Safety of the two-step tuberculin skin test in Indian health care workers

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ARTICLE INFO

Article history:
Received 25 September 2014
Accepted 2 October 2014
Available online 23 October 2014

Keywords:
Tuberculosis
Tuberculin skin test (TST)
Two-step tuberculin skin test
Healthcare workers
Adverse events
Latent TB infection (LTBI)

ABSTRACT

Background: Health care workers (HCW) in low and middle income countries are at high risk of nosocomial tuberculosis infection. Periodic screening of health workers for both TB disease and infection can play a critical role in TB infection control. Occupational health programs that implement serial tuberculin skin testing (TST) are advised to use a two-step baseline TST. This helps to ensure that boosting of waned immune response is not mistaken as new TB infection (i.e. conversion). However, there are no data on safety of the two-step TST in the Indian context where HCWs are repeatedly exposed.

Materials and methods: Nursing students were recruited from 2007 to 2009 at the Christian Medical College and Hospital, Vellore, India. Consenting nursing students were screened with a baseline two-step TST at the time of recruitment. From 2007 to 2008 adverse events were recorded when reported during the TST reading (Cohort A). Nurses recruited in the final study year (2009) answered an investigator administered questionnaire assessing all likely side-effects (Cohort B). This information was extracted from the case report forms and analysed.

Results: Between 2007 and 09, 800 trainees consented to participate in the annual TB screening study and 779 did not have a past history of TB or recall a positive TST and were selected to administer TST. Of these, 755 returned for reading the result and had complete data and were included for the final analysis – 623 subjects in (cohort A) and 132 in (cohort B). These were included for the final analysis. 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.
Introduction

For more than a hundred years, the tuberculin skin test (TST) has remained the mainstay for the testing of latent tuberculosis infection (LTBI). A new alternative test for LTBI is now available, the interferon-γ assay (IGRA) [1]. In theory, IGRA have many potential benefits over the conventional TST, but may not necessarily be preferred in high TB incidence settings [2].

The World Health Organization (WHO) has made the following recommendations [3]:

- “There is insufficient data and low quality evidence on the performance of IGRA in low- and middle-income countries, typically, those with a high TB and/or HIV burden.”
- “IGRAs are more costly and technically complex to do than the TST. Given comparable performance, but increased cost, replacing TST by IGRA as a public health intervention in resource-constrained settings is not recommended.”

Therefore, TST continues to be recommended for large-scale screening in high TB burden countries, including India.

With the advent of MDR and XDR strains of TB, the high risk of nosocomial TB in high burden settings has regained focus. Until recently, TB infection control (TBIC) has been neglected in TB endemic countries [4]. The stop TB partnership created a subgroup on TBIC, and WHO released guidelines for TBIC in resource-limited settings in 2009 [5]. The estimated prevalence of LTBI among HCWs in low- and middle-income countries is 54%, with an annual risk of TB infection (ARTI) ranging from 0.5% to 14.3% [6]. The median annual incidence of TB infection in low- and middle-income countries attributable to health care work has been estimated at 5.8% [6].

Studies conducted on health care trainees in this tertiary care hospital showed the prevalence of LTBI was 47.8% in nursing students [7], with an ARTI of 7.8% [8].

High prevalence of LTBI in health care workers (HCWs) and the very high ARTI is presumably due to the exposure to large numbers of diagnosed and undiagnosed smear-positive pulmonary TB cases, managed at the hospital and worsened by inadequate implementation of TBIC policies. These realities are common across Indian health care facilities [9,10]. Therefore, there is a strong case for the implementation of regular screening for TB infection in HCWs and health care trainees [11]. In a developing country like India, with its high-burden of TB, the simplicity and low cost of the TST makes it a more feasible screening test. Guidelines for occupational serial testing of HCWs suggest that all newly recruited HCWs should undergo a baseline 2-step TST, unless they have documented prior positive TST. In the absence of a baseline two-step TST, distinguishing boosting from conversions (new infection) is difficult. Boosting of TST upon re-testing in the absence of new infection is due to recall of waned immunity. It is common and is nonspecific as it is associated with remote TB infection, non-tuberculous mycobacterial sensitivity, and BCG vaccination. If serial TST is planned, an initial 2-step TST is required. Otherwise, false positive TST due to boosting might be misinterpreted as conversions. However, there are no data from India on safety of doing a two-step TST in HCWs who are repeatedly exposed.

Subjects and methods

Study population

This study, described in previous publications [7,8], was conducted at the Christian Medical College (CMC), Vellore, a large (2200 beds) tertiary referral medical school in Vellore, a town in Southern India. All nursing students were prospectively approached for participation in a cohort study to assess prevalence and risk factors for LTBI and the annual rate of TB infection. The study protocol was approved by the institutional review boards of CMC, Vellore and McGill University Health Centre, Montreal. All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki.

The College of Nursing at CMC offers several different training programs (Diploma, BSc, Post Diploma courses, Fellowship courses, MSc, Doctoral [PhD]) and, on average, 500–600 students are in training at any given time.

Methods

All students who provided informed consent to participate in the screening were enrolled. Students completed a written case report form (CRF), providing information on demographics, socio-economic and educational status, previous work in health care, and details on exposure to active TB patients in the hospital and in the community. A symptom screen was done for current active TB, and an assessment for any underlying immune-compromising condition or treatment was made. Examination included inspection for a BCG scar.

Students were tested with TST at baseline using the two-step TST protocol [12]. Two tuberculin units (0.1 ml) of RT23 PPD (Staten Serum Institute, Copenhagen) were injected intradermally. After 48–72 h, the induration was measured by a trained reader. An induration of ≥10 mm was considered positive at baseline [13]. If TST was negative (<10 mm) at baseline, participants underwent the second step of the TST testing at 7–14 days to determine boosting.

After the first TST test in these subjects, those recruited in 2007–2008 were educated about adverse events associated with the TST that could be expected, such as: blistering, fever,
body aches, itching at the site of TST, etc. They were asked to report any adverse event at the time of reading of results and these were recorded in the case report forms (CRF). For the purpose of this study, this group was categorized as cohort A. During the 3rd year (2009), the students were merely told that side-effects could be expected, without providing a comprehensive list of specific adverse events. While reading the TST, an investigator ran a checklist of adverse events (Table 1), facilitating a guided self-report of side-effects. This group was categorized as cohort B. Subjects from both the groups who had a negative TST underwent repeat TST testing 7–14 days later. If any additional adverse events were encountered, they were noted in the CRF.

Results

Of the students admitted to the various programs during the period 2007–2009, 800 consented to participate in the annual TB screening study and 779 did not have a past history of TB or recall a positive TST and were selected for TST testing. Of these, 755 returned for reading the results and had complete data and were included for the final analysis: 623 subjects in (cohort A) and 132 in (cohort B). The characteristics of the study population are enumerated in Table 2.

The TST results are captured in Table 3. A total of 334 subjects in cohort A and 82 subjects in cohort B had a negative TST and had a repeat TST (second step of the 2-step TST).

The adverse events reported are enumerated in Table 4. In cohort A, the vast majority (98.7%) of the subjects did not report experiencing any adverse events; a small fraction (1.3%, 8 subjects) reported adverse events, which were not serious. Blistering was seen in only 2 subjects (0.3%) and only 1 subject showed signs of local infection and this promptly responded to a course of oral antibiotic. Only 2 subjects had fever and 1 of them also had body aches and they were prescribed an antipyretic.

In cohort B, the investigator elicited self-reported symptoms that were encountered in 20% of the subjects, while the majority (75%) did not report any symptoms. All those who reported symptoms (25%) had itching and also local pain, except 1. One subject reported fever. These subjects received symptomatic treatment as required, and none of them required any specific treatment or hospitalization.

The subjects who had 2-step TST reported the same side-effects, and none of them had a severe reaction.

Discussion

The rise of MDR and XDR strains of TB has led to a rise in concern in the HCW community. In high burden settings like India, with inadequate or no triage of infectious outpatients with proven or suspected TB, overcrowding and poor ventilation, HCWs and healthcare trainees are constrained to come into close contact with infectious TB patients. In this context it is essential to evolve sound TBIC protocols, and the WHO guidelines of 2009 are a step in the right direction [5,14]. However, in a high burden setting, due to logistical constrains, notwithstanding the best intentions, the risks will continue to exist. In such a situation, there should be a high index of suspicion with regards to TB, resulting in prompt diagnosis and appropriate anti-TB treatment for health workers. The goal should be to prevent TB disease to the extent possible. In this regard, the diagnosis of LTBI by periodic screening is a strategy that has been found to be useful, and there is anecdotal evidence for its efficacy [14]; this strategy is therefore recommended for all HCWs [11].

Traditionally, screening HCWs for LTBI was done with the TST; however, there are some limitations for its use in serial testing HCWs. Particular problems have arisen with the use of repeated tuberculin tests to detect new infection in high-risk populations such as initially tuberculin-negative contacts of active cases, and workers with occupational exposure. This has revealed that tuberculin reactions may decrease in size (reversion) or increase in size because of: (1) random variability from differences in administration, reading, or biologic response; (2) immunologic recall of pre-existing delayed type hypersensitivity to mycobacterial antigens (boosting); or (3) new infection (conversion) [15]. In recent years, the introduction of novel IGRAs has provided an alternative to the 100-year-old TST, as well as a dilemma to the medical fraternity, with regard to the choice of the most appropriate test. There are two IGRAs commercially available: the TSPOT.TB assay (Oxford Immunotech, Abingdon, UK) and the QuantiFERON-TB Gold In-Tube (QFT) assay (Cellestis Ltd, Carnegie, Australia). The advantages IGRA assays may have over the TST include: no influence of prior BCG vaccination or non-TB mycobacterial (NTM) infection. Furthermore, IGRAs are in vitro tests and eliminate concerns regarding adverse events or boosting and do not require a return visit [1,8,16–18]. The use of IGRAs for HCWs is increasing and there are several published studies and two systematic reviews published [8,19–21]. While these assays show promise for screening in low incidence settings, they appear to have a lower sensitivity in high incidence settings such as India [8,16,19]. The predictive (prognostic) value of both TST and IGRA for identifying those at highest risk of progressing to active TB disease appears to be limited, especially in high TB burden settings [3,8,3]. Finally, IGRAs are substantially more expensive and require skilled laboratory personnel to run the tests.

<table>
<thead>
<tr>
<th>Table 1 – Adverse events questionnaire.</th>
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<tbody>
<tr>
<td><strong>Adverse Event Check list (Cohort –B)</strong></td>
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<tr>
<td><strong>Skin effects</strong></td>
</tr>
<tr>
<td>o None</td>
</tr>
<tr>
<td>o Discoloration</td>
</tr>
<tr>
<td>o Immediate reaction</td>
</tr>
<tr>
<td>o Blistering</td>
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<tr>
<td>o Ulceration</td>
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<tr>
<td>o Scar formation</td>
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<tr>
<td><strong>Pain</strong></td>
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<tr>
<td>o Mild</td>
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<tr>
<td>o Moderate</td>
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<tr>
<td>o Severe</td>
</tr>
<tr>
<td><strong>Itching</strong></td>
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<tr>
<td><strong>Fever</strong></td>
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<tr>
<td><strong>Other</strong></td>
</tr>
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In this study the safety and good tolerance of TST was demonstrated when used for screening HCWs. The adverse events encountered were extremely low and trivial. Although investigator-elicited self reporting of invariably minor symptoms was encountered in nearly 20% of the subjects, the adverse events that were reported were much lower (1.3%). The difference between the two modes of eliciting patient experience is to be expected, with the subjects becoming constrained to report even trivial symptoms while self-reporting on administration of a questionnaire.

The time-tested, simple and inexpensive TST, therefore, remains a safe and fairly well tolerated test for screening of TB in HCWs and health care trainees. In resource limited settings, TST should remain the test of choice and has the potential for wider use as a screening tool due to the lower skills required and the lesser cost. These studies have shown that young health care trainees are under great risk of LTBI [1,7–9]. While this study had addressed only the risk for nursing trainees, the scenario is probably no different for medical and other allied health sciences trainees. It is recommended that the model that was adopted for this study be applied to all health care trainees. This entails screening at entry to the program and annually thereafter. It is not recommended to provide prophylactic treatment for those that are positive at the first point of testing at entry, since the benefit is more for those who converted relatively recently, and there is no way of knowing which of the positives fall in this category. Furthermore, in a high prevalence country like India, the prevalence of LTBI at entry could be high, thus administration and supervising prophylaxis at such a large scale would pose logistical challenges. For these reasons, it is preferred to reserve prophylactic treatment only for the recent converters detected on annual screening. This group is most likely to benefit from prophylactic treatment and therefore more likely to comply with it. It is imperative to rule out active TB disease before initiation of preventive therapy.

In conclusion, TST is a simple and inexpensive tool for screening of HCWs and health care trainees in high burden, resource limited settings. It is recommended that a wide scale screening of HCWs and health care trainees be implemented.

**Conflict of interest**

None.

**REFERENCES**


[12] ATS, Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America. (IDSA), September 1999, and the sections of this statement, Am. J. Respir. Crit. Care Med. 161 (2000) S221–S247.


