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MAJOR ARTICLE

Risk of Tuberculosis Infection and Disease for Health Care Workers: An Updated Meta-Analysis

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Background. Tuberculosis (TB) remains a major challenge to global health. Healthcare workers (HCWs) appear to be at increased risk of TB compared with the general population, despite efforts to scale up infection control and reduce nosocomial TB transmission. This review aims to provide an updated estimate of the occupational risk of latent TB infection (LTBI) and active TB among HCWs compared with the general population.

Methods. A systematic review was performed to identify studies published over the last 10 years reporting TB prevalence or incidence among HCWs and a control group. Pooled effect estimates were calculated to determine the risk of infection.

Results. Twenty-one studies met the inclusion criteria, providing data on 30 961 HCWs across 16 countries. Prevalence of LTBI among HCWs was 37%, and mean incidence rate of active TB was 97/100 000 per year. Compared with the general population, the risk of LTBI was greater for HCWs (odds ratio [OR], 2.27; 95% confidence interval [CI], 1.61–3.20), and the incidence rate ratio for active TB was 2.94 (95% CI, 1.67–5.19). Comparing tuberculin skin test and interferon-gamma release assay, OR for LTBI was found to be 1.72 and 5.61, respectively.

Conclusions. The overall risk of both LTBI and TB to HCWs continues to be significantly higher than that of the general population, consistent with previous findings. This study highlights the continuing need for improvements in infection control and HCW screening programs.

Keywords. healthcare workers; incidence; occupational risk; prevalence; tuberculosis.

According to the World Health Organization (WHO), there were 10.4 million new cases of tuberculosis (TB) in 2015 and 1.4 million deaths [1], representing a significant challenge to global health. India, Indonesia, China, Nigeria, Pakistan, and South Africa accounted for 60% of incident cases, suggesting that further reduction in TB cases is likely dependent on improved prevention and care in these countries to reduce the considerable gap between number of incident cases and those that are identified and treated appropriately [1].

To combat the epidemic, the WHO introduced their "END TB" Strategy in 2015, which aims to reduce TB incidence by 95% by 2030 [2], and infection control was included as a key component of this strategy. This is particularly important for healthcare workers (HCWs) who, through nosocomial transmission, are likely to have increased exposure to TB and therefore are at greater risk of contributing to TB transmission.

Healthcare workers are known to be at high risk of latent TB infection (LTBI) and active TB disease through occupational exposure to patients with active TB [3], and pathogen sequencing is now able to track transmission in healthcare settings [4, 5]. Although this has been explored in previous reviews, there is a need to update estimates in light of changing TB prevalence and infection control policies. Previous reviews have covered large periods of time [6–8], and since then TB treatment and control has greatly improved. This outcome is likely to have had a significant impact on their results. Our study aims to review the current TB risk to HCWs, which is particularly pertinent because it occurs at the beginning of the Sustainable Development Goals and the WHO's END TB strategy. The primary aims of this review and meta-analysis are to (1) provide an updated estimate of the occupational risk of LTBI and active TB to HCWs compared with the general population and (2) to compare the incidence or prevalence between the 2 groups.

METHODS

This meta-analysis was reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9].

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Search Strategy

Electronic searches were performed using Ovid in MEDLINE, Embase, and Global Health up to March 23, 2016. Studies published before January 1, 2006 were excluded due to their comprehensive coverage in earlier reviews and because our focus was on more recent estimates. The search strategy is described in detail in Supplementary Appendix.

Healthcare workers were first defined broadly according to the WHO definition of "people engaged in the promotion, protection or improvement of the health of the population" [10] and then more specifically as those used in healthcare and in direct contact with patients. Control groups included (1) administrative HCWs who were not in direct contact with patients as well as (2) comparable groups of non-HCWs. Studies that used national data to calculate population prevalence or incidence were included as long as the method of calculation was clear and the comparison was appropriate. Studies that used reference data for the general population were excluded if their estimates were taken from other studies and it was not clear how this had been calculated, meaning the comparison could not be guaranteed to be appropriate.

Observational studies included cohort and case-control studies, including cross-sectional studies. Conference abstracts were excluded due to an inability to extract the relevant data and to assess methodological quality. Reviews and case reports were excluded.

Comorbidities such as human immunodeficiency virus (HIV), chronic kidney disease, and diabetes were excluded if the primary aim of the study was to compare TB in these groups to populations without comorbidity, because of the well known increased risk of infection in these populations [11–13]. However, if populations of HCWs and non-HCWs were later found to include these groups, they were not excluded from the analysis. The initial screen had no language limitations, but the final full-text screen only included studies published in English. No geographic limitations were applied.

Attempts were made to include studies looking at both incidence and prevalence of both LTBI and active TB disease. After we screened the initial papers, it became apparent that those using incidence had focused on active TB disease, whereas those using prevalence focused on LTBI, and so these were analyzed separately to produce a more reliable comparison. This means that, throughout this paper, references to prevalence refer to LTBI, whereas incidence refers to active disease. Prevalence of LTBI was either stated in papers as a primary outcome or an assumption was made by using tuberculin skin test (TST) or interferon-gamma release assay (IGRA) (mainly TST >10 mm or 5 mm in those who were HIV positive). Studies that used TB notification rates were assumed to be referring to incidence rates (IRs) of active TB; however, a lack of a clear positive definition was highlighted in the score the paper received in the quality assessment. If both TST and IGRA were used in a paper, TST was used to analyze prevalence because this was the more commonly used test and therefore allowed investigators to obtain a more reliable comparison.

The following information was extracted from all studies according to a predetermined data extraction form: title, date of publication, author, country of study, language of study, funding source, study design, length of study, diagnostic method, type of HCW, type of control group, and whether the study assessed incidence of active TB or prevalence of LTBI.

For studies investigating prevalence of LTBI, the number of HCWs and controls and the number of cases (positive TST or IGRA) in both HCWs and controls were recorded. If studies implemented multiple testing methods, then only the initial results were used because later screening may have biased results due to increased awareness of occupational TB risk.

For studies investigating incidence of active disease, the number of cases (diagnosis of TB by various methods) and person-years (py) among HCWs were recorded, if available. If only cases and IR were given, these were used to calculate the py of the study, and if the IR for multiple years had been recorded for different years of the study, the mean of these was calculated. For the control groups only, IR per 100 000 per annum was available for all studies; therefore, this denominator was used for all control groups.

Quality Assessment

Methodological quality of studies was assessed using items of the STROBE checklist [14], and, using this approach, studies were ranked into high (>55), medium (≤55), and low (≤45) quality. Although all studies were included in the original meta-analysis, subgroup analysis was later done excluding low-quality studies.

Statistical Methods

Meta-Analysis

From the data extracted from each study, using total number of cases among HCWs and total number of HCW participants, a pooled prevalence estimate of LTBI among HCWs was calculated. The Mantel-Haenszel (MH) method for dichotomous outcomes was then used to calculate odds ratios (ORs). For studies investigating incidence of active TB, the MH method was used to calculate IR ratios (IRRs). Ninety-five percent confidence intervals (CIs) were generated for all estimates. If a study included data for both incidence of active TB and prevalence of LTBI, it was included in both meta-analyses. All meta-analyses were conducted using random-effects models.

To investigate possible causes of heterogeneity, subgroup analysis was performed. First, low-quality studies were excluded. Then, from the remaining studies, analyses were performed by TB burden and TB/HIV coinfection burden according to WHO-defined groups [15], method of diagnosis, and income group according to World Bank definitions [16].

An additional subgroup analysis was then performed, which included only the incidence studies that either reported py for the control groups or reported incidence for which py could be calculated. All analyses were carried out using R.

RESULTS

Study Characteristics

From an initial screen of 2152 publications, 21 met the inclusion criteria and were included in the meta-analysis (Figure 1). Twelve studies investigated prevalence of LTBI among HCWs (9 cross-sectional studies, 3 cohort studies), 8 investigated incidence of active TB (7 cohort studies and 1 cross-sectional study), and 1 cohort study compared both. Only 1 study included a matched control group [17], whereas the others were unmatched. A total of 8 studies were included from Asia, 5 from Africa, 5 from Europe, and 3 from South America. Four studies investigated HCWs with high exposure to TB, whereas the remainder looked at HCWs in general. The control groups included school workers, nonmedical students, administrative employees, and reference data for the general population. Study characteristics are summarized in Tables 1 and 2.

Quality Assessment and Within Study Bias

Most papers had clear inclusion criteria for HCWs and control groups, thereby reducing selection bias; however, the objectivity of diagnostic methods used varied between studies, with some having clear definitions of a positive result. Nonetheless, others failed to define which exact method was used to determine a positive result. Withdrawal rates also varied between studies and did introduce an element of attrition bias to some reports.

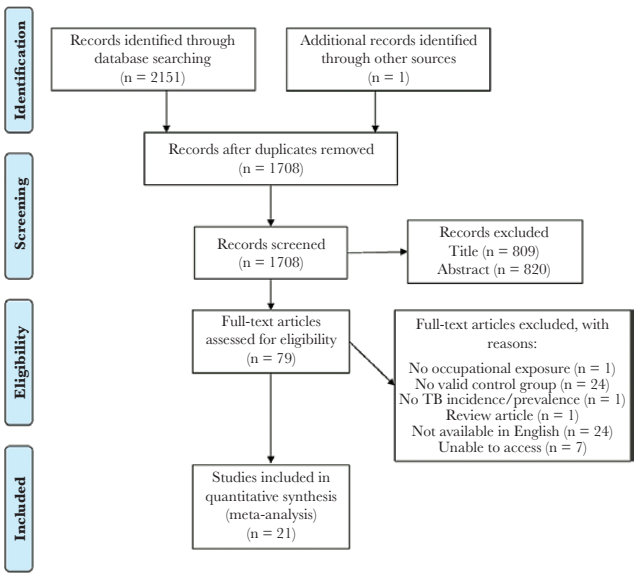

Figure 1. Flow diagram illustrating literature search and study selection. Abbreviation: TB, tuberculosis.

There was considerable heterogeneity between studies, and many studies included small sample sizes, as demonstrated by the wide and overlapping CIs generated. Therefore, a funnel plot to assess publication bias was deemed to be unreliable.

Prevalence of Latent Tuberculosis Infection

The pooled prevalence estimate for LTBI among HCWs was 37% (95% CI, 28%–47%), with 6 studies reporting prevalence of more than 50%, although estimates ranged from 0.5% to 62%. The lowest prevalence rates were seen in 2 of the 3 studies that compared medical or nursing students to the general population. Of the 3 studies comparing HCWs with an especially high likelihood of TB exposure, the prevalence was towards the higher end of the range, except for the 1 study that was carried out in a high-income country (HIC). The OR for LTBI in HCWs was 2.27 (95% CI, 1.61–3.20) (Figure 2), compared with the general population.

Subgroup analyses were carried out, which were restricted to high- and medium-quality studies. When the analysis was restricted to high-burden countries (HBCs), the OR for LTBI was 2.23 (95% CI, 1.37–3.62), compared with 1.74 (95% CI, 0.46–6.54) for countries without a high TB burden. The risk of LTBI was higher in countries with a high TB/HIV coinfection burden (OR, 2.25; 95% CI, 1.48–3.43), compared with countries without a high TB/HIV coinfection burden (OR, 1.18; 95% CI, 0.05–28.9).

The risk of TB infection was lower in studies that used TST (OR, 1.72; 95% CI, 1.17–2.52) compared with studies that used IGRA (OR, 5.61; 95% CI, 3.19–9.89). This difference was explored by comparing the prevalence estimates in both the HCW and control groups. The TST gave a pooled prevalence estimate of 37% (95% CI, 27%–49%) for HCWs and 24% (95% CI, 17%–35%) for the control groups, whereas IGRA gave results of 28% (95% CI, 10%–57%) and 8% (95% CI, 4.4%–15%), respectively, suggesting that the difference in OR arises mainly from a reduced number of cases among the control groups rather than among HCWs.

Incidence of Active Tuberculosis

The pooled estimate for incidence of active TB among HCWs was 97/100 000 py (range, 42 to 4393/100 0000 py), whereas the IRR for active TB among HCWs compared with the general population was 2.94 (95% CI, 1.67–5.19) (Figure 3). When low-quality studies were excluded, the IRR was 1.99 (95% CI, 1.47–2.69). Restricting the analysis to low- and middle-income countries (LMICs) gave an IRR of 2.09 (CI, 1.39–3.14), compared with 1.66 (95% CI, 1.13–2.45) in non-LMICs. In HBCs, IRR was 2.44 (95% CI, 1.67–3.54), compared with 1.50 (95% CI, 1.10–2.04) in non-HBCs. Finally, in countries with a high burden of TB/HIV coinfection, IRR was 2.44 (95% CI, 1.69–3.54); in those without a high burden of TB/HIV coinfection, IRR was 1.50 (95% CI, 1.10–2.04).

Table 1. Characteristics of Included Studies Reporting Prevalence

Author	Country	WHO HBC	High TB/ HIV Burden	Income Group	Study Design	Study Size	HCWs	No. of HCWs	Controls	No. of Controls	Method of Dx	No. of Cases/ HCW	Prevalence among HCWs (%)	Odds Ratio	Study Quality
Agaya et al [18]	Kenya	Yes	Yes	Lower-Middle	Cross-sectional	1230	G	898	SW	332	TST	534	59.5	1.58 (1.22; 2.03)	HIGH(56)
Corbett et al [3]	Zimbabwe	Yes	Yes	Low	Cohort	785	S	342	NS	443	TST	183	54.0	0.90 (0.68; 1.20)	HIGH(57)
Drobniewski et al [19]	Russia	Yes	Yes	High	Cross-sectional	392	G	262	NS	130	IGRA	107	40.8	10.53 (4.94; 22.43)	HIGH(57)
Durando et al [20]	Italy	No	No	High	Cross-sectional	721	S	585	NS	136	TST	3	0.5	0.23 (0.05; 1.14)	MEDIUM(52)
Franco and Zanetta [21]	Brazil	Yes	Yes	Upper-Middle	Cross-sectional	333	H	169	A	164	TST	101	59.8	1.28 (0.83; 1.98)	MEDIUM(54)
Maciel et al [22]	Brazil	Yes	Yes	Upper-Middle	Cohort	837	S	619	NS	218	TST	114	18.4	3.88 (2.09; 7.18)	LOW(43)
Sawhney et al [23]	India	Yes	Yes	Lower-Middle	Cohort	200	G	100	A	100	TST	20	20.0	2.53 (1.09; 5.87)	LOW(41)
Nikokar et al [24]	Iran	No	No	Upper-Middle	Cross-sectional	366	G	185	SW	181	TST	113	61.1	2.03 (1.34; 3.070)	LOW(35)
Powell et al [25]	Vietnam	Yes	Yes	Lower-Middle	Cross-sectional	1111	G	956	SW	155	TST	380	39.7	1.90 (1.29; 2.78)	HIGH(58)
Rutanga et al [26]	Rwanda	No	Yes	Low	Cross-sectional	1371	G	1023	SW	348	TST	635	62.1	2.58 (2.01; 3.32)	HIGH(59)
Storla et al [27]	Norway	No	No	High	Cohort	203	H	155	A	48	TST	42	27.1	5.58 (1.64; 18.91)	MEDIUM(46)
Zhu et al [28]	China	Yes	Yes	Upper-Middle	Cross-sectional	105	G	20	R	85	IGRA	6	30.0	4.78 (1.40: 16.34)	MEDIUM(54)
van Rie et al [29]	South Africa	Yes	Yes	Upper-Middle	Cross-sectional	199	H	120	NS	79	TST	68	56.7	3.61 (1.95; 6.69)	MEDIUM(54)

Abbreviations: A, administrative employee; Dx, diagnosis; G, general healthcare workers; H, healthcare workers working specifically with TB; HBC, high-burden country; HCWs, healthcare workers; HIV, human immunodeficiency virus; IGRA, interferon-gamma release assay; NS, nonclinical students; R, reference data for wider population; S, medical or nursing students; SW, school workers; TB, tuberculosis; TST, tuberculin skin test; WHO, World Health Organization.

Table 2. Characteristics of Included Studies Reporting Incidence

Author	Country	WHO HBC	High TB/HIV Burden	Income Group	Study Design	HCWs	Person-Years/ HCWs	Controls	Method of Dx	No. of Cases/ HCW	Incidence Among HCWs/100 000 per Annum	IRR	Study Quality
Chen et al [30]	China	Yes	Yes	Upper-Middle	Cohort	G	181 724	R	N	142	78.3	1.91 (1.35; 2.70)	MEDIUM(48)
Chu et al [17]	Taiwan	No	No	High	Cohort	G	101 505	R	Rx	62	61.08	1.65 (1.10; 2.48)	HIGH(56)
Claassens et al [31]	South Africa	Yes	Yes	Upper-Middle	Cohort	HR	250	R	Rx	11	4393	2.35 (1.30; 4.24)	MEDIUM(52)
Corbett et al [3]	Zimbabwe	Yes	Yes	Low	Cohort	S	155	NS	T	30	19 300	3.23 (2.25; 4.62)	HIGH(57)
Klimuk et al [32]	Belarus	No	No	Upper-Middle	Cohort	H	5445	R	N	23	426	9.82 (5.92; 16.30)	LOW(39)
Pan et al [33]	Taiwan	No	No	High	Cohort	G	4980	R	C	3	63.1	1.83 (0.56; 5.95)	MEDIUM(54)
Pazin-Filho et al [34]	Brazil	Yes	Yes	Upper-Middle	Cohort	G	4520	R	C	5	110.6	2.63 (1.04; 6.66)	LOW (24)
Skodric-Trifuno et al [35]	Serbia	No	No	Upper-Middle	Cohort	G	57 279	R	C	24	41.9	1.23 (0.73; 2.08)	MEDIUM(49)
Sotgiu et al [36]	Romania	No	No	Upper-Middle	Cross-sectional	G	5303	R	C	50	942.8	9.72 (6.91; 13.67)	LOW(42)

Abbreviations: C, culture positive; Dx, diagnosis; G, general healthcare workers; H, healthcare workers working specifically with TB; HBC, high-burden country; HCWs, healthcare workers; HIV, human immunodeficiency virus; HR, healthcare researchers; IRR, incidence rate ratio; N, not given; NS, nonclinical students; R, reference data for wider population; Rx, recorded treatment; S, medical or nursing students; TB, tuberculosis; WHO, World Health Organization.

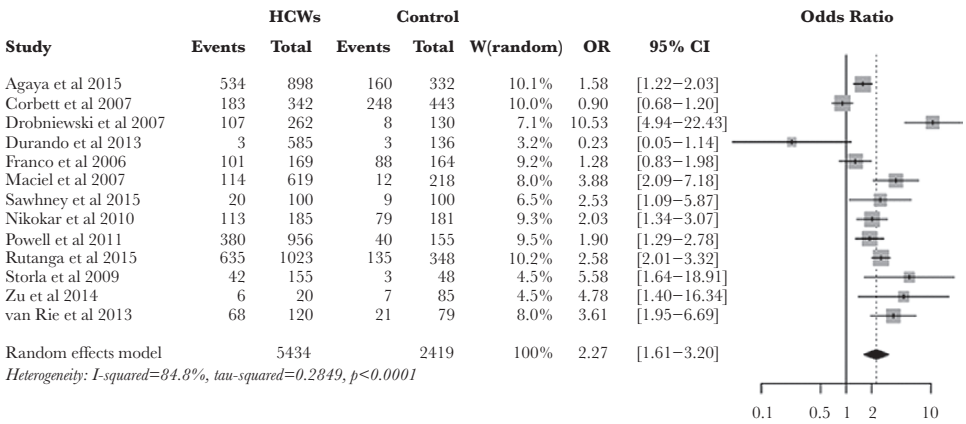

Figure 2. Forest plot showing pooled odds ratio (OR) for latent tuberculosis infection among healthcare workers (HCWs). Abbreviation: CI, confidence interval.

DISCUSSION

This study provides an update to previous work [6–8] and is the first meta-analysis to restrict analyses to studies that included control groups. This allows direct comparison of HCWs with the local population, providing a more reliable estimate of their relative risk for LTBI and active TB. The pooled prevalence estimate for LTBI in HCWs was 37% in our study, and the risk of LTBI among HCWs is more than twice that of control populations. The prevalence findings are lower than previously published reports [7, 8], and our risk to HCWs of LTBI compared with the general population is of a similar magnitude to previous findings [7, 37]. For example, a review published in 2007 found that HCWs had a 2–3 times increased morbidity risk when matched for employment and socioeconomic status [8], and the studies in our analysis that compared HCWs and school workers found the risk to HCWs to be approximately double. Our findings are consistent with previous studies, but we found a reduced overall prevalence of LTBI in HCWs, which is consistent with a decrease among the general population, as found in the most recent WHO TB report [1]. We unexpectedly found that the risk decreased when the analysis was restricted to LMICs, possibly due to the small number of studies included in our meta-analysis, which may not give a comprehensive view of risk in LMICs. A 2008 review found a lower risk in HICs; the annual incidence of TB infection attributable to working in healthcare was 1.1% in HICs compared with 5.8% in LMICs [8]. The considerable heterogeneity in our analysis, although a limitation, may also may highlight the large variation in LTBI risk to HCWs.

HCWs were found to have an approximately 3 times greater risk of active TB compared with the general population, although there was substantial variability between studies. The findings illustrate how TB estimates may vary considerably within and between countries: for example, 2 studies in China and Taiwan showed IRs of active TB to be 78.3% and 61.1%, respectively [17, 30]. In addition, while looking at the prevalence of LTBI, 2 studies in Brazil showed very different prevalence estimates of 18.4% and 59.8% [21, 22]. These findings suggest that adaptation of national infection control policies may be required at the regional level.

Among the studies investigating prevalence of LTBI, a significant reduction in heterogeneity was only observed when the analysis was restricted to studies using IGRA. This increased the estimated risk to HCWs, as a result of a reduction in cases among the control group. Although this finding suggests that IGRA is a more specific and discriminatory tool

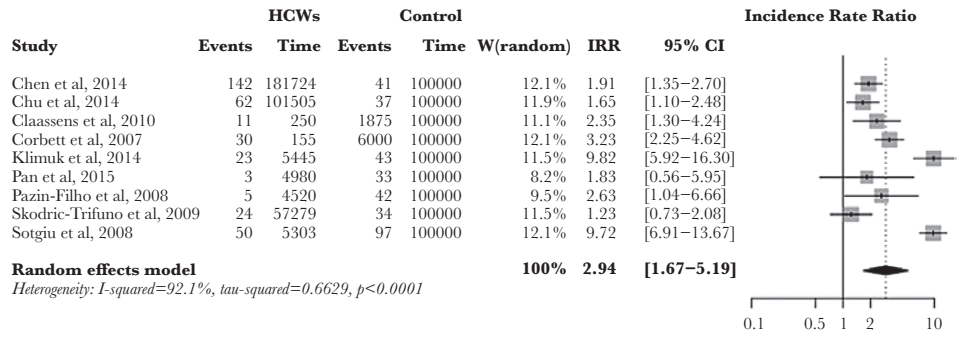

Figure 3. Forest plot showing pooled incidence rate ratio (IRR) for active tuberculosis among healthcare workers (HCWs). Abbreviation: CI, confidence interval.

among the general population, there appear to be limitations for its use in screening HCWs. A recent study found that the rate of positive results among HCWs in a low-burden setting was greatly increased when screening was switched from TST to IGRA, and subsequent follow-up using IGRA produced a significant reversion rate in those who had originally tested positive [38]. This demonstrates the low reproducibility of IGRA among HCWs, which has been corroborated in other settings with a low TB burden [39]. Therefore, our finding that IGRA appeared to be more discriminatory in areas of a high TB burden cannot be applied to all settings, highlighting that further research is needed to determine TB screening in specific populations.

There are a number of limitations to note. First, there was substantial heterogeneity, reflecting the different settings and populations included in the review. Second, there appears to have been an element of publication bias with a paucity of small studies showing negative results, possibly leading to an overestimation of the TB risk to HCWs. The low number of studies and significant heterogeneity between them reflects the limited evidence base and highlights the need for high-quality, comparative studies. Few studies recorded information on important confounders such as Bacillus Calmette-Guérin vaccination status, magnitude of TB exposure, and extent of infection control policies. Finally, including only English-language studies may have resulted in a language bias in our search; nevertheless, studies included here cover all continents where TB is a significant, occupational concern.

CONCLUSIONS

In conclusion, the most recent data show that HCWs globally remain at increased risk of both latent and active TB compared with the general population, despite an absolute decrease in TB prevalence. These findings should encourage even greater attention to prevention measures and screening for HCWs in all settings as part of efforts to achieve the WHO targets for 2030 [23].

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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