Review Article

A systematic review and meta-analysis of Latent tuberculosis infection in Health care workers in Iran

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Abstract

Background: Health care workers (HCWs) are more likely to get latent tuberculosis infection (LTBI) because of the direct contact they may have with patients and carriers. Therefore, this study aimed to assess the prevalence of LTBI in HCWs.

Materials and Methods: In the present study, we searched from 1st 2010 to the end of 2021 in various databases such as; PubMed, Scopus, Web of sciences, and Google Scholar for studies presented LTBI in HCWS. After applying inclusion and exclusion criteria and quality assessment, obtained data were analyzed by Comprehensive Meta-analysis (CMV) software.

Results: In total, 22 studies met the eligibility criteria to include in the present systematic review and meta-analysis. The combined prevalence of LTBI was reported by 25.9% (95% CI: 19.3-33.7). No publication bias was seen among studies included based on Eger's regression test (p=0.04).

Conclusion: Our study showed a high prevalence of LTBI in HCWs. Therefore, periodical screening of HCWs with Suitable tests is essential to prevent this high prevalence. According to the results of this systematic review and meta-analysis, the rate of LTBI in Iranian HCWs is high. Therefore, periodical screening and diagnostic tests such as TST are necessary for the timely diagnosis and treatment of these individuals to prevent changing LTBI to an active form of tuberculosis.

Keywords: Health care worker, Latent tuberculosis infection, Patient

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Introduction

Tuberculosis is one of the most common infectious diseases caused by different types of Mycobacteria, especially *Mycobacterium tuberculosis*[1-4]. This infection is the most significant cause of death among infectious diseases[5-7]. It has a tenth rank among global diseases[8-10].

However, many infections do not lead to tuberculosis; about 90-95% of infections are asymptomatic or generally latent[11-13]. The natural immune response to *Mycobacterium tuberculosis* antigens leads to Latent tuberculosis infection (LTBI) without symptoms of active tuberculosis (TB)[14,15]. Colonization of alveolar macrophages is caused by *Mycobacterium tuberculosis* and, lastly, form granuloma[16,17]. Also, *Mycobacterium*

tuberculosis is ingested through resident alveolar macrophages and tissue dendritic cells (DC) by the phagocytosis process[18, 19].

Conditions including direct exposure of HCWs to TB patients, direct contact with clinical specimens such as; sputum and blood products from patients with suspected tuberculosis, and long work hours in closed high-risk places such as health centers and hospitals raise the risk of tuberculosis infection[20-22].

Work experience, age, and employment status of HCWs, in addition to using personal protective equipment, proper ventilation of Ward space, infection control department, and isolated rooms, can affect the prevalence of latent tuberculosis in HCWs[11, 23-26].

According to estimations in high-income countries, the risk of TB in HCWs is twice as high in the general population. This rate is five times higher than the general population in countries with low and middle income[21, 25, 27].

So far, various methods to identify and diagnose Latent tuberculosis infection have been introduced, the most important of which include the Tuberculin skin test (TST) and IFN-gamma release assay[28, 29]. Tests in a specific way assess the state of the individual's immune system, and they have some advantages and disadvantages. Studies showed that QuantiFERON-TB Gold (QFT) tests have higher sensitivity and specificity in identifying latent TB patients[30]. The tuberculin skin test has Limitations in latent TB diagnosis[31]. Therefore, regarding the importance of LTBI in HCWs, we aimed to evaluate the prevalence of LTBI in HCWs from Iran.

Methods

Strategy search: In the present study, we searched from 1st 2010 to the end of 2021 in various databases such as; PubMed, Scopus, Web of sciences, and Google Scholar for studies that presented LTBI in HCWS following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Mesh words used for searching were; 'latent tuberculosis,' 'LTB, 'healthcare worker,' 'HCW,' 'QuantiFERON test,' 'TST test,' and 'Iran.'

Eligibility Criteria: We included original cross-sectional studies that reported the prevalence of LTBI in Iranian HCWs. In addition, studies that conducted TST tests for the detection of LTBI entered the present study. Meta-analysis, systematic reviews, case reports, meetings, congress, reports, and studies with missed and unclear data are excluded from the current study.

Quality appraisal: For quality assessment, the Newcastle-Ottawa Scale (NOS) checklist was used[32]. The quality of studies is determined according to three levels of scoring. A score of 5 or less determined weak quality; score of 5- 6 was defined as the medium, and the score of 7-10 was described as the high-quality. Lastly, the moderate to high-quality studies were selected for inclusion in the current systematic review and Meat-analysis.

Data extraction: Two researchers independently reviewed inclusive studies included in the present review. Using the designed forms, they entered the desired data; the year of publication, sample size, the prevalence of LTBI, first author, location, and TST test. If these two researchers had a problem extracting data, they shared it with a third person or entered the data through an agreement.

Statistical analysis: The studies were analyzed by Comprehensive meta-analysis software. A random-effect model was applied to determine the combined prevalence with a 95% confidence interval (CI) due to heterogeneity in the studies included. In addition, bias in the publication of studies was evaluated visually by a Funnel plot. Egger's regression test was used to assess discrimination in the studies further.

Results

Selection studies: As shown in Figure 1, at first, 402 studies were detected through searching in different databases, then 113 duplicate studies were removed, 289 articles were screened, after deleting some studies with reasons, at last, 22 articles from 2010 to end of 2021 met eligibility criteria for inclusion in the present systematic review and Meta-analysis.

Study characteristics: Among 22 studies that met eligibility criteria for inclusion, two from Ahvaz, three from Teheran, two from Zahedan, three from Mashhad, one from Kermanshah, one from Semnan, one from Kermanshah, one from Hamedan, two from babol, one from Yazd, one from Shiraz, one from Urmia, one from Khoram Abad, one from Qazvin, and one from throughout Iran.

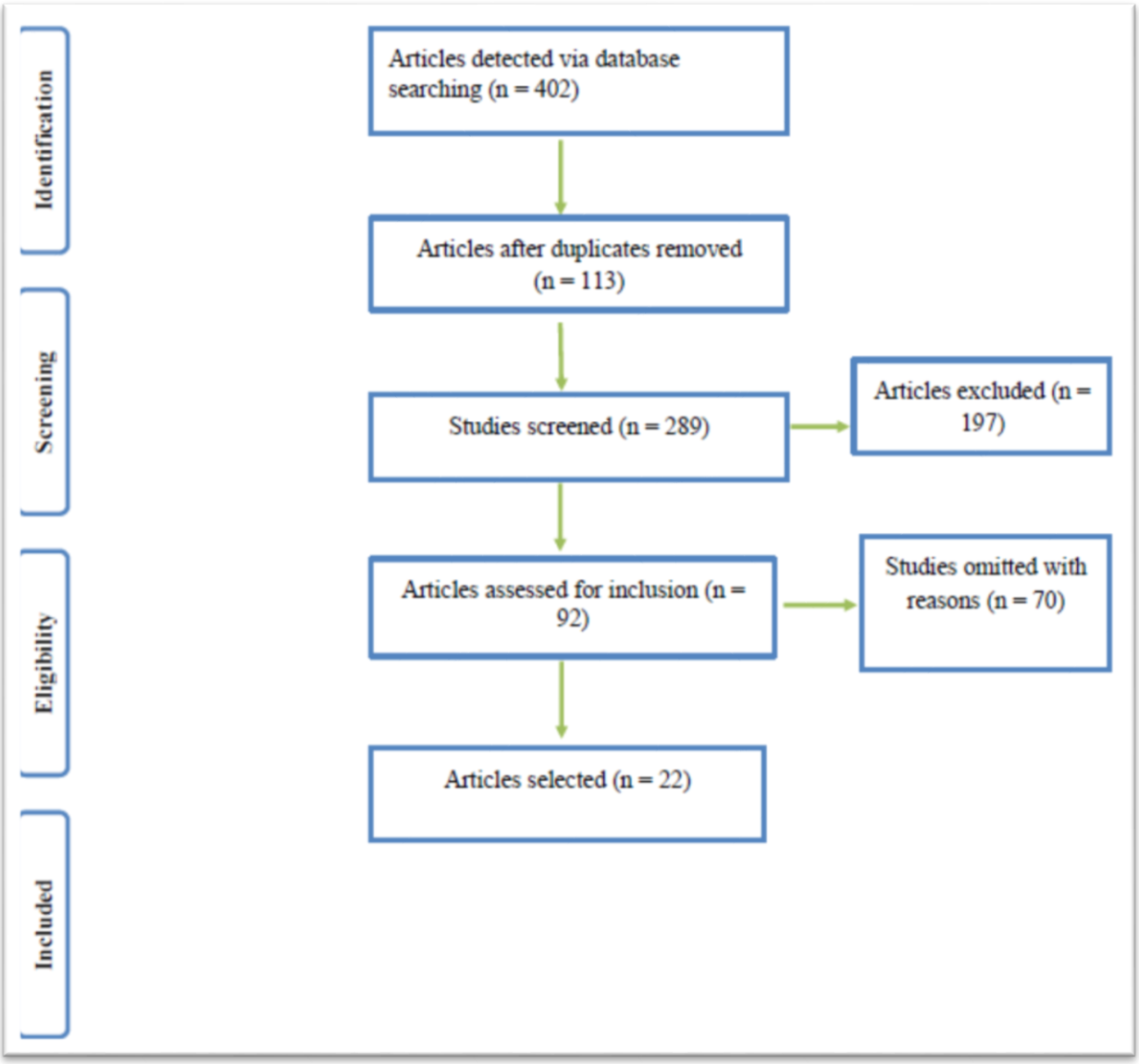

Figure 1. Flow diagram of selected studies

Overall effects

The combined prevalence of LTBI in HCWs: As abstracted in figure 2 and Table 1, the prevalence of LTBI in Iranian HCWs varied between 5.4%-60%. The pooled prevalence of LTBI in Iranian HCWs was reported by 25.9% (95% CI: 19.3-33.7), Z=5.45, I^2= 97.3, Q= 802.3.

Presence of publication bias: The publication bias in this study was evaluated by Egger's tests. According to the Funnel plot, as shown in Figure 3, there was publication bias. The publication bias by Egger's test was calculated at 0.04; therefore, there is no publication bias in the studies included.

Discussion

As stated in the results section, the prevalence of LTBI in Iranian HCWs varied widely in different parts of our country, about 5.4% to 60%. Due to this, the following reasons could be mentioned; Geographical area, type of sampling in different studies, type of personal protection, public health in medical and health centers, the obedience to health protocols in other geographical areas, exposure to carriers, and positive TB patients, proper ventilation, infection control in hospitals and health- Therapeutic centers[11, 20, 24].

Table 1: Characteristics studies selected for the present meta-analysis from HCWs.

First author	Publication	Location	Sample size	LTB(n)%	TST(mm)
Sharafkhani	2010	Urmia	409	225(55)	225
Besharat	2012	Chaharmahal	1424	698(49)	698
Nassaji	2012	Semnan	180	52(28.8)	52
Hashemi Shahri	2012	Zahedan	134	85(63.4)	85
Talebi Taher	2013	Tehran	200	105(52.5)	105
Alijani	2013	Zahedan	75	45(60.3)	45
Taheri	2013	Shiraz	89	7(8)	7
Behnaz	2013	Yazd	54	21(39.6)	21
Habibi	2013	Mashhad	195	77(39.5)	77
Vaziri	2013	Kermanshah	69	33(47.8)	33
Hashemi	2014	Hamedan	245	93(38)	93
Nazer	2015	Khoram abad	223	40(18)	40
Tavanaee	2015	Mashhad	200	14(7)	14
Ghafouri	2015	Mashhad	476	71(14.9)	71
Allami	2015	Qazvin	213	32(14.6)	32
Salmanzadeh	2016	Ahvaz	87	27(31)	27
Mostafavi	2016	Tehran	244	39(16)	39
Nasehi	2017	throughout Iran	689	171(24.8)	6.47
Bayani	2018	Babol	400	59(14.8)	-
Keshavarz Valian	2018	Tehran	101	47(46.5)	-
Bavarsad	2019	Ahvaz	513	67(13.1)	>10
Bayani	2018	Babol	400	59(14.7)	-

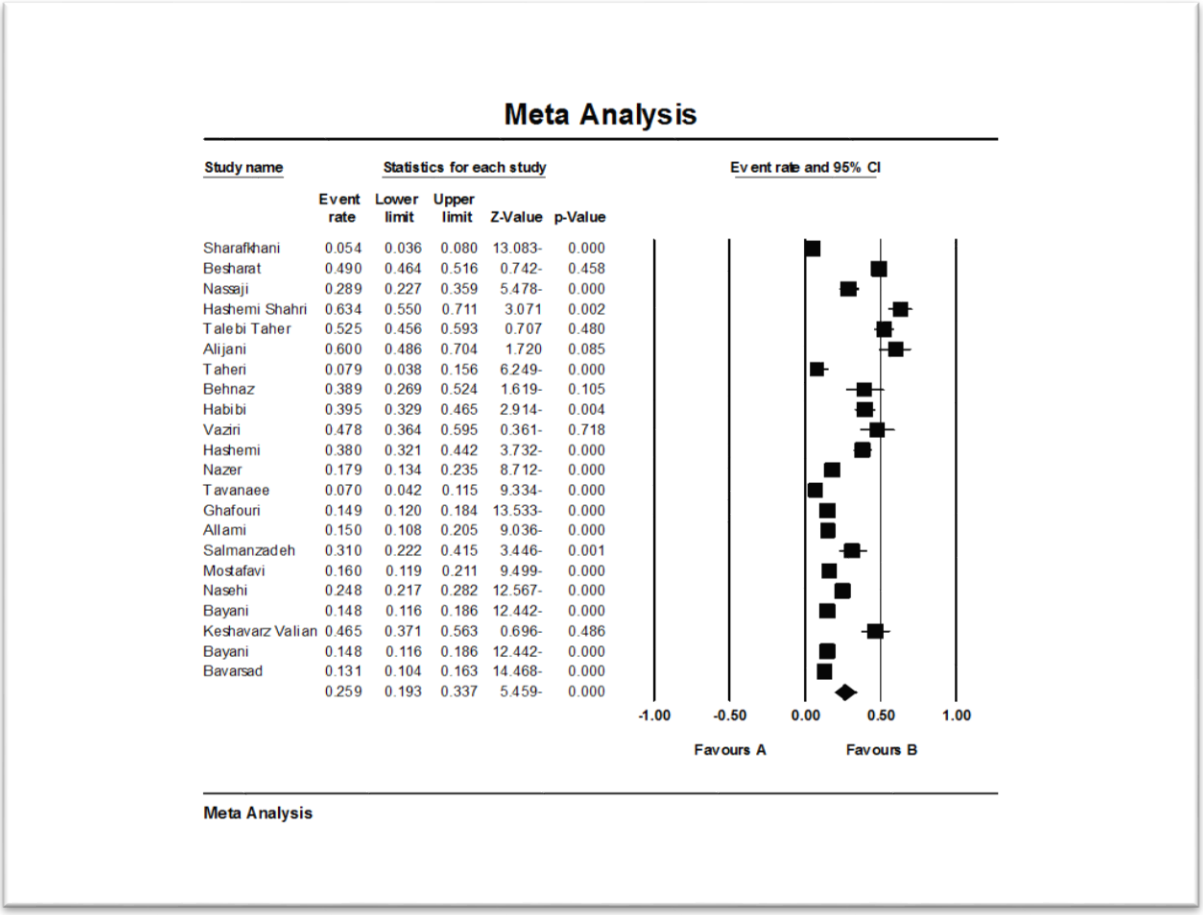

Figure 2. Forest plot for Latent tuberculosis infection in Iranian Health care workers

Our review showed a high combined prevalence of LTBI among HCWs, about 25%. Therefore, preventive

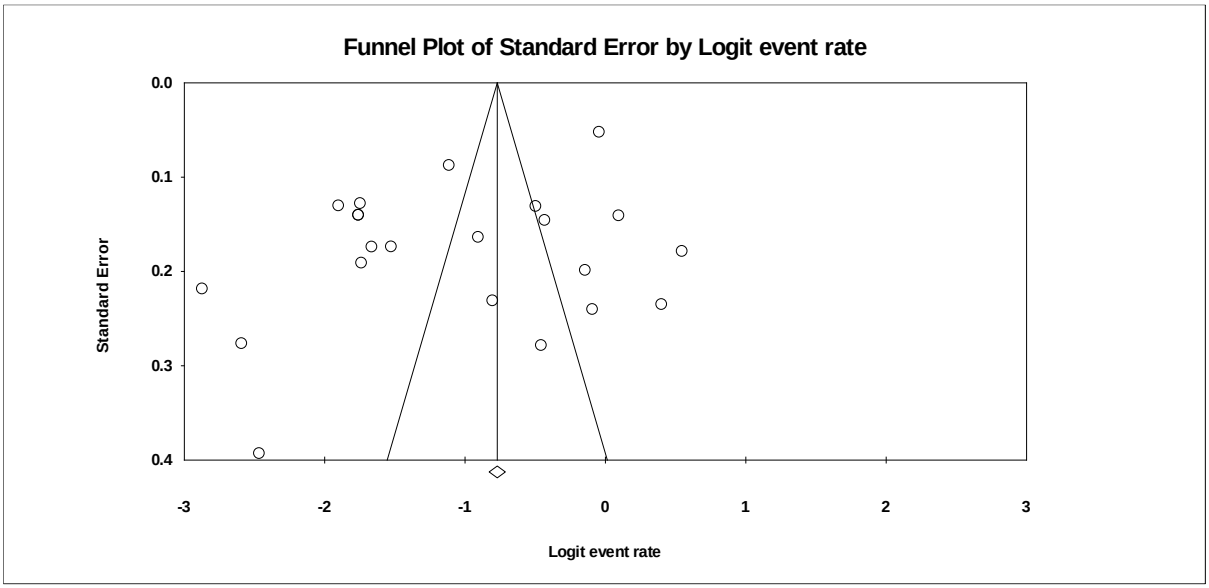

Figure 3. Funnel plot for Latent tuberculosis infection in Iranian Health care workers

measures are necessary[33]. According to the results of studies, health workers are at higher risk of contracting tuberculosis, so periodic tests such as TST can be beneficial in diagnosing LTBI in these people. Moreover, if LTBI is diagnosed with prophylaxis, it can be prevented from changing into active pulmonary tuberculosis[34]. In hospitals at the potential transmission risk, TST should be performed once every three months until conditions for tuberculosis control are provided. In high-income countries, screening personnel in Pulmonary and Laboratory wards is recommended annually and in other departments every three years[35]. However, in low-income countries, it often doesn't perform routinely[21]. The high rate of LTBI in Iranian HCWs reported from Zahedan with a prevalence of 60%; this probably referred to neighboring this region with countries with high TB rates of tuberculosis, such as Pakistan and Afghanistan[36]. In compliance with our findings, a global systematic review and Meta-analysis reported the highest prevalence in Eastern Mediterranean countries (19.4%), wherein the pooled estimation found the lowest prevalence of LTBI for North American and West Pacific countries (<5%)[37]. Our findings confirmed data reported by WHO (2015), the incidence of LTBI in the general population of Iran was described (16/100000 people)[38]. Contrary to our results, Studies from Thailand, Uganda, and the Netherlands reported LTBI prevalence of about 63%, 57%, and 42%, respectively. This data is justifiable because Iran is an intermediate region[39, 40].

Conclusion

According to the results of this systematic review and meta-analysis, the rate of LTBI in Iranian HCWs is high. Therefore, periodical screening and diagnostic tests such as TST are necessary for the timely diagnosis and treatment of these individuals to prevent changing LTBI to an active form of tuberculosis.

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References

1. Heidarnezhad F, Asnaashari A, Rezaee SA, Ghezelsofla R, Ghazvini K, Valizadeh N, et al. Evaluation of Interleukin17and Interleukin 23 expression in patients with active and latent tuberculosis infection. Iranian journal of basic medical sciences. 2016;19(8):844.
2. Safdari H, Sadeghi A, Ghazvini K, Mohammadi S, Derakhshan M. Prevalence of Mycobacterium tuberculosis in the samples referred to the tuberculosis research laboratory in Mashhad Ghaem Hospital during 2005-2006. Iranian Journal of Microbiology. 2009;1(3):20-2.
3. Sterling TR, Njie G, Zenner D, Cohn DL, Reves R, Ahmed A, et al. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. Wiley Online Library; 2020. p. 1196-206.
4. Reid MJ, Arinaminpathy N, Bloom A, Bloom BR, Boehme C, Chaisson R, et al. Building a tuberculosis-free world: The Lancet Commission on tuberculosis. The Lancet. 2019;393(10178):1331-84.
5. Mirzayev F, Viney K, Linh NN, Gonzalez-Angulo L, Gegia M, Jaramillo E, et al. World Health Organization recommendations on the

treatment of drug-resistant tuberculosis, 2020 update. European Respiratory Journal. 2021;57(6).
6. Organization WH. WHO consolidated guidelines on drug-resistant tuberculosis treatment: World Health Organization; 2019.
7. Dijkman K, Sombroek CC, Vervenne RA, Hofman SO, Boot C, Remarque EJ, et al. Prevention of tuberculosis infection and disease by local BCG in repeatedly exposed rhesus macaques. Nature medicine. 2019;25(2):255-62.
8. Organization WH. Global tuberculosis report 2013: World Health Organization; 2013.
9. Sharma SK, Mohan A, Kohli M. Extrapulmonary tuberculosis. Expert Review of Respiratory Medicine. 2021(just-accepted).
10. Organization WH. WHO operational handbook on tuberculosis: module 3: diagnosis: rapid diagnostics for tuberculosis detection. 2021.
11. Christopher DJ, Daley P, Armstrong L, James P, Gupta R, Premkumar B, et al. Tuberculosis infection among young nursing trainees in South India. PLoS One. 2010;5(4):e10408.
12. Conradie F, Diacon AH, Ngubane N, Howell P, Everitt D, Crook AM, et al. Treatment of highly drug-resistant pulmonary tuberculosis. New England Journal of Medicine. 2020;382(10):893-902.
13. Oh CE, Ortiz-Brizuela E, Bastos ML, Menzies D. Comparing the diagnostic performance of QuantiFERON-TB gold plus to other tests of latent tuberculosis infection: a systematic review and meta-analysis. Clinical Infectious Diseases. 2021;73(5):e1116-e25.
14. Apriani L, McAllister S, Sharples K, Alisjahbana B, Ruslami R, Hill PC, et al. Latent tuberculosis infection in healthcare workers in low-and middle-income countries: an updated systematic review. European Respiratory Journal. 2019;53(4).
15. Marx FM, Hauer B, Menzies NA, Haas W, Perumal N. Targeting screening and treatment for latent tuberculosis infection towards asylum seekers from high-incidence countries–a model-based cost-effectiveness analysis. BMC public health. 2021;21(1):1-16.
16. Harding E. WHO global progress report on tuberculosis elimination. The Lancet Respiratory Medicine. 2020;8(1):19.
17. Deutsch-Feldman M, Pratt RH, Price SF, Tsang CA, Self JL. Tuberculosis—United States, 2020. Morbidity and Mortality Weekly Report. 2021;70(12):409.
18. Korbel DS, Schneider BE, Schaible UE. Innate immunity in tuberculosis: myths and truth. Microbes and Infection. 2008;10(9):995-1004.
19. North RJ, Jung Y-J. Immunity to tuberculosis. Annu Rev Immunol. 2004;22:599-623.
20. Yanai H, Limpakarnjanarat K, Uthaivoravit W, Mastro T D, Mori T, Tappero J W. Risk of Mycobacterium tuberculosis infection and disease among health care workers, Chiang Rai, Thailand. The International Journal of Tuberculosis and Lung Disease. 2003;7(1):36-45.
21. Kassim S, Zuber P, Wiktor S, Diomande F, Coulibaly I, Coulibaly D, et al. Tuberculin skin testing to assess the occupational risk of Mycobacterium tuberculosis infection among health care workers in Abidjan, Cote d'Ivoire. The International Journal of Tuberculosis and Lung Disease. 2000;4(4):321-6.
22. Janagond AB, Ganesan V, Kumar GV, Ramesh A, Anand P, Mariappan M. Screening of health-care workers for latent tuberculosis infection in a Tertiary Care Hospital. International journal of mycobacteriology. 2017;6(3):253.
23. Garber E, San Gabriel P, Lambert L, Saiman L. A survey of latent tuberculosis infection among laboratory healthcare workers in New York City. Infection Control & Hospital Epidemiology. 2003;24(11):801-6.
24. Joshi R, Reingold AL, Menzies D, Pai M. Tuberculosis among health-care workers in low-and middle-income countries: a systematic review. PLoS medicine. 2006;3(12):e494.
25. Yeon JH, Seong H, Hur H, Park Y, Kim YA, Park YS, et al. Prevalence and risk factors of latent tuberculosis among Korean healthcare workers using whole-blood interferon-γ release assay. Scientific reports. 2018;8(1):1-5.
26. Erawati M, Andriany M. The prevalence and demographic risk factors for latent tuberculosis infection (LTBI) among healthcare workers in Semarang, Indonesia. Journal of multidisciplinary healthcare. 2020;13:197.
27. Sanghavi DM, Gilman RH, Lescano-Guevara AG, Checkley W, Cabrera LZ, Cardenas V. Hyperendemic pulmonary tuberculosis in a Peruvian shantytown. American Journal of Epidemiology. 1998;148(4):384-9.
28. Brock I, Weldingh K, Lillebaek T, Follmann F, Andersen P. Comparison of tuberculin skin test and new specific blood test in tuberculosis contacts. American journal of respiratory and critical care medicine. 2004;170(1):65-9.
29. Zhou G, Luo Q, Luo S, Teng Z, Ji Z, Yang J, et al. Interferon-γ release assays or tuberculin skin test for detection and management of latent tuberculosis infection: a systematic review and meta-analysis. The Lancet Infectious Diseases. 2020;20(12):1457-69.
30. Kang YA, Lee HW, Yoon HI, Cho B, Han SK, Shim Y-S, et al. Discrepancy between the tuberculin skin test and the whole-blood interferon γ assay for the diagnosis of latent tuberculosis infection in an intermediate tuberculosis-burden country. Jama. 2005;293(22):2756-61.
31. Mori T, Sakatani M, Yamagishi F, Takashima T, Kawabe Y, Nagao K, et al. Specific detection of tuberculosis infection: an interferon-γ–based assay using new antigens. American journal of respiratory and critical care medicine. 2004;170(1):59-64.
32. Poorolajal J, Cheraghi Z, Irani AD, Rezaeian S. Quality of cohort studies reporting post the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. Epidemiology and health. 2011;33.
33. Mansury D, Ghavidel M, Ghazvini K. Latent tuberculosis infection in health care workers. Tehran University Medical Journal TUMS Publications. 2018;75(10):708-14.
34. Getahun H, Matteelli A, Abubakar I, Aziz MA, Baddeley A, Barreira D, et al. Management of latent Mycobacterium tuberculosis infection: WHO guidelines for low tuberculosis burden countries. European Respiratory Journal. 2015;46(6):1563-76.
35. Schablon A, Harling M, Diel R, Nienhaus A. Risk of latent TB infection in individuals employed in the healthcare sector in Germany: a multicentre prevalence study. BMC infectious diseases. 2010;10(1):1-10.
36. Velayati A, Farnia P, Masjedi M, Ibrahim T, Tabarsi P, Haroun R, et al. Totally drug-resistant tuberculosis strains: evidence of adaptation at the cellular level. European Respiratory Journal. 2009;34(5):1202-3.
37. Peters C, Kozak A, Nienhaus A, Schablon A. Risk of Occupational

Latent Tuberculosis Infection among Health Personnel Measured by Interferon-Gamma Release Assays in Low Incidence Countries—A Systematic Review and Meta-Analysis. International journal of environmental research and public health. 2020;17(2):581.
38. Nasehi M, Hashemi-Shahraki A, Doosti-Irani A, Sharafi S, Mostafavi E. Prevalence of latent tuberculosis infection among tuberculosis laboratory workers in Iran. Epidemiology and Health. 2017;39.
39. Mumpe-Mwanja D, Verver S, Yeka A, Etwom A, Waako J, Ssengooba W, et al. Prevalence and risk factors of latent Tuberculosis among adolescents in rural Eastern Uganda. African health sciences. 2015;15(3):851-60.
40. Nasreen S, Shokoohi M, Malvankar-Mehta MS. Prevalence of latent tuberculosis among health care workers in high burden countries: a systematic review and meta-analysis. PloS one. 2016;11(10):e0164034.