Screening of Health-care Workers for Latent Tuberculosis Infection in a Tertiary Care Hospital

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Abstract

Background: Health-care workers (HCWs) are at increased risk of acquiring tuberculosis (TB) than the general population. While national-level data on the burden of TB in general population is available from reliable sources, nationally representative data on latent tuberculosis infection (LTBI) burden in HCWs in the high burden countries is lacking. Methods: A prospective study was carried out to assess the risk of TB infection among HCWs who directly engage in medical duties. HCWs were recruited between January 2014 and December 2015. A structured questionnaire was used for risk assessment of TB infection among HCWs, including sociodemographic characteristics (e.g., age, gender, period of professional work, and employed position), knowledge of TB prevention and control, and history of professional work. A single-step tuberculin skin test (TST) using 5 international units (IU; 0.1 ml) of tuberculin (purified protein derivative from Mycobacterium bovis Bacillus Calmette–Guérin [BCG]). TB infection was determined using a TST induration ≥10 mm as a cutoff point for TST positivity. TST-positive participants were further subjected to detailed clinical evaluation and chest radiography to rule out active TB. The associations between TB infection and the sociodemographic characteristics, duration of possible exposure to TB while on medical duties, BCG vaccination, and knowledge about TB were estimated using Chi-square test. A two-sided \( P < 0.05 \) indicated statistical significance. Results: A total of 206 eligible HCWs signed the informed consent and completed the questionnaires between January 2014 and December 2015. The age of the participants ranged from 18 to 71 years, with a mean age of 27.13 years. TST induration size (mean 6.37 mm) the TST results suggested that 36.8% (76/206) were infected with TB using a TST induration ≥10 mm as a cut-off point. All 76 TST-positive HCWs showed no evidence of active TB in clinical evaluation and chest radiography. However, during the study, two HCWs developed pulmonary TB (both TST baseline test negative). Statistical analysis suggested that age, duration of employment as a health-care professional, literacy status, and working in medical wards/OP/Intensive Care Unit were significantly associated with TB infection. Conclusions: Many studies propose serial tests of LTBI as effective occupational protection strategies. However, practically, it is not feasible because it has to be done at frequent intervals, but how frequently to be done is not clear. Another concern is even if found to have LTBI, there are no clear consensus guidelines about the treatment in high prevalence settings. The prevalence of LTBI is so high in countries like India that affected HCWs could not be exempted from working in high-risk areas. The depth of knowledge of TB prevention and control among HCWs should be improved by regular infection control training.

Keywords: Latent tuberculosis, Mantoux test, tuberculin

INTRODUCTION

Health-care workers (HCWs) are at increased risk of acquiring tuberculosis (TB) than the general population. While national-level data on the burden of TB in general population is available from sources such as World Health Organization (WHO), nationally representative data on LTBI burden in HCWs in the high burden countries is lacking. Latent tuberculosis infection (LTBI) does not produce disease manifestations and is not infectious albeit it results in persistent immune response against Mycobacterium tuberculosis antigens.\(^1\)

However, there remains a 10-15% lifetime risk of developing active TB. There is no gold standard test for diagnosis of LTBI. Tuberculin skin test (TST) and blood interferon-gamma release assay (IGRA) tests are performed to diagnose LTBI. The WHO recommends that Bacillus Calmette–Guérin (BCG) vaccine be
administered during infancy in TB endemic countries. Center for disease control (CDC) guidelines state that TST reactivity caused by BCG vaccine generally wanes with the passage of time. A person with a history of BCG vaccination can be tested and treated for LTBI if they react to the TST. TST reactions should be interpreted based on risk stratification regardless of BCG vaccination history. Furthermore, CDC states that considering comparable performance between TST and IGRA but increased cost, replacing TST with IGRA in low-income and other middle-income countries is not recommended.[5]

The present study was conducted in a tertiary hospital with 350 beds. Suspect cases of pulmonary TB are referred to the department of pulmonary medicine which acts as Revisited National Tuberculosis Control Programme (RNTCP) cell. Under RNTCP, two sputum samples are checked by the microbiologist and treatment of positive cases monitored by a dedicated health-care worker. Annually, around 300 new cases are detected in the hospital. Patients were treated on ambulatory basis as well as inpatients. During the early months of the study, all positive cases were admitted to the medical wards and allotted corner beds. There were no separate wards for pulmonary TB patients. There is no provision of negative pressure room for TB cases. N95 respirators were not available regularly to the health-care workers. Given the high prevalence of TB cases in the hospital and lack of stringent infection control practices, this study was proposed. During the later period of the study, separate ward for sputum positive cases was allotted. Patients who remain positive after the intensive phase of treatment were checked for rifampicin resistance by gene expert TB under RNTCP. However, no separate ward for MDR TB cases has been provided.

**Methods**

**Study design and settings**

A prospective study was carried out between January 2014 and December 2015 to assess the risk of TB infection among HCWs who directly engage in medical duties. Participants included nurses, laboratory technicians, paramedical technicians, and housekeeping workers. All the HCWs who were engaged in medical duties for more than 6 months were eligible. Each HCW was recruited by their department supervisor and encouraged to complete a self-administered and standard questionnaire. TST was performed on all potential participants unless they declined to take or were not available during the study. The study was approved by the Ethics Committees of the Institute. Out of 321 health-care workers, 206 consented to participate in the study. This includes 130 nurses, 5 technical staff, 28 laboratory technicians, and 43 housekeeping staff. Eleven workers with history of TB were not included. The study was conducted after obtaining institutional ethics committee approval, and all the participants provided written informed consent before recruitment.

**Data collection and tuberculin skin test**

A structured questionnaire was used for risk assessment of TB infection among HCWs, including sociodemographic characteristics (e.g., age, gender, period of professional work, and employed position), knowledge of TB prevention and control, history of professional work, and clinical work. A single-step TST using 10 international units (IU; 0.1 ml) of tuberculin (purified protein derivative from *Mycobacterium bovis* BCG, (Span diagnostics). The TST was administered using the Mantoux method by experienced staff, and participants returned 48–72 h after TST inoculation to obtain results, which were confirmed independently by two microbiologists. The horizontal diameter of induration size was measured using a standardized ruler, and the results obtained by the two microbiologists were averaged. LTBI was determined using a TST induration ≥10 mm as a cutoff point for TST positivity. However, BCG vaccination history was recorded for all the participants recorded, and its effect on the results was evaluated.

TST-positive participants were further subjected to detailed clinical evaluation and chest X-ray examination to rule out active TB. The associations between TB infection and the sociodemographic characteristics, experiences of medical duties, BCG vaccination, and knowledge about TB were estimated using Chi-square test. A two-sided *P* < 0.05 indicated statistical significance.

**Results**

A total of 206 eligible HCWs signed the informed consent and completed the questionnaires between January 2014 and December 2015. The age of the participants ranged from 18 to 71 years, with a mean age of 27.13 years. Eight were males. Of the participants, 78.6% (162/206) reported having received a BCG vaccination at birth. Mean TST induration size was 6.37 mm. The TST results showed that 36.8% (76/206) were infected with TB using a TST induration ≥10 mm as a cutoff point. All 76 TST-positive HCWs revealed no evidence of active TB on clinical and radiological evaluation. Statistical analysis suggested that age, duration of employment as a health-care professional, literacy status, and working in medical wards/OP/Intensive Care Unit were significantly associated with TB infection [Tables 1 and 2]. Other factors such as sex, body mass index, contact with TB patient in hostel/house/neighborhood, BCG vaccination, and knowledge about TB were not significantly associated with TB infection [Tables 1, 3 and 4]. Out of 206 health-care workers, 15 had generalized/systemic (more than one anatomical surface apart from test site) urticaria. We identified one participant with bulla, one with a bleb, and one with blister [Figures 1-3]. They were treated with skin emollients and antihistamines. There were no major adverse reactions.

**Discussion**

The results suggest that more than one-third of the HCWs had LTBI. This is likely due to high exposure to TB patients in the absence of optimum TB control measures in the high background TB prevalence in India in general and our study...
setting in particular. Studies on latent TB among HCWs have only been conducted in disparate regions of the country.

In 2005, Pai et al.\(^3\) estimated the prevalence of LTBI among 720 health-care workers with a single-step tuberculin test and found the prevalence of 41%. In 2006, Pai et al.\(^4\) performed serial testing of tuberculin test and IGRA among 216 medical and nursing students; 22% were TST-positive, and 18% were QFT-positive at baseline. Among 147 participants with concordant baseline negative results, TST conversions occurred in 13.6%, and QFT conversions occurred in 11.6% participants. In 2010, Christopher et al.\(^5\) estimated the prevalence of 50.2% with serial tuberculin testing among 468 nursing students. In the multivariate analysis, TST positivity was strongly associated with time spent in health care. This is in concordance with the present study. Vijaykumar and Gopalakrishnan\(^6\) studied the prevalence of LTBI in 85 nursing students with serial testing of TST and IGRA and concluded that combination of TST and IGRA is ideal for screening to detect LTBI and modification of IGRA result interpretation is needed to be of significance in TB endemic countries.

Table 1: Association between demographic characteristics and latent tuberculosis infection

| Factors                  | LTBI (%) | P     |
|--------------------------|----------|-------|
| Sex                      |          |       |
| Female                   | 64/198 (32.3) | 0.71  |
| Male                     | 3/8 (37.5)    |       |
| Age                      |          |       |
| <30                      | 33/145 (22.7) | 0.0071|
| 30-39                    | 12/39 (30.7)  |       |
| >40                      | 12/22 (54.5)  |       |
| Education                |          |       |
| Illiterate               | 19/42 (45.2)  | 0.000162|
| Primary school           | 0/26 (0)    |       |
| Bachelor degree          | 34/138 (24.6) |       |
| BMI                      |          |       |
| ≤18.5                    | 13/61 (21.3)  | 0.903 |
| 18.5-25 (94)             | 29/121 (23.9) |       |
| >25 (18)                 | 6/24 (25)    |       |
| BCG vaccination          |          |       |
| Yes                      | 52/162 (32)   | 0.2738|
| No                       | 18/44 (40.9)  |       |

LTBI: Latent tuberculosis infection, BMI: Body mass index, BCG: Bacillus Calmette-Guérin

Table 2: Association between medical work and latent tuberculosis infection

| Factors                                    | LTBI (%) | P      |
|--------------------------------------------|----------|--------|
| Duration of professional exposure to TB patients (years) |           |        |
| <1                                         | 5/74 (6.7)    | 0.0021 |
| 1-5                                        | 28/110 (25.4) |       |
| >5                                         | 7/22 (31.8)   |       |
| Area of work                               |           |        |
| Medical                                    | 32/117 (27.3) | 0.04703|
| Surgical                                   | 9/59 (15.2)   |       |
| Laboratory                                 | 3/30 (10)    |       |

LTBI: Latent tuberculosis infection, TB: Tuberculosis

Table 3: Association between habit and latent tuberculosis infection

| Factors                                    | LTBI (%) | P     |
|--------------------------------------------|----------|-------|
| Immunocompromised status                   |          |       |
| Diabetes                                   |          |       |
| Yes                                        | 1/4 (25) | 0.597 |
| No                                         | 31/202 (15.3) |       |
| Steroid use                                |          |       |
| Yes                                        | 1/4 (25) | 0.2969|
| No                                         | 19/202 (9.4) |       |
| Known TB patient in house/hostel           |          |       |
| Yes                                        | 2/12 (16.66) | 0.8716|
| No                                         | 29/194 (14.9) |       |
| Known TB patient in neighborhood            |          |       |
| Yes                                        | 0/4 (0) | 0.5578|
| No                                         | 16/202 (7.9) |       |

LTBI: Latent tuberculosis infection, TB: Tuberculosis

Table 4: Association between knowledge of tuberculosis and latent tuberculosis infection

| Score | LTBI (%) | P     |
|-------|----------|-------|
| 0-5   | 6/21 (28.5) | 0.6664|
| 6-10  | 22/62 (35.48) |       |
| >10   | 36/123 (29.2) |       |

LTBI: Latent tuberculosis infection

that combination of TST and IGRA is ideal for screening to detect LTBI and modification of IGRA result interpretation is needed to be of significance in TB endemic countries.

There is also a growing recognition that LTBI is a spectrum, and accumulating evidence suggests that none of the existing LTBI tests can resolve this spectrum, particularly with onetime testing.\(^9\) In 2011, Joshi et al.\(^10\) performed a cross-sectional comparison of TST and QFT in a cohort of 726 HCWs with young trainees making up half the cohort. A total of 360 (50%) HCWs were found to be positive using either the TST or QFT assay at baseline, and 226 (31%) were found to be positive using both tests. Six years after the baseline survey, HCWs were followed up. Of the 674 HCWs followed, 14 had developed active TB disease. Incidence rates of TB disease in the TST and QFT positive and negative subgroups were similar. In the present study, one of the participants negative for latent TB by Mantoux test went on to develop sputum positive pulmonary TB (Grade 3+) in the next 4 months. Current LTBI tests may not be able to identify the subset that is at highest risk of future disease, as confirmed by a new meta-analysis.\(^11\) Therefore, the search for more predictive biomarkers or combinations of biomarkers and risk factors must continue.

TST has evolved over 100 years; despite all the stern scrutiny and standardizing measures, this test is still not devoid of side effects. Although adverse reactions to TST are uncommon, local allergic reactions to tuberculin or its components can occur in 2%–3% of those tested.\(^12\) Studies have authenticated
the fact that there is no linear relation between tuberculin dose and the skin reaction observed and hence, our results cannot be ascribed to using higher strengths of TU. In this study, only minor side effects were observed. In 2014, Christopher et al. screened 755 nursing students for baseline two-step TST. In 623 individuals, adverse events were recorded when reported during the TST reading and 132 individuals answered an investigator administered questionnaire assessing all likely side-effects. In cohort A only 1.3% reported adverse events. In cohort B, as per the investigator administered questionnaire; 25% reported minor side effects. Itching and local pain were the most common side effects encountered. There were no major adverse events reported. In particular, the adverse events were similar in the second step of the test and not more severe.

Important concern overuse of screening tests in health-care workers is about the treatment. In the present study, participants who were found to have latent TB infection were not offered treatment in accordance with WHO guidelines. Resource-limited countries and other middle-income countries should implement existing WHO guidelines for latent TB treatment on people living with HIV and child contacts below 5 years of age as a priority. But the infected individuals were explained about the chances of developing active TB and educated about the infection control measures. Despite, two participants (both TST baseline negative) developed pulmonary TB during the study.

**Limitation of the study**

Only one step TST was done. A negative test was not followed by another test to check booster phenomenon and testing at regular intervals not done to detect seroconversion. HIV testing was not included in the study which has definite implications. The risk of progression from LTBI to TB disease is 7% to 10% each year for those with both LTBI and untreated HIV infection. Those with LTBI who are not HIV infected have a 10% risk over their lifetime. The prevalence of latent TB among the general population in India is not known.

**Conclusion**

Most TB control programs in low- and middle-income countries have focused on case detection and treatment using the DOTS strategy. However, occupational infection control measures are not implemented as regular tasks in the TB infection control programs because of the high TB burden and limited resources. Many studies propose serial tests of LTBI as effective occupational protection strategies. However, practically it is not feasible because it has to be done at frequent intervals but how frequently to be done is not clear. The prevalence of latent TB is so high that the affected HCWs could not be exempted from working in high-risk areas. The depth of knowledge of TB prevention and control among HCWs should be improved by regular infection control training. There should be uniformity in the policy of TB treatment and care. Patients should be treated on ambulatory basis as much as possible. Consistent N95 respirator use by HCWs while attending suspected or diagnosed TB patients and by confirmed sputum positive TB patients themselves must be emphasized. Future research is needed to identify and test the effectiveness of feasible and affordable environmental control strategies.
and respiratory protection measures in resource-constrained settings.

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**Conflicts of interest**

There are no conflicts of interest.

**References**

1. World Health Organization. Guidelines on the Management of Latent Tuberculosis Infection. Spain: WHO; 2015.
2. Centre for Disease Control and Prevention. Latent Tuberculosis Infection: A Guide for Primary Health Care Providers. Atlanta, Georgia: CDC; 2014.
3. Pai M, Gokhale K, Joshi R, Dogra S, Kalantri S, Mendiratta DK, et al. Mycobacterium tuberculosis infection in health care workers in rural India: Comparison of a whole-blood interferon gamma assay with tuberculin skin testing. JAMA 2005;293:2746-55.
4. Pai M, Joshi R, Dogra S, Mendiratta DK, Narang P, Kalantri S, et al. Serial testing of health care workers for tuberculosis using interferon-gamma assay. Am J Respir Crit Care Med 2006;174:349-55.
5. 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:e10408.
6. Vijaykumar GS, Gopulakrishnan R. Detection of latent tuberculosis infection in nursing students by combined TST and IGRA serial testing. J Med Sci Clin Res 2014;2:567-74.
7. Barry CE 3rd, Boshoff H, Dartois V, Dick T, Ehrt S, Flynn J, et al. The spectrum of latent tuberculosis: Rethinking the biology and intervention strategies. Nat Rev Microbiol 2009;7:845-55.
8. Mack U, Migliori GB, Sester M, Rieder HL, Ehlers S, Goletti D, et al. LTBI: Latent tuberculosis infection or lasting immune responses to M. tuberculosis? A TBNET consensus statement. Eur Respir J 2009;33:956-73.
9. Pai M. Spectrum of latent tuberculosis – Existing tests cannot resolve the underlying phenotypes. Nat Rev Microbiol 2010;8:242.
10. Joshi R, Narang U, Zwerling A, Jain D, Jain V, Kalantri S, et al. Predictive value of latent tuberculosis tests in Indian healthcare workers: A cohort study. Eur Respir J 2011;38:1475-7.
11. Rangaka MX, Wilkinson KA, Glynn JR, Ling D, Menzies D, Mwansa-Kambafwile J, et al. Predictive value of interferon-γ release assays for incident active tuberculosis: A systematic review and meta-analysis. Lancet Infect Dis 2012;12:45-55.
12. Al Jahdali HH, Baharoon S, Abba AA, Memish ZA, Alrajhi AA, AlBarrak A, et al. Saudi guidelines for testing and treatment of latent tuberculosis infection. Ann Saudi Med 2010;30:38-49.
13. Dimoliatis ID, Liaskos CA. Six Mantoux tuberculin skin tests with 1, 2, 5, 10, 20, and 50 units in a healthy male without side-effects – Is skin reaction a linear function of tuberculin dose? Cases J 2008;1:115.
14. Christopher DJ, Shankar D, Datey A, Zwerling A, Pai M. Safety of the two-step tuberculin skin test in Indian health care workers. Int J Mycobacteriol 2014;3:247-51.