Original Article

Utility of the Interferon-Gamma Release Assay for Latent Tuberculosis Infection Screening among Indian Health-Care Workers

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Abstract

Background: The utility of interferon-gamma release assays (IGRAs) for latent tuberculosis infection (LTBI) screening among health-care workers (HCWs) in low- and middle-income countries (LMICs) remains unclear. **Methods:** This was a prospective cohort study among HCW trainees undergoing annual LTBI screening via tuberculin skin test (TST) and QuantiFERON® TB Gold Test-in-tube (QFT-GIT) in Pune, India. TST induration ≥ 10 mm and QFT-GIT ≥ 0.35 IU/ml were considered positive. Test concordance was evaluated at entry among the entire cohort and at 1 year among baseline TST-negative participants with follow-up testing. Overall test agreement was evaluated at both timepoints using the kappa statistic: fair (k < 0.40), good (0.41 ≥ k ≤0.60), or strong (k > 0.60). **Results:** Of 200 participants, prevalent LTBI was detected in 42 (21%) via TST and 45 (23%) via QFT-GIT; QFT-GIT was positive in 27/42 (64%) TST-positive and 18/158 (11%) TST-negative trainees. Annual TST conversion was 28% (40/142) and included 11 trainees with baseline TST-/IGRA+; QFT-GIT was positive in 17/40 (43%) TST-positive and 5/102 (5%) TST-negative trainees. Overall test concordance was 84% (k = 0.52; 95% confidence interval [CI]: 0.38–0.66) and 80% (k = 0.44; 95% CI: 0.29–0.59) at baseline and 12 months, respectively. **Conclusions:** We observed good overall agreement between TST and QFT-GIT, and QFT-GIT detected additional LTBI cases among TST-negative trainees with possible early detection of LTBI conversion. Overall, our results support the use of IGRA for annual LTBI screening among HCWs in a high burden LMIC setting.

Keywords: Concordant and discordant test results, health-care workers, latent tuberculosis infection, Quanti FERON® TB Gold Test-in-tube (QFT-GIT), tuberculin skin test

Introduction

Tuberculosis (TB) poses a significant risk to health-care workers (HCWs), particularly in low- and middle-income countries (LMICs).[1-3] In India, the 2018 TB notification rate was at least 6-fold higher among HCWs than the general population.[4] Critical World Health Organization (WHO)-recommended interventions include infection prevention and control measures as well as regular HCW latent tuberculosis infection (LTBI) screening along with preventive TB treatment.[5] However, which screening test should be used, the tuberculin skin test (TST) or the interferon gamma release assay (IGRA) for LTBI, remains unclear.

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The limitations of TST (e.g., Bacillus Calmette–Guerin [BCG] cross-reaction, persistent positivity, and arbitrary induration cutoffs[6]) and IGRA (e.g., unexplained conversions/reversions[7]) are well known. Notably, 2018 WHO guidelines

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deem the two tests to be equivalently imprecise and recommend either for LTBI screening among high-risk population groups, yet this strong recommendation is based on very low-quality evidence.[8] Currently, IGRAs are more commonly used in high-income settings[9] due to the inter-rater variability in assessing TST induration.[10] There is, however, little evidence concerning the utility of IGRA and the concordance of TST and IGRA among HCWs with high TB exposure from LMIC health-care settings.

In the context of the world's largest underlying TB burden, India reports high rates of LTBI and TB disease among HCWs.[1,11-14] Currently, LTBI screening remains limited to TST due to presumed inaccuracy.[15] We examined the concordance of TST and IGRA during annual LTBI screening among a prospective longitudinal cohort of HCW trainees established at a large public teaching hospital in Pune. Our results may have implications for the use of IGRA among HCWs in India and other high TB burden LMIC settings.

Methods

Between May 2016 and December 2017, a prospective cohort of HCW trainees (medical residents and nursing students) was established at Byramjee Jeejeebhoy Government Medical College (BJGMC) in Pune, India. The primary outcome was LTBI incidence. Study methods have been described in detail elsewhere.[16] Briefly, the cohort included medical residents and nursing students ages ≥18 years with no previous history of active TB. Following written informed consent, detailed demographic and clinical histories of the participants were recorded in clinical record form.[16] Participants underwent LTBI testing via TST and QuantiFERON® TB Gold Test-in-tube (QFT-GIT; Cellestis Ltd.) at study entry and 12 months; additional QFT-GIT testing was done at 1, 3, 6, and 9 months. Immediately following the 3 ml blood collection for QFT-GIT (performed and analyzed according to manufacturer instructions), TST (Span Diagnostics, India) was administered (5 units of purified protein derivative), and the reaction was read at 48–72 h. TST induration ≥10 mm and QFT-GIT ≥0.35 IU/ml were considered positive. The study was approved by the Ethics Committee and Institutional Review Board at BJGMC, India, and Johns Hopkins University, USA.

For this analysis, we examined TST and IGRA results at baseline among the overall cohort and at 12 months among a subcohort of baseline TST-negative HCWs. For each timepoint, test results were summarized as TST+/IGRA+, TST−/IGRA−, TST+/IGRA−, or TST-/IGRA+; we calculated the proportion of TST-positive cases detected by IGRA (TST+/IGRA+) and the proportion of TST-negative cases identified as LTBI by IGRA (i.e., additional LTBI cases identified by IGRA; TST−/IGRA+). To assess overall test concordance, we calculated the proportion of concordant results (TST+/IGRA + plus TST−/IGRA−) at both timepoints and assessed agreement using the kappa statistic (k) with 95% confidence interval (CI); agreement was categorized as fair (k < 0.40), good (0.41 ≥ k ≤0.60), or strong (k > 0.60).[17] All analyses were performed using STATA version 13.1(STATA 13.1, Copyright 1985-2015 StataCorp LP, StataCorp, Lakeway Drive, College Station, Texas ,USA).

Results

Study population characteristics have been described elsewhere.[16] Briefly, the overall cohort (n = 200) was comprised of 90 (45%) nursing students and 110 (55%) medical residents, the median age was 25 (interquartile range, 19–27) years, and 89 (45%) reported exposure to a sputum smear-positive TB patient in the past 1 year.

Table 1 summarizes TST and IGRA results at study entry and 12 months. Baseline LTBI prevalence was 21% (n = 42) and 22% (n = 45) via TST and IGRA, respectively. QFT-GIT detected 27 (64%) of the 42 TST-positive HCWs (i.e., TST+/IGRA+) and identified 18 (11%) additional LTBI cases among the 158 TST-negative HCWs. Of these TST−/IGRA + HCWs, 53% (n = 10/18) reported contact with a sputum smear-positive TB patient, and interferon-gamma levels ranged between 0.41 IU/ml and 6.96 IU/ml; 50% (n = 9/18) had QFT-GIT >0.7 IU/ml.

The analysis at 12 months included 142 HCWs who were TST negative at entry and had TST and IGRA results at 1 year [Table 1]. Annual LTBI incidence (conversion at 1 year) was 28% (n = 40) via TST; of these, 11 (28%) HCWs were identified by IGRA at study entry (i.e., baseline TST−/IGRA+). QFT-GIT detected 17 (43%) of the 40 TST-positive HCWs (TST+/IGRA+) and identified 5 (5%) additional LTBI cases among the 102 HCWs who remained TST negative. Of these TST−/IGRA + HCWs, 40% (2/5) reported exposure to a sputum smear-positive TB patient in the past 12 months, and interferon-gamma levels ranged between 0.35 IU/ml and 2.18 IU/ml; one had QFT-GIT > 0.70 IU/ml.

Overall test concordance was observed in 167/200 (84%, k = 0.52; 95% CI: 0.38–0.66) at baseline and 114/142 (80%, k = 0.44; 95% CI: 0.29–0.59) at 1 year, corresponding to good agreement.

Discussion

This prospective cohort study suggests good overall agreement between TST and IGRA during annual LTBI screening among HCW trainees in India.[18-20] In addition, QFT-GIT identified LTBI among TST-negative HCWs with possible early LTBI detection among 28% of HCW trainees before TST conversion was observed in annual follow-up. Overall, our study provides country-specific data supporting the use of IGRA among HCWs.

In our cohort, LTBI prevalence was nearly equivalent whether determined by TST or IGRA. A recent systematic review of studies conducted among HCWs in LMICs between 2005 and 2017 also reported similar pooled LTBI prevalence in high TB burden countries via TST (55%; n = 5 studies) and

Table 1: Summary of concordant and discordant results of the tuberculin skin test and interferon-gamma release assay during annual latent tuberculosis infection screening among health-care worker trainees in Pune, India

Interferon-gamma release assay[a]	Tuberculin skin test		Total
	≥10 mm (positive)	<10 mm (negative)	
Baseline (IU/ml)			
≥0.35 (positive)	27	18	45
<0.35 (negative)	15	140	155
Total	42	158	200
12 months (IU/ml)			
≥0.35 (positive)	17	5	22
<0.35 (negative)	23	97	120
Total	40	102	142

[a]QuantiFERON® TB Gold Test-in-tube (Cellestis Ltd.)

IGRA (56%; *n* = 3 studies).[7] Fewer studies have assessed overall agreement between IGRA and TST among HCWs in similar settings. Compared to the good baseline test agreement observed in our relatively small cohort (84%; k = 0.52), an analysis of prevalent LTBI among HCWs in Brazil (*n* = 664) found low test agreement (69%; k = 0.31),[21] yet agreement was found to be high (81.4%; k = 0.61) in a study among 726 HCWs in rural India.[13] Notably, our longitudinal study design allowed us to follow LTBI status over time, revealing that 61% of the additional LTBI cases identified by QFT-GIT at entry (i.e., TST−/IGRA+) had TST conversion at 1-year follow-up. Although QFT-GIT levels have not yet been optimized for the Indian population,[22] our findings suggest early LTBI detection among 28% of HCWs with annual TST conversion; applying the certainty cutoff, QFT-GIT >0.70 IU/ml would still identify 10 additional HCWs as LTBI positive.

Our study provides new data supporting the most recent WHO LTBI guidelines. In the context of good test concordance, the decision to limit LTBI screening to TST in India should be driven by factors other than individual test precision.[8] Particularly in health-care settings with existing laboratory infrastructure and expertise, IGRA may be better positioned than TST to overcome barriers to regular LTBI screening among HCWs in LMICs. Specifically, low perceived TB risk, complacency, and TB stigma among clinic staff/hospital administrators may be mitigated by the one-visit convenience of a single blood draw.[23,24] IGRA also eliminates the impact of BCG cross-reaction, boosting with serial screening, and global shortages make it an attractive option for health-care institutions in LMICs.[5,25]

Conclusion

Finally, the potential for early detection of LTBI status conversion suggested by our study might allow for earlier initiation of preventive TB treatment among some HCWs.

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Conflicts of interest

There are no conflicts of interest.

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