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

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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. http://bit.ly/2MN8Gvu

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ABSTRACT In 1999, the World Health Organization (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-γ 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 individuals, as this constitutes an enormous source of potential active tuberculosis.

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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*, but without clinical symptoms of active tuberculosis (TB), which is the definition of latent TB infection (LTBI) [1]. This estimate has since been referred to frequently, but had 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 re-infection 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 at the beginning of the new millennium [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 calculated from the incidence of smear-positive cases using the Styblo [7] rule, derived from empirical data and assumptions on duration of infectiousness and transmissions per year. The ratio assumes that each smear-positive case transmits 10 infections per year; whereas a newer estimate suggested that this number could be as low as two to six infections [8]. In addition, the Styblo rule assumes that the duration of infectiousness is in general 2 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 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 do not involve assumptions on transmission rates or infectiousness, but incorporate local conditions.

TST has traditionally been used as a screening tool for LTBI due to low direct costs and ease of use. In recent decades, commercial interferon-γ release assays (IGRAs) have been introduced, which solely contain antigens that are absent in bacille 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 nontuberculous 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 material section F) [14]. The protocol was registered on PROSPERO (www.crd.york.ac.uk/prospero/; CRD42019125380).

Studies that reported on the prevalence of LTBI diagnosed with IGRA and/or TST were eligible. Two investigators (A. Cohen and V.D. Mathiasen) searched the databases MEDLINE, Embase, Scopus and Web of Science for articles published between January 1, 2005 and July 30, 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 available in supplementary material section 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 nontuberculous mycobacteria.

Full texts were obtained for all studies identified by either A. Cohen or V.D. Mathiasen as potentially relevant.

Study eligibility and quality assessment

Following deletion of duplicates, A. Cohen and V.D. Mathiasen screened titles, abstracts or entire articles for exclusion criteria and determined which studies met the eligibility criteria (supplementary material section B). Only studies with a sample size of ⩾200 were included, to avoid selection bias from small studies. Meta-analyses, reviews, cost-effectiveness analyses and nonhuman 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, HIV-positive patients and 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 (Strengthening the Reporting of Observational Studies in Epidemiology) 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 material section 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 included participants. Enrolment data were used for the full study enrolment when data for selected subgroups were missing. Furthermore, 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-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 manufacturers' 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 in July 2018 from the WHO 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 per 100 000 person-years), intermediate (11–120 cases per 100 000 person-years) and high (>120 cases per 100 000 person-years). 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 uncertainty, we sequentially performed statistical analysis on an 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 the WHO framework towards TB 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. 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 prioritised 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 3) in a worst-case scenario 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^{-1}) 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 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. First, 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 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 [27] method. Clopper–Pearson 95% confidence intervals 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. Then 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. Furthermore, 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 prevalence 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 texts were assessed for eligibility, and 682 were excluded. 88 quantitative studies fulfilled the criteria for inclusion (figure 1; studies listed in supplementary material section 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 per 100 000 in the United Arab Emirates [28] to 781 per 100 000 in South Africa [106]. The mean age reported ranged from ∼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-GIT (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 T-SPOT.TB (n=5547) [31, 62, 65, 72, 90, 104, 114] and two of these included simultaneous QFT-GIT [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]. 67 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]. 20 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 material section 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

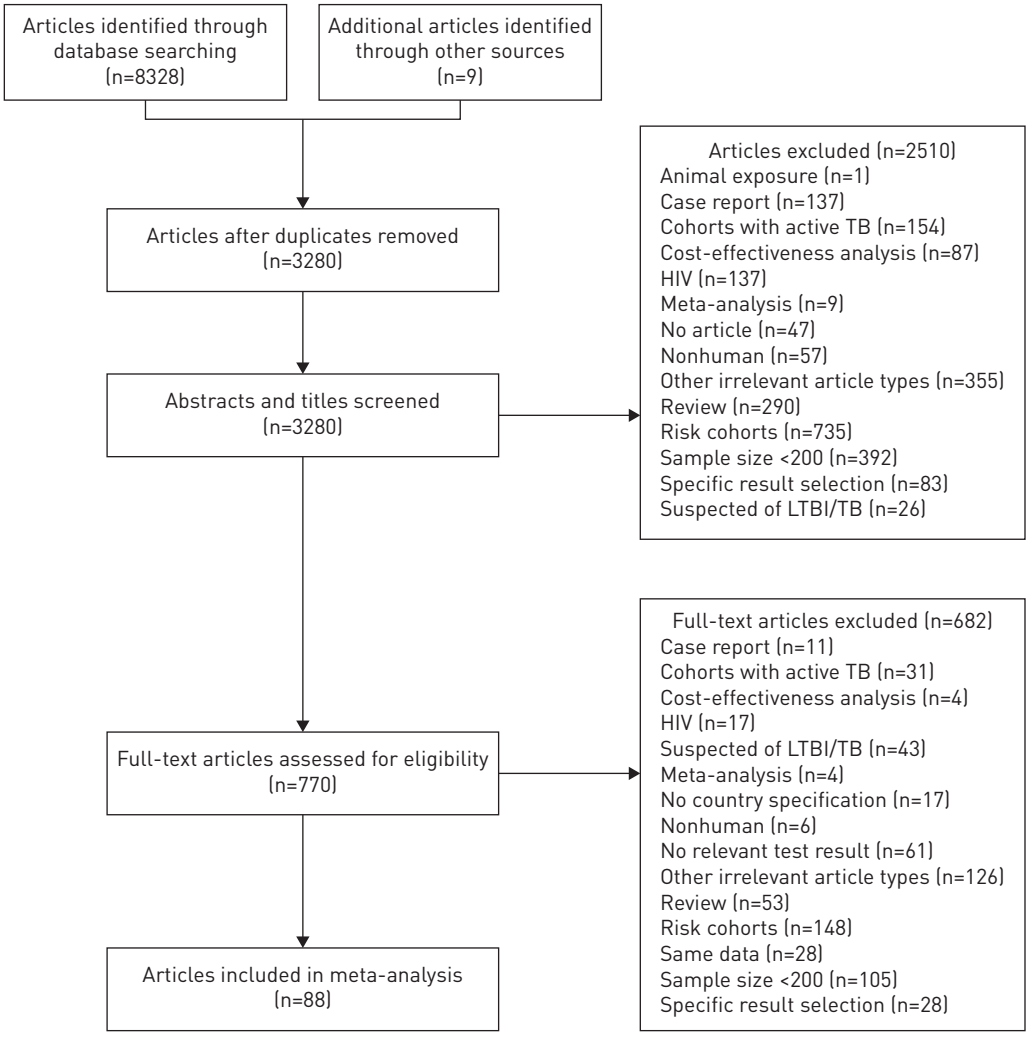

FIGURE 1 Study selection. Flow chart of study inclusion. Studies are listed in supplementary material section D. TB: tuberculosis; LTBI: latent TB infection.

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 coloured the countries in a lighter version of aforementioned colours.

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 figures 3 and 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 heterogenicity of the low, intermediate and high

TABLE 1 Pooled sample sizes of included studies

	IGRA sample size	TST sample size	Total sample size
TB incidence intervals			
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)

Data are presented as n (%). Pooled sample sizes by interferon-γ release assay (IGRA), tuberculin skin test (TST) (10-mm cut-off) and in total. Categorisation of countries in tuberculosis (TB) incidence intervals is listed in supplementary material section E.

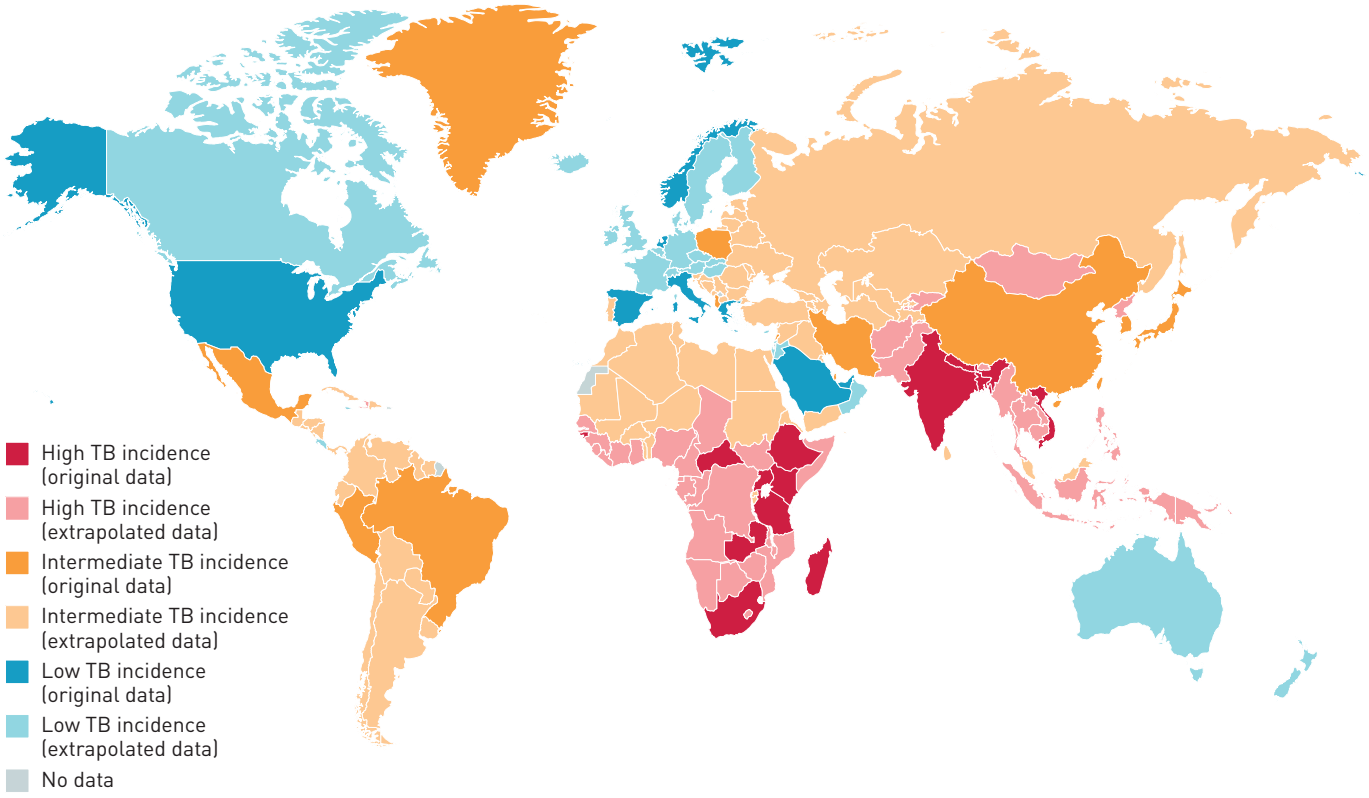

FIGURE 2 World map of countries by tuberculosis (TB) incidence. High, intermediate and low active TB incidence countries are shown, corresponding to average latent TB infection (LTBI) prevalence of 28–36%, 19–20% and 3–5%, respectively (from figures 3 and 4). Darker shades of the colours indicate areas with original LTBI prevalence data, lighter shaded colours indicate countries where the weighted estimate of the country's TB incidence interval has been used.

TB incidence interval, calculated with I^2 statistics, was 97%, 99% and 99%, respectively, for IGRA and 100% for all three incidence intervals with TST.

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 results as positive, global prevalence was estimated to be 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, respectively. 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 2). 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 to 8 points out of a possible 8 (references available in supplementary material section C). Most studies employed convenience sampling (n=60 out of 88). Information on response rate was presented in 42 (47.7%) out of 88 studies. Indeterminate results were reported in 30 (73.2%) out of 41 studies on IGRA, of which four had indeterminate results constituting >5% of all results [31, 60, 65, 96]. 27 (40.3%) out of 67 studies reported a 15-mm TST cut-off, 56 (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

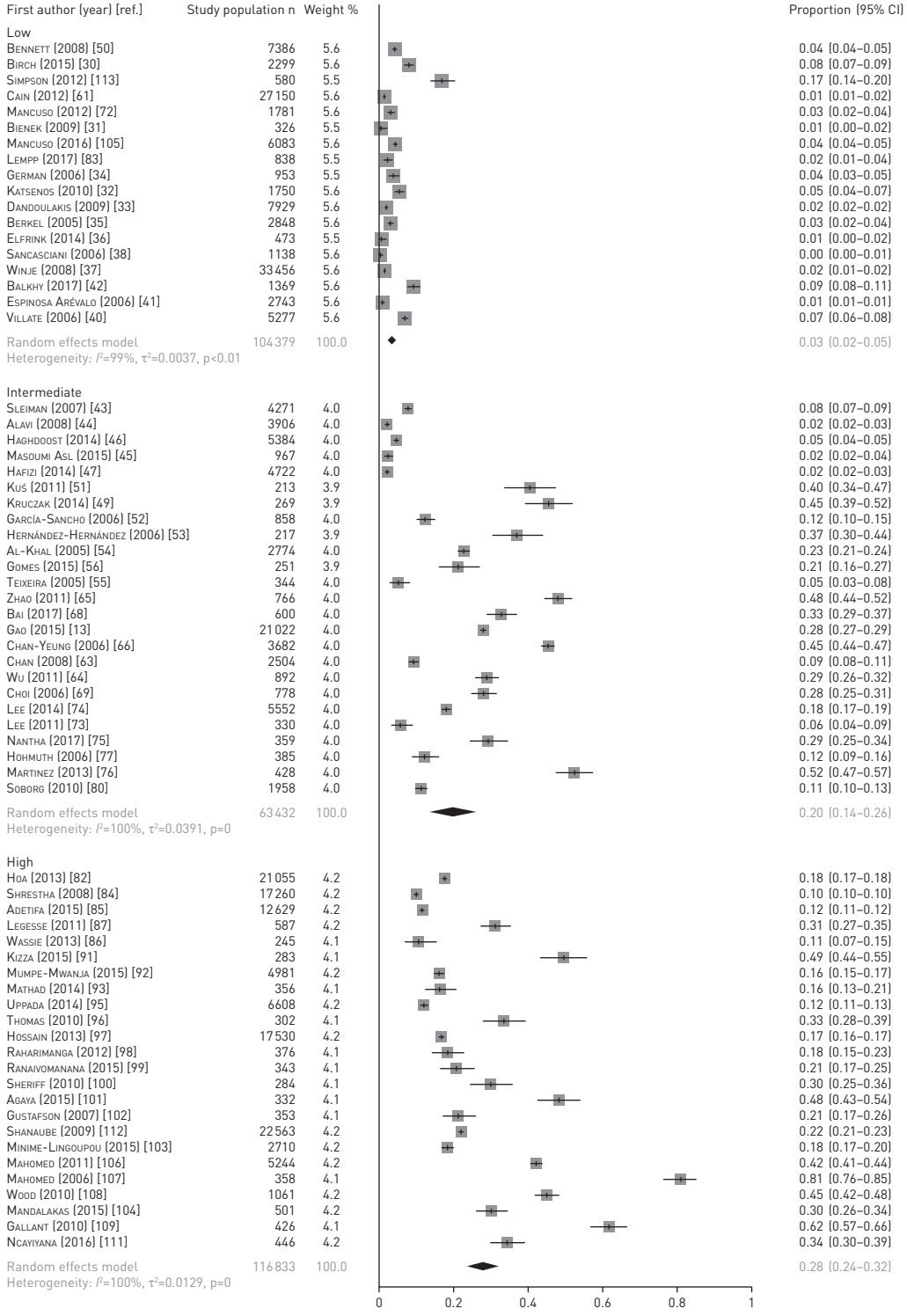

FIGURE 3 Forest plot of tuberculin skin test (TST) data. Prevalence of latent tuberculosis infection by tuberculosis incidence intervals using random effects model. Latent infection based on TST with a 10-mm cut-off.

for preventive therapy. Data were gathered from >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 annual risk of infection-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

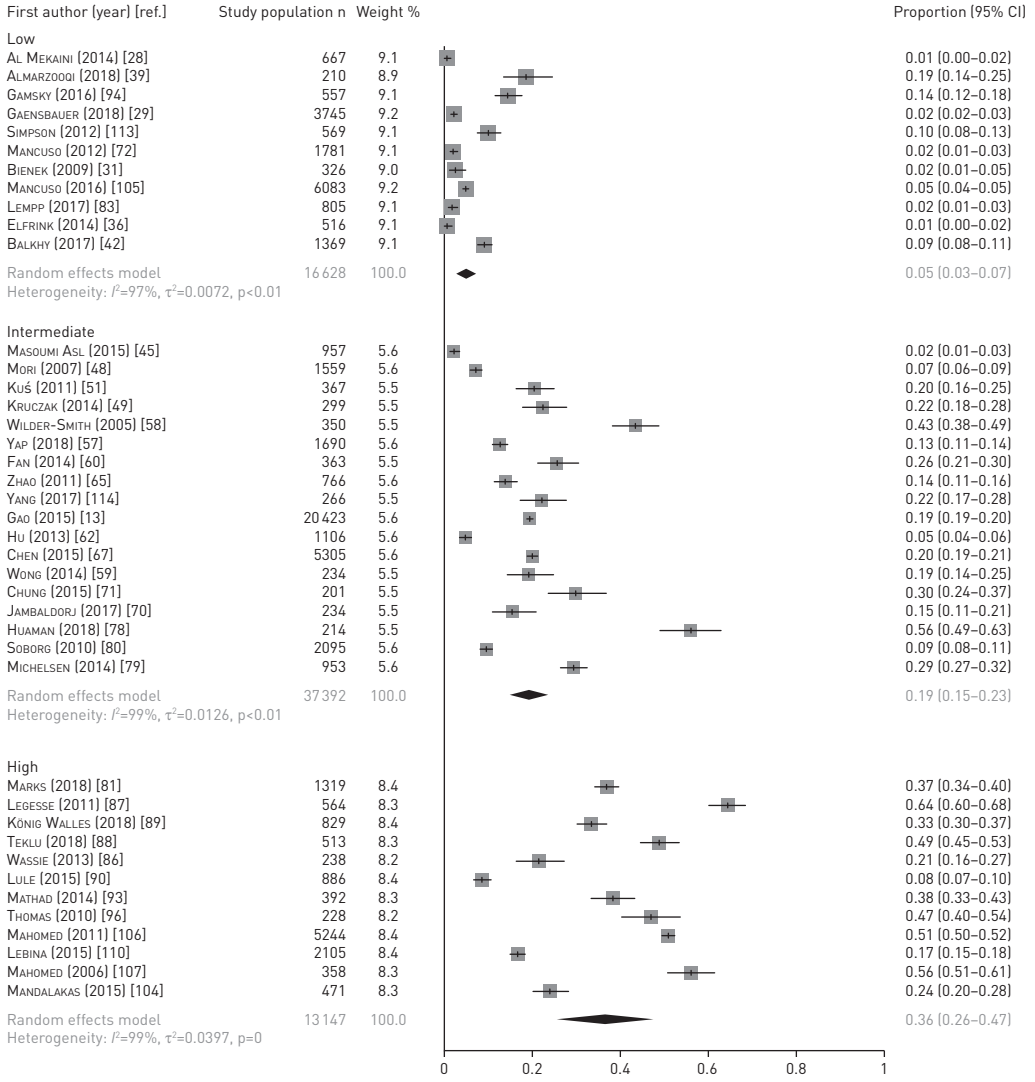

FIGURE 4 Forest plot of interferon-γ release assay (IGRA) data. Prevalence of latent tuberculosis infection by tuberculosis incidence intervals using random effects model. Latent infection based on IGRA with indeterminate excluded.

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; the reductions are in many aspects, although not completely, aligned with the new prevalences modelled by Houben and Dodd [2].

In accordance with the previous WHO estimates from 1999 [1] as well as with the new estimates by Houben and Dodd [2], we found that Southeast Asia is the region with the highest LTBI prevalence. 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 and Dodd [2] 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 1990s. This could partly explain the slower pace in reducing LTBI prevalence in Africa, as is indicated by our estimates. Sub-Saharan Africa in particular is a high-endemic region, and active TB is prioritised 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 with 20.7% (IGRA) and 20.3% (TST) whereas Houben and Dodd [2] 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 Western Pacific region population.

TABLE 2 New and old estimates of latent tuberculosis infection (LTBI) prevalence by World Health Organization (WHO) region

	1999 WHO estimates [1]	2016 Houben and Dodd estimates [2]	New estimates including IGRA data	
	TST[#]	ARI based on TST surveys and WHO TB prevalence data	TST[¶]	IGRA
WHO region				
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)

Data are presented as % or % (95% CI). Global and regional prevalences of LTBI displaying 1999 WHO estimates [1], new modelling estimates from 2016 by Houben and Dodd [2] and our current estimates, including interferon-γ release assay (IGRA) survey data. TST: tuberculin skin test; ARI: annual risk of infection; TB: tuberculosis. [#]: partly based on annual risk of infection and Styblo's rule; [¶]: 10-mm cut-off for TST.

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 *M. tuberculosis* 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. Furthermore, 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^{-1} 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. 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]. Impaired immunity such as HIV may have higher impact on TST results than IGRAs.

Our study has several limitations. First, 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. Second, 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. Third, age was assumed to be 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 material section D, the LTBI prevalence data illustrate a consistent effect of age when comparing populations of younger and older surveyed study participants (*i.e.* South Africa 16–56%, Mexico 12–36.9%, Singapore 12.6–43.4%, Spain 0.9–9.3% and USA 1.5–8%), but that does not necessarily 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. Fourth, 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 undoubtedly diverse, yet an indication that the prevalences should be interpreted with caution. Fifth, 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 and Dodd [2], we found remarkably comparable estimates. 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 surveys, 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, it is estimated that only 6.8% of all those with LTBI are Australian-born [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. Furthermore, models using the Styblo rule will 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. For instance, children 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 aged >15 years. With no golden standard for diagnosing LTBI, and no method available to measure viable *M. tuberculosis* 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 recognised as a considerable obstacle, and as a point of intervention, in reaching the End TB Strategy goals of 2050.

Author contributions: C. Wejse and A. Cohen conceived and designed the study. All data were collected by A. Cohen and V.D. Mathiasen. A. Cohen and V.D. Mathiasen had access to all obtained data and conducted statistical analyses. A. Cohen drafted the first manuscript with contributions from V.D. Mathiasen, T. Schön and C. Wejse. All authors interpreted data as well as contributed with intellectual content to the final manuscript. C. Wejse and T. Schön were study supervisors. All authors agree with the results and conclusions of this article.

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