Latent Tuberculosis Infection Screening for Laboratory Personnel Using Interferon- γ Release Assay and Tuberculin Skin Test in Korea: An Intermediate Incidence Setting

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Background: Though recent reports have indicated a higher prevalence of latent tuberculosis infection (LTBI) in laboratory personnel than in other healthcare workers, these studies included only a limited number of laboratory personnel. **Methods:** We have thus focused on the laboratory personnel, who had a high level of exposure to specimens from patients with TB. We recruited 173 laboratory personnel and performed QuantiFERON-TB Gold In-Tube test (QFT-G) and tuberculin skin test (TST). **Results:** QFT-G was positive in 21.4% of the enrolled laboratory personnel, and TST was positive in 33.3%. The agreement between the two tests was fair ($\kappa = 0.234$). In multivariate analyses, household contact

with TB patients ($P = 0.013$), the laboratory sections of microbiology ($P = 0.045$) and chemistry/immunology ($P = 0.014$) were shown to be significantly associated with positive QFT-G results. **Conclusion:** Our data show a high prevalence of TST and QFT-G positivity in laboratory personnel and emphasize the importance of LTBI screening for laboratory personnel. In BCG-vaccinated populations with an intermediate incidence setting, QFT-G seems to be superior to TST as a screening tool for the detection of LTBI. Further study, including results of follow-up tests will be helpful for confirmation of our findings. J. Clin. Lab. Anal. 25:382–388, 2011. © 2011 Wiley Periodicals, Inc.

Key words: tuberculosis; laboratory personnel; QuantiFERON-TB Gold In-Tube test; tuberculin skin test

INTRODUCTION

The incidence of tuberculosis (TB) infection has decreased in Korea, but it is still in the intermediate range (1,2). Healthcare workers (HCW) have been known to be at high risk for TB infection due to occupational exposures to patients with TB infection or specimens with *Mycobacterium tuberculosis* (*M. tuberculosis*) (3,4). According to the guidelines for preventing transmission of TB infection in HCW, all HCW should receive regular TB screening using the tuberculin skin test (TST) or interferon-gamma (INF- γ) release assay (IGRA) (3,5). In Korea, TB screening in HCW has been performed to detect active TB using chest radiography, and latent TB infection (LTBI) of HCW has not been a great issue. Moreover, according to Korean national policy, all infants are required to be vaccinated using Bacille Calmette-Guérin (BCG) vaccine. The usefulness of TST to detect LTBI is therefore limited due to the possibility of false positives as a result

of BCG vaccination (6,7). Regarding the prevalence of LTBI in HCW, few studies have been conducted in high or intermediate incidence settings. In these settings, evaluation of LTBI by only TST may be influenced by previous BCG vaccination or nontuberculous mycobacteria (NTM) exposure (8), and more specific and sensitive assays are needed (9,10). IGRA is based on the release of INF- γ from sensitized T cells in individuals with TB infection, and has emerged as a promising diagnostic alternative. IGRAs have been known to have a high specificity and may therefore play an important

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role especially in populations with a high incidence of BCG vaccination (4,6). QuantiFERON-TB assay (Cellestis Limited, Carnegie, Australia) was the first commercially available IGRA, and QuantiFERON-TB Gold In-Tube test (QFT-G) has been recently developed.

In this study, we evaluated the prevalence of LTBI in Korean laboratory personnel using QFT-G and TST, and assessed risk factors related to the positive test results. A few recent reports showed higher prevalence of LTBI in laboratory personnel than other HCW, but they included only a limited number of laboratory personnel (4,8). We thus focused on laboratory personnel, who had a high level of exposure to specimens from patients with TB. To the best of our knowledge, this is the first large-scale study on the prevalence of LTBI in laboratory personnel in an intermediate incidence setting.

METHODS

Participants

We recruited 173 laboratory personnel working at the departments of laboratory medicine and pathology in Konkuk University Medical Center and at Seoul Clinical Laboratory from May to August 2010. Konkuk University Medical Center is a tertiary university hospital with 900 beds, and its laboratory performs seven million laboratory tests annually. Seoul Clinical Laboratory is a reference laboratory performing 20 million clinical laboratory tests annually, referred from about 3,600 hospitals. Using a standardized questionnaire, we collected data on sex, education level, history of BCG vaccination, and history of contact with patients with TB or with specimens from patients with TB. We also assessed present workplace, duration of work in healthcare profession, job category, and household contact with TB patients. The written informed consent was obtained from every participant and the study protocol was approved by the Institutional Review Boards of Konkuk University Medical Center.

TST and QFT-G

We performed TST on the volar side of the forearm using 2-TU dose of purified protein derivative (PPD) RT23 (Statens Serum Institut, Copenhagen, Denmark) based on the Mantoux method (11). TST was administered by one certified nurse and induration was read after 48–72hr by two experienced experts to minimize inter-reader variability. There was no discordant result. Indurations of at least 10 mm were considered positive, and 15-mm cut-off points were also used (3,11).

QFT-G was performed according to the manufacturer's recommendation. In brief, peripheral blood was collected into three 1-mL heparin-containing tubes. The

first tube was a negative control, the second one was a positive control for T-cell mitogen phytohemagglutinin, and the third one included peptides such as ESAT-6, CFP-10, and TB7.7. After 24 hr of incubation, the release of IFN- γ in response to these peptides was measured by enzyme-linked immunosorbent assay. The result was considered positive, if 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 positive control for mitogen was less than 0.5 IU/ml. The readers of every test were blinded to the result of the other test. All participating subjects had no evidence of active TB by clinical or regular chest radiograph.

Statistical Analysis

Agreement between TST and QFT-G was assessed using κ coefficient. A κ coefficient greater than 0.81 was considered as very good agreement, a κ coefficient of 0.61–0.80 as good agreement, 0.41–0.60 as moderate agreement, 0.21–0.40 as fair agreement, and a κ coefficient of less than 0.20 as poor agreement. For the risk factors for test positivity, an odds ratio (OR) with a 95% confidence interval (95% CI) was obtained using conditional logistic regression. We also calculated adjusted OR with multiple covariates. Statistical analysis was performed using SPSS Software (version 12.0; SPSS Inc., Chicago, IL) and MedCalc Software (version 11.2.1; MedCalc Software, Mariakerke, Belgium). A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Characteristics of the Laboratory Personnel

Baseline characteristics of the participants are shown in Table 1. Their median age was 32 years (range: 22–67

TABLE 1. Characteristics of the 173 Laboratory Personnel Who Participated in This Study

Characteristics	N (%)
Age, median (range), years	32 (22–67)
Sex, male: female	71:102
Sections in laboratory	
Microbiology	22 (12.7)
Molecular diagnostics	23 (13.3)
Chemistry/immunology	79 (45.6)
Pathology/hematology	22 (12.7)
Clerical part	18 (10.4)
Physicians	9 (5.2)
Duration of healthcare profession, median (range), years	7 (0.2–42)
History of exposure to TB patients or specimens	61 (35.2)
Household contact with TB patients	18/173 (10.4)

TB, tuberculosis.

years) and 41.0% (71/173) were male. They all were vaccinated with BCG at least once during infancy and/or at school in accordance with national policy. Median duration of work in healthcare profession was 7 years (range: 0.2–42 years). Sixty-one laboratory personnel (35.2%) reported that they had worked in a setting where they were exposed to TB patients or specimens from TB patients for at least 1 year, and 18 (10.4%) reported that they had a history of household contact with active TB patients.

Agreements Between QFT-G and TST

QFT-G was positive in 21.4% (37/173) of the laboratory personnel, and there were no indeterminate results. TST results were available in 156 individuals and were positive in 52 (33.3%) individuals with a 10-mm cut-off and in 30 (19.2%) individuals with a 15-mm cut-off. The distribution of QFT-G positivity according to TST results are shown in Table 2. Although there was a tendency that the QFT-G-positive rate increased when the TST was positive (>10 mm), QFT-G-positive results were also observed even with a negative TST. Agreements between QFT-G and TST are presented in Table 3. Agreement was fair with a 10-mm cut-off of the TST (69.2%; $\kappa = 0.234$; 95% CI, 0.054–0.414) and did not change with a 15-mm cut-off of TST (76.9%; $\kappa = 0.276$; 95% CI, 0.068–0.483).

Risk Factors for QFT-G and TST

The risk factors for QFT-G and TST were analyzed using both univariate and multivariate logistic regression analyses. With univariate analyses, positive QFT-G results were significantly associated with an age older

than 40 years ($P = 0.013$; OR = 4.28; 95% CI, 1.36–13.45), duration of healthcare profession longer than 10 years ($P = 0.023$; OR = 4.75; 95% CI, 1.23–18.26), history of household contact with TB patients ($P = 0.003$; OR = 4.53; 95% CI, 1.65–12.48), and laboratory sections of microbiology and chemistry/immunology ($P = 0.030$; OR = 4.53; 95% CI, 1.16–17.82 and $P = 0.033$; OR = 3.48; 95% CI, 1.10–10.98, respectively). With multivariate logistic regression analyses, positive QFT-G results were significantly associated with household contact with TB patients ($P = 0.013$; OR = 4.08; 95% CI, 1.34–12.45) and the sections of microbiology and chemistry/immunology ($P = 0.045$; OR = 4.76; 95% CI, 1.03–21.89 and $P = 0.014$; OR = 4.73; 95% CI, 1.36–16.44, respectively) (Table 4).

With respect to the TST, age, duration of healthcare profession, male sex, and physician were significantly associated with TST positivity on the basis of univariate analysis. However, section of chemistry/immunology was the only risk factor associated with TST positivity on the basis of multivariate analysis ($P = 0.046$; OR, 2.77; 95% CI, 1.01–7.53). Both QFT-G and TST showed increased positivity as age and duration of healthcare profession in the laboratory increased. There was no association between QFT-G or TST response and the history of contact with TB patients or specimens from TB patients (Table 4).

DISCUSSION

Until recently, TST was the only test used for the diagnosis of LTBI (8,12). Because the PPD used in TST is a mixture of antigens, a response to PPD can occur in the presence of *Mycobacterium bovis*, BCG, or some

TABLE 2. Positivity of QFT-G by TST Diameters

	<5 mm	5– <10 mm	10– <15 mm	>15 mm	Total
TST	75	29	22	30	156
QFT-G positive	9 (12.0%)	5 (17.2%)	5 (22.7%)	13 (19.2%)	32 (20.5%)

TST, tuberculin skin test; QFT-G, QuantiFERON-TB Gold In-Tube test.

TABLE 3. Agreements Between TST and QFT-G by TST Cut-Off Point

	TST cut-off 10 mm		TST cut-off 15 mm	
	Positive	Negative	Positive	Negative
QFT-G positive (20.5%)	18	14	13	19
QFT-G negative (79.5%)	34	90	17	107
Total agreement	108/156 (69.2%)		120/156 (76.9%)	
κ (95% CI)	0.234 (0.05–0.41)		0.276 (0.07–0.48)	

TST, tuberculin skin test; QFT-G, QuantiFERON-TB Gold In-Tube test; CI, confidence interval.

TABLE 4. Risk Factors Associated With Positive TST and QFT-G

	TST with 10-mm cut-off			QFT-G		
	Positivity, <i>N</i> (%)	Adjusted OR (95% CI)	<i>P</i>	Positivity, <i>N</i> (%)	Adjusted OR (95% CI)	<i>P</i>
<i>Sex</i>						
Male	27/61 (44.3)	1		17/71 (23.9)	1	
Female	25/89 (28.1)	0.47 (0.20–1.07)	0.074	20/102 (19.6)	0.73 (0.31–1.73)	0.485
<i>Age (years)</i>						
20–29	6/45 (13.3)	1		7/58 (12.3)	1	
30–39	38/83 (45.8)	3.04 (0.62–14.83)	0.167	21/92 (22.8)	1.14 (0.21–6.10)	0.874
≥40	8/22 (14.7)	1.40 (0.15–12.57)	0.762	9/24 (37.5)	2.03 (0.19–21.08)	0.332
<i>Laboratory sections</i>						
Clerical/pathology	9/40 (22.5)	1		4/43 (9.3)	1	
Microbiology	9/22 (40.9)	2.31 (0.62–8.66)	0.211	7/22 (31.8)	4.76 (1.03–21.89)	0.045
Molecular diagnostics	7/23 (30.4)	1.32 (0.36–4.82)	0.672	3/23 (13.0)	1.65 (0.30–8.95)	0.557
Chemistry/immunology	24/57 (42.1)	2.77 (1.01–7.53)	0.046	20/76 (26.3)	4.73 (1.36–16.44)	0.014
Physician	3/8 (37.5)	2.83 (0.45–17.86)	0.267	3/9 (33.3)	3.22 (0.44–23.49)	0.249
<i>Duration of healthcare profession (years)</i>						
≤2	2/27 (7.4)	1		3/37 (8.1)	1	
2–5	11/30 (36.7)	5.25 (0.84–32.59)	0.074	7/34 (20.6)	3.02 (0.33–16.33)	0.199
6–10	22/52 (42.3)	3.26 (0.37–28.43)	0.285	14/58 (24.1)	3.23 (0.37–27.87)	0.285
>10	17/41 (41.5)	5.19 (0.49–54.15)	0.169	13/44 (29.5)	3.10 (0.27–34.86)	0.385
<i>History of exposure to TB patients (years)</i>						
≤1	41/129 (31.8)	1		31/151 (20.5)	1	
>1	11/21 (52.4)	1.8 (0.57–5.63)	0.313	6/22 (27.3)	1.29 (0.37–4.47)	0.685
<i>History of exposure to TB specimens (years)</i>						
≤1	28/94 (29.8)	1		23/112 (20.5)	1	
>1	24/56 (42.9)	1.12 (0.46–2.75)	0.794	14/61 (35.3)	0.93 (0.36–2.38)	0.879
<i>Household contact with TB patients</i>						
No	44/134 (32.8)	1		28/155 (18.1)	1	
Yes	816 (50.0)	2.00 (0.63–6.33)	0.238	9/18 (50.0)	4.08 (1.34–12.45)	0.013

TST, tuberculin skin test; QFT-G, QuantiFERON-TB Gold In-Tube test; OR, odds ratio; CI, confidence interval; TB, tuberculosis. Logistic regression analysis was used for the statistical analysis.

NTM (8,12). As a consequence, the diagnosis of LTBI using TST is limited, especially in BCG-vaccinated populations. In Korea, the incidence rate of TB is considered intermediate (73/10⁵ cases per year) (1,2,13), and BCG vaccination is obligatory for infants. In many studies, IGRA including QFT-G showed high specificity and sensitivity, and was proved to be useful in BCG-vaccinated populations (6,9,13). QFT-G is an in vitro immunosorbent assay using whole blood, and could be easily used as a routine screening test for LTBI in most laboratories.

This study showed a high prevalence of QFT-G positivity (21.4%) in the Korean laboratory personnel, and it was higher than that of newly employed Korean nurses (14.3%) and low-risk Koreans (8.4%) (1,14). Higher prevalence of LTBI in laboratory personnel than in other HCW was also demonstrated in previous studies (8,15). However, there has been no large-scale study that specifically focused on the issue of LTBI in laboratory personnel. To the best of our knowledge, this

is the first study that focused on laboratory personnel from an intermediate incidence setting and also compared the prevalence among laboratory sections in addition to other risk factors. Compared with the data from Japan and India, which are considered a low and a high incidence setting, respectively, the prevalence of QFT-G positivity in the laboratory personnel in Korea was slightly higher than that in Japan (19.0% in laboratory personnel, 9.9% in all HCW) and lower than that in India (54.0% in laboratory personnel, 40.0% in all HCW [Please check footnotes a and b in Table 5]) (4,8) (Table 5). Very recently, a few large-scale studies reported that the prevalence of LTBI in HCW was 9.9% in Germany and 25.9% in Portugal, and it was also higher than the general population. Although technicians were included in these studies, the exact prevalence in laboratory personnel was not reported (16,17) (Table 5). Prevalence of QFT-G positivity could be influenced by age, duration of exposure, and degree of exposure of the study populations. Moreover, our

TABLE 5. Studies on the Prevalence of LTBI in Laboratory Personnel Using TST and QFT-G

Studies	Study population	Prevalence of LTBI by		BCG vaccination status	Incidence of TB in area studied
		TST	QFT-G		
Pai et al. (8)	Total HCW (<i>N</i> = 726)	41%	40%	71%	High
	Laboratory personnel (<i>N</i> = 39)	59%	54%		(200/100,000)
Harada et al. (4)	Total HCW (<i>N</i> = 332)	93.1%	9.9%	> 90%	Low
	Laboratory personnel (<i>N</i> = 21)	NR	19%	Extensive vaccination policy (at infancy and one or more additional vaccination at older ages)	(20–25/100,000)
Schablon et al. (16)	Total HCW (<i>N</i> = 2,028)	24%	9.9%	45%	Low
	Technician (<i>N</i> = 176) ^a	NR	14.2%		(6.1/100,000)
Torres Costa et al. (17)	Total HCW (<i>N</i> = 5,209)	55.2%	25.9% ^b	60%	Low
	Technician (<i>N</i> = 461) ^a	48.8%	NR		(29.4/100,000)
This study (2010)	Laboratory personnel (<i>N</i> = 173)	33.3%	21.4%	> 90%	Intermediate
				Mandatory at infancy	(70/100,000)

HCW, healthcare worker; LTBI, latent tuberculosis infection; TST, tuberculin skin test; QFT-G, QuantiFERON-TB Gold In-Tube test; BCG, bacille Calmette-Guérin; TB, tuberculosis; NR, not reported.

^aIncluded laboratory personnel and other technicians such as radiology staff.

^bQFT-G performed only in a subgroup.

data together with the previous data show that the prevalence of QFT-G positivity in laboratory personnel would be dependent on the incidence of TB in general population.

Agreements between TST and QFT-G were reported to be highly variable (8,13,18,19). In contrast to previous studies from highly endemic areas (8,20), the agreement in our study was fair (*k* coefficient = 0.234). The reasons for this disagreement would be the differences of LTBI prevalence, BCG vaccination policy, and subjectiveness of TST procedures and reading. The results of one Japanese study showed a very high TST-positive rate (more than 90% of HCW). This may be due to differences in interpretation or the result of Japanese national policy, which stipulates extensive BCG vaccination—BCG is vaccinated in early childhood and additionally at older ages as well, or if HCW with a negative TST are hired (4). Although all infants are to be vaccinated with BCG in Korea, additional vaccination in adulthood is optional and not as strict as in Japan. This may be a reason for the lower TST positivity (33.3% with 10 mm cut-off) in our study than in the Japanese study. Subjectiveness of TST reading could be another reason for the different results. TST results are not easy to read, and this should be carried out carefully by a designated, trained HCW (3). In our study, TST reading was performed by two, experienced experts from the Korean Institute of Tuberculosis. In contrast to the Japanese study, the study on HCW from India showed a strong agreement between the results of TST and IFN- γ assay and a little impact of BCG vaccination on TST results (8). Because

the positive reaction of BCG is known to lessen after several years (3,15,21), the effect of vaccination may be different according to the amount of time since vaccination.

With respect to risk factors, age and duration of laboratory profession, which might reflect cumulative exposure to TB, were significantly associated with the positivity of both QFT-G and TST on the basis of univariate analysis, and this was similar to the previous findings (8,15,22–24). On the basis of univariate and multivariate analyses, a history of household contact with TB patients and working in sections of the laboratory with comparatively higher risk were identified as significant risk factors for LTBI. Risk variability according to the laboratory sections might indicate the different degree of exposure intensity. The microbiology sections dealt more frequently with specimen processing, such as centrifugation and inoculation, than other sections did, such as clerical part and pathology. However, the high positivity in the chemistry/immunology section needs to be evaluated for another reason. Owing to the intermediate incidence rate of TB in Korea, many individuals had a history of household contact with TB patients, which was another significant risk factor for LTBI. It can be expected that transmission control would be less strict in household contact compared with the exposure in laboratories. It is important to note that these risk factors were significantly associated with QFT-G positivity, not with TST positivity. QFT-G results appear to be more reliable than TST results. Moreover, the progression rate of positive QFT-G test was reported to be much higher than that of positive TST in recent studies

(25,26). However, this study is a cross-sectional evaluation for the prevalence of LTBI and serial changes or conversion of QFT-G or TST over time could not be evaluated. Thus, we have a limitation on distinction between recent and previous exposure. Another limitation of our study is that there were no control groups, so we could not show how much higher the positive rate was in laboratory personnel as compared with control groups.

According to the Centers for Disease Control and Prevention guideline, laboratory staffs and technicians should be included in a TB screening program, and HCW who are possibly exposed to persons with TB disease or to clinical specimens that might contain *M. tuberculosis* are classified as medium risk in terms of TB screening program (3). They should receive baseline TB screening on being hired using TST or IGRA and follow-up screening annually (3). In Korea, LTBI screening is not yet routinely performed on HCW; 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. However, a study using a computerized, cost comparison model for TB screening in HCW showed that the QFT-G-only model was cheaper than the TST-only model and required fewer clinical visits (27). A few recent studies also reported that IGRA was feasible and cost-effective (28–30).

In conclusion, this study is the largest study on the prevalence of LTBI in laboratory personnel, especially in an intermediate incidence setting. Our data imply that laboratory personnel show high positivity of QFT-G and TST. The high prevalence of LTBI in laboratory personnel underscores the necessity for national or at least institutional guidelines for TB screening in HCW who are at an increased risk of TB exposure. In BCG-vaccinated populations with an intermediate incidence setting, QFT-G appears to be superior to TST as a screening tool for the detection of LTBI.

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