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Detection of latent tuberculosis infection among laboratory personnel at a University Hospital in Eastern Saudi Arabia using an interferon gamma release assay

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Summary
Background/aims: A few recent reports have demonstrated an elevated prevalence of latent tuberculosis infection (LTBI) among laboratory personnel. We sought to evaluate the prevalence of LTBI among laboratory personnel using the QuantiFERON-TB Gold In-Tube (QFT-GIT) assay and to assess the risk factors associated with positive test results.
Methods: The study population included laboratory personnel who were working in the routine diagnostic laboratories of different departments of a university hospital. Subjects were interviewed using a standardized questionnaire that assessed information related to risk factors for LTBI and underwent the QFT-GIT assay.
Results: Positive QFT-GIT tests results were detected in 19.4% (26/134) of the laboratory personnel. The following factors were significantly associated with positive QFT-GIT results: age $\geq$ 30 years [odds ratio (OR): 4.741, 95% CI: 1.41—17.50, $P = 0.004$]; duration of employment in the healthcare profession >10 years ($P < 0.0001$); and non-Saudi nationality (OR: 21.67, 95% CI: 6.69—73.94, $P < 0.0001$).

Abbreviations: LTBI, latent tuberculosis infection; TST, tuberculin skin test; MTB, *Mycobacterium tuberculosis*; BCG, Bacillus Calmette-Guérin; NTM, non-tuberculous mycobacteria; RD1, region of difference; IFN-γ, interferon gamma; IGRAs, interferon gamma release assays; ESAT-6, early secreted antigenic target 6; CFP-10, culture filtrate protein 10; CDC, Centers for Disease Control and Prevention; HCWs, health care workers; QFT-GIT, QuantiFERON-TB Gold In-Tube; OR, odds ratio; CI, confidence interval.

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Conclusion: These data highlight the need for effective institutional TB infection control plans. Additionally, our data reinforce the necessities of pre-employment and regular LTBI screening of laboratory personnel and the importance of offering preventive therapies to positive subjects to prevent the progression to active disease.

Introduction

Tuberculosis in Saudi Arabia is still not fully controlled, despite the enormous efforts exerted by the Ministry of Health. Saudi Arabia is still a country in the intermediate prevalence category [1]. Several factors may play vital roles in the ongoing transmission of TB in Saudi Arabia, including a high number of expatriates, the Hajj pilgrimage, Omra, and the social habits of Saudi citizens.

The current treatment strategy for active TB is inadequate for disease elimination, partially due to latent TB infections (LTBIs). It has been estimated that one-third of the world population has an LTBI [2], with an annual risk of 0.1% of developing active TB [3]. Therefore, identifying and treating latently infected subjects who are at an increased risk of progressing to active disease are key elements of TB control programs [4]. Such preventive treatment diminishes the risk of subsequently developing active TB by approximately 90% [5].

Over the last century, the tuberculin skin test (TST) has been the traditional testing method for the diagnosis of LTBI in different populations throughout the world [6]. However, the TST has many limitations. The test uses a relatively crude mix of antigens from *Mycobacterium tuberculosis* (MTB); as a result, false-positive reactions can occur because of previous Bacillus Calmette-Guérin (BCG) vaccination or sensitization to non-tuberculous mycobacteria (NTM) [7].

To overcome the relatively low specificity associated with the TST, antigens encoded in the region of difference (RD1) of the MTB genome were used to develop T lymphocyte-based interferon (IFN)-γ release assays (IGRAs), which became commercially available in 2005. IGRAs measure the cellular immune responses to a few MTB-specific antigens, including early secreted antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10) of the RD1 in comparison with the mixed non-specific antigens used in the TST [8].

IGRAs are standardized, quality-controlled laboratory tests that provide results within 24 h. They have excellent specificity and are unaffected by BCG and NTM [7,9]. Unlike the TST, they require a single patient visit, the result is read by an instrument and, thus, is objective, and they do not have a 'booster' effect. IGRAs appear to be at least as sensitive as the TST [7].

IGRAs may seem too expensive at first glance. However, taking into account the expense of follow-up examinations due to false-positive TST results, the overall cost associated with IGRA screening is fairly acceptable. The use of IGRAs is steadily increasing in low or intermediate incidence countries. In 2005 and in 2010, the US Centers for Disease Control and Prevention (CDC) recommended that IGRAs be used in all situations in which the TST is currently used [10].

Health care workers (HCWs) have been known to be at a high risk for TB infections due to occupational exposures to patients with TB infections or specimens with MTB [11]. Additionally, HCWs are at a particular risk for the progression to TB disease [12]. Regarding the prevalence of LTBI among HCWs, few studies have been conducted in high or intermediate incidence settings. Furthermore, many of these studies used the TST and were thus hampered by its low specificity and its cross reactivity with BCG and NTM infections [13].

According to Saudi national policy, as well as countries of East Asia, from which most of the expatriates are always recruited, all infants are required to be vaccinated with BCG. The usefulness of the TST in detecting LTBI is therefore limited due to the possibility of false positives as a result of BCG vaccination [7].

A few recent reports showed a higher prevalence of LTBI in laboratory personnel than in other HCWs, but they included only a limited number of laboratory personnel [8,11,14]. There has been no large-scale study that specifically focused on the issue of LTBI in laboratory personnel who have a high level of exposure to specimens from patients with TB. This study was undertaken to evaluate the prevalence of LTBI among laboratory personnel at a university hospital using IGRAs and to assess the risk factors related to positive test results.

Materials and methods

Study design

A cross sectional comparative survey was conducted. The study protocol was approved by the institutional ethics committee.

Study population

All laboratory personnel (technologist and supervisors) affiliated with the routine diagnostic laboratories at a university hospital in eastern Saudi Arabia during the time of the study were invited to participate in the study. The routine diagnostic laboratories included the departments of microbiology, immunology/serology, and hematology/blood bank. The study was conducted over a period of 6 months (January 2012—June 2012). The total number of subjects available for the study was 156. The number of participants after applying the exclusion criteria was 149, while seven subjects were excluded from the study. Ten personnel were enrolled in a pilot study then excluded from the study. Thus, the participants of the study were 139 laboratory personnel.

Exclusion criteria included a positive history of active TB, a history of household contact with TB patients, clinical evidence of active TB, and the use of immunosuppressive drugs.

Study objectives and procedures were explained to each of the study participants, and it was clearly explained to participants that the results would be confidential. A written informed consent was obtained from each participant prior to inclusion in the study.

All participants were interviewed using a standardized questionnaire, and data were collected by the researcher [15]. The questionnaire provided information on possible risk factors for LTBI, including data on age, sex, nationality, education level, present workplace, duration of work in the healthcare profession, and any history of previous TST.

The questionnaire was reviewed by an expert panel for suitability and efficacy. A pilot study was conducted on 10 randomly selected personnel who were excluded from the main study.

Interferon-γ release assay

For the IGRA, the QuantiFERON-TB Gold In-Tube (QFT-GIT) test was used according to the manufacturer's protocol (Cellestis Ltd., Carnegie, Australia). In brief, venipuncture was performed and 3 ml of whole blood was collected into three 1-ml heparinized tubes. One tube served as the negative control containing only heparin. The second tube served as the positive control containing the T cell mitogen phytohemagglutinin, and the third tube included the peptides ESAT-6, CFP-10 and TB7.7. After being incubated upright at 37 °C for 24 h, the specimens were centrifuged at 2000—3000 rpm for 15 min. The supernatant was frozen at −20 °C for further analysis. The release of IFN-γ in response to MTB peptides was measured by an enzyme-linked immunosorbent assay. The results were calculated using the QFT software. The result was considered positive if the IFN-γ was at least 0.35 IU/ml. It was considered indeterminate if the corrected IFN-γ release for tuberculin-specific antigen was less than 0.35 IU/ml and the positive control for mitogen was less than 0.5 IU/ml.

Statistical analysis

Data were entered in computer using SPSS for windows version 17.0 (SPSS Inc., Chicago, IL). The data were described using the frequency, the distribution, the mean, and the standard deviation. Univariate analyses were conducted using the Chi-square test and Fisher's exact test for qualitative variables. The odds ratio (95% CI) was calculated to quantify the risk of different factors. The significance of the results was at 5%.

Results

A total of 139 laboratory personnel joined the study. Due to indeterminate QFT-GIT assay results, five were excluded from the analysis. Baseline characteristics of the study participants are shown in Table 1. Their mean age was 33.0 ± 9.2 years, with a range of 21—60 years. Males constituted 53.7% of the study participants (72 participants). The mean duration of work in the health care profession was 6.9 ± 7.9 years, with a range of 0.08—37.0 years. The highest contribution was from the microbiology department (59 subjects, 44%). Participants from other departments included 61 laboratory technicians from the immunology/serology and hematology/blood bank labs. There were 14 trainees who rotated between different laboratory sections, spending two months in each department (non-mutually exclusive). The majority of the study population (97 participants, 72.4%) had Saudi nationality. East Asians were the most frequent non-Saudi participants (34/134, 25.4%). The QFT-GIT was positive in 19.4% (26) of the study participants.

Table 1 Characteristics of the study participants.

Characteristic	No. (%)
Age (years): range (mean ± SD)	21–60 (33.0 ± 9.2)
Gender	
Male	72 (53.7)
Female	62 (46.3)
Duration of work (years): range (mean ± SD)	0.08–37.0 (6.9 ± 7.9)
Workplace	
Microbiology department	59 (44.0)
Non-microbiology departments	61 (45.5)
Trainees (rotators)	14 (10.5)
Nationality	
Saudi	97 (72.4)
East Asia	34 (25.4)
Middle East	3 (2.2)
TST history	
Negative TST in medical history	28 (20.9)
Positive TST in medical history	8 (6.0)
No TST in medical history	86 (64.1)
Not sure about TST in medical history	12 (9.0)
Results	
Negative	108 (80.6)
Positive	26 (19.4)

Risk factors for a positive QFT-GIT test were analyzed. Positive QFT-GIT results were significantly associated with the non-Saudi nationality (OR: 21.67, 95% CI: 6.69–73.94, $P < 0.0001$). An age ≥ 30 years was associated with an increased risk of QFT-GIT positivity (OR: 4.741, 95% CI: 1.41–17.50, $P = 0.004$), as well as duration of work in healthcare service ($P < 0.0001$). Trainees ($n = 14$), who rotated between different laboratory sections, were all negative for the QFT-GIT (Table 2). No statistically significant association was observed between test positivity and gender, workplace or the TST status of the study participants, after excluding those who were not sure about their status from the analysis.

Discussion

The global burden of TB remains enormous, with an estimated 8.7 million new cases and 1.4 million deaths in 2011 [16]. Furthermore, it has been estimated that one third of the world population has LTBI [2], and approximately 10% of LTB-infected subjects will progress to active TB during their lifetime [17]. The importance of increasing the specificity for the diagnostic tests lies in reducing LTBI overestimation, subsequently reducing the wasted resources on treating false positives; these resources could instead be allocated to latently infected subjects. In addition, using the more specific IGRAs would save HCWs and other TB contacts

Table 2 Correlation between QFT-GIT positivity and socio-demographic data, the work history and the TST status of the study participants.

Item	Categories	Positivity, no. (%)	OR (95% CI)	Significance
Gender	Male	16/72 (22.2)	1	
	Female	10/62 (16.1)	0.67 (0.26–1.75)	$\chi^2 = 0.79$ $P = 0.374$
Age	20–29	4/54 (7.4)	1	
	≥30	22/80 (27.5)	4.741 (1.41–17.50)*	$\chi^2 = 8.32$ $P = 0.004$*
Duration of work	≤2	0/47 (0.0)	1	
	2–5	4/31 (12.9)	NA	$^{FE}P = 0.022$*
	6–10	6/32 (18.8)	NA	$^{FE}P = 0.003$*
	>10	16/24 (66.7)	NA	$\chi^2 = 40.45 P < 0.0001$*
Workplace	Micro	11/59 (42.3)	1	
	Non-micro	15/61 (57.7)	1.42 (0.55–3.75)	$\chi^2 = 0.62$ $P = 0.429$
	Trainee	0/14 (0.0)	0.0	$^{FE}P = 0.109$
Nationality	Saudi	6/97 (6.2)	1	
	Non-Saudi	20/34 (54.1)	21.67 (6.69–73.94)*	$\chi^2 = 43.85 P < 0.0001$*
TST status	Positive TST in medical history	3/8 (37.5)	1	
	Negative TST in medical history	5/28 (17.9)	0.36 (0.05–2.76)	$^{FE}P = 0.338$
	No TST in medical history	12/86 (14.0)	0.27 (0.05–1.66)	$^{FE}P = 0.113$

χ^2, Chi-square test; FA, Fisher's exact test; NA, OR is undefined.
* Statistically significant at $P \leq 0.05$.

from unnecessary follow-up and potential adverse effects of chemotherapy. With the IGRAs, we have, for the first time, a test that allows for valid statements regarding the LTBI prevalence. The use of IGRAs is increasingly recommended, particularly in BCG-vaccinated populations [18].

Recently, a few large-scale studies addressed the prevalence of LTBI among HCWs, and it was found to be significantly higher than in the general population [19—21]. Although laboratory technicians were included in these studies, the exact prevalence in laboratory personnel was not reported [20,21]. A higher prevalence of LTBI in laboratory personnel than in other HCWs was demonstrated in few studies [8,14]. However, only limited data on this issue are available in the literature. Additionally, to the best of our knowledge, this is the first study in Saudi Arabia focusing on laboratory personnel. We detected a prevalence of 19.4% (26/134) of QFT-GIT positivity. Comparing our results with the few data in the literature, the prevalence of LTBI among laboratory personnel were found to be 21.4% in Korea [15], 19% in Japan [11], and 54% in India [8], three countries that represent intermediate, low, and high incidence settings, respectively. Bearing in mind that Saudi Arabia is an intermediate TB burden country, the data show that the prevalence of IGRA positivity in laboratory personnel would be dependent on the incidence of TB in the general population.

In the present study, the prevalence of LTBI assessed by QFT-GIT correlated significantly with age. In the subgroup with participants under 30 years old, the LTBI prevalence was 7.4%, while in the subgroup with participants above 30, the prevalence increased to 27.5%. Similar results were obtained from Germany, Portugal, and French HCWs when the youngest and oldest age categories were compared [22]. The higher LTBI prevalence in older participants might be explained by longer exposure time at work or by a cohort effect. We also observed that the length of work in the healthcare sector was a significant predictor for LTBI, which might reflect the cumulative exposure to TB. The significant correlation between the level of IFN-γ and both age ($P = 0.004$) and the length of employment ($P < 0.0001$) detected in the present study was in agreement with many other studies [15,19,20,23].

Especially in fields with an increased risk of TB exposure, effective control measures are important tools to reduce TB transmission. Moon et al. found that working in sections of the laboratory with a comparatively higher risk was a significant risk factor for LTBI [15]. Other investigators documented the higher prevalence of LTBI among HCWs who worked in departments with increased contact with TB patients [23,24]. In the present study, however, no statement could be made regarding the occupational risk when comparing the results of different laboratory sections. Similarly, Schablon et al., who investigated LTBI in healthcare sector employees in Germany, observed no statistically significant association of IGRA positivity with the workplace [20]. Because of the inadequate data in the literature, it is difficult to evaluate the tuberculosis risk in different laboratory sections. Risk variability according to the laboratory sections might indicate the different degree of exposure intensity. Although the microbiology section deals more frequently than others with specimen processing, such as centrifugation and inoculation, working in microbiology laboratory was not a predictor for IGRA positivity in this study. This could be explained by the fact that the microbiology laboratory is dealing with cultures and isolates of infectious organisms, which renders laboratory personnel working there more familiar with the appropriate protective measures.

In this study, the prevalence of QFT-GIT positivity was significantly associated with non-Saudi nationalities ($P < 0.0001$), of which the East Asian nationality constituted a majority. In Riyadh, the prevalence of LTBI among two-year new hires of HCWs was investigated. The highest significant positive TST rates were found among HCWs coming from sub-Saharan countries (61.1%) compared with Saudi HCWs with the lowest positive rates (5%) as a reference group [25]. Unfortunately, even though the majority of expatriates are from endemic places, LTBI screening is not implemented in many healthcare institutes among the routine tests given to newly hired employees.

We observed no statistically significant associations with gender, workplace or TST status. We found no positive IGRA results among the 14 trainees who rotated between different laboratory sections, which could be explained by the short duration of exposure.

According to the CDC guidelines, HCWs who are possibly exposed to persons with TB disease or to clinical specimens that might contain MTB are classified as medium risk in terms of the TB screening program [4]. They should receive baseline TB screening when hired and a follow-up screening annually [4]. Furthermore, the treatment of LTBI among HCWs should be encouraged to prevent the progression to TB disease [12]. Although Saudi Arabia is a country with intermediate prevalence of TB [1], regular screening of HCWs, including laboratory personnel, for LTBI is not being strictly adhered to. This might be due to the inaccuracy and inconvenience of the TST. Although IGRA would be reliable and easy to perform in BCG-vaccinated

populations, its higher cost was regarded as a barrier against routine screening. Nevertheless, recent studies reported that IGRA was feasible and cost-effective [26,27].

Very few studies have been performed on disease progression in IGRA positive individuals [28,29]. The data indicated that the progression rate, within the 103 weeks of observation, for IGRA positive subjects (14.6%) was higher than the rate for TST positive subjects estimated by the same investigators (2.3%) [28], as well as the rate estimated by the WHO [30] for a lifetime after a positive TST (5—10%).

Several limitations in our study had to be addressed. First, a larger number of participants are needed to improve the significance of testing. Second, the population is a mixture of many nationalities with different patterns of exposure and different patterns of TB prevalence. Finally, this study is a cross-sectional evaluation for the prevalence of LTBI, and serial changes or the conversion of QFT-GIT over time could not be evaluated. Thus, we have a limitation on the distinction between recent and previous exposure.

Conclusion

In conclusion, this study is one of the few studies on the prevalence of LTBI among laboratory personnel. The data obtained demonstrated that the prevalence of QFT-GIT positivity in laboratory personnel would be dependent on the incidence of TB in the general population. The putative risk factors for QFT-GIT positivity could be age, the duration of work in the health care profession as well as a non-Saudi nationality. Our data emphasize the need to design and implement a simple, effective, and affordable institutional TB infection-control plan to prevent LTBI among laboratory personnel. Additionally, we emphasize the necessity of screening for LTBI both as a routine pre-employment investigation and as a part of periodic HCWs checkups. This will support TB control through chemoprophylaxis and prevent cross-infection. Larger cohort studies are needed to evaluate the individual risks of active TB development in latently infected subjects and the effectiveness of preventive therapy based on IFN-γ test results.

Authors' contributions

MIH: conception and design of the study, laboratory work, analysis and interpretation of data, drafting the article, final approval of the version submitted.

AED: laboratory work, acquisition of data, analysis and interpretation of data, revising the article for important intellectual content, final approval of the version submitted.

Conflict of interest

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Ethical approval: Not required.

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