

RESEARCH NOTE

QUANTIFERON®-TB GOLD IN-TUBE TEST FOR DIAGNOSING LATENT TUBERCULOSIS INFECTION AMONG CLINICAL-YEAR THAI MEDICAL STUDENTS

Benjawan Phetsuksiri¹, Somchai Sangkitporn¹, Janisara Rudeeaneksin¹, Sopa Srisunggam¹, Supranee Bunchoo¹ and Thana Khawcharoenporn²

¹National Institute of Health, Department of Medical Sciences, Ministry of Public Health, Nonthaburi; ²Division of Infectious Diseases, Faculty of Medicine, Thammasat University, Pathum Thani, Thailand

Abstract. Persons with latent tuberculosis infection (LTBI) are at-risk for developing subsequent active tuberculosis (TB). Screening for LTBI is important, especially in healthcare workers (HCWs) who have increased risk of acquiring TB. The new LTBI screening test, QuantiFERON®-TB Gold In-tube Test (QFT-IT) is now available in Thailand. However, data on the rate of positive test and factors associated with test positivity are limited among Thai medical students. We conducted a cross sectional study among clinical-year medical students (fourth to sixth year students) at Thammasat University, Thailand. All students who consented to participate in this study had the QFT-IT and a LTBI risk assessment during June 2014 as part of a health screening program. A total of 204 subjects were included in the program; their median age was 22 years (range: 20-34 years), 52% were female, 94% had a history of Bacillus Calmette-Guérin vaccination. Twenty subjects (10%) had a positive QFT-IT test and were presumed to have LTBI. The median interferon- γ (IFN- γ) level was 0.01 (range: 0-7.37 IU/ml). Independent factors associated with QFT-IT positivity were a history of direct TB contacts [adjusted odds ratio (aOR)=3.78; $p=0.006$], being a sixth year student (aOR=2.76; $p=0.03$) and having a history of working on a ward with active TB patients without having direct TB contacts (aOR=2.69; $p=0.04$). The QFT-IT was useful in screening our study subjects and should be considered as a screening tool in this population due to the high incidence of QFT-IT positivity.

Keywords: QuantiFERON®-TB Gold In-tube Test, latent tuberculosis infection, clinical-year, medical students, Thailand

Correspondence: Dr Thana Khawcharoenporn, Division of Infectious Diseases, Faculty of Medicine, Thammasat University, Pathum Thani, Thailand.
Tel: 66 (0) 81 836 5576; Fax: 66 (0) 2926 9793
E-mail: thanak30@yahoo.com

INTRODUCTION

Tuberculosis (TB) is a major public health problem in Thailand. The estimated prevalence of TB in the general Thai population is 172 per 100,000 (WHO, 2014). TB

screening and prevention are important to reduce TB incidence, especially in at-risk populations, such as healthcare workers (HCWs) (Khawcharoenporn *et al*, 2011). The currently available screening tests for latent tuberculosis infection (LTBI) in Thailand are the tuberculin skin test (TST) and the interferon- γ release assays (IGRAs). The TST has limitations, such as false positive results from previous *Bacillus Calmette-Guérin* (BCG) vaccination and non-tuberculous mycobacterial infections, administrative and interpretative errors and the requirement of two clinic visits (Khawcharoenporn *et al*, 2011). The IGRAs have gained popularity as a test to diagnose LTBI (CDC, 2010).

IGRAs have been demonstrated to be more sensitive and specific than the TST, especially among BCG-vaccinated persons or those from TB-endemic settings (Khawcharoenporn *et al*, 2011). However, false positive IGRA tests occur in infections due to *Mycobacterium kansasii*, *Mycobacterium szulgai*, *Mycobacterium marinum* and *Mycobacterium gordonae* (Andersen *et al*, 2000), due to incorrect blood sample collection, and improper handling of the specimen (Andersen *et al*, 2007). There is no gold standard test to diagnose LTBI. The interferon (IFN)- γ cut-off level of ≥ 0.35 IU/ml for a positive QuantiFERON®-TB Gold In-tube Test (Cellestis, Carnegie, Victoria, Australia) (QFT-IT) is derived from studies of active TB cases (CDC, 2010). However, the utility of diagnosing LTBI among Thai medical students using the QFT-IT has not been evaluated before. In addition, data on factors associated with positive QFT-IT among the students is limited.

MATERIALS AND METHODS

We conducted a cross sectional study

among fourth to sixth year medical students at Thammasat University during their clinical clerkship at Thammasat University Hospital (TUH) to determine how many of them had positive QFT-IT and also factors associated with QFT-IT positivity. This study was approved by Faculty of Medicine, Thammasat University Ethics Committee. Inclusion criteria were all the fourth to sixth year medical students participated in the TUH annual health screening program in June 2014. Exclusion criteria were students with prior or current active TB and receipt of TST or IGRA within the prior 12-month period. Data obtained from each subject included demographics, working history, history of BCG vaccination, and LTBI risks. All subjects were screened for active TB by assessing symptoms including fever, coughing more than 2 weeks, night sweat and weight loss of more than 10% within one month and by chest radiograph. All study subjects had a QFT-IT. The test was conducted following the manufacturer's guidelines (Mazurek *et al*, 2010). The IFN- γ level was calculated by subtracting TB antigen response with nil response. The nil response indicates the presence of any residual gamma interferon found in the subject's blood due to an infection with an organism requiring cell mediated immunity/T cell immunity.

Direct TB contact was defined as staying in the same closed-ventilation room with active pulmonary TB case without airborne isolation protection. A history of working on a TB ward and the year of study were recorded.

All analyses were performed using SPSS, version 15.0 (SPSS, Chicago, IL). Categorical variables were compared using the Pearson's χ^2 or Fisher's exact test when appropriate. Continuous variables were compared using the Mann-Whitney

Table 1
 Characteristics of study subjects by QuantiFERON®-TB Gold In-tube Test (QFT-IT) results.

Characteristics	Number (%) except where noted (n = 204)	QFT-IT positive, number (%) (n =20)	QFT-IT negative, number (%) (n = 184)	p-value
Age (years, median, range)	22 (20-34)	23 (20-25)	22 (20-34)	0.32
Female sex	106 (52)	12 (60)	94 (51)	0.45
Study year		0.07		
4	85 (42)	7 (35)	78 (42)	
5	60 (29)	3 (15)	57 (31)	
6	59 (29)	10 (50)	49 (27)	
History of working on a ward with active TB patients without direct TB contact for at least 1 month	118 (58)	16 (80)	102 (55)	0.04
Working duration on the wards (days, median, range)	380 (5-1,825)	730 (10-1,095)	365 (5-1,825)	0.07
History of a direct TB contacts	28 (14)	7 (35)	21 (11)	0.006
History of BCG vaccination	192 (94)	18 (90)	174 (95)	0.33
Interferon- γ level (IU/ml, median, range)	0.01 (0-7.37)	0.90 (0.39-7.37)	0.01 (0-0.33)	<0.001

BCG, Bacillus Calmette-Guérin; LTBI, latent tuberculosis infection; TB, tuberculosis.

U test. A *p*-value <0.05 was considered statistically significant. Adjusted odd ratios (aORs) and 95% confidence intervals (CIs) were calculated by multivariable logistic regression analysis to determine factors associated with a positive QFT-IT.

RESULTS

A total of 204 students were included in this study. The characteristics of the students are summarized in Table 1. Using an IFN- γ cut-off level of ≥ 0.35 IU/ml, 20 students (10%) had a positive QFT-IT. When comparing students with positive and negative QFT-IT results, those with a positive result were more-likely to have a history of a direct TB contacts and a history of working on a ward with active TB patients without direct TB contacts (Table 1). On multivariable logistic regression

analysis, having a history of a direct TB contacts (aOR=3.78; 95% CI: 1.47-9.69; *p*=0.006), being a sixth year student (aOR=2.76; 95% CI: 1.08-7.02; *p*=0.03) and having a history of working on a ward with active TB patients without direct TB contacts (aOR=2.69; 95% CI: 1.05-8.37; *p*=0.04) were all significantly associated with a positive QFT-IT result.

DISCUSSION

This is the first study using QFT-IT to diagnose LTBI among clinical-year medical students in Southeast Asia. Ten percent of all subjects had a positive QFT-IT test, which was higher than the rates of positive QFT-IT among healthcare professional students in TB low prevalence countries but comparable to or lower than the rates of positive QFT-IT in TB high

Table 2
Summary of studies using the QuantiFERON-TB® (QFT) to screen for latent tuberculosis infection among healthcare professional students.

Reference	Country	TB incidence (cases/100,000) ^a	Study type	Sample size	Type of QFT	Study population	QFT positivity rate	Factors associated with QFT positivity
Pai <i>et al.</i> , 2006	India	217	Prospective cohort	216	QFT-IT	Medical and nursing students	18%	No data
Zwerling <i>et al.</i> , 2013	India	217	Prospective cohort	226	QFT-IT	Medical and nursing students	28%	Days spent working on medical wards
Eum <i>et al.</i> , 2008	South Korea	80	Cross sectional	48	QFT-IT	BCC-vaccinated medical students	10%	No data
Dagnew <i>et al.</i> , 2012	Ethiopia	192	Cross sectional	107	QFT-IT	Male medical and paramedic students	44%	Older age, Khat ^b consumption
Jung <i>et al.</i> , 2012	South Korea	80	Cross sectional	153	QFT-IT	Medical students	5%	No data
Our study	Thailand	172	Prospective cohort	204	QFT-IT	Medical students	10%	History of direct TB contacts, higher study year, history of working on a ward with active TB patients without direct TB contacts
Veeser <i>et al.</i> , 2007	United States	3	Retrospective chart review	54	QFT-IT	Students of University Health Services	15%	No data
Hotta <i>et al.</i> , 2007	Japan	17	Cross sectional	207	QFT	Medical, nursing and dental students	1%	No data
Schablon <i>et al.</i> , 2013	Germany	8	Prospective cohort	194	QFT-IT	Healthcare professional students	2%	No data
Lamberti <i>et al.</i> , 2015	Italy	6	Cross sectional	1,577	QFT-IT	Nursing students	0.1% ^c	No data
Lamberti <i>et al.</i> , 2014	Italy	6	Cross sectional	3,374	QFT-IT	Healthcare professional students	1% ^c	Older age, higher study year
Lamberti <i>et al.</i> , 2017	Italy	6	Cross sectional	281	QFT-IT	Undergraduate and postgraduate dental students	3% ^c	Higher study year ^d

^aBased on the World Health Organization tuberculosis country profiles (WHO, 2014). ^bA plant named *Catha edulis*. ^cMost participants were tested positive for tuberculin skin test first, then had QFT. Some participants were tested by QFT as the first test. ^dThis factor was associated with tuberculin skin test and/or QFT positivity. BCG, Bacillus Calmette-Guérin; QFT, QuantiFERON®-TB Test; QFT-IT, QuantiFERON®-TB Gold In-tube Test; TB, tuberculosis.

prevalence countries (Table 2).

The risk factors associated with a positive QFT-IT in this study were history of a direct TB contacts, being a sixth year student and having a history of working on a ward with active TB patients without direct TB contacts. Other studies reported that older age, higher study year and number of days spent working on medical wards were risk factors associated with a positive QFT-IT among healthcare professional students (Dagnev *et al*, 2012; Zwerling *et al*, 2013; Lamberti *et al*, 2014; Lamberti *et al*, 2017). These reported factors were consistent with our study's results which suggest that infection control measures need to be strictly implemented not just for the active TB patients but the students need to be educated in preventive methods and given appropriate protection.

Limitations of this study include the small sample size of the included subjects and the single site study. The study results may not be generalizable to other medical students in Thailand.

In conclusion, the QFT-IT positivity rate among our study subjects was high. The risk factors associated with QFT-IT positivity were history of a direct TB contacts, being a sixth year student and having a history of working on a ward with active TB patients without direct TB contacts. The QFT-IT was useful in screening our study subjects and should be considered as a screening tool in this population due to the high incidence of QFT-IT positivity.

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