Evaluation of the QuantiFERON®-TB Gold In-Tube assay and tuberculin skin test for the diagnosis of *Mycobacterium tuberculosis* infection in northeastern Thailand

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Summary

Background: **The diagnosis of latent *Mycobacterium tuberculosis* infection (LTBI) is currently based on the immunological response of T-cells to *M. tuberculosis* (MTB) antigens. However, the QuantiFERON®-TB Gold In-Tube assay (QFT) has not yet been evaluated in the Thai adult population.**

Objective: **To evaluate the diagnostic performance and determine predictors of discordant results between the QFT and tuberculin skin test (TST).**

Methods: **Active tuberculosis (ATB) patients (n=54), close contacts (CCs) living in the same household as a TB patient (n=100) and healthy controls (HCs) (n=60) were interviewed and underwent the QFT and TST at Srinagarind Hospital in Thailand. Various cut-off values for the QFT (0.25-0.35 IU/mL) and TST (5-15 mm) were applied.**

Results: **The maximum agreement rate between the tests was 71.5% (κ=0.41) with cut-offs of 0.35 IU/mL and 10 mm or 0.25 IU/mL and 10 mm. Based on standard cut-off values (0.35 IU/mL and 10 mm) and using ATB patients and HCs as positive and negative controls, the TST was more sensitive than the QFT (87.0% vs. 66.7%, respectively), whereas the QFT was more specific than the TST (83.3% vs. 70.0%, respectively). Being underweight (OR 3.86, 95%CI 1.3-11.48) or overweight (OR 5.9, 95%CI 1.24-28.16) was significantly associated with TST+/QFT- results. Diabetes (OR 32.56, 95%CI 1.73-613.49) and poor or fair nutrition (OR 7.4, 95%CI 1.23-44.57) were significantly associated with TST-/QFT+ results.**

Conclusion: **The TST should be used as a screening test based on its higher sensitivity, whereas the QFT should be used as a confirmatory test because of its higher specificity.** ***(Asian Pac J Allergy Immunol 2015;33:236-44)***

Keywords: *Interferon-gamma release assay, latent tuberculosis infection, Mantoux test, Mycobacterium tuberculosis, tuberculin skin test*

Introduction

Tuberculosis (TB) remains a major public health problem, as one-third of the world's population is infected with *Mycobacterium tuberculosis* (MTB). Identifying active and latent TB infection (LTBI) cases and determining appropriate prophylactic interventions are necessary for effective TB control. However, there is no gold standard for the identification of LTBI cases, and such infections are commonly inferred based on immunological responses (e.g., T-cell response). The interferon-gamma release assay (IGRA) is a well-known test that is often used instead of the tuberculin skin test (TST) for LTBI screening due to increased specificity and faster results.[1] However, the guidelines for using the TST and IGRA as screening methods for MTB infections are unclear and vary among geographical regions.[2]

The TST detects MTB sensitization via a delayed-type hypersensitivity response to crude

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Submitted date: 14/10/2014
Accepted date: 4/2/2015

MTB antigens from purified protein derivatives (PPDs); however, these antigens may cross-react with environmental mycobacteria and the BCG vaccine.[3] IGRAs measure interferon-gamma (IFN-γ) release in response to specific MTB antigens, which improves the specificity.[4] There are two main commercially available IGRAs: the QuantiFERON In-Tube® (ELISA-based test, Cellestis Australia) and the T-SPOT.TB® assay (ELISPOT-based test, Oxford Immunotech, UK). In 2005, a third-generation ELISA-based test, the QuantiFERON®-TB Gold In-Tube assay (QFT), was approved by the Food and Drug Administration (FDA) as a diagnostic test for MTB infection.[5] The QFT was reported to have higher sensitivity and specificity than the TST.[4,6,7] However, the efficacies of the QFT and TST can vary depending on the tested population and region.[4,6]

For effective control of TB, parallel management of active TB and LTBI is a more effective approach. However, the current guidelines for LTBI management in Thailand are still not clear due to the focus on more urgent issues such as active TB, drug-resistant TB and HIV infection-associated TB. Additionally, Thailand has a high TB burden, and administration of the BCG vaccine is promoted as a national health policy. Therefore, Thailand is a suitable region for evaluating MTB screening tests. Previously, LTBI in Thailand was studied using the TST.[8-11] Only one study has compared the performance of the IGRA with that of the TST in Thailand. This study revealed that the results of the IGRA (QFT and T-SPOT.TB) tests were not significantly different from those of the TST in a Thai pediatric population.[12] Evaluations of the tests in different populations, such as adult individuals who live in the same household as TB patients and are in close contact with these patients, and verification using active TB patients and healthy individuals with unknown TB exposure are still needed.

Our current study evaluated the diagnostic performance of the QFT and TST using various cut-offs and determined factors associated with discordance between these tests in northeastern Thailand.

Methods

Setting and population

Participants (n=214) from Srinagarind Hospital in Khon Kaen, Thailand were enrolled between September 1st, 2012 and March 31st, 2014. These participants included patients with new, active pulmonary TB (ATB) (n=54) who tested positive for the disease based on acid-fast bacilli (AFB) and/or MTB growth in culture, patients with a positive PCR-TB result, people in close contact (CC) with TB patients who were living in the same household (n=100), and healthy controls (HCs) with no known TB exposure risk (n=60). The HC group comprised healthy individuals who received a health check-up at Srinagarind Hospital. Members of HC group were interviewed to exclude individuals with a potential risk of TB exposure. All participants provided written informed consent, completed a TB risk assessment questionnaire, and underwent a physical examination. Blood samples were obtained from the participants prior to performing the TST. Demographic data and information regarding any underlying diseases were collected. A chest X-ray and anti-HIV test were performed in all ATB patients. This study was approved by the Research Ethics Committee (HE551100) of Khon Kaen University, Thailand.

Inclusion and exclusion criteria

New, symptomatic ATB patients with positive AFB, a positive Xpert MTB/RIF assay (Cepheid, Sunnyvale, USA) result, or MTB growth culture from sputum were defined as the "ATB" group. Participants living in the same house with an ATB patient for ≥2 weeks before the patient started TB treatment were defined as the "CC" group. Healthy subjects without TB signs and symptoms, normal results from a chest X-ray, and no history of TB infection or TB exposure were defined as the "HC" group. Individuals with LTBIs were defined as people without active TB symptoms who had a normal chest X-ray and positive results in both the QFT and TST.

HIV-positive ATB patients were excluded. CC and HC participants were excluded if they developed active TB, were HIV positive, received an immunosuppressive agent, or had a positive TST result within 3 weeks of recruitment. Participants with an indeterminate QFT result were also excluded from the study population.

QFT

The QFT was performed according to the manufacturer's instructions on the same day as the TST. Briefly, venous blood samples were obtained from volunteers and placed in three 1-mL QFT tubes. The samples were mixed, delivered to the laboratory, and incubated at 37°C for 21 h. After

incubation, the samples were processed and tested to determine IFN-γ levels (IU/mL). The results were considered positive when the IFN-γ concentration of the sample exposed to MTB-specific antigens minus the IFN-γ concentration of the negative control was ≥0.35 IU/mL (or other cut-off values) and when the IFN-γ concentration in the sample was ≥25% of that in the negative control sample. Other QFT cut-off values (0.25-0.35 IU/mL) were also evaluated.

TST

The TST was performed by trained nurses according to the Mantoux technique. On enrollment, 0.1 mL (5 TU) of PPDs (RT23; Statens Serum Institut, Copenhagen, Denmark) was injected intradermally on the volar aspect of the forearm. After 48 h, the transverse diameter of the TST induration was determined by two trained nurses. The results were considered positive when the average TST diameter was ≥ 10 mm. Other TST cut-off values were also evaluated.

Data analysis

The means were compared using Student's t-test or one-way analysis of variance (ANOVA). Comparisons of group size and concordance between the TST and QFT were performed using a Chi-square test or Fisher's exact test. Kappa scores were used for measuring agreement between tests. Predictors of discordance between the TST and QFT were analyzed by logistic regression. A correlation analysis was performed between the TST and QFT using linear regression. A P-value <0.05 was considered significant. SPSS version 16 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis.

Results

Participant characteristics

We obtained complete demographic data for all 214 participants recruited for the study. Most participants were female (135/214, 63.08%). A total of 62.96% (34/54) of the ATB patients were male, which was significantly higher than the proportions observed in the CC group (32 males/100 patients, 32%) and the HC group (13 males/60 patients, 21.67%) (p <0.001). The mean age of all participants was 41.63±18.48 years (range 6-83). Only 5.1% (11/214) of the participants were younger than ten years. Individuals in the ATB group were significantly older than individuals in the CC (p <0.001) and HC groups (p =0.005). The mean body mass index (BMI) of the ATB patients was significantly lower than that of the CC (p = 0.001) and HC subjects (p = 0.005). The majority (77.1%) of the participants were from Khon Kaen province and had an office-based occupation (31.78%). The ATB group was more likely to have diabetes mellitus (DM) (22.22%) compared with the CC group (6%) (p = 0.004) (Table 1).

Comparisons between TST and QFT among the study groups

Using the standard cut-off values of 10 mm and 0.35 IU/mL, the majority of the ATB patients showed positive TST (47/54, 87.04%) and QFT (36/54, 66.67%) results. The positive rates for both the TST and QFT were significantly higher in the ATB group compared to the CC (p < 0.001) and HC (p < 0.001) groups (Table 2). The positive rates were not significantly different between the CC and HC groups for the TST (39/100 [39%] vs. 18/60 [30%], respectively, p = 0.164) or QFT (20/100 [20%] vs. 10/60 [16.67%], respectively, p = 0.381). Overall, the positive rate for the TST was significantly higher than that for the QFT (104/214 [48.60%] vs. 66/214 [30.84%], respectively, p < 0.001) (Table 2).

Diagnostic performance of the TST and QFT

Using standard cut-off values and the ATB and HC groups as positive and negative controls for MTB infection, respectively, the sensitivity of the TST was higher than that of the QFT (87.04% vs. 66.67%, respectively), whereas the specificity of the QFT was higher than that of the TST (83.33% vs. 70.00%, respectively) (Table 3). For the TST and QFT, the positive predictive value (PPV) (72.31 vs. 78.26%, respectively) and negative predictive value (NPV) (85.71 vs. 73.53%, respectively) are shown in Table 3. The induration size in the TST and the IFN-γ level in the QFT were found to be significantly correlated within the total population (p < 0.001, R=0.394) and within individual groups (data not shown).

Agreement between the TST and QFT using various cut-off values

The overall agreement between the TST and QFT in all participant groups (ATB, CC and HC) using the standard cut-off values was 71.5% (κ = 0.41) (Table 4). Comparing the cut-off values of 10 mm and 0.25 IU/mL with the standard cut-off values, a similar agreement rate was achieved for all groups (71.5%), and a slightly higher agreement rate (83/114 cases, 72.8%) was achieved for the combined ATB and HC groups when the cut-off values of 10 mm and 0.25 IU/mL were used. The use of other cut-off values yielded lower overall

Table 1. Demographic and clinical data.

Characteristics	Study groups (n, (%))			Total (n=214)
	ATB (n=54)	CC (n=100)	HC (n=60)	
Male gender	34 (62.96)	32 (32)	13 (21.67)	79 (36.92)
Age				
Average [±SD]	49.50 [±15.55]	38.34 [±20.89]	40.03 [±14.35]	41.63 [±18.48]
≤20	2 (3.7)	29 (29)	5 (8.33)	36 (16.82)
>20-40	15 (27.78)	20 (20)	27 (45)	62 (28.97)
>40-60	22 (40.74)	37 (37)	22 (36.67)	81 (37.85)
>60	15 (27.78)	14 (14)	6 (10)	35 (16.36)
BMI				
Average [±SD]	20.32 [±3.23]	22.65 [±5.11]	22.87 [±3.25]	22.13 [±4.34]
≤18.5	19 (35.19)	25 (25)	5 (8.33)	49 (22.90)
>18.5-25	30 (55.56)	46 (46)	41 (68.33)	117 (54.67)
>25	5 (9.26)	29 (29)	14 (23.33)	48 (22.43)
Living inside KK	40 (74.07)	77 (77)	48 (80)	165 (77.10)
Occupations				
Farmer	9 (16.67)	12 (12)	1 (1.67)	22 (10.28)
General servant	11 (20.37)	13 (13)	13 (21.67)	37 (17.29)
Officer	18 (33.33)	17 (17)	33 (55)	68 (31.78)
Student	3 (5.56)	29 (29)	9 (15)	41 (19.16)
Merchant	4 (7.41)	11 (11)	2 (3.33)	17 (7.94)
No occupation	9 (16.67)	18 (18)	2 (3.33)	29 (13.55)
BCG vaccination	42 (77.78)	86 (86)	55 (91.67)	183 (85.51)
Smoking	19 (35.19)	9 (9)	6 (10)	34 (15.89)
Alcohol consumption	24 (44.44)	24 (24)	16 (26.67)	64 (29.91)
Diabetes mellitus	12 (22.22)	6 (6)	0 (0)	18 (8.41)
Nutrition status				
Excellent	3 (5.56)	33 (33)	13 (21.67)	49 (22.9)
Good	28 (51.85)	58 (58)	43 (71.67)	129 (60.28)
Fair	16 (29.63)	9 (9)	4 (6.67)	29 (13.55)
Poor	7 (12.96)	0 (0)	0 (0)	7 (3.27)

SD: standard deviation, ATB: active TB patients, CC: individuals in close contact with a TB patient, HC: healthy controls. Nutritional status: the current status at the time of the participant's interview.

agreement rates or lower positive agreement rates (data not shown).

Predictors of discordance between QFT and TST results

Predictors of discordance between the QFT and TST results were analyzed in the ATB, CC and HC groups (Table 5). Multivariate regression analysis revealed that participants with a low BMI (OR 3.86, 95% CI 1.3-11.48) or high BMI (OR 5.9, 95% CI 1.24-28.16) were significantly more likely to have a TST+/QFT- result than those with a normal BMI, compared to concordant positive results. Participants with DM (OR 32.56, 95% CI 1.73-613.49) and poor or fair nutrition (OR 7.4, 95% CI 1.23-44.57) were significantly more likely to have a TST-/QFT+ result than non-DM subjects and those with excellent or good nutrition, respectively, compared to concordant negative results. DM patients were more likely to have a TST+/QFT- result (OR 13.55, 95% CI 1.4-131.56) compared to concordant negative results. Other predictors such as gender, age, location, smoking, and alcohol consumption showed insignificant ORs. TST+/QFT- discordance was found in both BCG-vaccinated (44/183, 24.0%) and non-vaccinated (6/31, 19.4%) participants, and TST-/QFT+ discordance was found in both vaccinated (7/183, 3.8%) and non-vaccinated participants (4/31, 12.9%).

Table 2. Comparison of results between the TST and QFT in individuals who were in close contact with TB patients, healthy individuals, and active TB patients.

Tested groups	TST: induration size (mm)				QFT: IFN-γ level (IU/mL)			
	Positive cases		Negative cases		Positive cases		Negative cases	
	n	x̄ (±SD)	n	x̄ (±SD)	n	x̄ (±SD)	n	x̄ (±SD)
ATB (n=54)	47	19.09 (3.81)	7	1.29 (2.21)	36	2.69 (2.5)	18	0.11 (0.09)
CC (n=100)	39	15.14 (4.82)	61	1.45 (2.74)	20	3.49 (3.08)	80	0.05 (0.07)
HC (n=60)	18	13.56 (3.33)	42	2.52 (3.49)	10	1.45 (1.43)	50	0.05 (0.07)
Total (n=214)	104	16.65 (4.70)	110	1.85 (3.05)	66	2.74 (2.62)	148	0.06 (0.08)

ATB: active TB patients, CC: individuals in close contact with a TB patient, HC: healthy controls, TST: tuberculin skin test, QFT: QuantiFERON®-TB Gold In-Tube assay, TST+ refers to an induration size of ≥ 10 mm. QFT+ refers to ≥ 0.35 IU/mL.

Discussion

In Thailand, the TST is used as the main screening test for MTB infection. Most studies of LTBI in Thailand have used the TST.[8-11] Only one study recently evaluated the IGRA tests and the TST in a pediatric population.[12] Our study further analyzed both the QFT and TST in various adult subpopulations (ATB, HC and CC groups) in northeast Thailand. We found that the TST showed higher sensitivity, whereas the QFT showed higher specificity. The factors associated with discordant results included BMI, nutrition, and DM.

The performance of the IGRA is generally superior to that of the TST, especially in BCG-vaccinated populations.[4] In particular, the greater false-positive rate associated with the TST is likely caused by various factors, including cross-reactivity to the BCG vaccine.[13,14] Among Asian countries with standard cut-off for the QFT, the test had a higher sensitivity in Vietnam (a high TB burden country in which a 10 mm cut-off is used for the TST),[15] Korea (an intermediate TB burden country in which a 10 mm cut-off is used for the TST),[16] and Japan (an intermediate TB burden country in which a 5 mm cut-off is used for the TST),[17] whereas the TST had a higher sensitivity in Indonesia (a high TB burden country in which a 10 mm cut-off is used for the TST).[18] Furthermore, the performance of the QFT was not superior to that of the TST in low-income countries.[19] Our study showed that the TST had a higher sensitivity and NPV, whereas the QFT had a higher specificity and PPV. Based on our results, the TST had a sensitivity of 87%, and the QFT had a specificity of 83%. These values are slightly different from the average values reported in a previous meta-analysis (77% sensitivity for the TST and 96% specificity for the QFT).[4] Our results are also concordant with a meta-analysis showing that the TST had a higher sensitivity but lower specificity than the QFT.[4] A recent study performed in a pediatric population in Thailand showed that there were no statistically significant differences between the performances of the two tests. Our study population is at high risk of developing TB, as the burden of TB in Thailand is high. A previous report showed that the TST had higher sensitivity in high-risk populations.[20] The QFT was less sensitive in Indian and Malay populations than in a Chinese population,[21] indicating the influence of ethnicity on test sensitivity. Concordance between TST and QFT results also varies among individuals with different diseases, including rheumatoid arthritis (κ=0.22)[22] and HIV infection (κ=0.44);[23] additionally, it varies among individuals in prison (κ=0.8).[24] In our study population, the agreement rate between the two tests was moderate (κ=0.41). Therefore, the performances of the TST and QFT were complementary in our study population, and a moderate agreement rate was noted.

Table 3. Diagnostic performance of the QFT and TST for *M. tuberculosis* infection

Performances	TST	QFT
	Values (95% CI)	Values (95% CI)
Sensitivity (%)	87.04 (78.08-96.00)	66.67 (54.10-79.24)
Specificity (%)	70.00 (58.40-81.60)	83.33 (73.90-92.76)
PPV (%)	72.31 (61.43-83.19)	78.26 (66.34-90.18)
NPV (%)	85.71 (75.91-95.51)	73.53 (63.04-84.02)

The diagnostic performances of the TST and QFT were determined using the ATB group as a positive control and the HC group as a negative control. TST: tuberculin skin test, QFT: QuantiFERON®-TB Gold In-Tube assay, TST+ refers to an induration size of ≥ 10 mm. QFT+ refers to ≥ 0.35 IU/mL.

Table 4. Rates of agreement between the TST and QFT in individuals who were in close contact with TB patients, healthy individuals, and active TB patients

Two test agreement	ATB (n=54)	CC (n=100)	HC (n=60)	ATB + HC (n=114)	Total (n=214)
TST^+: QFT^+	33	15	7	40	55
TST^+: QFT^-	14	24	12	26	50
TST^-: QFT^+	3	5	3	6	11
TST^-: QFT^-	4	56	38	42	98
Positive agreement (%)	61.11	15.00	11.67	35.09	25.70
Negative agreement (%)	7.41	56.00	63.33	36.84	45.79
Total agreement (%)	68.52	71.00	75.00	71.93	71.50
Kappa (κ)	0.33	0.27	0.16	0.44	0.41

TST: tuberculin skin test, QFT: QuantiFERON®-TB Gold In-Tube assay, TST+ refers to an induration size of ≥ 10 mm. QFT+ refers to ≥ 0.35 IU/mL.

Thailand implemented BCG vaccination as a national health policy four decades ago. Furthermore, there is a high incidence of HIV in Thailand.[25] In our study population, one-fifth of the participants had a TST^+/QFT^- result. One major contributing factor to this result may be the BCG vaccine, which causes false-positive TST results.[13] Indeed, 86% of participants in our study had a BCG scar, which was used as an indicator of vaccination. HIV infection affects CD4- T-cells and subsequently influences T-cell-based tests; [23] thus, we excluded HIV-infected cases from our study population. Multivariate analysis of predictors of discordant results between the TST and QFT showed that a BCG vaccine was insignificantly associated with a TST^+/QFT^- discordant result. Although insignificant, vaccinated individuals with a QFT^+ result were more likely to have a TST^- result, indicating that the BCG vaccine was partly associated with a false-positive QFT result. Other factors may have caused false-negative TST results because 5.6% of the microbiologically confirmed ATB patients were TST^- despite being QFT^+. On the other hand, 26% of the ATB patients were QFT^- despite being TST^+. HIV infection and immunocompromised status were evaluated in the ATB patients, and the QFT was performed according to the manufacturer's protocol to ensure that false-positive results occurred due to other factors.

The immune status of an individual is associated with various demographic and risk factors. Previous studies reported that increased age was associated with decreased immunity and false-negative results for the QFT and TST.[26,27] Smoking and alcohol consumption were also suggested as risk factors for TB.[28,29] Previously, TST-/QFT+ and TST+/QFT- discordance was associated with HIV infection, gender, age, and ethnicity.[26] However, we found that age, gender, smoking, and alcohol consumption were not risk factors for discordant TST/QFT results in our study population. BMI is associated with immunity,[30] and we found that a high or low BMI was a risk factor for a TST+/QFT- result. Additionally, poor nutrition was a risk factor for a TST-/QFT+ result. Underweight or overweight individuals may have dysfunctional T-cell responses, leading to TST/QFT discordant results. Additionally, DM may be associated with TB because this condition can diminish immune responses.[31] We found that DM was associated with the ATB group but not the CC group. Additionally, we found that DM was associated with discordant TST+/QFT- and TST-/QFT+ results. However, it should be noted that the analysis of DM yielded values with a broad CI. Our findings showed that host factors related to the immune response affected discordant TST/QFT results.

The establishment of TST and IGRA guidelines is fundamentally important for LTBI control. The WHO recommends use of the TST and IGRA in groups that are at high risk for LTBI, such as individuals who are in close contact with TB patients, healthcare workers and immunosuppressed patients.[32] Many MTB screening guidelines vary based on geographical region. Two-step (TST followed by IGRA for confirmation) and one-step (IGRA or TST alone) approaches have been suggested.[2] A previous study reported that the performances of the TST and IGRA were comparable,[33] whereas other studies in populations with a low TB burden reported that the IGRA had a higher sensitivity and specificity compared with the TST.[4,6] The results from our study indicate that the diagnostic performance of the QFT is different from that of the TST, and these tests can compensate for each other. Additionally, the cut-off values for both tests also vary according to geographical location.[34,35] We showed that the standard cut-off values (10 mm for the TST and 0.35 IU/mL for the QFT) were appropriate for discrimination in our study population. Due to the higher sensitivity of the

Table 5. Predictors of discordance between TST and QFT results based on a multivariate regression analysis.

Predictors	Adjusted odd ratio (95% CI) of predictors for TST-QFT discordance			
	TST^-:QFT^+ vs. TST^+:QFT^+ (n=66)	**TST^+:QFT^- vs. TST^+:QFT^+ (n=105)**	**TST^-:QFT^+ vs. TST^-:QFT^- (n=109)**	**TST^+:QFT^- vs TST^-:QFT^- (n=148)**
Male gender	2.31 (0.33-16.23)	1.14 (0.39-3.36)	0.19 (0.03-1.01)	0.50 (0.21-1.22)
Age (years)				
≤20	0.14 (0.02-1.08)	0.33 (0.09-1.29)	2.50 (0.45-13.79)	1.23 (0.46-3.29)
>20-60	Reference	Reference	Reference	Reference
>60	0.43 (0.02-9.37)	0.40 (0.07-2.38)	4.27 (0.3-60.87)	2.57 (0.69-9.56)
BMI				
≤18.5	1.83 (0.3-11.1)	**3.86 (1.3-11.48)***	0.49 (0.04-5.79)	0.32 (0.09-1.12)
>18.5-25	Reference	Reference	Reference	Reference
>25	1.36 (0.08-22.97)	**5.9 (1.24-28.16)***	0.63 (0.03-12.84)	0.32 (0.07-1.37)
BCG vaccination	5.22 (0.7-38.99)	1.13 (0.29-4.44)	0.22 (0.03-1.48)	2.21 (0.61-8.06)
Smoking	7.99 (0.6-106.93)	1.70 (0.51-5.74)	0.42 (0.03-6.28)	2.43 (0.62-9.59)
Alcohol consumption	0.56 (0.08-4.11)	1.29 (0.45-3.69)	3.14 (0.52-18.9)	0.86 (0.33-2.25)
Diabetes mellitus	0.61 (0.09-4.2)	1.57 (0.37-6.58)	**32.56 (1.73-613.49)***	**13.55 (1.4-131.56)***
Poor or fair nutrition	0.33 (0.04-2.61)	1.69 (0.44-6.44)	**7.40 (1.23-44.57)***	0.69 (0.25-1.95)

All three groups of participants (ATB: active TB patients, CC: individuals in close contact with TB patients, HC: healthy controls) were used to analyze predictors of discordance between the TST and QFT results. The standard cut-off values for TST and QFT were 10 mm and 0.35 IU/mL, respectively. TST: tuberculin skin test, QFT: QuantiFERON®-TB Gold In-Tube assay, KK: Khon Kaen province, BMI: body mass index, "+": positive, "-": negative, OR: odds ratio, BCG: Bacillus Calmette–Guérin. *Values refer to a significant odds ratio.

TST and higher specificity of the QFT, the TST should be used in LTBI screening in Thailand, and the results should be confirmed using an IGRA (such as the QFT). In Thailand, the TB problem has gradually improved as a result of intensive control strategies. In the near future, TB control strategies in Thailand might be extended to cover LTBI. The use of the TST for contact investigation in children who are in close contact with TB patients is recommended by the Bureau of Tuberculosis in Thailand. The QFT has recently been applied in Thailand; however, guidelines for LTBI diagnosis have not yet been established. Therefore, we have provided information to facilitate the establishment of LTBI diagnostic guidelines in Thailand. The sufficiency of the TST alone for LTBI diagnosis in a pediatric population was previously suggested.[12] Our evaluation of the two tests in a Thai adult population suggested that use of the TST, which has higher sensitivity, may be appropriate for screening LTBI, while use of the QFT, which has higher specificity, may be appropriate for confirmation. In Thailand, the cost of the QFT is still quite high compared with that of the TST. However, the cost of the TST might be increasing due to the shortage of purified protein derivatives (PPDs) that were provided by the Thai Red Cross Society. Use of the QFT as a confirmatory test should be more cost effective. The QFT is more convenient because it requires only one blood sample and therefore one patient visit. The QFT is also becoming more readily available in many government and private hospitals in Thailand. Although the TST still has many disadvantages, including a low specificity and the need for two patient visits, the QFT cannot replace the TST due to its lower sensitivity. Because these two tests showed compensatory performance in a Thai adult population, they could potentially be used in combination for the diagnosis of LTBI in Thailand. Thus, the use of an IGRA (such as the QFT) to confirm a positive TST result might be considered for maximal efficiency of LTBI diagnosis.

There were limitations to our study. This was a prospective study performed within 1 year of data collection. However, predictors of discordance were not determined in particular groups due to the small sample size. Because there is no diagnostic gold

standard for LTBI, we used HC and ATB as negative and positive control cases, respectively. However, use of HC as negative controls for MTB infection is limiting due to the high prevalence of TB in the community. Nevertheless, the use of microbiologically confirmed TB cases and the exclusion of HIV-infected and immunocompromised individuals from the ATB group ensured this group's validity as a positive control. The HC group was interviewed, and individuals who were more likely to have been exposed to TB were excluded. Concordant results between the TST and QFT were used to determine the LTBI status in the HC and CC groups. Although the QFT and TST were recently evaluated in Thai children, our study fills the gap in knowledge regarding use of the QFT and TST in adults who are in close contact with TB patients. AFB and/or culture was used to identify TB patients and healthy controls with no known risk of exposure who served as positive and negative controls, respectively. Furthermore, we also provide information about the factors underlying discordant results between the two tests as well as other related aspects.

In this study, we showed that the QFT and TST were complementary. The results of these tests should be carefully interpreted. The QFT could not be replaced with the TST in this study population. The TST should be used as a screening test based on its higher sensitivity, whereas the QFT should be used as a confirmatory test because of its higher specificity.

Acknowledgements

This study was supported by a 2013 general supportive research grant from Khon Kaen University, Thailand. The microbiology clinical laboratory at Srinagarind Hospital provided the sputum cultures and laboratory results. We would like to thank RCEID for laboratory support. The authors declare that there are no conflicts of interest.

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