.17 [0.16; 0.17]
Raharimanga V., 2012 376 4.1% 0.18 [0.15; 0.23]
Ranaivomanana P., 2015 343 4.1% 0.21 [0.17; 0.25]
Sheriff F.G., 2010 284 4.1% 0.30 [0.25; 0.36]
Agaya J., 2015 332 4.1% 0.48 [0.43; 0.54]
Gustafson P., 2007 353 4.1% 0.21 [0.17; 0.26]
Shanaube K., 2009 22563 4.2% 0.22 [0.21; 0.23]
Minime-Lingoupou F., 2015 2710 4.2% 0.18 [0.17; 0.20]
Mahomed H., 2011 5244 4.2% 0.42 [0.41; 0.44]
Mahomed H., 2006 358 4.1% 0.81 [0.76; 0.85]
Wood R., 2010 1061 4.2% 0.45 [0.42; 0.48]
Mandalakas A.M., 2015 501 4.2% 0.30 [0.26; 0.34]
Gallant C.J., 2010 426 4.1% 0.62 [0.57; 0.66]
Ncayiyana J.R., 2016 446 4.2% 0.34 [0.30; 0.39]
Random effects model 116833 100.0% 0.28 [0.24; 0.32]
Heterogeneity: $I^2$ = 100%, $\tau^2$ = 0.0129, $p$ = 0
0
0.2
0.4
0.6
0.8
1


First author
Study population
Weight
Proportion
95%-CI
LOW
Al Mekaini L.A., 2014 667 9.1% 0.01 [0.00; 0.02]
Almarzoogi F., 2018 210 8.9% 0.19 [0.14; 0.25]
Gamsky T.E., 2016 557 9.1% 0.14 [0.12; 0.18]
Gaensbauer J., 2018 3745 9.2% 0.02 [0.02; 0.03]
Simpson T., 2012 569 9.1% 0.10 [0.08; 0.13]
Mancuso J.D., 2012 1781 9.1% 0.02 [0.01; 0.03]
Bienek D.R., 2009 326 9.0% 0.02 [0.01; 0.05]
Mancuso J.D., 2016 6083 9.2% 0.05 [0.04; 0.05]
Lemp J.M., 2017 805 9.1% 0.02 [0.01; 0.03]
Elfrink F., 2014 516 9.1% 0.01 [0.00; 0.02]
Balkhy K., 2017 1369 9.1% 0.09 [0.08; 0.11]
Random effects model 16628 100.0% 0.05 [0.03; 0.07]
Heterogeneity: $I^2$ = 97%, $\tau^2$ = 0.0072, $p$ < 0.01
INTERMEDIATE
Masoumi Asl H., 2015 967 5.6% 0.02 [0.01; 0.03]
Mori T., 2007 1559 5.6% 0.07 [0.06; 0.09]
Kus J., 2011 367 5.5% 0.20 [0.16; 0.25]
Kruczak K., 2014 299 5.5% 0.22 [0.18; 0.28]
Wilder-Smith A., 2005 350 5.5% 0.43 [0.38; 0.49]
Yap P., 2018 1690 5.6% 0.13 [0.11; 0.14]
Fan W.C., 2014 363 5.5% 0.26 [0.21; 0.30]
Zhao J., 2011 766 5.6% 0.14 [0.11; 0.16]
Yang X., 2017 266 5.5% 0.22 [0.17; 0.28]
Gao L., 2015 20423 5.6% 0.19 [0.19; 0.20]
Hu Y., 2013 1106 5.6% 0.05 [0.04; 0.06]
Chen C., 2015 5305 5.6% 0.20 [0.19; 0.21]
Wong S.H., 2014 234 5.5% 0.19 [0.14; 0.25]
Chung W., 2015 201 5.5% 0.30 [0.24; 0.37]
Jambaldorj E., 2017 234 5.5% 0.15 [0.11; 0.21]
Huaman M.A., 2018 214 5.5% 0.56 [0.49; 0.63]
Soborg B., 2010 2095 5.6% 0.09 [0.08; 0.11]
Michelsen S.W., 2014 953 5.6% 0.29 [0.27; 0.32]
Random effects model 37392 100.0% 0.19 [0.15; 0.23]
Heterogeneity: $I^2$ = 99%, $\tau^2$ = 0.0126, $p$ < 0.01
HIGH
Marks G.B., 2018 1319 8.4% 0.37 [0.34; 0.40]
Legesse M., 2011 564 8.3% 0.64 [0.60; 0.68]
König Walles J., 2018 829 8.4% 0.33 [0.30; 0.37]
Teklu T., 2018 513 8.3% 0.49 [0.45; 0.53]
Wassie L., 2013 238 8.2% 0.21 [0.16; 0.27]
Lule S.A., 2015 886 8.4% 0.08 [0.07; 0.10]
Mathad J.S., 2014 392 8.3% 0.38 [0.33; 0.43]
Thomas T.A., 2010 228 8.2% 0.47 [0.40; 0.54]
Mahomed H., 2011 5244 8.4% 0.51 [0.50; 0.52]
Lebina L., 2015 2105 8.4% 0.17 [0.15; 0.18]
Mahomed H., 2006 358 8.3% 0.56 [0.51; 0.61]
Mandalakas A.M., 2015 471 8.3% 0.24 [0.20; 0.28]
Random effects model 13147 100.0% 0.36 [0.26; 0.47]
Heterogeneity: $I^2$ = 99%, $\tau^2$ = 0.0397, $p$ = 0
0
0.2
0.4
0.6
0.8
1

# Supplementary material

## The global prevalence of latent tuberculosis: a systematic review and meta-analysis

### Supplementary A. Search strategies

The following list shows the stepwise searches in the applied databases 30th of July 2018, resulting in the total number of abstracts screened.

MEDLINE

| # | Searches | Results |
|---|---|---|
| 1 | "Latent Tuberculosis" OR "Latent Tuberculosis"[Mesh] | 3891 |
| 2 | "Tuberculosis" AND "Prevalence" AND "Latent" | 943 |
| 3 | "Tuberculin Test"[mesh] OR "Tuberculin test" OR “Tuberculin tests” OR "Tuberculin skin test" OR “Tuberculin skin tests” OR "TST*" OR "Mantoux*" | 19 136 |
| 4 | "Interferon-gamma Release Tests"[mesh] OR "Interferon-gamma" OR “Interferon-gamma release assay” OR “Interferon-gamma release assays” OR “Interferon-gamma release test” OR “Interferon-gamma release tests” OR "IGRA*" OR "Quantiferon*" OR "QFT*" OR "T-SPOT.TB*" OR “Enzyme-Linked Immunospot Assay” OR “Enzyme-linked Immunospot Assays” OR "Enzyme-Linked Immunospot Assay"[mesh] | 87 491 |
| 5 | (#1 AND #3) OR (#1 AND #4) | 2128 |
| 6 | (#2 OR #5)<br>Filters activated: Humans. Publication date from 2005/01/01 to 2018/07/30. | **2024** |

Embase

| # | Searches | Results |
|---|---|---|
| 1 | exp latent tuberculosis/ | 4304 |
| 2 | “latent tuberculosis”.ab,ti | 4204 |
| 3 | 1 or 2 | 5899 |
| 4 | ("Tuberculosis" and "Prevalence" and "Latent").ab,ti. | 1200 |
| 5 | exp tuberculin test/ | 20 006 |
| 6 | ("Tuberculin test" or "Tuberculin tests" or "Tuberculin skin test" or "Tuberculin skin tests" or TST* or Mantoux*).ab,ti. | 15 607 |
| 7 | 5 or 6 | 28 249 |
| 8 | exp interferon gamma release assay/ | 2793 |
| 9 | exp enzyme linked immunospot assay/ | 9915 |
| 10 | ("interferon-gamma release assay" or "interferon-gamma release assays" or "interferon-gamma release test" or "interferon-gamma release tests" or "Interferon-gamma" or "enzyme linked immunospot assay" or "enzyme linked immunospot assays" or "IGRA" or Quantiferon* or QFT* or "T-SPOT.TB").ab,ti. | 54 582 |
| 11 | 8 or 9 or 10 | 63 586 |
| 12 | 3 and 7 | 2640 |
| 13 | 3 and 11 | 2407 |
| 14 | 4 or 12 or 13 | 3863 |
| 15 | limit 14 to (human and yr="2005 -Current" and article) | **1936** |

Scopus

| # | Searches | Results |
|---|---|---|
| 1 | TITLE-ABS-KEY ( "Latent tuberculosis" ) | 5281 |
| 2 | TITLE-ABS-KEY ( "Tuberculosis" AND "Prevalence" AND "Latent") | 1293 |
| 3 | TITLE-ABS-KEY ( "Tuberculin test" OR "Tuberculin tests" OR "Tuberculin skin test" OR "Tuberculin skin tests" OR "TST*" OR "mantoux" ) | 31 039 |
| 4 | TITLE-ABS-KEY ( "Interferon-gamma" OR "Interferon-gamma release assay" OR "Interferon-gamma release assays" OR "Interferon-gamma release test" OR "Interferon-gamma release tests" OR "Enzyme-Linked Immunospot Assay" OR "Enzyme-linked Immunospot Assays" ) | 71 287 |
| 5 | TITLE-ABS-KEY (" IGRA*" OR "Quantiferon*" OR "QFT" OR "T-SPOT.TB*" ) | 6170 |
| 6 | (#4 OR #5) | 75 236 |
| 7 | (#1 AND #3) | 2430 |
| 8 | (#1 AND #6) | 2132 |
| 9 | (#2 OR #7 OR #8)<br>Filters activated: Articles.<br>Publication date from 2005 to 2018/07/30. | **2394** |

Web of Science

| # | Searches | Results |
|---|---|---|
| 1 | **TOPIC:** ("Latent tuberculosis") | 4316 |
| 2 | **TOPIC:** ("Tuberculosis" AND "Prevalence" AND "Latent") | 1027 |
| 3 | **TOPIC:** ("Tuberculin test" OR “Tuberculin tests” OR "Tuberculin skin test" OR “Tuberculin skin tests” OR "TST*" OR "Mantoux*") | 10 713 |
| 4 | **TOPIC:** ("Interferon-gamma" OR “Interferon-gamma release assay” OR “Interferon-gamma release assays” OR “Interferon-gamma release test” OR “Interferon-gamma release tests” OR "IGRA*" OR "Quantiferon*" OR "QFT*" OR "T-SPOT.TB*" OR “Enzyme-Linked Immunospot Assay” OR “Enzyme-linked Immunospot Assays”) | 77 515 |
| 5 | #1 AND #3 | 1388 |
| 6 | #1 AND #4 | 1708 |
| 7 | #5 OR #6 | 2138 |
| 8 | #2 OR #7<br>Filters activated: Articles<br>Publication date from 2005 to 2018/07/30.<br>(Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI) | **1974** |

**Supplementary B. Exclusion criteria**

1. The article is a review or meta-analysis.
2. The article is a case report or case series.
3. The study is a cost-effectiveness analysis.
4. The study population is non-human.
5. The study population is tested with neither the skin tuberculin test nor a variant of the interferon-gamma release assay (QFT-G, QFT-GIT, QFT-Plus, T-SPOT.TB).
6. The sample size of neither test is $\geq 200$.
7. The study was published before 2005.
8. The study includes an intervention before testing that could affect results.
9. Test results are not stratified according to country
10. The study population is selected with culture or radiographic findings indicating infection with any mycobacteria as a mandatory criterion.
11. The study population is selected with specific results of TST or IGRA as a mandatory criterion.
12. The study population is a high-risk group: Drug users, prison inmates, psychiatric patients, indigenous, healthcare workers, homeless, HIV positive, part of a contact investigation or refugee/migrant screening, pre- or post-organ transplanted, sarcoidosis, silicosis, miners, patients with end-stage renal disease and/or in dialysis, patients with inflammatory mediated disease (IMID) or patients with diabetes mellitus.

**Supplementary C. Quality Assessment**

The table summarizes the quality assessment of all included reports using the following quality assessment framework. Studies are listed in the same order as Supplementary D (by WHO countries and incidence rates per 100,000).

Scoring matrix for 4 quality assessment elements:

C.1. Quality of sampling method

0 Convenience
1 Randomization
2 Multisite randomization / National survey

C.2. Quality of selection method

0 No exclusion criterion stated / risk factor is an exclusion criterion
1 Exclusion criterion stated (risk factor is not a criterion)
2 Means of identification of TB is stated

C.3. Response rate

0 Not recorded/reported
1 Reported and under 65%
2 Reported and 65% or above

C.4. Quality of prevalence assessment

0 TST cut-off at 10 mm was not present / Indeterminate IGRA results were not stated.
1 TST cut-off at 10 mm was present / Indeterminate IGRA results were stated.
2 TST cut-off at 5 or 15 mm was present as well / Indeterminate IGRA results constituted < 10%.

| First author and publication year | C.1. Quality of sampling method | C.2. Quality of selection method | C.3. Response rate | C.4. Quality of prevalence assessment | Total |
|---|---|---|---|---|---|
| Al Mekaini, L.A. 2014 | 2 | 0 | 0 | 2 | 4 |
| Almarzoogi, F. 2018 | 0 | 1 | 1 | 0 | 2 |
| Bennett D.E. 2008 | 2 | 0 | 2 | 1 | 5 |
| Cain, K.P. 2012 | 0 | 0 | 0 | 0 | 0 |
| Mancuso, J.D. 2012 | 0 | 1 | 2 | 2 | 5 |
| Lempp, J.M. 2017 | 0 | 1 | 2 | 2 / 2 | 5 / 5 |
| Gamsky, T.E. 2016 | 0 | 1 | 0 | 2 | 3 |
| Mancuso, J.D. 2016 | 2 | 2 | 2 | 1 / 2 | 7 / 8 |
| Simpson, T. 2012 | 0 | 0 | 0 | 2 | 2 |
| Gaensbauer, J. 2018 | 0 | 1 | 0 | 0 | 1 |
| Birch, S.J. 2015 | 0 | 0 | 0 | 0 | 0 |
| Bienek, D.R. 2009 | 0 | 1 | 0 | 1 / 1 | 2 / 2 |
| Katsenos, S. 2010 | 0 | 2 | 0 | 2 | 4 |
| Dandoulakis, M. 2009 | 0 | 0 | 0 | 1 | 1 |
| German, V. 2006 | 0 | 0 | 0 | 0 | 0 |
| Berkel, G.M. 2005 | 0 | 1 | 0 | 2 | 3 |
| Elfrink, F. 2014 | 0 | 1 | 2 | 1 / 0 | 3 / 4 |
| Winje, B.A. 2008 | 2 | 2 | 2 | 0 | 6 |
| Sancasciani, D. 2006 | 0 | 0 | 1 | 1 | 2 |
| Villate, J.I. 2006 | 0 | 1 | 2 | 2 | 5 |
| Espinosa Arévalo, M. 2006 | 0 | 0 | 0 | 0 | 0 |
| Balkhy, H.H. 2017 | 2 | 1 | 2 | 1 / 2 | 7 / 8 |
| Sleiman, R. 2007 | 1 | 2 | 2 | 2 | 7 |
| Alavi, S.M. 2008 | 2 | 2 | 2 | 2 | 8 |
| Asl, H.M. 2015 | 2 | 2 | 0 | 2 / 0 | 4 / 6 |
| Haghdoost, A.A. 2014 | 2 | 0 | 2 | 1 | 5 |
| Hafizi, H. 2014 | 2 | 1 | 0 | 2 | 5 |
| Mori, T. 2007 | 0 | 0 | 0 | 0 | 0 |
| Kruczak, K. 2014 | 0 | 0 | 0 | 1 / 2 | 1 / 2 |
| Kuś, J. 2011 | 0 | 1 | 0 | 2 / 2 | 3 / 3 |
| Garcia-Sancho, F.M.C. 2006 | 2 | 2 | 1 | 2 | 7 |

| | | | | | |
|---|---|---|---|---|---|
| Hernández-Hernández, E. 2006 | 0 | 2 | 2 | 1 | 5 |
| Al-Khal, A.L. 2005 | 0 | 0 | 0 | 2 | 2 |
| Teixeira, E.G. 2005 | 0 | 1 | 2 | 1 | 4 |
| Gomes, C.M. 2015 | 0 | 0 | 0 | 2 | 2 |
| Yap, P. 2015 | 2 | 0 | 1 | 2 | 5 |
| Wilder-Smith, A. 2005 | 0 | 1 | 2 | 2 | 5 |
| Gao, L. 2015 | 2 | 2 | 2 | 2 | 8 |
| Wong, S.H. 2014 | 0 | 0 | 0 | 2 | 2 |
| Fan, W.C. 2014 | 0 | 2 | 0 | 2 | 4 |
| Hu, Y. 2014 | 2 | 2 | 0 | 0 | 4 |
| Chan, P.C. 2008 | 0 | 0 | 0 | 1 | 1 |
| Wu, X. 2011 | 0 | 0 | 0 | 2 | 2 |
| Zhao, J. 2011 | 0 | 2 | 0 | 2 / 2 | 4 / 4 |
| Chan-Yeung, M. 2006 | 0 | 1 | 2 | 1 | 4 |
| Chen, C. 2015 | 0 | 1 | 2 | 2 | 5 |
| Bai, X. 2017 | 0 | 0 | 0 | 0 | 0 |
| Yang, X. 2017 | 0 | 0 | 1 | 0 | 1 |
| Choi, C.M. 2006 | 0 | 2 | 0 | 2 | 4 |
| Jambaldorj, E. 2017 | 0 | 2 | 0 | 0 | 2 |
| Chung, W. 2015 | 0 | 2 | 0 | 2 | 4 |
| Lee, H. 2011 | 0 | 0 | 0 | 0 | 0 |
| Lee, S.W. 2014 | 0 | 2 | 0 | 2 | 4 |
| Nantha, S.Y. 2017 | 0 | 1 | 1 | 1 | 3 |
| Martinez, L. 2013 | 2 | 2 | 0 | 2 | 6 |
| Hohmuth, B.A. 2006 | 0 | 1 | 1 | 1 | 3 |
| Huaman, M.A. 2018 | 0 | 2 | 0 | 2 | 4 |
| Michelsen, S.W. 2014 | 0 | 0 | 2 | 2 | 4 |
| Soborg, B. 2010 | 0 | 0 | 2 | 2 | 4 |
| Marks, G.B. 2018 | 2 | 2 | 2 | 2 | 8 |
| Hoa, N.B. 2013 | 2 | 1 | 2 | 1 | 6 |
| Shrestha, K.B. 2008 | 2 | 1 | 2 | 1 | 6 |
| Adetifa, I.M. 2011 | 2 | 1 | 1 | 1 | 5 |
| Wassie, L. 2013 | 2 | 1 | 0 | 1 / 2 | 4 / 5 |

| | | | | | |
|---|---|---|---|---|---|
| Legesse, M. 2011 | 2 | 1 | 0 | 2 / 2 | 5 / 5 |
| Teklu, T. 2018 | 2 | 1 | 0 | 2 | 5 |
| König Walles, J. 2018 | 0 | 0 | 0 | 2 | 2 |
| Lule, S.A. 2015 | 0 | 1 | 1 | 0 | 2 |
| Kizza, F.N. 2015 | 2 | 0 | 0 | 1 | 3 |
| Mumpe-Mwanja, D. 2015 | 0 | 0 | 2 | 0 | 2 |
| Mathad, J.S. 2014 | 0 | 1 | 0 | 1 | 2 |
| Uppada, D.R. 2014 | 0 | 1 | 0 | 1 | 2 |
| Thomas, T.A. 2010 | 0 | 1 | 2 | 1 / 1 | 4 / 4 |
| Hossain, S. 2013 | 2 | 0 | 2 | 0 | 4 |
| Raharimanga, V. 2012 | 0 | 1 | 2 | 2 | 5 |
| Ranaivomanana, P. 2015 | 0 | 2 | 2 | 0 | 4 |
| Sheriff, F.G. 2010 | 0 | 2 | 2 | 1 | 5 |
| Agaya, J. 2015 | 1 | 0 | 2 | 1 | 4 |
| Gustafson, P. 2007 | 1 | 2 | 0 | 1 | 4 |
| Minime-Lingoupou, F. 2015 | 0 | 1 | 2 | 2 | 5 |
| Mandalakas, A.M. 2015 | 0 | 2 | 0 | 1 / 1 | 3 / 3 |
| Mahomed, H. 2011 | 0 | 2 | 1 | 2 / 2 | 5 / 5 |
| Mahomed, H. 2006 | 0 | 2 | 0 | 2 / 0 | 4 / 2 |
| Wood, R. 2010 | 0 | 1 | 0 | 2 | 3 |
| Gallant, C.J. 2010 | 0 | 1 | 0 | 0 | 1 |
| Lebina, L. 2015 | 0 | 1 | 0 | 2 | 3 |
| Ncayiyana, J.R. 2016 | 1 | 0 | 1 | 0 | 2 |
| Shanaube, K. 2009 | 2 | 0 | 1 | 2 | 5 |

**Supplementary D. Supplementary table of LTBI prevalence studies included in the review (by WHO countries and incidence rates per 100,000)**

*IGRA prevalence is presented with indeterminate excluded in both the denominator and the numerator. TST prevalence is presented with 10 mm cut-offs or the closest possible**.** Twenty-eight of 88 studies stated randomization strategies.

In total, 58 studies stated exclusion criteria; 25 studies stated diagnostic strategies for identifying active TB and 31 directly stated current TB disease as an exclusion criterion. 42 studies reported a response rate.

| WHO TB incidence per 100,000 | Country | Study date | Study area | Sampling method | Age | Sample size (IGRA/TST) | IGRA prevalence* | TST prevalence* | First author and year of publication |
|---|---|---|---|---|---|---|---|---|---|
| 0.8 | United Arab Emirates | 2013/04-2013/09 | 7 ambulatories in 1 state | Randomly selected children | 1-19 yrs | 669 | 0.6% | - | Al Mekaini, L.A. 2014 [28] |
| | United Arab Emirates | 2016/08-2017/05 | 5 departments at 1 hospital | Convenience sampling | 42 yrs (mean) | 210 | 18.6% | - | Almarzoogi, F. 2018 [29] |
| 3.1 | United States of America | 1999-2000 | National multicentre | Random, probability cluster sampling | ≥ 1 yrs | 7386 | - | 4.2% | Bennett, D.E. 2008 [30] |
| | United States of America | 2002/03-2006/12 | 95 health departments, 1 state | Convenience sampling | - | 27150 | - | 1.5% | Cain, K.P. 2012 [31] |
| | United States of America | 2009/04-2009/05 | 1 military base | Convenience sampling | 18-29 yrs | 1781 | 2.0% | 3.2% | Mancuso, J.D. 2012 [32] |
| | United States of America | 2004/01-2004/02 | 1 military base | Convenience sampling | - | 810/838 | 1.7% | 2.3% | Lempp, J.M. 2017 [33] |
| | United States of America | 2007/01-2013/10 | Emergency responders in one county | Convenience sampling | - | 565 | 14.4% | - | Gamsky, T.E. 2016 [34] |
| | United States of America | 2011-2012 | National Health and Nutrition Examination Survey | Probability cluster sampling | > 6 yrs | 6083 | 4.8% | 4.4% | Mancuso, J.D. 2016 [35] |
| | United States of America | 2008/01-2009/06 | Public health screening | Convenience sampling | - | 580 | 10.0% | 16.9% | Simpson, T. 2012 [36] |
| | United States of America | 2011/01-2014/08 | 14 school-based health centers, 3 paediatric primary care clinics, and 6 family medicine clinics | Convenience sampling | 8 yrs (mean) | 3745 | 2.1% | - | Gaensbauer, J. 2018 [37] |
| | United States of America | 2012-2013 | 1 university | Convenience sampling | - | 2299 | - | 8.0% | Birch, S.J. 2015 [38] |
| | United States of America | - | Recruit training boot camp | Convenience sampling | 18-14 yrs | 326 | 2.5% | 0.6% | Bienek, D.R. 2009 [39] |
| 4.4 | Greece | 2007/11-2008/11 | 1 military base | Convenience sampling | 24.3 yrs (mean) | 1750 | - | 5.5% | Katsenos, S. 2010 [40] |
| | Greece | 1990-2005 | 5 primary and 3 secondary schools | Convenience sampling | 6-14 yrs | 7929 | - | 2.0% | Dandoulakis, M 2009 [41] |
| | Greece | 2005/11-2006/02 | Military training center | Convenience sampling | 23.5 yrs (mean) | 953 | - | 3.9% | German, V. 2006 [42] |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 5.9 | Netherlands | 2000-2001 | 8 clinics, 1 state | Convenience sampling | -- | 2848 | - | 3.1% | Berkel, G.M. 2005 [43] |
| | Netherlands | 2008/12-2011/11 | Travel clinic | Convenience sampling | 25 yrs (median) | 516/473 | 0.6% | 0.6% | Elfrink, F. 2014 [44] |
| 6.1 | Norway | 2005-2006 | School children | Convenience sampling | 14-15 yrs | 33456 | - | 1.6% | Winje, B.A. 2008 [45] |
| 6.1 | Italy | 2002-2003 | 21 high schools | Convenience sampling | 18 yrs | 1138 | - | 0.4% | Sancasciani, S. 2006 [46] |
| 10 | Spain | 1998 | All children turning 7, 1 city | Convenience sampling | 7 yrs | 5277 | - | 7.0% | Villate, J.I. 2006 [47] |
| | Spain | - | 22 primary pediatric care clinics | Convenience sampling | 51.3 months (mean) | 2743 | - | 0.9% | Espinosa Arévalo, M. 2006 [48] |
| 10 | Saudi Arabia | 2010/07-2013/03 | 11 primary health centres | Stratified random sampling technique | 26.3 yrs (mean) | 1369 | 9.1% | 9.3% | Balkhy, H.H. 2017 [49] |
| 12 | Lebanon | 2004/02-2004/05 | Several schools | Convenience sampling | 3-19 yrs | 4271 | - | 7.8% | Sleiman, R. 2007 [50] |
| 14 | Iran | 2006-2007 | Children, southwest Iran | Randomized multi-cluster sampling | 10 yrs (mean) | 3906 | - | 2.2% | Alavi, S.M. 2008 [51] |
| | Iran | 2009/10-2010/03 | 24 schools, 11 day care centers | Multistage random sampling | 1-15 yrs | 967 | 2.2% | 2.5% | Asl, H.M. 2015 [52] |
| | Iran | 2012-2013 | 25 urban and 53 rural primary schools | Randomized multi-cluster sampling | 7 yrs (mean) | 5384 | - | 4.7% | Haghdoost, A.A. 2014 [53] |
| 16 | Albania | 2010 | National screening | Students | 10-13 yrs | 4722 | - | 2.2% | Hafizi, H. 2014 [54] |
| 16 | Japan | 2003/09-2013/10 | 1 rural community | Community screening | 40-69 yrs | 1559 | 7.1% | - | Mori, T. 2007 [55] |
| 18 | Poland | 2007/07-2009/09 | 3 long term care facilities and community, 1 city | Convenience sampling | 49 yrs (mean) | 300/269 | 22.4% | 45.5% | Kruczak, K. 2014 [56] |
| | Poland | - | Blood donors and controls, 1 province | Convenience sampling | 43.8 yrs (mean) | 367/213 | 20.4% | 40.4% | Kuś, J. 2011 [57] |
| 22 | Mexico | 2000/09-2001/02 | Selected schools | Convenience sampling | 6 yrs (mean) | 858 | - | 12.4% | Garcia-Sancho, F.M.C. 2006 [58] |
| | Mexico | 1989/01-2000/12 | Renal donors | Convenience sampling | 31 yrs (median) | 217 | - | 36.9% | Hernández-Hernández, E. 2006 [59] |
| 23 | Qatar | 2000/01-2003/16 | Garment workers | Convenience sampling | 28.6 yrs (mean) | 2774 | - | 22.7% | Al-Khal, A.L. 2005 [60] |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 42 | Brazil | 2002/03-2003/09 | Preclinical medical students, 5 hospitals | Convenience sampling | 22 yrs (mean) | 344 | - | 5.2% | Teixeira, E.G. 2005 [61] |
| | Brazil | - | Primary care unit database | Convenience sampling | 50.2 yrs (mean) | 251 | - | 21.1% | Gomes, C.M. 2015 [62] |
| 51 | Singapore | 2014/04-2015/03 | Singapore | National household randomization | 18-19 yrs | 1690 | 12.6% | - | Yap, P. 2018 [63] |
| | Singapore | 2002 | Vaccination sites | Convenience sampling | 49.2 yrs (median) | 357 | 43.4% | - | Wilder-Smith, A. 2005 [64] |
| 64 | China | 2013/07-2013/09 | 4 areas | Multisite, randomisation | All | 21022/20979 | 19.4% | 28.0% | Gao, L. 2015 [13] |
| | China | - | Hong Kong | Convenience sampling | 48.3 yrs (mean) | 234 | 19.2% | - | Wong, S.H. 2014 [65] |
| | China | 2011/01-2012/08 | 4 hospitals, Taiwan | Convenience sampling | 17.8 yrs (mean) | 391 | 25.6% | - | Fan, W.C. 2014 [66] |
| | China | 2010/01-2010/08 | 8 schools, 7 districts | Convenience sampling | 11-18 yrs | 1106 | 4.7% | - | Hu, Y. 2013 [67] |
| | China | 2002-2004 | 1 city | City screening | 6-14 yrs | 2504 | - | 9.3% | Chan, P.C. 2008 [68] |
| | China | 2009/12-2010/03 | Military base | Convenience sampling | 17-24 yrs | 892 | - | 28.8% | Wu, X. 2011 [69] |
| | China | 2008 | 1 university | Convenience sampling | 17-24 yrs | 766 | 13.8% | 47.9% | Zhao, J. 2011 [70] |
| | China | 2006 | 35 old age homes, Hong Kong | Convenience sampling | 82.3 yrs (mean) | 3682 | - | 45.3% | Chan-Yeung, M. 2006 [71] |
| | China | 2013/07 | 2 villages, Eastern China | Convenience sampling | ≥ 5 yrs | 5305 | 20.0% | - | Chen, C. 2015 [72] |
| | China | 2014 | Army recruits Beijing | Convenience sampling | 19 yrs (mean) | 600 | - | 32.8% | Bai, X. 2017 [73] |
| | China | - | Vaccinated control group | Convenience sampling | 18-76 yrs | 266 | 22.2% | - | Yang, X. 2017 [114] |
| 77 | South Korea | 2005/03-2006/01 | 1 military base | Convenience sampling | 20 yrs (mean) | 788 | - | 28% | Choi, C.M. 2006 [74] |
| | South Korea | 2009/01-2015/12 | 1 hospital | Convenience sampling | 45.9 (mean) | 234 | 15.4% | - | Jambaldorj, E. 2017 [75] |
| | South Korea | 2012/08-2014/07 | Controls undergoing routine health examinations | Convenience sampling | ≥ 18 yrs | 201 | 29.9% | - | Chung, W. 2015 [76] |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | South Korea | 2006/05-2006/12 | Paediatric departments at 4 hospitals | Convenience sampling | 3-7 yrs | 330 | - | 5.8% | Lee, H. 2011 [77] |
| | South Korea | 2005 + 2008-2011 | Korean Reserve Force Battalion | Convenience sampling | 20 yrs (median) | 552 | - | 18.0% | Lee, S.W. 2014 [78] |
| 92 | Malaysia | 2014/10-2015/12 | Primary care clinic | Convenience sampling | 63 yrs (mean) | 359 | - | 29.2% | Nantha, S.Y. 2017 [79] |
| 117 | Peru | 2011/07-2012/01 | Cluster of shantytowns, 1 city | Convenience sampling | 32.7 yrs (median) | 428 | - | 52.3% | Martinez, L. 2013 [80] |
| | Peru | 2002/03-2003/08 | 1 university | Convenience sampling | 21.1 yrs (mean) | 385 | - | 12.2% | Hohmuth, B.A. 2006 [81] |
| | Peru | 2015/07-2017/03 | Large national public hospital networks | Convenience sampling | 62 yrs (median) | 215 | 56.1% | - | Huaman, M.A. 2018 [82] |
| 118 | Greenland | 2012/09-2013/04 | Birth cohort, 1 district | Convenience sampling | 5-30 yrs | 953 | 29.4% | - | Michelsen, S.W. 2014 [83] |
| | Greenland | 2006-2007 | Schoolchildren, 5 towns | Convenience sampling | ≥ 5 yrs | 2117/1958 | 9.4% | 11.3% | Soborg, B. 2010 [84] |
| 133 | Vietnam | 2015/06-2016/03 | 60 subcommunes | Randomized multi-cluster sampling | 41 (median) | 1319 | 36.8% | - | Marks, G.B. 2018 [85] |
| | Vietnam | 2006/09-2007/07 | Nationwide survey of school children | Stratified cluster sample survey | 6-14 yrs | 21055 | 17.6% | - | Hoa, N.B. 2013 [86] |
| 154 | Nepal | 2006/02-2006/09 | Nationwide survey of school children | Randomized multi-cluster sampling | 5-7 yrs | 17260 | 10.0% | - | Shrestha, K.B. 2008 [87] |
| 174 | Gambia | 2011 | Schools, national screening | Randomized multi-cluster sampling | 6-11 yrs | 12629 | - | 11.5% | Adetifa, I.M. 2011 [88] |
| 177 | Ethiopia | 2009/03-2009/09 | 7 schools, 1 city | Randomly picked schools | 14.8 yrs (median) | 245 | 21.4% | 10.6% | Wassie, L. 2013 [89] |
| | Ethiopia | 2010/04-2010/06 | Several administrative units, 1 community | Randomly picked administrative units | 30 yrs (median) | 570/587 | 64.4% | 31.2% | Legesse, M. 2011 [90] |
| | Ethiopia | 2015/05-2016/02 | Pastoral communities in southern Ethiopia | Randomly picked sub-districts | 37.2 yrs (mean) | 497 | 48.9% | - | Teklu, T. 2018 [91] |
| | Ethiopia | 2015/11-2016/08 | 3 public health clinics | Convenience sampling | - | 829 | 33.4% | - | König Walles, J. 2018 [92] |
| 201 | Uganda | - | 1 city | Convenience sampling | 5 yrs | 886 | 8.5% | - | Lule, S.A. 2015 [93] |
| | Uganda | - | 1 city | Randomized sampling | ≥ 15 yrs | 283 | - | 49.5% | Kizza, F.N. 2015 [94] |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Uganda | - | 1 university | Convenience sampling | 12-18 yrs | 4981 | - | 16.1% | Mumpe-Mwanja, D. 2015 [95] |
| 211 | India | 2011/01-2012/07 | 1 antenatal clinic | Convenience sampling | - | 401 | 38.3% | 16.3% | Mathad, J.S. 2014 [96] |
| | India | 2007/02-2008/05 | 1 school, 1 junior college | Convenience sampling | 11-18 yrs | 6608 | - | 12.0% | Uppada, D.R., 2014 [97] |
| 221 | Bangladesh | 2009/04-2009/06 | Slum area, 1 city | Convenience sampling | 12.5 yrs | 302 | 46.9% | 33.4% | Thomas, T.A. 2010 [98] |
| | Bangladesh | 2007-2009 | School children from 20 urban and 20 rural clusters | Randomized multi-cluster sampling | 5-14 yrs | 17530 | - | 16.7% | Hossain, S. 2013 [99] |
| 237 | Madagascar | 2008/04-2008/05 | 2 primary schools | Convenience sampling | 6-7 yrs | 376 | - | 18.4% | Raharimanga, V. 2012 [100] |
| | Madagascar | 2010/07-2010/10 | 2 primary and 2 secondary schools | Convenience sampling | 6-14 yrs | 343 | - | 20.7% | Ranaivomanana, P. 2015 [101] |
| 287 | Tanzania | 2008/06-2008/08 | 1 clinic | Convenience sampling | 25.3 yrs (mean) | 284 | - | 29.9% | Sheriff, F.G. 2010 [102] |
| 348 | Kenya | 2013/06-2013/10 | School workers from 34 primary and secondary schools | Randomized sampling | 36 yrs (median) | 332 | - | 48.2% | Agaya, J. 2015 [103] |
| 374 | Guinea Bissau | 1999/05-2000/11 | 1 neighbourhood | Randomized sampling | All | 353 | - | 21.2% | Gustafson, P. 2007 [104] |
| 407 | Central African Republic | 2011/02-2011/02 | 57 primary schools, 2 cities | Convenience sampling | 6-12 yrs | 2710 | - | 18.4% | Minime-Lingoupou, F. 2015 [105] |
| 781 | South Africa | 2008/01-2012/07 | Neighbourhood controls | Convenience sampling | 0.25-15 yrs | 471/501 | 24.0% | 30.1% | Mandalakas, A.M. 2015 [106] |
| | South Africa | - | 1 high school | Convenience sampling | 12-18 yrs | 5422 | 50.8 | 42.2% | Mahomed, H. 2011 [107] |
| | South Africa | - | Workplaces, 1 rural town | Convenience sampling | 18-40 yrs | 358 | 56.1% | 80.7% | Mahomed, H. 2006 [108] |
| | South Africa | 2006 | Townships, 1 city | Convenience sampling | 5-40 yrs | 1061 | - | 45.0% | Wood, R. 2010 [109] |
| | South Africa | - | 2 suburbs, 1 city | Convenience sampling | 13.9 yrs (mean) | 426 | - | 61.5% | Gallant, C.J. 2010 [110] |
| | South Africa | 2011/02-10 | Schools and creeches, 1 city | Randomly selected schools and creeches | 5-7 yrs | 2105 | 16.6% | - | Lebina, L. 2015 [111] |
| | South Africa | 2013/05-2014/03 | Urban township | Randomized sampling | 32 (median) | 446 | - | 34.3% | Ncayiyana, J.R. 2016 [112] |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 781/376 | South Africa & Zambia | 2005 | 98 schools, 2 countries | Randomized multi-cluster sampling | 6-11 yrs | 22563 | - | 22.0% | Shanaube, K. 2009 [113] |

## Supplementary E. WHO TB incidence intervals and categorization of countries

| TB incidence interval | Countries with original data | Countries prevalence was extrapolated to |
|---|---|---|
| Low<br>(0-10 cases / 100,000 person years$^{-1}$) | Greece, Italy, Netherlands, Norway, Saudi Arabia, Spain, United Arab Emirates, United States of America | Andorra, Antigua and Barbuda, Australia, Austria, Barbados, Belgium, Canada, Costa Rica, Cuba, Cyprus, Czech Republic, Denmark, Dominica, Finland, France, Germany, Grenada, Hungary, Iceland, Ireland, Israel, Jamaica, Jordan, Luxembourg, Monaco, New Zealand, Oman, Samoa, San Marino, Slovakia, Slovenia, St. Kitts and Nevis, St. Lucia, St. Vincent and the Grenadines, Sweden, Switzerland, Tonga, United Kingdom |
| Intermediate<br>(11-120 cases / 100,000 person years$^{-1}$) | Albania, Brazil, China, Greenland, Iran, Japan, Lebanon, Malaysia, Mexico, Peru, Poland, Qatar, Singapore, South Korea | Algeria, Argentina, Armenia, Azerbaijan, Bahamas, Bahrain, Belarus, Belize, Benin, Bolivia, Bosnia, Brunei, Bulgaria, Burkina Faso, Burundi, Chile, Colombia, Comoros, Cook Islands, Croatia, Dominican Republic, Ecuador, Egypt, El Salvador, Eritrea, Estonia, Fiji, Georgia, Guatemala, Guyana, Honduras, Iraq, Kazakhstan, Kuwait, Latvia, Libya, Lithuania, Maldives, Mali, Malta, Mauritania, Mauritius, Moldova, Montenegro, Morocco, Nauru, Nicaragua, Niger, Niue, Panama, Paraguay, Portugal, Romania, Russia, Rwanda, Sao Tome and Principe, Serbia, Seychelles, Solomon Islands, Sri Lanka, Sudan, Suriname, Syria, Tajikistan, the Former Yugoslav Republic of Macedonia, Togo, Trinidad and Tobago, Tunisia, Turkey, Turkmenistan, Ukraine, Uruguay, Uzbekistan, Vanuatu, Venezuela, Yemen |
| High<br>(>120 cases / 100,000 person years$^{-1}$) | Bangladesh, Central African Republic, Ethiopia, Gambia, Guinea Bissau, India, Kenya, Madagascar, Nepal, South Africa, Tanzania, Uganda, Vietnam, Zambia | Afghanistan, Angola, Bhutan, Botswana, Cambodia, Cameroon, Cape Verde, Chad, Congo, Cote d'Ivoire, Democratic Republic of the Congo, Djibouti, Equatorial Guinea, Gabon, Ghana, Guinea, Haiti, Indonesia, Kiribati, Kyrgyzstan, Laos, Lesotho, Liberia, Malawi, Marshall Islands, Micronesia (Federated States), Mongolia, Mozambique, Myanmar, Namibia, Nigeria, North Korea / Democratic People's Republic of Korea, Pakistan, Palau, Papua New Guinea, Philippines, Senegal, Sierra Leone, Somalia, South Sudan, Swaziland, Thailand, Timor-Leste, Tuvalu, Zimbabwe |
| Total countries | 36 | 159 |

## Supplementary F. PRISMA checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 3-4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 3-4 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 4 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 4 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 4 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 4 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 4 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 5 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 5 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 5 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | - |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 6-7 |

| **Section/topic** | **#** | **Checklist item** | **Reported** |
|---|---|---|---|

| | | | on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | - |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 6 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 7 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 7 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 8 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Fig 3-4 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 7-8, fig 3-4 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | - |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | - |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 8 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 8-11 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 11 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 12 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097.

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