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ORIGINAL ARTICLE

Prevalence of latent tuberculosis infection in BCG-vaccinated healthcare workers by using an interferon-gamma release assay and the tuberculin skin test in an intermediate tuberculosis burden country

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Background: The risk of healthcare workers (HCWs) acquiring tuberculosis (TB) infection is high. We determined the prevalence of latent TB infection (LTBI) in HCWs with a high Bacille Calmette-Guérin (BCG) vaccine coverage in an intermediate TB burden country by using an interferon-gamma release assay [QuantiFERON-TB Gold (QFT-G)] and by using the tuberculin skin test (TST). Risk factors associated with a positive test were determined.
Methods: This prospective cross-sectional study enrolled HCWs from a medical center in Taiwan. Participants were grouped into workers without exposure (Group 1) and workers who self-reported a history of TB exposure (Group 2). All participants completed a questionnaire to collect demographic information and risk factors for acquiring TB. The QFT-G test and the TST were administered and risk factors for a positive test were analyzed.
Results: We recruited 193 HCWs [149 (77.2%) female workers] with a mean age of 35.6 years. All were BCG-vaccinated. The prevalence of LTBI was 88.8% (based on the TST) and 14.5%

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(based on the QFT-G test). There was no difference between HCWs with and without known exposure to TB. Agreement between the tests was poor (i.e., the kappa value was less than 0.05). Multivariable logistic regression showed that only the QFT-G test was associated with age (35 years or greater) (adjusted OR, 2.53; $p = 0.03$).

Conclusion: By using the QFT-G test or TST, this study found a similar prevalence of LTBI in HCWs with and without known exposure to TB. This suggests that in intermediate TB burden countries exposure to TB may occur within the hospital and within the community. Compared to the TST, the QFT-G test was correlated better with age, which is a known risk factor for latent TB infection.

Introduction

Tuberculosis (TB) poses a significant occupational health problem in healthcare workers (HCWs) because of the increased risk of exposure to TB. HCWs generally have a higher incidence of TB than the general population. The incidence of TB among Malaysian HCWs during the years 2003—2006 was reportedly 73.4—77.7 per 100,000 workers, compared to 60.3—62.6 per 100,000 people in the general population.[1] In high TB burden settings such as India, HCWs are twice more likely to develop active TB, compared to the general population.[2] A systematic review of 51 studies on the performance of the interferon-gamma (IFN-γ) release assay (IGRA) in HCWs in cross-sectional and in serial testing studies showed that the prevalence and incidence of TB infection and disease were high among HCWs in low income and middle income countries; this mostly included countries with a high burden of TB and/or human immunodeficiency virus (HIV).[3]

Latent TB infections comprise a significant reservoir of future epidemics.[4] Targeted treatment of latent TB infection in high-risk groups is an important strategy in TB control. Therefore, the screening and treatment of HCWs for latent TB infection in low TB incidence countries is crucial in an infection control program.[5] However, the implementation of this strategy in high TB incidence countries is hindered by uncertainty in the ability of current diagnostic tests to accurately identify workers who will benefit from treatment.

Two tests are currently available for the diagnosis of latent TB infection: the tuberculin skin test (TST) and the IGRA test.[6] The primary drawbacks of the TST are: (1) poor specificity because of previous vaccination with the Bacille Calmette-Guérin (BCG) vaccine or because of exposure to nontuberculous mycobacterium, (2) the need for workers to make a return visit to have the test result interpreted, (3) the subjectivity involved in reading the test result, and (4) the boosting phenomenon.[7]

The QuantiFERON-TB Gold (QTF-G, Cellestis Limited, Melbourne, Australia) test is a whole blood IGRA that uses a mixture of two antigens that are specific for *Mycobacterium tuberculosis* and are encoded by the region of difference 1 (RD1). The antigens—early secreted antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10)—stimulate T lymphocytes to release interferon-gamma. These new assays have several advantages over the TST such as a higher specificity without cross-reactivity with BCG strains or environmental mycobacteria, logistic simplicity, and the requirement of only one worker visit.[7]

In 2011, Taiwan had an annual incidence of TB infection of 54.5 per 100,000 population.[8] Since 1965, the National Immunization Program has included neonatal BCG vaccination. The national coverage was 87% in 1975; 98% in 2001; and 97% thereafter.[9] Coverage reached 99.8% in 2004.[10]. The aim of this study was to: (1) determine (by using the TST and the QFT-G test) the prevalence of latent TB infection in HCWs in a country with an intermediate TB burden (i.e., 10—100 cases of TB per 100,000 population) and a high BCG vaccination coverage; (2) to compare the TST and the QFT-G test results in HCWs with and without known exposure to patients with active TB; and (3) to determine the risk factors for a positive test.

Methods

This prospective cross-sectional study was conducted from 2004 to 2008 in a 1408-bed medical center in southern Taiwan. The center annually services approximately 350 patients with TB. Study participants were recruited by posters and invited to participate by announcements in various departments and wards within the hospital. They were grouped into workers without a history of unprotected exposure to TB (Group 1) and workers with a self-reported history of unprotected exposure to TB (Group 2). The study protocol was approved by the Institutional Review Board of the Kaohsiung Veterans General Hospital.

All HCWs received medical evaluation and chest X-rays to exclude active TB disease, and received further medical evaluation if they were symptomatic (which included acid-fast staining and mycobacterial culture of the sputum). A questionnaire was administered to collect demographic data and included the participants' age, sex, occupation, BCG vaccination status, and risk factors for TB, such as having a past history of exposure to TB or having active TB disease.

Blood was drawn for QFT-G testing prior to the two-step TST. The participant's blood samples were delivered within 12 hours to the laboratory for analysis. The blood samples were mixed with specific antigens (ESAT-6 and CFP-10) of *Mycobacterium. tuberculosis* and incubated for 16—24 hours. Blood samples were also mixed with mitogen phytohemagglutinin (i.e., positive control) and saline (i.e., negative control). All values were interpreted after subtracting the value of the negative control, which was the background level. The QFT-G test results were interpreted as: "positive" if the IFN-γ level in response to either the ESAT-6 or CFP-10

was at least 0.35 IU/mL; "negative" if the IFN-γ level was less than 0.35 IU/mL and the IFN-γ level in response to mitogen (i.e., positive control) was at least 0.5 IU/mL; and "indeterminate" if the IFN-γ level was less than 0.35 IU/mL in response to ESAT-6 or CFP-10 and the positive control was less than 0.5 IU/mL, or if the negative control was greater than 0.7 IU/mL, irrespective of the IFN-γ response to ESAT-6 or CFP-10.

The TST was performed by giving 2TU tuberculin RT-23 intradermally (Statens Serum Institute, Copenhagen, Denmark) on the volar surface of the forearm. The diameter of the indurated area was measured 48—72 hours later by the intramural Mantoux method and was considered positive when the area was 10 mm or greater. A two-step tuberculin skin test was administered to all participants to avoid the booster phenomenon. If the first-step TST result was negative, the second-step TST was administered 1—3 weeks later. If either the baseline first-step TST result was positive or the first-step TST result was negative but the second-step TST result was positive, the participants were evaluated for TB disease. If the first- and second-step TST results were both negative, the person was classified as not infected with *M. tuberculosis*.

Statistical analysis

Data were analyzed using Stata Statistical Software: Release 10 (StataCorp LP, College Station, TX). The Pearson Chi-square analysis or the Fisher's exact test was used for comparing categorical variables. Continuous variables were compared by using the Student *t* test or the Wilcoxon rank sum test, as appropriate. Concordance between the TST and QFT-G test results was evaluated by the kappa coefficient (a κ value greater than 0.75 indicated excellent agreement; a κ value less than 0.4, poor agreement; and a κ value between 0.4 and 0.75, fair to good agreement).[11] Risk factors for QFT-G test and TST positivity were determined by using multivariable logistic regression analysis. Age and sex were included *a priori* in the final model.

Results

A total of 193 HCWs were recruited into the study, mostly women [149 (77.2%) women], with a mean age of 35.6 years [standard deviation (SD), 7.2 years] and an age range of 21.0 years to 54.4 years. All HCWs received the BCG vaccination either in infancy or during childhood. The occupations of the HCWs included 82 (42.5%) nurses; 60 (31.3%) administrative staff; 27 (14.0%) doctors, 23 (11.9%) laboratory technicians, and 1 (0.5%) from another occupation. Group 1 ($n = 111$) consisted of HCWs without known exposure to TB. Group 2 ($n = 82$) consisted of HCWs who self-reported a history of unprotected exposure to patients with active TB. There was no difference between the baseline characteristics of the two groups, except that there were more females in Group 1 (Table 1).

Table 1 Baseline characteristics of BCG-vaccinated healthcare workers who were grouped by workers denying TB exposure (Group 1) and workers with a self-reported history of unprotected TB exposure (Group 2) to patients with tuberculosis ($n = 193$)

Characteristic	Group 1 ($n = 111$)	Group 2 ($n = 82$)	*p*
Age (y), mean (SD)	36.1 (8.2)	34.8 (5.5)	0.19
Sex (female)	96 (86.5)	53 (64.6)	<0.001
BCG vaccination	111 (100.0)	82 (100.0)	—
Occupation			
Nurse	48 (43.2)	34 (41.5)	—
Doctor	14 (12.6)	13 (15.9)	—
Laboratory technician	22 (19.8)	1 (1.2)	—
Administrative staff	27 (24.3)	33 (40.2)	—
Other	0 (0.0)	1 (1.2)	—
Self-reported exposure to TB	0 (0.0)	82 (100.0)	—

Data are presented as *n* (%), unless otherwise indicated.
BCG = Bacille Calmette-Guérin; HCWs = healthcare workers; SD = standard deviation; TB = tuberculosis.

Prevalence of latent TB infection, as assessed by the QFT-G test

The prevalence of latent TB infection in the 193 HCWs, based on QFT-G positivity, was 14.5% [95% confidence interval (95% CI), 9.9-20.3]. The QFT-G response was indeterminate in 7.8% (95% CI, 4.4-12.5). There was no significant difference between the prevalence of QFT-G positivity in HCWs with (15.3%) and without (13.4%) known exposure to patients with active TB ($p = 0.14$). The prevalence of latent TB infection was significantly higher (based on the QFT-G test) in HCWs who were 35 years or older (22.1%) than in workers who were younger than 35 years (9.8%; $p = 0.02$). On multivariable logistic regression analysis, an age older than 35 years was associated with a positive QFT-G test result [adjusted odds ratio (OR), 2.53; 95% CI, 1.07-5.98; $p = 0.03$], after adjusting for sex and history of exposure to TB (Table 2).

Prevalence of latent TB infection, as assessed by TST

The TST was administered to 187 HCWs (three participants each in Group 1 and Group 2 refused the TST); 179 HCWs completed the two-step TST (Table 3). Fig. 1 shows the distribution of the size of the TST induration in the two HCW groups. The two-step TST was overall positive in 88.8% (95% CI, 83.3—93.0) of the HCWs, when using the 10 mm cut-off criterion, and positive in 66.9% (95% CI, 59.2—74.0) of the HCWs, when using the 15-mm cut-off criterion. In Group 1, 93 (91.2 %) participants (95% CI, 83.9—95.9) had positive TST results when using the 10-mm cut-off value, compared to 61 (66.3%) participants (95% CI, 55.7—75.8) when using the 15-mm cut-off value.

In Group 2, the TST was positive in 66 (85.7%) participants (95% CI, 75.9—92.6) when using the 10-mm cut-off value, and positive in 50 (67.6%) participants (95% CI, 55.7—78.0) when using the 15-mm cut-off value. There were no significant differences between the two groups in

Table 2 Multivariate logistic regression analysis of the risk factors for a positive QuantiFERON-TB Gold test result or tuberculin skin test result in BCG-vaccinated healthcare workers

	QFT-G positive (n = 178)[b]			TST positive[a] (n = 179)		
Variables	Adjusted OR[c]	95% CI	p	Adjusted OR[c]	95% CI	p
Age ≥35 y	2.54	1.08–6.01	0.03	2.53	0.92–6.98	0.07
Sex	0.56	0.17–1.78	0.32	1.64	0.49–5.53	0.43
Exposure to TB	1.12	0.47–2.64	0.80	0.53	0.20–1.42	0.21

[a] A two-step TST was administered and considered positive if the induration was ≥10 mm.
[b] Fifteen patients were excluded who had indeterminate results on the QuantiFERON-TB Gold test.
[c] Multivariate analysis was adjusted for age, sex, and exposure to TB.
BCG = Bacille Calmette-Guérin; CI = confidence interval; OR = odds ratio; QFT-G = QuantiFERON-TB Gold; TB = tuberculosis; TST = tuberculin skin test.

the size of the TST induration or in the proportion (91.2% vs. 85.7%) of positive results when using the TST at a 10-mm cut-off value (p = 0.25) or when using other cut-off criteria (Table 3). On multivariable logistic regression analysis, neither age, sex, nor a history of exposure to TB was associated with a positive TST (Table 2).

Booster effect of the two-step TST

A two-step TST increased the proportion of TST positivity from 74.9% to 88.8% when using the cut-off criteria of 10 mm (p = 0.001). Fig. 2 shows the booster effect of the two-step TST when using other cut-off criteria. Differences between TST positivity after boosting was significantly different across all cut-offs values of the TST.

Table 3 Tuberculin skin test and QuantiFERON TB-Gold test results of BCG-vaccinated healthcare workers who are grouped by workers without TB exposure (Group 1) and workers with known TB exposure (Group 2) to patients with active tuberculosis (n = 193)

Characteristic	Group 1 (n = 111)	Group 2 (n = 82)	p
TST induration[a] (mm)	(n = 108)	(n = 79)	
One-step	12.0 (9.0–18.0)	13.0 (10.0–18.0)	0.65
Two-step	13.0 (10.0–15.0)	15.0 (8.0–18.0)	0.15
TST positivity at various cut-offs[b]			
10 mm	91.2	85.7	0.25
15 mm	66.3	67.6	0.86
18 mm	39.3	51.4	0.13
20 mm	22.7	33.9	0.15
QuantiFERON-TB GOLD test[c]	(n = 111)	(n = 82)	
Positive	17 (15.3)	11 (13.4)	0.14
Indeterminate (ID)	5 (4.5)	10 (12.2)	

Data are presented as [a]median (IQR), [b]%, or [c]n (%).
BCG = Bacille Calmette-Guérin; ID = indeterminate response; IQR = interquartile range; TB = tuberculosis; TST = tuberculin skin test.

Correlation between TST and QFT-G

There was a poor correlation between the TST and QFT-G positivity when using various TST cut-off values. The overall agreement ranged from 24.0% to 67.7% for TST cut-offs varying between 10 mm and 20 mm, and kappa values of less than 0.05 (Table 4).

Discussion

In this study, the prevalence of latent TB infection among BCG-vaccinated HCWs in Taiwan was 14.5% (95% CI, 9.9–20.3, based on the QFT-G test), and 88.8% (95% CI, 83.3–93.0, based on the two-step TST). This was higher than the prevalence reported in low incidence countries such as Melbourne, Australia where Vinton et al[12] reported a positive rate of 6.7% by using the QFT In-tube test in 358 healthcare staff. However, the prevalence was similar to the prevalence reported in the general Taiwanese population in which the TST was positive in 44.4% of 135 healthy adults and QFT-G in 16.8% of 135 healthy adults from the community in the Kaohsiung area and with a mean age of 48.3 years (range, 27–69 years); 95.5% of the study participants were BCG-vaccinated.[13] The prevalence rates, based on QFT-G, did not differ between HCWs and healthy adults, even when subgroup comparisons were performed between people younger than 35 years (9.8% vs. 12.5%, respectively; p = 0.58) and people 35 years and older (22.1% vs. 18.1%, respectively; p = 0.48; unpublished data).[13] This suggests that HCWs in intermediate TB burden countries face a risk of exposure to TB similar to the risk in the community, and that appropriate personal protection equipment and good infection control practices employed within a hospital effectively mitigated the transmission of TB in healthcare settings. Our infection control program for TB is part of our hospital infection control policy in which all patients with suspected pulmonary TB and patients who have sputum smears positive for acid-fast bacilli are immediately transferred to the negative pressure ward for isolation. The treatment of patients is performed promptly. In addition, timely automatic electronic notification of a positive sputum smear is sent to physicians and automatic

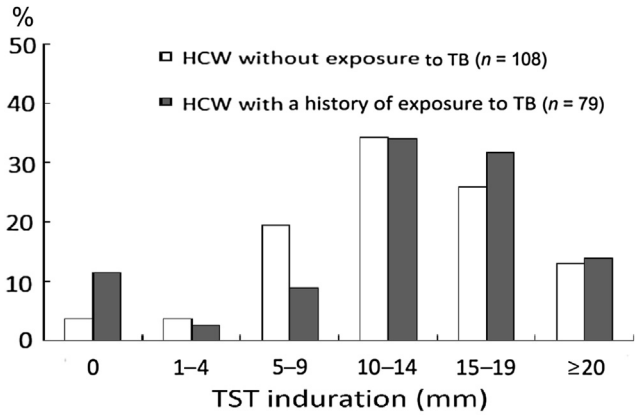

Figure 1. The distribution of the tuberculin skin test induration measured in healthcare workers (HCWs; $n = 193$) with and without a self-reported history of exposure to patients with active tuberculosis. TST = tuberculin skin test.

e-mails are sent by radiologists and pathologists whenever TB is suspected based on chest X-rays or based on histopathologic results of specimen biopsies. Surveillance of HCWs for TB is by annual chest X-rays. Contacts are screened for symptoms and receive a chest X-ray to rule out active disease. The TST is not administered routinely because of high rates of BCG vaccination.

The highly discordant results between the TST and the QFT-G test have been reported in countries in which BCG vaccination has been widely used.[5] In a study performed in 332 Japanese HCWs (95% of whom were BCG-vaccinated), 9.9% had positive QFT-G results and 93.1% had an induration diameter of 10 mm on the Mantoux test.[14] It has nevertheless been shown that in HCWs with a high rate of BCG vaccination and discordant QFT-G and TST results, a positive QFT-G test result was associated with the presence of known risk factors for TB exposure, whereas a positive TST was associated most strongly with a history of BCG vaccination.[10] Our study showed that, compared to the TST, the QFT-G test was correlated better with age, which is a known risk factor for TB infection.[15] Our findings supported the general consensus that the TST should not solely be relied on for diagnosing latent TB infection in populations with a high BCG vaccination coverage.[16]

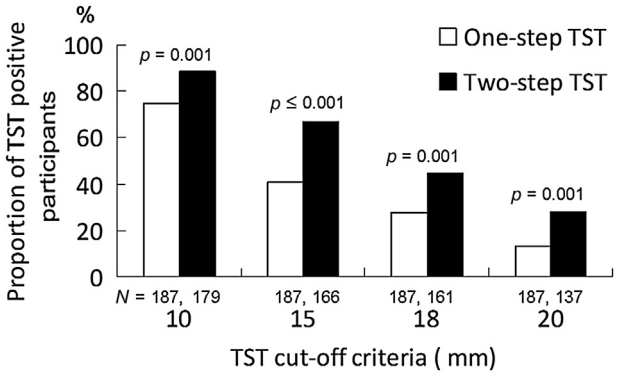

Figure 2. Booster effect of the two-step tuberculin skin test, assessed by using different cut-off values in healthcare workers in Taiwan.

Table 4 Correlation between the QuantiFERON-TB-Gold test results and the one-step and two-step tuberculin skin test results, assessed at different cut-off values in TST indurations in BCG-vaccinated healthcare workers in Taiwan

One step			
TST cut-off (mm)	Overall agreement (%)	Kappa value	95% CI
10 mm	34.7	0.02	−0.05 to 0.09
15 mm	56.1	−0.01	−0.11 to 0.13
18 mm	65.3	0.01	−0.13 to 0.15
20 mm	74.6	0.01	−0.14 to 0.15
Two-step			
TST cut-off (mm)	Overall agreement (%)	Kappa value	95% CI
10 mm	24.0	0.00	−0.05 to 0.05
15 mm	40.3	0.03	−0.05 to 0.12
18 mm	56.4	0.05	−0.07 to 0.17
20 mm	67.7	0.05	−0.11 to 0.21

BCG = Bacille Calmette-Guérin; CI = confidence interval; TB = tuberculosis; TST = tuberculin skin test.

When using the QFT-G test and the TST, the prevalence of latent TB infection in HCWs with and without known exposure to patients with active TB was similar in our study. This suggests that HCWs who did not report exposure to TB may have been unknowingly exposed to TB either within the hospital or in the community. It has been proposed that repeated exposure in high TB-incidence settings may attenuate the predictive ability of a single cross-sectional TST or IGRA result. In general, IGRAs appear to perform better in low TB-incidence settings.[2] Studies in Austria and Germany demonstrate IGRAs have a better predictive value in low endemic areas than in endemic countries with a high TB burden.[17] In settings with a high TB burden, all existing tests for latent TB infection—including the TST and IGRAs—may have only a modest predictive value and may not identify people who are at highest risk of progressing to TB disease.[2]

Our study showed that in an intermediate TB burden country with a high coverage of BCG vaccination, high discordance is observed between the QFT-G and the TST, and that a positive TST result may not identify people who are truly infected because of cross-reactivity with the BCG strain. Compared to the TST, the QFT-G test was correlated better with age, which is a known risk factor for TB. However, further longitudinal studies need to be performed to determine the predictive value for the development of active TB disease in this setting.

The strengths of this study are that this is one of the few studies that evaluated IGRA and TST in a head-to-head comparison in BCG-vaccinated HCWs from an intermediate TB burden country. This study showed that the cross-reactivity of the BCG vaccine with the TST is a significant problem when interpreting a positive TST result if the BCG vaccination has previously been administered in infancy with booster doses in childhood. This study also showed

that the QFT-G test may provide a better estimate of the burden of disease in HCWs in intermediate TB incidence countries.

The limitations of this study are that there is no gold standard for the diagnosis of latent TB infection. However, past studies have demonstrated that the QFT-G test is better correlated with risk factors for TB and is more specific than the TST, especially in BCG-vaccinated people.[18,19] Further longitudinal studies need to be performed to determine which test can better identify individuals with latent TB infection who will benefit from treatment, especially in intermediate TB incidence countries.[20]

In conclusion, by using the QFT-G test and the TST, this study demonstrated a similar prevalence of latent TB infection in HCWs with and without known exposure to patients with TB, and demonstrated a high rate of discordance between the TST and the QFT-G test in HCWs who have received BCG vaccination. This finding suggests that in a country with an intermediate TB burden, TB infection may occur in the hospital and within a community. This study also supports the general consensus that the TST should not be solely relied on for diagnosing latent TB in populations with a high BCG vaccination coverage and that the QFT-G test (compared to the TST) appears to be better correlated with age, which is a known risk factor for TB infection. Based on the QFT-G test results, the prevalence of latent TB infection may provide public health authorities with a better estimate of the burden of disease among HCWs in Taiwan, thereby to enable planning of future policies for TB control.

Conflicts of interest

The authors declare that they have no financial or nonfinancial conflicts of interest related to the subject matter or materials discussed in the manuscript.

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