RISK FACTORS FOR LATENT TUBERCULOSIS INFECTION AMONG HEALTH-CARE WORKERS IN NORTHEASTERN THAILAND

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Abstract. Health-care workers (HCWs) are a high-risk population for acquiring *Mycobacterium tuberculosis* infection. Understanding the risk factors for latent tuberculosis infection (LTBI) could provide information to facilitate an appropriate tuberculosis (TB) control program. We aimed to determine the prevalence of, and risk factors for LTBI among HCWs in northeastern Thailand. Between 1 November 2013 and 30 September 2015, we examined 112 HCWs at Srinagarind Hospital, Khon Kaen Province in northeastern Thailand using the QuantiFERON®-TB Gold In-Tube (QFT) assay. Twenty-one [18.8%; 95% confidence interval (CI): 11.5-26.0%] HCWs had a positive QFT result — all of whom were determined to have LTBI. The exposure risks and demographic data obtained from a questionnaire were compared between the 21 subjects who had a positive QFT assay and the 91 subjects who had a negative QFT assay. Multivariate analysis showed factors significantly associated with a positive QFT assay were: age ≥30 years (OR=18.88; 95%CI: 1.52-234.36), having worked as a nurse (OR=2.78; 95%CI: 1.19-6.49), having been employed at that job for ≥10 years (OR=8.78; 95%CI: 1.26-61.29) and having been exposed to known TB patients (OR=13.32: 95%CI: 1.61-110.04). Appropriate guidelines need to be developed, especially for these at-risk workers to prevent LTBI. These high-risk workers should also be considered for regular TB screening.

Keywords: latent tuberculosis infection, risk factors, health-care workers, interferon-gamma release assay, northeastern Thailand

INTRODUCTION

Health care workers (HCWs) are at higher risk of contracting *Mycobacterium tuberculosis* (*Mtb*) infection, especially in low- and middle-income countries (Jensen *et al*, 2005; Joshi *et al*, 2006). Inhalation of *Mtb* can lead to asymptomatic latent tuberculosis infection (LTBI). Approximately, 5-10% of people with LTBI develop tuberculosis (TB) (WHO, 2015). According to the WHO, Thailand is among 22 high TB-burden countries with an estimated 120,000 (95% uncertainly interval: 61,000-190,000) new TB cases annually (WHO, 2015). The prevalence of LTBI among Thai

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HCWs is estimated to be at least 50% (Do *et al*, 1999; Yanai *et al*, 2003). Detecting the presence of LTBI and determining the risk factors for LTBI among HCWs are fundamental for prevention and control of TB among HCWs.

Several studies have investigated the occupational risk factors for LTBI among HCWs in Thailand (Do *et al*, 1999; Yanai *et al*, 2003; Sawanyawisuth *et al*, 2009) and other countries (Borroto *et al*, 2011; Zhou *et al*, 2014; Rutanga *et al*, 2015). Those studies used the tuberculin skin test (TST) as the diagnostic method, which can have false-positive results due to previous Bacillus Calmette–Guérin (BCG) vaccination (Khawcharoenporn *et al*, 2011) and infection with nontuberculous mycobacteria (NTM) (Farhat *et al*, 2006). Newborns in Thailand have been given the BCG vaccine for the past 40 years. NTM infections are common in Thailand (Kheawon *et al*, 2013; Thanachartwet *et al*, 2014). The prevalence of LTBI and risk factors for it among HCWs in Thailand remain unclear.

The interferon gamma release assay (IGRA) is very accurate and specific (Andersen *et al*, 2000). It measures IFN-γ released from memory immune cells induced by specific *Mtb* antigens including ESAT-6, CFP-10 and TB-7.7. These antigens are not found in BCG vaccine strains or in most NTMs (Diel *et al*, 2010; 2011). Several studies have used an *in vitro* blood ELISA-based IGRA to study LTBI in HCWs (Casas *et al*, 2009; Lien *et al*, 2009; He *et al*, 2012; Whitaker *et al*, 2013). The drawbacks of the TST to screen for LTBI in HCWs caused us to select the QuantiFERON®-TB Gold In-Tube (QFT) assay for our study to estimate the prevalence of and occupational risk factors for LTBI among HCWs in northeastern Thailand.

MATERIALS AND METHODS

Study population and data collection

This study was conducted between 1 November 2013 and 30 September 2015 among 112 HCWs: 31 nurses, 12 nursing assistants, 22 physicians, 2 pharmacists, 10 medical technologists working in the microbiology laboratory, 7 housekeepers, 6 molecular laboratory staff, 5 administrative/clerical workers, 2 senior researchers and 15 research assistants working in the TB laboratory. All these workers had been employed at Srinagarind Hospital, Khon Kaen University, Thailand, for at least 1 year and had at least one of the following occupational risks: dealing with TB patients and working in a TB-associated area or TB laboratory. All participants were healthy with no symptoms of active TB and had normal chest radiograph in annual health checkup. Any participant positive in a QuantiFERON®-TB Gold In-Tube (QFT) test was regarded as having LTBI. Informed consent was provided by all volunteers. Demographic data and occupational risk factors for LTBI were collected using a risk-assessment questionnaire. Recorded data included a history of BCG vaccination and details of underlying diseases/conditions, including lung disease, diabetes mellitus, liver disease, kidney disease and thalassemia. None of the study subjects had received immunosuppressive agents or had undergone a TST during the three-week period prior to study participation. No participant developed active TB after the start of the study. This study was approved by the Khon Kaen University Ethics Committee in Human Research (Ethics number HE561342).

QuantiFERON®-TB Gold In-Tube test

The QFT assay (Cellestis, Melbourne, Australia) was used in this study to diagnose LTBI among study subjects. We

obtained a venous blood sample from each participant. Each sample was distributed into three QFT blood collection tubes as follows: TB-antigen (coated with *Mtb*-specific antigen), nil-control (negative control) and mitogen-control (positive control). The tubes were gently shaken and incubated at 37°C for 24 hours. The plasmas from each blood sample set were collected by centrifugation for 15 minutes at 3,000 RCF (*g*) and stored separately at -80°C until used. The IFN-γ level in each plasma was measured by ELISA according to the manufacturer's protocol. A QFT result was considered positive when the IFN-γ level in the TB-antigen tube minus the value for the nil-control tube (TB-antigen minus nil value) was ≥ 0.35 IU/ml and when the TB minus nil value was ≥25% of the IFN-γ concentration of the nil control.

Statistical analysis

The demographic data for those with positive QFT and negative QFT results were compared using the Student's *t*-test, Mann-Whitney test and Pearson chi-square test, depending on the type of variable. Associations between risk factors and QFT results were evaluated using the Pearson chi-square test and the Fisher's exact test where appropriate. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Multivariate logistic regression analysis was used to evaluate relationships of risk factors to QFT results by adjusting for age, employment length and household TB history. A $p<0.05$ was considered significant. SPSS version 16.0 software (SPSS, Chicago, IL) was used to perform statistical calculations.

RESULTS

Prevalence of latent tuberculosis infection among study subjects

Study subjects consisted of 112 HCWs, of whom 70.5% (79/112) were female. The mean (±SD) age of study subjects was 38.28 (±10.18) years. There was no significant difference in mean age between females and males (p=0.31). The mean (±SD) body mass index (BMI) of study subjects was 22.71±4.05 kg/m^2. Twenty-one subjects (18.8%; 95%CI: 11.52-25.98) had a positive QFT assay. None of the study subjects had an indeterminate QFT-assay result. Among the six study subjects with a history of successfully treated active TB, only one had a positive QFT assay.

Demographic factors and risks for latent tuberculosis infection

Of the 21 study subjects with a positive QFT-assay result, 17 (81.0%) were females. The female-to-male ratio of QFT-positive subjects was 4.25:1. Of the 91 study subjects with a negative QFT-assay result, 62 (68.1%) were females (female-to-male ratio of 2.14:1). Of those with a positive QFT-assay result, the mean age was 42 (range: 26-51) years and the mean BMI was 23.76 (±4.1) kg/m^2. Of those with a negative QFT-assay result, the mean age was 37 (range: 23-60) years and the mean BMI was 22.47 (±4.0) kg/m^2. The difference in mean ages between HCWs with a negative and positive QFT-assay result was significant (p=0.039) but the difference in mean BMI values was insignificant (p=0.188).

On univariate analysis, study subjects aged ≥30 years were more likely (OR= 10.33; 95%CI: 1.32-80.64) to have LTBI than those aged <30 years (Table 1).

Occupational factors and latent tuberculosis infection

In our study, nurses were more likely to have a positive QFT-assay result (OR= 10.42; 95%CI: 2.10-51.61) (Table 2). Study subjects who worked in the inpatient TB treatment department were more likely (OR=11.00; 95%CI: 1.33-90.89) to have a

Table 1
Associations between demographic factors and latent tuberculosis infection among study subjects.

Factor	QFT (*n*, %)		Univariate analysis		
	Positive (*n*=21)	Negative (*n*=91)	OR	95%CI	*p*-value
Gender					
Male	4 (19.0)	29 (31.9)	1		
Female	17 (81.0)	62 (68.1)	1.988	0.614-6.437	0.245
Age (year)					
<30	1 (4.8)	31 (34.1)	1		
≥30	20 (95.2)	60 (65.9)	10.333	1.324-80.640	0.007
BMI (kg/m^2)					
<25	14 (66.7)	69 (75.8)	1		
≥25	7 (33.3)	22 (24.2)	1.568	0.562-4.377	0.388
BCG vaccination[a]					
Yes	11 (91.7)	62 (95.4)	1		
No	1 (8.3)	3 (4.6)	1.879	0.179-19.745	0.500
Education					
Below bachelor	2 (9.5)	20 (22.0)	1		
Bachelor	10 (47.6)	49 (53.8)	2.041	0.410-10.157	0.376
Master	6 (28.6)	16 (17.6)	3.750	0.665-21.154	0.118
Doctorate	3 (14.3)	6 (6.6)	5.000	0.671-37.256	0.096

[a]Only 77 participants had information concerning BCG vaccination. QFT, QuantiFERON®-TB Gold In-Tube; OR, odds ratio; CI, confidence interval; BMI, body mass index; BCG, Bacille Calmette-Guérin.

positive QFT result. Study subjects who worked at the study institution for ≥10 years were significantly more likely to have a positive QFT-assay result (OR=5.93; 95%CI: 1.85-19.03), as were those with a history of exposure to a known TB patient (OR=9.84; 95%CI: 1.26-76.82).

Underlying diseases/conditions and association with latent tuberculosis infection

Study subjects with a history of liver disease were more likely to have LTBI than those who did not (OR=7.24; 95%CI: 1.12-46.66) (Table 3). Other underlying diseases/conditions were not found to be significantly association with LTBI.

Multivariate analysis of factors associated with latent tuberculosis infection

On multivariate analysis, factors associated with LTBI were: age ≥30 years (OR=18.88; 95%CI: 1.52-234.36), having worked as a nurse (OR=2.78; 95%CI: 1.19-6.49), having been employed for ≥10 years in the same job capacity at the study site (OR=8.78; 95%CI: 1.26-61.29) and having been exposed to a known TB case (OR=13.32; 95%CI: 1.61-110.04) (Table 4).

DISCUSSION

Thailand has a high TB disease burden. We postulated the prevalence of LTBI

Table 2
Associations between occupational factors and latent tuberculosis infection among study subjects.

Factor	QFT (*n*, %)		Univariate analysis		
	Positive (*n*=21)	Negative (*n*=91)	OR	95%CI	*p*-value
Occupation					
Housekeepers/general duties	1 (4.8)	6 (6.6)	1[a]		
Administrative clerk	0 (0)	5 (5.5)			
Molecular laboratory staff	0 (0)	6 (6.6)			
TB research assistant	0 (0)	15 (16.5)			
Senior TB researcher	1 (4.8)	1 (1.1)			
Microbiology laboratory staff	2 (9.5)	8 (8.8)	4.125	0.502-33.911	0.209
Physician	2 (9.5)	20 (22.0)	2.357[b]	0.363-15.310[b]	0.388[b]
Pharmacist	1 (4.8)	1 (1.1)			
Nurse assistant	2 (9.5)	10 (11.0)	3.300	0.411-26.514	0.266
Nurse	12 (57.1)	19 (20.9)	10.421	2.104-51.607	0.001
Work location					
TB research laboratory	1 (4.8)	22 (24.2)	1		
Clinical microbiology laboratory	2 (9.5)	10 (11.0)	4.400	0.356-54.367	0.266
Outpatient department	2 (9.5)	8 (8.8)	5.500	0.437-69.264	0.212
Inpatient department	13 (61.9)	26 (28.5)	11.000	1.331-90.886	0.008
Employment length in years					
<10	4 (19.0)	53 (58.2)	1		
≥10	17 (81.0)	38 (44.8)	5.928	1.847-19.025	0.001
Hours worked per day					
≤8	11 (52.4)	49 (53.8)	1		
>8	10 (47.6)	42 (46.2)	1.061	0.410-2.743	0.903
Known TB exposure in the hospital					
No	1 (4.8)	30 (33.0)	1		
Yes	20 (95.2)	61 (67.0)	9.836	1.259-76.817	0.009
Type of exposure[c]					
Specimens	3 (15.0)	33 (37.1)	1		
Patients	17 (85.0)	56 (62.9)	3.339	0.910-12.260	0.058
Frequency of handling TB specimens or patients per week[c]					
0-1	7 (33.3)	24 (35.3)	1		
2-5	10 (47.6)	26 (38.2)	1.319	0.433-4.017	0.620
6-10	2 (9.5)	3 (4.4)	2.286	0.316-16.512	0.581
>10	2 (9.5)	15 (22.1)	0.457	0.084-2.499	0.460

[a]The reference groups for occupational risk included housekeepers/those with general duties, administrative/clerical, molecular laboratory staff, TB research assistants and senior TB researchers. [b]Physicians and pharmacists were combined for analysis because of the small number in the latter group and because both groups worked in the inpatient department. [c]Only available data were analyzed (*n*=109 for type of exposure, *n*=89 for frequency of handling TB specimens or patients per week). QFT, QuantiFERON®-TB Gold In-Tube; OR, odds ratio; CI, confidence interval; TB, tuberculosis.

Table 3
Associations between underlying disease/conditions and latent tuberculosis infection among study subjects.

Factor	QFT (*n*, %)		Univariate analysis		
	Positive (*n*=21)	Negative (*n*=91)	OR	95%CI	*p*-value
Nutritional status[a]					
Moderate	2 (9.5)	16 (17.6)	1		
Good	10 (47.6)	44 (48.4)	1.818	0.356-9.210	0.718
Excellent	9 (42.9)	31 (34.0)	2.323	0.448-12.054	0.474
Smoking					
No	20 (95.2)	87 (95.6)	1		
Yes	1 (4.8)	4 (4.4)	1.088	0.115-10.262	1.000
Alcohol consumption					
No	18 (85.7)	61 (67.0)	1		
Yes	3 (14.3)	30 (33.0)	0.339	0.093-1.241	0.091
Diabetes mellitus[b]					
No	15 (88.2)	81 (98.8)	1		
Yes	2 (11.8)	1 (1.2)	10.800	0.920-126.77	0.075
Liver disease[b]					
No	17 (85.0)	82 (97.6)	1		
Yes	3 (15.0)	2 (2.4)	7.235	1.122-46.658	0.048
Kidney disease[b]					
No	19 (100)	86 (100)	NA		
Yes	0 (0)	0 (0)	NA		
Lung disease[b]					
No	19 (95.0)	84 (100)	NA		
Yes	1 (5.0)	0 (0)	NA		
Thalassemia[b]					
No	16 (88.9)	80 (92.0)	1		
Yes	2 (11.1)	7 (8.0)	1.429	0.271-7.518	0.650
Household TB					
No	19 (90.5)	83 (91.2)	1		
Yes	2 (9.5)	8 (8.8)	1.092	0.214-5.561	1.000

[a]No participant exhibited poor nutrition. [b]Only available data (*n*=99 for diabetes mellitus, *n*=104 for liver disease, *n*=105 for kidney disease, *n*=104 for lung disease and *n*=105 for thalassemia) were analyzed. Household TB refers to the history of having a patient with active TB living in the same house. QFT, QuantiFERON®-TB Gold In-Tube; OR, odds ratio; CI, confidence interval; NA, not analyzed; TB, tuberculosis.

in the general community and among study subjects would be high. The World Health Organization (WHO, 2015) estimates the global prevalence of LTBI to be one-fourth to one-third of the population (WHO, 2015). In our study, the prevalence of LTBI among the study population of HCWs was 18.8%, lower than postulated. A previous study of the prevalence of LTBI in HCWs at Srinagarind Hospital, based

Table 4
Associations between selected factors and latent tuberculosis infection on multivariate analysis among study subjects.

Factor	Adjusted OR	95%CI	*p*-value
Age in years			
<30	1		
≥30	18.880	1.521-234.358	0.022
Occupations			
Reference group	1[a]		
Nurses	2.778	1.189-6.494	0.018
Work location			
Research lab	1		
Inpatient department	2.774	0.938-8.204	0.065
Employment length in years			
<10	1		
≥10	8.778	1.257-61.290	0.028
Known TB exposure			
No	1		
Yes	13.318	1.612-110.040	0.016
Liver disease[b]			
No	1		
Yes	6.859	0.955-49.266	0.056

[a]The reference groups for occupational risk included housekeepers/those with general duties, administrative/clerical, molecular laboratory staff, TB research assistants and senior TB researchers. [b]Only available data were analyzed (n=104 for liver disease). Multivariate analysis used age, employment length and household TB contacts to adjust. OR, odds ratio; CI, confidence interval; TB, tuberculosis.

on TST results, was 26.1% (Sawanyawisuth *et al*, 2009). Although higher than our figure, this could be due to false-positive TST results as a consequence of previous BCG vaccination or previous infection with NTM (Farhat *et al*, 2006; de Souza *et al*, 2014). In contrast, two previous studies of LTBI among HCWs in northern Thailand using TST found prevalences of 68% and 63% (Do *et al*, 1999; Yanai *et al*, 2003). Our study subjects were at high risk for TB exposure because they worked with TB patients or in a TB laboratory. Those much higher prevalences could be due to false-positive TST results or a higher prevalence of TB due to a different study population. Other studies using the TST found high prevalences of LTBI in HCWs: 38% in Canada (Schwartzman *et al*, 1996), 79% in Ivory Coast (Kassim *et al*, 2000) and 57% in Uganda (Kayanja *et al*, 2005). Studies using the QFT found lower prevalences of LTBI: 8.9% in Poland (Targowski *et al*, 2014), 27% in Brazil (de Souza *et al*, 2014) and 20.6% in Turkey (Bozkanat *et al*, 2016). No previous studies in Thailand have used the QFT assay to determine the association between selected risk factors and LTBI among HCWs.

In our study, nurses were more likely to have a positive QFT-assay result compared to other study subjects. This is

similar to previous studies (Do *et al*, 1999; Garcia-Garcia *et al*, 2001; Keskiner *et al*, 2004; Roth *et al*, 2005). Working directly with TB patients over time increases the risk for contracting TB. However, some studies did not find an association between having LTBI and being a HCW (Lien *et al*, 2009; Borroto *et al*, 2011; He *et al*, 2012; Zhang *et al*, 2013). On univariate analysis, working in the inpatient department was significantly associated with a positive QFT-assay result. A similar result was found in a previous study (Sawanyawisuth *et al*, 2009). This could be due to greater frequency and longer duration of exposure to active TB patients. At our study hospital, the outpatient department is better ventilated than the inpatient department, and there are stricter policies about wearing personal protective equipment, such as masks. These might be preventive factors. However, on multivariate analysis, we did not find an association between work location and a positive QFT-assay result. Other studies also reported finding no association between work area and LTBI (Do *et al*, 1999; Yanai *et al*, 2003; Powell *et al*, 2011; Zhang *et al*, 2013). Some studies have reported a positive association between length of career as a HCW and risk of contracting LTBI (Do *et al*, 1999; Yanai *et al*, 2003; He *et al*, 2012; Zhou *et al*, 2014). In our study, those who had been employed as HCWs for ≥10 years were more likely to have a positive QFT-assay result. This is in agreement with two studies from China (He *et al*, 2012; Zhang *et al*, 2013). Longer duration of employment as a HCW has been found to be significantly associated with positive TST and QFT-assay results (Pai *et al*, 2005).

Exposure to active TB cases is probably a risk for developing LTBI. In our study, subjects exposed to known TB cases were significantly more likely to have a positive QFT-assay result. In a study from Cuba, HCWs with an exposure to TB patients had twice the risk of having LTBI (Borroto *et al*, 2011). The frequency of exposure to TB patients has been reported to be associated with LTBI in several studies (Do *et al*, 1999; He *et al*, 2012; Whitaker *et al*, 2013). However, we did not see this association in our study. A previous study also reported that HCW frequency of exposure to TB patients was not significantly associated with a positive TST (Yanai *et al*, 2003). HCWs who frequently deal with TB patients may be more aware of personal protection methods against TB, such as wearing an N95 mask. Inversely, HCWs who deal with TB patients less frequently may be more careless regarding personal protective equipment.

Underlying disease might increase the risk of LTBI. In our study, only liver disease was associated with LTBI, but this result did not remain significant on multivariate analysis. Other conditions/diseases such as diabetes mellitus, kidney disease and lung disease were not associated with LTBI in our study. Most HCWs were healthy, therefore they were not an appropriate set of subjects for study of underlying diseases and conditions associated with LTBI.

A QFT result can become negative due to clearance of the TB or presence of localized infection when the memory T-cell response may subside over time (Bocchino *et al*, 2010). In our study, 5 out of 6 subjects with a history of TB had a negative QFT-assay result. The reversion of previous active TB status into negative QFT-assay result of these 5 subjects probably indicates TB clearance. The one individual with a persistent positive QFT-assay result might have had a persistent LTBI, have become re-infected with TB,

or have been infected with an NTM (such as *M. gastri, M. kansasii* or *M. marinum).* Distinguishing among these possibilities is necessary for treatment, control and prevention measures.

One limitation of our study was selection bias because we recruited participants from particular areas in the hospital, especially areas at high risk for TB exposure. Some medical information was based on a questionnaire only, rather than examination or laboratory testing. A history of household TB contact was not significantly associated with a positive QFT-assay result in our study. However, this could be confounded by the risk of TB exposure at the work place. To maximize the sample size, we did not exclude those with a previous history of active TB or household TB contacts. However, only one subject with a previous history of TB and two subjects with a history of household TB contacts had a positive QFT-assay result. Furthermore, we also added household TB contact as a factor to be adjusted in the multivariate analysis.

In conclusion, the factors significantly associated with a positive QFT-assay result among study subjects were: age ≥30 years, employment as a HCW for ≥10 years and having a history of exposure to a known TB patient. Nurses were more likely to have a positive QFT-assay result. This information can inform control programs and management policies of TB control among HCWs.

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