Latent tuberculosis infection in healthcare workers in low- and middle-income countries: an updated systematic review

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ABSTRACT Healthcare workers (HCWs) are at increased risk of latent tuberculosis (TB) infection (LTBI) and TB disease.

We conducted an updated systematic review of the prevalence and incidence of LTBI in HCWs in low- and middle-income countries (LMICs), associated factors, and infection control practices. We searched MEDLINE, Embase and Web of Science (January 1, 2005–June 20, 2017) for studies published in any language. We obtained pooled estimates using random effects methods and investigated heterogeneity using meta-regression.

85 studies (32 630 subjects) were included from 26 LMICs. Prevalence of a positive tuberculin skin test (TST) was 14–98% (mean 49%); prevalence of a positive interferon-γ release assay (IGRA) was 9–86% (mean 39%). Countries with TB incidence ⩾300 per 100 000 had the highest prevalence (TST: pooled estimate 55%, 95% CI 41–69%; IGRA: pooled estimate 56%, 95% CI 39–73%). Annual incidence estimated from the TST was 1–38% (mean 17%); annual incidence estimated from the IGRA was 10–30% (mean 18%). The prevalence and incidence of a positive test was associated with years of work, work location, TB contact and job category. Only 15 studies reported on infection control measures in healthcare facilities, with limited implementation.

HCWs in LMICs in high TB incidence settings remain at increased risk of acquiring LTBI. There is an urgent need for robust implementation of infection control measures.

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Introduction

Healthcare workers (HCWs), especially in high tuberculosis (TB) incidence countries, are at increased risk of latent TB infection (LTBI) and TB disease due to exposure to TB cases and variable implementation of infection control practices [1–3]. World Health Organization (WHO) guidelines (2009) advise regular screening for TB in HCWs and routine reporting [4]. A systematic review by Joshi *et al.* [1] of 51 studies from low- and middle-income countries (LMICs) published from 1999 to 2005 reported that the prevalence of LTBI (tuberculin skin test (TST) positive) among HCWs ranged from 33% to 79%. Reported independent risk factors for LTBI included working in medical wards, participation in procedures such as sputum collection and autopsy, and a history of TB patient contact. The annual incidence of LTBI ranged from 0.5% to 14.3%. Reported independent risk factors for TST conversion were a higher level of clinical training, nursing occupation and recent exposure to TB [1].

Interferon-γ release assays (IGRAs) have emerged as alternative diagnostic tests for LTBI [5, 6]. They are not subject to sensitisation or boosting [3], but they have much higher rates of largely unexplained test conversions and reversions [3, 7]. Studies reporting the prevalence and incidence of LTBI in HCWs in LMICs conducted since the 2006 review by Joshi *et al.* [1] have used the TST, IGRA or both to diagnose LTBI [8–13]. Although two systematic reviews have been carried out recently, one included only studies using the TST [14] and the other included only studies with a comparison group of non-HCWs [2]. We conducted a comprehensive systematic review of the prevalence and incidence of LTBI in HCWs in LMICs, along with factors associated with LTBI. Including studies that used the TST and/or IGRA, we aimed to describe the prevalence and incidence of LTBI in HCWs in LMICs, and to identify associated risk factors, with a particular emphasis on infection control practices.

Methods

This systematic review was reported according to PRISMA guidelines [15]. The protocol was registered with the PROSPERO register of systematic reviews (identifier CRD42017079494).

Search strategy

We searched the MEDLINE, Embase and Web of Science electronic databases for primary studies in any language. The previous systematic review by Joshi *et al.* [1] was up to December 2005; therefore, our search was limited to the period from January 1, 2005 to June 20, 2017. Since this was an update, we did not wish to include any studies such as those published in 2005 that had been included in the Joshi *et al.* [1] review. If previously included, they were excluded from our review.

Initially, three broad concepts were used to identify the medical subject headings (MeSH) and key words in the databases: “latent tuberculosis”, “healthcare workers” and “occupational exposure”. Several key words were used for “latent tuberculosis” (“latent tuberculosis”, “tuberculin test”, “interferon-gamma release test”, “IGRA”), “healthcare workers” (“healthcare worker”, “health personnel”, “physician”, “medical staff”, “hospital staff”, “nurses”, “community health worker”, “nursing students”, “medical student”) and “occupational exposure” (“occupational exposure”, “infectious disease transmission”, “occupational disease”, “nosocomial exposure”). All key words were searched for in the title, abstract and field key words. Both key words and subjects identified in the databases were used together with “OR”. The key words for the concepts of “healthcare workers” and “occupational exposure” were used together with “OR”, and then these results were combined using “AND” with “latent tuberculosis” to obtain the final result (details of the complete search strategy are provided in supplementary table S1).

In addition, we examined references cited in studies and reviews identified as being potentially relevant. We contacted authors of studies for further information if required.

Study selection

Two reviewers (L.A. and S.M.) independently screened the citations (title and abstract) identified. We obtained full-text versions of all studies identified by either reviewer as being potentially relevant. The two reviewers independently assessed the full texts for inclusion, using pre-specified criteria. Differences were resolved by consensus.

We included studies that reported data on the prevalence or incidence of LTBI in HCWs. Based on the WHO World Health Report 2006, the term “health workers” was defined as “all people engaged in actions whose primary intent is to enhance health” [16]. There are two broad types of HCWs: those that deliver health services, either personal or non-personal, called “health service providers”, and those not engaged in the direct provision of health services, called “health management and support workers” [16]. We included studies that reported any part-time or full-time HCWs. We also included studies that reported data on healthcare students (HCSs), including nursing, medical, paramedical, pharmacy and dental students.

We included cross-sectional TST and IGRA surveys, cohort studies reporting TST and IGRA conversion rates, and retrospective or prospective studies on the incidence of LTBI.

We excluded: 1) case reports or case series of LTBI, 2) studies with 10 or fewer participants, 3) commentaries, 4) editorials and reviews, 5) letters that did not report original data, 6) studies evaluating the TST or IGRA for treatment monitoring in HCWs (*i.e.* not diagnostic purposes), 7) for incidence, short-term serial testing studies (within 1 month), 8) non-commercial/in-house IGRAs, 9) TST or IGRA testing in the context of a known nosocomial outbreak or single-point source exposure or contact tracing following TB diagnosis, 10) conference abstracts, and 11) immunological or diagnostic studies with no prevalence or incidence data.

Included studies were conducted in one or more of the 139 countries classified by the World Bank as LMICs, with gross national income per capita less than USD12 475 for the 2017 fiscal year [17].

Data extraction

The two reviewers independently extracted data from a subset of the studies (20%). The interrater agreement between the two reviewers was high ⩾95%. Any disagreement was settled by consensus. Subsequently, one reviewer (L.A.) extracted data from the full set of included studies. Data extracted onto a Google Form (www.google.com/forms/about) included: author, country, survey year, TB incidence rate, study and participant type, number of participants, healthcare facility, test used, bacille Calmette–Guérin (BCG) vaccination status, prevalence of LTBI (with 95% confidence interval), LTBI incidence (with 95% confidence interval), results of analyses of occupational and non-occupational risk factors, TB infection control measures, demographic data, and other relevant details about HCWs. Definitions for healthcare facility, HCW, LTBI prevalence (defined as test positivity), LTBI incidence (defined as test conversion), including test definitions of IGRA and TST positivity and conversion, and risk factor of exposures are described in the supplementary methods. LTBI prevalence and incidence, or conversion, results were extracted and reported separately for the TST and IGRA, in view of previously published evidence that results of these two tests may be discordant.

Quality assessment

We assessed the quality of studies based on the Cochrane Group guidelines for observational studies [18], according to five criteria: 1) sampling strategy, 2) response rate ⩾80% for a cross-sectional study and retention rate ⩾90% for a cohort study, 3) method of measurement of TB exposure, 4) TST or IGRA performance, and 5) reported results (supplementary table S2). Any disagreement was resolved by consensus.

Data synthesis, meta-analysis and meta-regression

We evaluated the clinical heterogeneity of the studies, in particular with respect to the type of test used, TB incidence in the general population and type of participants included (HCWs or HCSs). We then evaluated the statistical heterogeneity as assessed by the I^2 statistic. Since significant heterogeneity (I^2>75%) was present, we carried out a stratified analysis and a meta-regression. We used random effects methods to obtained pooled estimates and 95% confidence intervals [19]. Forest plots were generated for each subgroup analysis. The meta-regression was performed using logistic regression in a generalised estimating equation framework to allow for correlations between prevalence estimates from the same study [20]. Data were analysed using Stata version 14.2 (StataCorp, College Station, TX, USA).

Results

Description of included studies

A total of 3537 records and four full-text articles from other systematic reviews were screened (figure 1); 168 full-text articles were assessed for eligibility and 83 articles were excluded. 85 studies met the inclusion criteria, representing 32 630 subjects from 26 LMICs [8–13, 21–99] (supplementary table S3). Annual TB incidence rates in countries included ranged from 8 per 100 000 in Cuba [25] to 977 per 100 000 in South Africa [61].

Prevalence of LTBI measured by TST and IGRA

The prevalence of a positive TST was measured in 66 studies [8–13, 21, 22, 24–28, 30, 31, 33–37, 39, 40, 42, 45–56, 58–60, 62–66, 69–71, 73–76, 78–82, 84–86, 88, 89, 91–95, 97] and of a positive IGRA in 36 studies [8–12, 22, 23, 26, 34, 37, 38, 41, 44, 47–49, 52, 55–57, 62, 67, 68, 70, 76, 78, 82, 87, 89–94, 96, 98, 99] (supplementary table S4a and b). The forest plot (figure 2) shows the variability in the estimates of prevalence of a positive TST; estimates ranged from 1% to 98% and there was evidence of heterogeneity (p<0.0005). Based on TST results, the prevalence of LTBI in HCWs ranged from 8% to 98% (mean 49%) and in HCSs ranged from 1% to 74% (mean 32%). The prevalence of a positive IGRA ranged from 9% to

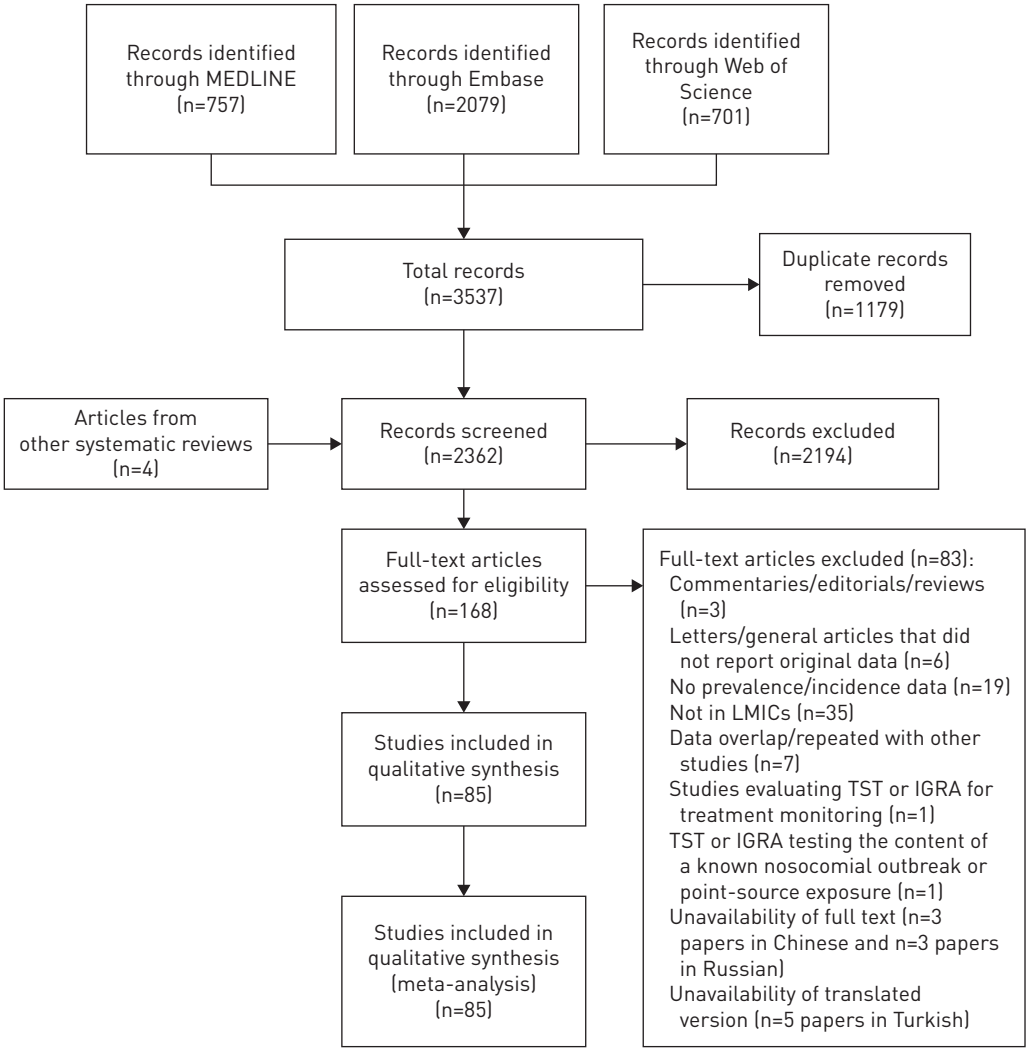

FIGURE 1 Flowchart of literature search. LMICs: low- and middle-income countries; TST: tuberculin skin test; IGRA: interferon-γ release assay.

86% (p-value for heterogeneity=0.01) (figure 3). The prevalence in HCWs ranged from 9% to 86% (mean 39%) and in HCSs ranged from 10% to 44% (mean 24%).

Nurses had the highest prevalence of positive TSTs (pooled estimate 54%, 95% CI 46–61%), followed by physicians (48%, 95% CI 30–65%), allied health professionals (45%, 95% CI 35–55%) and general services (45%, 95% CI 30–60%) (table 1). General services staff had the highest prevalence of positive IGRAs (pooled estimate 60%, 95% CI 54–66%), followed by physicians (35%, 95% CI 22–49%), nurses (34%, 95% CI 22–46%) and allied health professionals (31%, 95% CI 23–40%).

Studies conducted in high TB incidence countries (⩾300 per 100 000 population) had the highest prevalence of positive TSTs (pooled estimate 55%, 95% CI 41–69%) and positive IGRAs (56%, 95% CI 39–73%) (table 1 and supplementary figure S1). After stratification by type of participants and then by TB incidence, studies conducted in countries with the lowest TB incidence had the lowest prevalence of LTBI in all types of HCWs and HCSs as measured by the TST or IGRA (supplementary table S4c).

When stratified by study quality, studies with high quality had the lowest prevalence (TST: pooled estimate 41%, 95% CI 34–49%; IGRA: pooled estimate 30%, 95% CI 19–41%) compared with medium- and low-quality studies (table 1). 26 studies investigated the prevalence of LTBI using both the TST and IGRA [8–12, 22, 26, 34, 37, 47–49, 52, 55, 56, 62, 70, 76, 78, 80, 82, 89, 91–94]: the prevalence of LTBI measured by the TST was higher (pooled estimate 52%, 95% CI 41–62%) compared with the IGRA (38%, 95% CI 38–52%) (supplementary figure S2).

For comparison with the review by Joshi *et al.* [1], we restricted our analysis to studies from five countries (Brazil, India, South Africa, Thailand and Turkey) included in that review (six studies [100–105]) and our

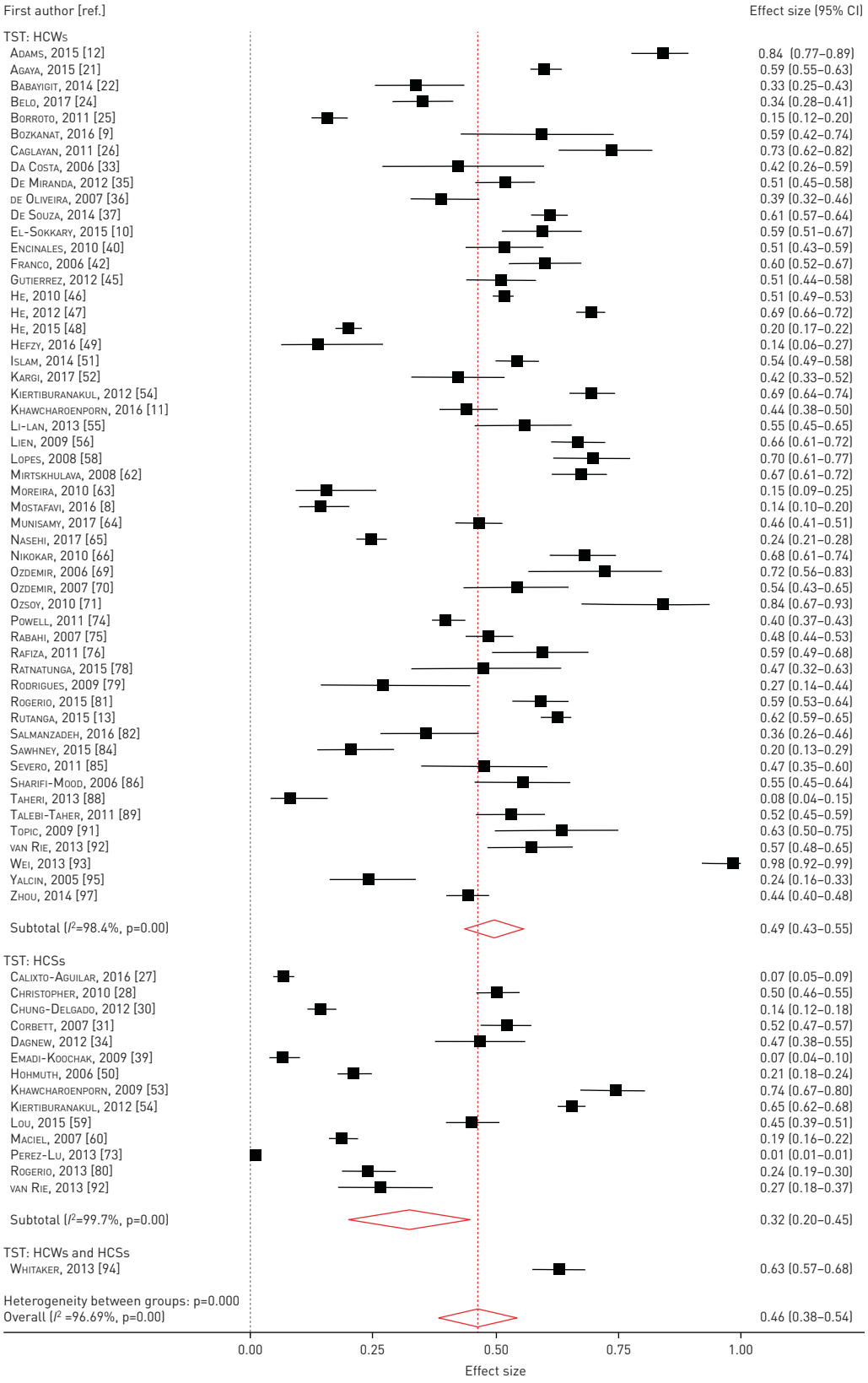

FIGURE 2 Forest plot for the prevalence of latent tuberculosis infection in healthcare workers (HCWs) and healthcare students (HCSs) measured by the tuberculin skin test (TST).

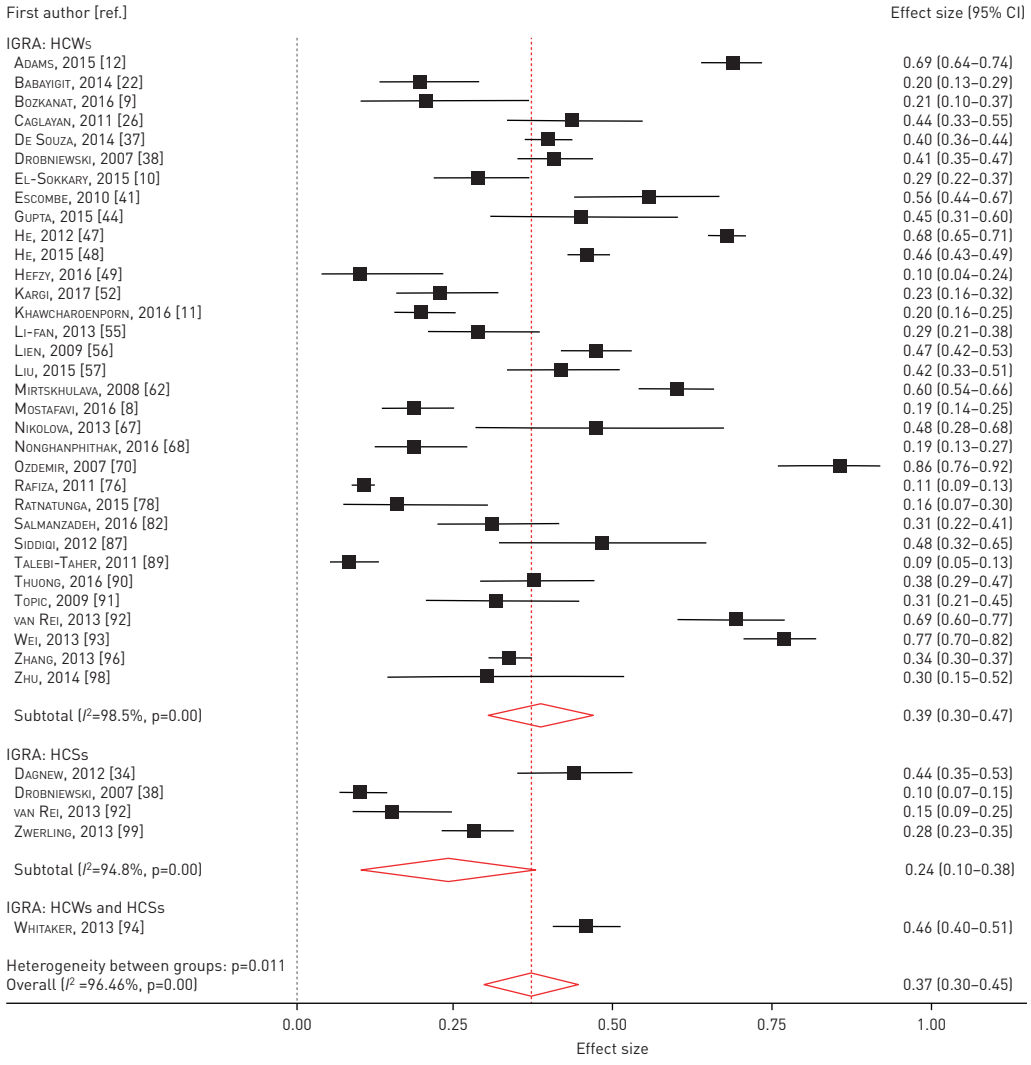

FIGURE 3 Forest plot for the prevalence of latent tuberculosis infection in healthcare workers (HCWs) and healthcare students (HCSs) measured by the interferon-γ release assay (IGRA).

review (23 studies [9, 11, 12, 22, 26, 33, 35–37, 42, 52, 54, 58, 63, 69–71, 75, 79, 81, 84, 92, 95]). The LTBI prevalence measured by the TST in HCWs in our review was slightly lower (pooled estimate 51%, 95% CI 44–58%) than Joshi *et al.*'s [1] estimate (55%, 95% CI 44–65%) (supplementary figure S3). Using the same approach in HCSs, when restricted to four countries (Brazil, India, Iran and Uganda), the prevalence of LTBI was higher in five studies from our review [28, 39, 59, 60, 80] (pooled estimate 29%, 95% CI 13–45%) than seven studies from Joshi *et al.*'s [1] review [103, 106–111] (24%, 95% CI 14–34%) (supplementary figure S4).

We fitted a meta-regression model using all studies, which provided prevalence estimates (75 studies and 164 prevalence estimates). Studies conducted in high annual TB incidence countries (⩾300 and 200–299 per 100 000 population) were statistically significantly associated with LTBI prevalence (OR 8.4, p<0.001 and 2.9, p=0.040, respectively). HCSs had a statistically significantly lower risk of LTBI (OR 0.3, p=0.003) (supplementary table S4d).

Risk factors associated with LTBI prevalence

28 studies reported factors associated with a positive TST [8, 13, 21, 24, 25, 28, 30, 34, 36, 37, 46–48, 52–55, 58, 59, 62, 64, 65, 74, 81, 85, 92, 94, 97] (supplementary table S5). In table 2 we provide a summary of risk factors examined and those found statistically significant and not significant. Estimates are not provided due to the potential bias from selective reporting of statistically significant results. Among HCWs, occupational risk factors of more years of work [13, 21, 37, 46, 47, 58, 62, 97] and work location [46, 64, 81, 97] were statistically significantly associated with LTBI prevalence. In some studies, job category [64, 65] and contact with a TB patient [21, 25] were independent occupational risk factors.

TABLE 1 Prevalence of latent tuberculosis (TB) infection (LTBI) measured by the tuberculin skin test (TST) and interferon-γ release assay (IGRA): differences by study quality

Study description	All studies			High- and medium-quality studies		
	Study data		Prevalence pooled estimate (95% CI) %	Study data		Prevalence pooled estimate (95% CI) %
	Studies n	IQR for prevalence estimate %		Studies n	IQR for prevalence estimate %	
Prevalence of LTBI measured by TST						
Overall	66	28–60	46 (38–54)	38	24–59	44 (37–51)
Stratified by type of participants						
Healthcare workers	53	39–61	49 (43–55)	29	34–59	47 (40–54)
Physicians	11	41–55	48 (30–65)	6	28–55	46 (19–73)
Nurses	20	44–65	54 (46–61)	10	48–64	54 (43–65)
Allied health professionals	23	28–63	45 (35–55)	15	26–61	40 (28–52)
General services[#]	7	40–53	45 (30–60)	5	51–53	45 (28–63)
Healthcare students	14	16–49	32 (20–45)	9	19–50	34 (21–46)
Stratified by TB incidence per 100 000						
0–24	14	14–52	34 (24–44)	5	14–52	32 (19–46)
25–99	31	43–61	51 (43–59)	20	43–61	45 (36–54)
100–199	9	14–63	36 (21–51)	5	14–63	30 (13–46)
200–299	7	46–60	51 (40–62)	4	46–60	56 (45–66)
⩾300	5	45–60	55 (41–69)	4	45–60	57 (41–74)
Stratified by study quality						
High	22	22–57	41 (34–49)	22	22–57	41 (34–49)
Medium	16	32–64	48 (34–61)	16	32–64	48 (34–61)
Low	28	38–64	48 (33–64)			
Prevalence of LTBI measured by IGRA						
Overall	36	22–47	37 (30–45)	12	21–52	40 (26–54)
Healthcare workers	33	20–43	39 (30–47)	12	26–52	41 (26–56)
Physicians	13	21–53	35 (22–49)	6	35–55	47 (33–61)
Nurses	18	22–40	34 (22–46)	7	30–39	36 (18–54)
Allied health professionals	21	17–38	31 (23–40)	9	19–58	34 (17–50)
General services[#]	2	29–59	60 (54–66)	1		74 (66–80)
Healthcare students	4	14–32	24 (10–38)	1		10 (7–15)
Stratified by TB incidence per 100 000						
0–24	7	14–26	20 (13–26)	2	21–26	22 (18–27)
25–99	16	28–46	41 (28–53)	8	24–51	39 (26–54)
100–199	7	29–52	41 (28–50)	1		47 (42–53)
200–299	3	36–44	38 (26–50)	0		
⩾300	3	48–59	56 (39–73)	1		69 (64–74)
Stratified by study quality						
High	8	28–48	30 (19–41)	8	28–48	30 (19–41)
Medium	4	30–53	60 (44–77)	4	30–53	60 (44–77)
Low	24	22–46	36 (28–44)			

[#]: general services included cleaners, drivers and housekeepers.

In HCSs, years spent in healthcare after entry to a clinical programme [28] and contact with a TB patient [59] were independent risk factors. Male sex [21, 47, 54, 74], age [37, 46, 74, 94], BCG scar/history of BCG vaccination [37, 46, 48, 54], education level [65, 81], household contact with TB [47, 81], smoking status [36, 48], chronic disease [64, 65], immunosuppression [24] and diabetes mellitus [64] were independent non-occupational risk factors in HCWs. Similarly in HCSs, male sex [54, 59], BCG scar/history of BCG vaccination [53, 54], older age [34], TB knowledge [34] and course of study [59] were associated with a higher LTBI prevalence.

21 studies reported risk factors associated with higher prevalence of LTBI determined by the IGRA [8, 10, 22, 34, 37, 38, 47, 48, 52, 55, 56, 62, 68, 70, 76, 90, 92–94, 96, 99] (supplementary table S5). In summary (table 2), among HCWs, a positive IGRA was associated with more years of work [10, 22, 37, 47, 48, 62, 68, 96], job category [10, 68, 76, 93, 96], contact with a TB patient [55, 68], type of facility [22, 56], work location [38], contact with a co-worker with TB [47] and average daily time with direct patient contact in the preceding year [47]. No occupational factors were significantly associated with a positive IGRA in HCSs. Non-occupational factors significantly associated with a positive IGRA in HCWs included older age

TABLE 2 Summary of risk factors associated with the prevalence of latent tuberculosis (TB) infection measured by the tuberculin skin test (TST) or interferon-γ release assay (IGRA)

Factors	Occupational			Factors	Non-occupational		
	Studies assessed n	Studies showing statistically significant (p<0.05) association n [refs]	Studies showing no statistically significant association n [refs]		Studies assessed n	Studies showing statistically significant (p<0.05) association n [refs]	Studies showing no statistically significant association n [refs]
Healthcare workers (measured by TST)[#]							
Years of work	16	8 [13, 21, 37, 46, 47, 58, 62, 97]	8 [8, 24, 48, 55, 64, 65, 81, 85]	Male sex	20	4 [21, 47, 54, 74]	16 [8, 13, 24, 25, 36, 37, 46, 48, 52, 62, 64, 65, 81, 85, 92, 97]
Work location	9	4 [46, 64, 81, 97]	5 [13, 21, 37, 74, 85]	Age	18	4 [37, 47, 74, 94]	14 [8, 24, 36, 47, 48, 52, 54, 62, 64, 65, 81, 85, 92, 97]
Job category	13	2 [64, 65]	11 [8, 13, 21, 24, 37, 46, 55, 62, 74, 85, 92]	BCG scar/vaccination	13	4 [37, 46, 48, 54]	9 [8, 24, 25, 47, 52, 62, 81, 85, 97]
Contact with a TB patient	7	2 [21, 25]	5 [8, 24, 55, 62, 65]	Education level	8	2 [65, 81]	6 [8, 46–48, 62, 97]
Type of facility	4	1 [97]	3 [13, 21, 47]	Household contact with TB	5	2 [47, 81]	3 [24, 37, 92]
Ever had co-workers with TB	2	1 [47]	1 [24]	Smoking status	9	2 [36, 48]	7 [24, 37, 46, 47, 65, 85, 97]
Cared for a TB patient in last year	1	1 [47]		Chronic disease	2	2 [64, 65]	
Last professional contact with pulmonary TB patients	1	1 [58]		Immunosuppression	2	1 [24]	1 [81]
Had TB infection control or TB training	3	1 [47]	2 [81, 97]	Diabetes mellitus	1	1 [64]	
Aware of TB infection control guidelines	1	1 [47]					
Healthcare students (measured by TST)[¶]							
Time (years) spent in healthcare work after entry	2	1 [28]	1 [34]	Male sex	6	2 [54, 59]	4 [28, 30, 53, 92]
Contact with a TB patient	3	1 [59]	2 [28, 53]	BCG scar/vaccination	4	2 [53, 54]	2 [28, 34]
				Age	7	1 [34]	6 [28, 30, 53, 54, 59, 92]
				TB knowledge	2	1 [92]	1 [59]
				Course type	1	1 [59]	

Continued

TABLE 2 Continued

Factors	Occupational			Factors	Non-occupational		
	Studies assessed n	Studies showing statistically significant (p<0.05) association n [refs]	Studies showing no statistically significant association n [refs]		Studies assessed n	Studies showing statistically significant (p<0.05) association n [refs]	Studies showing no statistically significant association n [refs]
Healthcare workers (measured by IGRA)[+]							
Years of work	16	8 [10, 22, 37, 47, 48, 62, 68, 96]	8 [8, 38, 52, 55, 56, 70, 76, 93]	Age	15	5 [47, 62, 68, 76, 93]	10 [10, 37, 38, 48, 52, 55, 56, 90, 92, 96]
Job category	13	5 [10, 68, 76, 93, 96]	8 [8, 37, 52, 55, 56, 62, 90, 92]	Male sex	14	4 [37, 48, 52, 76]	10 [10, 38, 47, 55, 56, 62, 68, 90, 92, 96]
Contact with a TB patient	4	2 [55, 68]	2 [8, 62]	Household contact with TB	5	3 [10, 76, 96]	2 [37, 92]
Type of facility	3	2 [22, 56]	1 [47]	BCG scar/vaccination	9	2 [37, 47]	7 [10, 48, 52, 55, 62, 68, 93]
Work location	5	1 [38]	4 [37, 76, 90, 96]	Education level	7	2 [48, 56]	5 [47, 62, 68, 76, 96]
Ever had co-workers with TB	1	1 [47]		Body mass index	4	2 [56, 90]	2 [68, 76]
Average daily time in patient last year	1	1 [47]		Granulysin concentration	1	1 [90]	
				Diabetes mellitus	1	1 [10]	
Healthcare workers (measured by IGRA)[§]							
				Age	2	1 [34]	1 [92]
				Khat consumption[f]	1	1 [34]	

BCG: bacille Calmette–Guérin. Factors assessed in studies that were not found to be significantly significant: [#]: HIV status [13, 21, 92], alcohol consumption [36, 37, 97], income [46, 48, 97], TB knowledge score [92]; [¶]: smoking status [30, 59], alcohol consumption [30, 59], body mass index [30, 34], HIV status [59], education [28], income [28], religion [28], household contact with TB [92]; [+]: cared for a TB patient in last year [47], had TB infection control training [47], mask use [56], smoking status [10, 37, 47, 48], income [48, 76], comorbidity [37, 76], alcohol consumption [37], hepatitis C virus [10], TB knowledge score [92]; [§]: number of days spent working on medical wards [99], religion [34], BCG scar/vaccination [34], body mass index [34], male sex [92], HIV [92], household contact with TB [92], TB knowledge score [92]; [f]: khat (*Catha edulis* is plant grown commonly in the horn of Africa; the leaves of khat are chewed by people for its stimulant action).

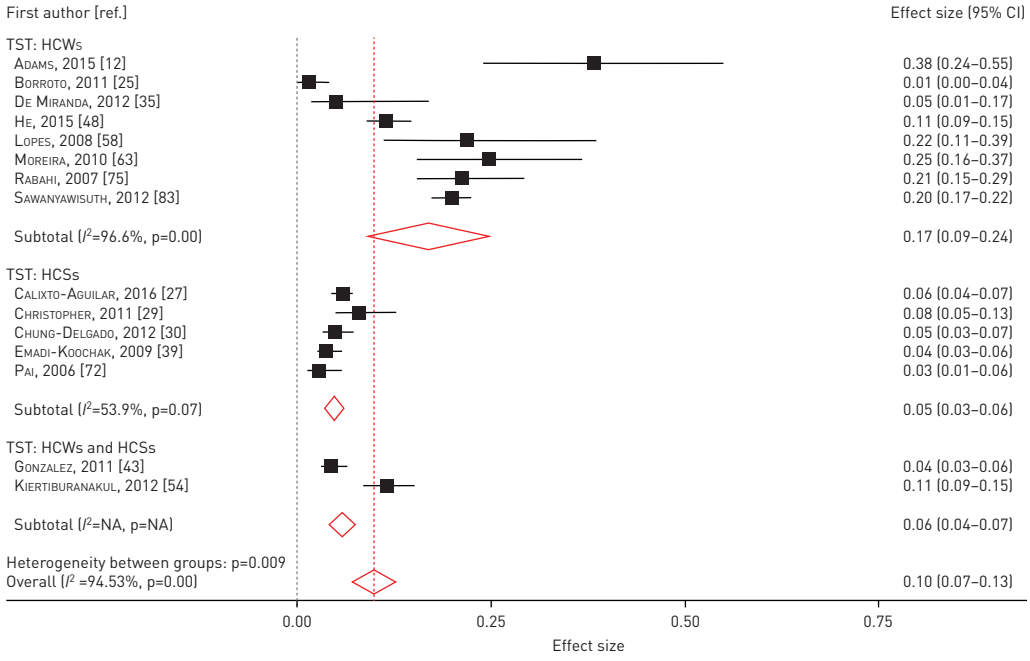

FIGURE 4 Forest plot for the incidence of latent tuberculosis infection in healthcare workers (HCWs) and healthcare students (HCSs) measured by the tuberculin skin test (TST). NA: not applicable.

[47, 62, 68, 76, 93], male sex [37, 48, 52, 76], household contact [10, 76, 96], BCG scar/vaccination [37, 47], level of education [48, 56], body mass index (BMI) [56, 90], granulysin concentration [90] and diabetes mellitus [10]. In HCSs, older age and khat consumption were the only significant non-occupational factors [34]. Factors assessed in studies that were not found to be statistically significant are listed in the footnotes to table 2.

Incidence of LTBI measured by TST and IGRA conversion

The annual LTBI incidence (defined as test conversion after 1 year) was reported in 15 studies using the TST [12, 25, 27, 29, 30, 35, 39, 43, 48, 54, 58, 63, 72, 75, 83] and five studies using the IGRA [12, 41, 48, 72, 77] (supplementary table S6a and b). The forest plot (figure 4) shows the variability in the estimates of incidence of LTBI using the TST; estimates ranged from 1% to 38% with evidence of significant heterogeneity (p<0.009). The incidence of LTBI in HCWs ranged from 1% to 38% (mean 17%) and in HCSs ranged from 3% to 8% (mean 5%). For the IGRA, the overall range in incidence estimates was 8–30% (p-value for heterogeneity=0.016) (figure 5). The incidence in HCWs ranged from 10% to 30% (mean 18%) and in HCSs was 8% (one study).

Among HCWs, in studies that used the TST, allied health personnel had the highest annual LTBI incidence (pooled estimate 15%, 95% CI 3–27%) followed by physicians (9%, 95% CI 0–18%) and nurses (9%, 95% CI 6–12%). In studies that used the IGRA, physicians had the highest annual incidence (pooled

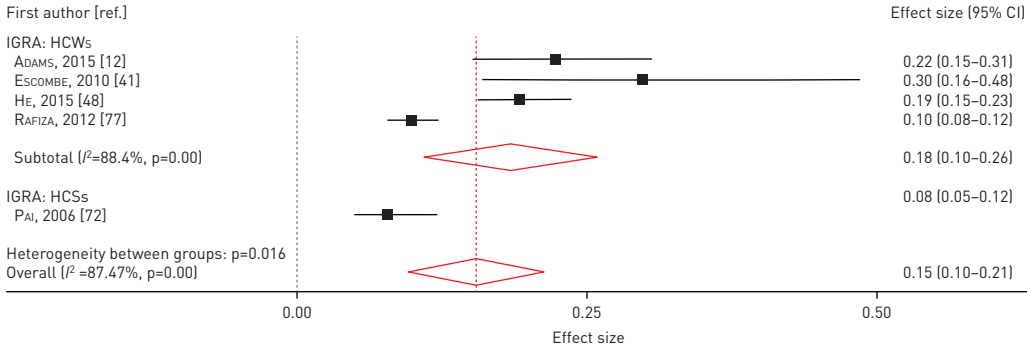

FIGURE 5 Forest plot for the incidence of latent tuberculosis infection in healthcare workers (HCWs) and healthcare students (HCSs) measured by the interferon-γ release assay (IGRA).

estimate 19%, 95% CI 15–23%) followed by nurses (10%, 95% CI 8–13%) and allied health professionals (10%, 95% CI 6–15%) (table 3).

Studies conducted in countries with TB incidence ⩾300 per 100 000 population had the highest annual incidence of LTBI among HCWs as measured by the TST (pooled estimate 38%, 95% CI 24–55%). In studies that used the IGRA, there was no clear trend, likely due to the low number of studies included (n=5) (table 3 and supplementary figure S5).

In two studies using both the TST and IGRA [12, 48], the annual incidence with the TST was lower (pooled estimate 12%, 95% CI 9–15%) than with the IGRA (20%, 95% CI 12–27) (supplementary figure S6). The annual IGRA reversion rate (pooled estimate) was 17% (95% CI 7–26%) in the five studies where it was reported [12, 41, 48, 72, 77] (table 3 and supplementary table S6c).

TABLE 3 Annual incidence of latent tuberculosis (TB) infection (LTBI) measured by the tuberculin skin test (TST) and interferon-γ release assay (IGRA): differences by study quality

Study description	All studies			High- and medium-quality studies		
	Study data		Annual incidence pooled estimate (95% CI) %	Study data		Annual incidence pooled estimate (95% CI) %
	Studies n	IQR for incidence estimate %		Studies n	IQR for incidence estimate %	
Annual incidence of LTBI measured by TST						
Overall	15	4–21	10 (7–13)	11	5–22	10 (7–13)
Stratified by type of participants						
Healthcare workers	8	10–23	17 (9–24)	6	14–24	18 (9–27)
Physicians	3	6–14	9 (0–18)	1		11 (9–15)
Nurses	2	12–24	9 (6–12)	0		
Allied health professionals	3	11–22	15 (3–27)	1		25 (16–37)
General services[#]	0			0		
Healthcare students	5	4–6	5 (3–6)	4	4–6	5 (3–6)
Stratified by TB incidence per 100 000						
0–24	3	3–4	3 (1–5)	1		1 (0–4)
25–99	5	11–22	16 (9–22)	4	19–23	19 (11–26)
100–199	2	5–5	5 (4–6)	2	5–5	5 (4–6)
200–299	4	7–13	10 (2–19)	3	5–10	7 (2–13)
⩾300	1		38 (24–55)	1		38 (24–55)
Stratified by study quality						
High	3	5–15	7 (3–11)	3	5–15	7 (3–11)
Medium	8	7–21	11 (7–16)	8	7–21	11 (7–16)
Low	4	4–9	8 (1–16)			
Annual incidence of LTBI measured by IGRA						
Overall	5	10–22	15 (10–21)	5	10–22	15 (10–21)
Stratified by type of participants						
Healthcare workers	4	10–22	18 (10–26)	4	10–22	18 (10–26)
Physicians	1		19 (15–23)	1		19 (15–23)
Nurses	1		10 (8–13)	1		10 (8–13)
Allied health professionals	1		10 (6–15)	1		10 (6–15)
General services[#]	0			0		
Healthcare students	1		8 (5–12)	1		8 (5–12)
Stratified by TB incidence per 100 000						
0–24	0			0		
25–99	2	12–17	12 (10–14)	2		12 (10–14)
100–199	1		30 (16–48)	1		30 (16–48)
200–299	1		8 (5–12)	1		8 (5–12)
⩾300	1		22 (15–31)	1		22 (15–31)
Stratified by study quality						
High	0			0		
Medium	5	10–22	15 (10–21)	5	10–22	15 (10–21)
Low	0					
IGRA reversion rate (annual)	5	7–21	17 (7–26)	5	7–21	17 (7–26)

[#]: general services included cleaners, drivers and housekeepers.

In studies that used the TST, when stratified by study quality, high-quality studies had the lowest incidence (pooled estimate 7%, 95% CI 3–11%) compared with medium-quality studies (11%, 95% CI 7–16%) and low-quality studies (8%, 95% CI 1–16). In studies that used the IGRA, none were assessed as low quality (table 3).

Risk factors associated with the incidence of LTBI

10 studies reported information on risk factors associated with TST conversion [12, 29–32, 48, 61, 73, 83, 94] (supplementary table S7). In summary (table 4), among HCWs, TST conversion was associated with occupational risk factors including job category [83], contact with TB patient [32], years of work [48] and engaged in counselling a TB patient [12]. In HCSs, days spent caring for pulmonary TB patients [29], involvement in sputum collection [29], ever performed or assisted in sputum collection [29] and career type [73] were independent occupational factors. Non-occupational factors in HCWs included male sex [83]; in HCSs, only older age [73] was associated with TST conversion.

Six cohort studies reported factors associated with IGRA conversion [12, 48, 61, 77, 94, 99] (supplementary table S7). Among HCWs, IGRA conversion was associated with work location [77], engaged in counselling a TB patient [12] and minutes spent on diagnosing one patient [61]. Increasing age was the only non-occupational factor [112]. There were no statistically significant factors found in HCSs studies. Factors assessed in studies that were not found to be statistically significant are listed in the footnotes to table 4.

Infection control measures in healthcare facilities

Of the 85 studies included in this review, only 15 reported on infection control measures in healthcare facilities [13, 28, 32, 35, 41, 42, 46, 50, 54, 58, 61, 74, 78, 99, 113] (summarised in supplementary table S8). None implemented a full programme of TB infection control measures. Nine studies reported inadequate implementation and no clear information was found in six studies. Five of the 15 studies reported a TB infection control policy [13, 28, 32, 46, 113]. One study reported on TB infection control training [32]. Implementation of patient triage and management was reported in six studies [13, 28, 32, 46, 74, 78], sputum management in one study [74], staff protection (personal respiratory protection) in four studies [28, 32, 35, 42] and environmental control in four studies [13, 32, 42, 46, 54, 74]. To assess the infection control measures, one study used the WHO guidelines [74] and one used the Centers for Disease Control and Prevention guidelines [58].

Discussion

In this systematic review we have found a high prevalence and incidence of LTBI in HCWs and HCSs in LMICs measured by the TST or IGRA. Nearly 50% of HCWs and 32% of HCSs were found to have a positive TST, while 39% and almost 25%, respectively, had a positive IGRA. HCWs from countries with an annual TB incidence ⩾300 per 100 000 had the highest prevalence of LTBI, with more than half found to be TST or IGRA positive. The annual incidence of LTBI was 17% in HCWs and 5% in HCSs when estimated from serial TSTs, and 18% and 8%, respectively, when estimated with IGRAs.

Strengths of our study include that we used multiple sources and databases to retrieve relevant studies. Paper selection and data extraction were conducted by two independent reviewers, subgroup analyses were used to accommodate heterogeneity across studies, and results were pooled only when studies were reasonably consistent in their methods. Our study does have some limitations. In the absence of a gold standard for diagnosing LTBI, there is no guarantee that prevalence and incidence estimates of LTBI are accurate. Both the TST and IGRA have several limitations. Due to the complexity of the data, in the final analysis we used the definition of LTBI based on the national guideline where the study was done or the standard definition as per the test manufacturer's recommendation. There was substantial heterogeneity, similar to previously published reviews [1, 14], reflecting the different tests, settings and populations included in the review. Although we stratified the prevalence and incidence estimates, due to the heterogeneity in our results, the pooled averages should be interpreted with caution. Although studies published in non-English languages were eligible, five Turkish papers were not accessible and could not be included in the final analysis [114–118]. We extracted data from their English abstracts and, apart from one study [117], the overall results were similar to those in our review (supplementary table S9). We were not able to conduct meta-analyses of the associations of risk factors with LTBI due to limited data. However, all associations are described in supplementary tables S5 and S7, in which all potential risk factors analysed by the authors in each study are summarised along with details regarding which associations were statistically significant. We did not include non-HCWs or non-HCSs in the analysis. A further limitation was not having general population estimates to compare with. The prevalence of LTBI in HCWs from our review was two times higher than the global LTBI prevalence of 23.0% estimated by Houben and Dodd [119], although the results of their modelling study may have limited comparability to

TABLE 4 Summary of risk factors associated with the incidence of latent tuberculosis (TB) infection measured by the tuberculin skin test (TST) or interferon-γ release assay (IGRA)

Factors	Occupational			Factors	Non-occupational		
	Studies assessed n	Studies showing statistically significant (p<0.05) association n [refs]	Studies showing no statistically significant association n [refs]		Studies assessed n	Studies showing statistically significant (p<0.05) association n [refs]	Studies showing no statistically significant association n [refs]
Healthcare workers (measured by TST)[#]							
Job category	3	1 [83]	2 [12, 32]	Male sex	3	1 [83]	2 [12, 32]
Contact with a TB patient	1	1 [32]					
Years of work	1	1 [48]					
Engaged in counselling a TB patient	1	1 [12]					
Healthcare students (measured by TST)[¶]							
Days spent caring for pulmonary TB patients	1	1 [29]		Age	4	1 [73]	3 [29–31]
Ever performed or assisted in sputum collection	1	1 [29]					
Careers	1	1 [73]					
Healthcare workers (measured by IGRA)[+]							
Work location	1	1 [77]					
Engaged in counselling a TB patient	1	1 [12]					
Minutes spent on diagnosing one patient	1	1 [48]					
Healthcare students (measured by IGRA)[§]							

BCG: bacille Calmette–Guérin. Factors assessed in studies that were not found to be significantly significant: [#]: work location [32], BCG scar/vaccination [12, 32, 48, 83], age [48], education [48], smoking status [12, 48], income [48], diabetes mellitus [12], alcohol consumption [12], HIV status [12]; [¶]: direct contact with sputum-positive TB [113], days spent working on isolation ward [113], days spent working on pulmonary ward [113], TB contact history [73], male sex [30, 31, 73], BCG scar/vaccination [31, 113], education [113], smoking status [30], income [113], alcohol consumption [30], HIV status [31], household contact with TB [31], type of students [31], body mass index [73]; [+]: years of work [48, 77], job category [12, 77], male sex [48, 77], age [48, 77], smoking status [12, 48], education [48], BCG scar/vaccination [48], income [48], diabetes mellitus [12], alcohol consumption [12], HIV status [12]; [§]: occupational exposures [99].

the results of direct testing in the studies included in this review. Uden *et al.* [2] found that HCWs and HCSs had more than two times the risk of LTBI than the general population, consistent with previous reports [1, 3]. Finally, estimating the prevalence and incidence of TB disease was beyond the scope of this review.

This review adds to the evidence that regardless of whether measured by the TST or IGRA, the prevalence of LTBI in HCWs in LMICs continues to be high, especially in high TB incidence countries. This is in keeping with previously published reports that have shown approximately half of HCWs were positive by the TST [1, 14]. When measured by the IGRA, our overall LTBI prevalence estimate was lower than that measured by the TST, but still high, and consistent with a previously published review in countries with a low and intermediate incidence of TB [3].

Similarly, our review showed that the overall incidence of LTBI in HCWs continues to be high in LMICs. The annual incidence, however, was higher when estimated using the IGRA compared with the TST, which is similar to a previous review [3]. We also found a high rate of IGRA reversion, consistent with previously published reviews in all countries, irrespective of the national TB incidence rates [3, 7]. The exact cause of the substantial rate of IGRA reversion is unexplained [3, 7] and raises concerns about the validity of serial IGRA to estimate new infections. Because of this, the WHO has discouraged the use of the IGRA for serial testing in HCWs in LMICs [112].

For HCSs, the prevalence and incidence of LTBI was lower than that seen in HCWs, and this was observed in studies that used the TST and/or IGRA. This is most likely due to their shorter exposure time compared with other HCWs. They do, however, require attention, similar to that needed for other HCWs, as their risk of LTBI is higher compared with the general population [2], as was shown in a Brazilian study in medical and nursing students where the risk of LTBI was more than three times greater than the general population [60].

Across all studies included in our systematic review, occupational factors found to be significantly associated with LTBI in HCWs and HCSs were those that involved more direct contact with a TB patient or prolonged exposure. This is similar to that reported in previous reviews [1, 14, 120]. Hence, these risk factors, along with the continuing high prevalence and incidence of LTBI in HCWs, are an indication that more needs to be done to ensure these workers and students receive the protection they require. The WHO released guidelines on TB infection control in healthcare settings in 2009 [4], yet in our review only 15 studies reported any TB infection control measures (the inadequacy of which was also reported by Joshi *et al.* [1] and Nasreen *et al.* [14]). In resource-limited countries, budget constraints may be cited as a reason for limited infection control measures. However, the basic control measures recommended in the 2009 WHO guidelines of early identification, isolation and treatment of those with presumptive TB, as well as open-window/door policies, education and training of HCWs, are all low-cost and effective measures that should be feasible in all settings, and provide important protection for these seemingly forgotten workers. Other measures, *e.g.* infrastructure modification to ensure appropriate natural ventilation/airflow and provision of personal protective measures, are more costly, but may also contribute towards a reduction of TB infection in HCWs. Moreover, it will be important to measure the effectiveness of implementation of infection control measures through monitoring and routine reporting of the number of HCWs who develop TB disease and infection each year in healthcare facilities.

In conclusion, HCWs in LMICs, especially in high TB incidence settings, continue to have an unacceptably high prevalence and incidence of TB infection. In resource-limited settings, basic control measures as recommended by the WHO, which are low cost and effective, are rarely implemented. TB programmes in high TB incidence countries must prioritise implementation of infection control measures in healthcare facilities to ensure protection for this highly vulnerable and essential group of HCWs.

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