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Comparison of Cost-effectiveness between the QuantiFERON-TB Gold-In-Tube and T-SPOT Tests for Screening Health-care Workers for Latent Tuberculosis Infection

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Abstract

Objective/Background: There are several methods used to screen for latent tuberculosis (TB) infection (LTBI) including the QuantiFERON-TB Gold-in-Tube (QFT-GIT) and T-SPOT-TB (T-SPOT) tests. Many studies have reported the equivalence of these two methods, but it is unclear which of them is more cost effective. We investigated the age and cost issues of these tests in screening for LTBI among health-care workers. **Materials and Methods:** One hundred and forty new employees during 2008–2011 in our hospital were screened using the QFT-GIT test, and 140 new employees during 2011–2014 were screened with the T-SPOT test for LTBI. The results of both tests were classified as positive, undetermined (retesting required), or negative. **Results:** There were six positive results (4.29%), eight undetermined results (5.71%), and 126 negative results (90.0%) with the QFT-GIT test. As for the T-SPOT test, there were eight positive results (5.71%), three undetermined results (2.14%), and 129 negative results (92.1%). Fourteen LTBI employees (6 in QFT-GIT and 8 in T-SPOT) were detected statistically equally using the two methods ($P = 0.79$). The total costs, including those incurred for retesting, were \$7,711.86 (US dollar) and \$6,525.42 for the QFT-GIT and T-SPOT tests (cost of one test is \$55.08 for QFT-GIT and \$46.61 for T-SPOT), respectively. **Conclusion:** T-SPOT is one of the options for screening for LTBI partly owing to the viewpoint of cost-effectiveness. Further prospective studies need to be considered for a definitive conclusion.

Keywords: Age, cost-effectiveness, QuantiFERON-TB Gold-in-Tube, T-SPOT, tuberculosis screening

INTRODUCTION

The tuberculin skin test (TST) is widely used for screening tuberculosis (TB), but it is sometimes difficult to discriminate between active and inactive TB because of Bacillus Calmette–Guerin (BCG) vaccination or atypical mycobacterial infection.^[1] QuantiFERON-TB Gold In-Tube (QFT-GIT) has higher specificity than the TST because it measures interferon-gamma (IFN- γ) produced by lymphocytes after the stimulation of special antigens to *Mycobacterium tuberculosis*, such as early secretory antigenic target 6 kDa or culture filtrate protein 10.^[1] QFT-GIT is widely used as the diagnostic method of choice in TB infection and for screening medical contacts.^[2] However, the test conditions are strict. For instance, a special blood collecting syringe and a careful technique for test process are required, and the bacterial culture needs to be started within

16 h of taking samples,^[3,4] resulting in a comparatively higher rate for requirement of retests by undetermined results in the first test.^[5] TB screening by QFT-GIT has been used in our institution for new employees as a baseline for TB screening.

However, cost-effectiveness is often an increasing concern because of the high frequency of requirements for retests. In this situation, T-SPOT-TB (T-SPOT) was approved as an extracorporeal diagnostic procedure in Japan and was

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permitted by medical insurance in 2012. It has the same principle of measurement as QFT-GIT but has easier test conditions because a unique collecting blood syringe is not required, and the materials can be stable for a longer period (32 h) than QFT-GIT with a heparin blood collecting syringe.^[6] Many studies have reported the equivalence of these two methods,^[2,7-10] but it is unclear which of them is more cost effective.

Meanwhile, the efficacy of TST is considered to be lower than that in other countries because of the higher rate of BCG vaccination in Japan. Therefore, latent TB infection (LTBI) screening by Interferon-Gamma Release Assays (IGRA) of QFT-GIT and T-SPOT needs to be performed, resulting in necessarily higher costs.^[11] In this situation, a comparison between these two methods is also necessary even when it comes to cost issues.^[12]

In this study, we have substituted T-SPOT for LTBI screening in new health-care employees, and we report our TB screening data comparing these two methods, especially focusing on the influence of age and cost-effectiveness.

MATERIALS AND METHODS

Examinees

New employees from October 2008 to September 2011 were screened for LTBI by QFT-GIT in the Hyogo Prefectural Rehabilitation Central Hospital, Kobe, Japan (330 beds), and new employees from October 2011 to June 2014 were screened by T-SPOT.

The total number of workers in the hospital is 445, which includes 58 physicians, 222 nurses or their assistants, 133 medical professionals, and 32 officers and others. The new employees in this study included both medical staff such as physicians and nurses and office workers. In addition, they were confirmed to have no findings of TB by chest X-ray. This study was approved by the Institutional Review Board committee in Hyogo Prefectural Rehabilitation Center Hospital as a retrospective study. All data were completely anonymized and deidentified before access and analysis. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Tests for latent tuberculosis

The results of QFT-GIT and T-SPOT were classified as positive, requiring retest (undetermined), or negative. All tests were graded by Mitsubishi Chemical Medicine Co. Ltd., (Tokyo, Japan). In QFT-GIT, the interpretation of positive, pending (undetermined), and negative results was based on the manufacturer's protocol.^[4] T-SPOT was likewise performed according to the manufacturer's protocol using a specific formula, and results of positive, undermined, or negative were also determined based on the manufacturer's protocol.^[6,13]

Diagnosis and treatment of latent tuberculosis infection

Those who had positive and pending (undetermined) results underwent a retest and chest X-ray scan. In addition, sputum culture and chest computer tomography were also performed if necessary.

Evaluation of age

We investigated how age affects LTBI diagnosis and compared these two methods (QFT-GIF and T-SPOT) – that is, we divided the participants into three age groups and compared the positive rates of LTBI in the two methods.

Evaluation of costs

The total costs for the initial test and retest for those with positive and undetermined results between QFT-GIF and T-SPOT were evaluated.

Statistical analyses

The statistical analysis for test reliability without undetermined results was performed with Fisher's exact test using EZR (Easy R),^[14] which is a reformed version of the R software.^[15]

RESULTS

Examinee backgrounds

The QFT-GIT group consisted of 140 examinees (30 males, 21.4%; 110 females, 78.6%) whose median age was 26 years (range 20–48 years). All examinees had no history of the disease and no physical symptoms. The T-SPOT group comprised 140 examinees (38 males, 27.2%; 102 females, 72.9%) whose median age was 26 years (range 20–53 years). There are no significant differences in these distributions ($P = 0.33$ and $P = 0.97$, respectively) [Table 1].

Latent tuberculosis infection tests and diagnosis

The QFT-GIT group had six positive (4.29%), eight undetermined (5.71%), and 126 negative (90.0%) results in 140 tests. The T-SPOT group had eight positive (5.71%), three undetermined (2.14%), and 129 negative results (92.1%) in 140 tests ($P = 0.32$) [Table 2].

Latent tuberculosis infection tests and age

We classified the age groups as follows: (1) 29 years or younger; (2) 30–39 years; and (3) 40 years or older. There was a

Table 1: Health-care examinees' backgrounds

	QFT-GIT (%)	T-SPOT (%)	<i>P</i>
Age			
Median	26	26	0.97
Range	20–48	20–53	
Sex			
Male	30 (21.4)	38 (27.2)	0.33
Female	110 (78.6)	102 (72.9)	
<i>n</i> , physician	4 (2.86)	7 (5.00)	0.64
<i>n</i> , nurse	85 (60.7)	80 (57.1)	
<i>n</i> , other staff	51 (36.4)	53 (37.9)	

QFT-GIT: QuantiFERON-TB Gold-in-Tube, T-SPOT: T-SPOT-TB, TB: Tuberculosis

significant difference in age groups in terms of the positive rate of LTBI tests only in T-SPOT ($P = 0.017$). A total of 14 employees (6 in QFT-GIT tests and 8 in T-SPOT tests) were diagnosed to have LTBI, and there was no significant difference between the two methods ($P = 0.79$). Of these 14 employees, one employee was diagnosed to have LTBI but had no active TB [Table 3].

Cost comparison between QuantiFERON-tuberculosis Gold-in-Tube and T-SPOT

Regarding cost issue, one test costs \$55.08 (U.S. dollar) in QFT-GIT and \$46.61 in T-SPOT. Moreover, as mentioned above, 13 examinees were required to take a retest in QFT-GIT, whereas 11 examinees were required to undergo a retest in T-SPOT including those with positive results and undetermined results (required for retest). Overall, the costs reached \$771.12 for QFT-GIT and \$512.71 for T-SPOT; if T-SPOT is used exclusively, this could result in a savings of \$258.41 in those examinee categories. Considering the number of examinees in this study, this difference suggests that the total costs amounted to \$7,711.86 for QFT-GIT ($n = 140$ examinees) and \$6,525.42 for T-SPOT ($n = 140$ examinees) [Table 4].

DISCUSSION

TB is still an international disease and is counted among the three major infectious diseases; it is rendered even more problematic by the involvement of human immunodeficiency

viral infection or acquired immunodeficiency syndrome.^[16] In Japan, the number of TB patients is gradually decreasing. For children, in particular, BCG vaccination has effectively reduced the number of TB patients.^[17]

Even in such a situation, there were about 24,000 newly diagnosed TB patients in a year, and the main cause of the decrease in TB patients was the suppression of disease in career patients who no longer discharge *M. tuberculosis*.^[18] The measures against those with the germ discharge are essential to prevent the spread of TB, and continuous reinforcement against TB is required.^[19]

TB screening is vital to have a good grasp on generational TB status as well as prevention, early detection, and stopping its spread. Medical checkups include TB tests and screening, especially for those who are in contact with TB patients.^[20] TST is considered a gold standard method in much of the literature; importantly, however, Japan presents a unique background because almost all of its entire population has received BCG vaccination,^[21] as a result of which TST may not be able to detect LTBI with higher sensitivity than the IFN- γ -based method.^[22,23] The methods measuring IFN- γ response may be useful in countries with high rates of BCG vaccination, such as Japan because *M. tuberculosis*-specific antigens are not affected by BCG vaccination.^[24]

In the comparison between these two new methods, the specificity of QFT-GIT and T-SPOT was equally high in a population with a truly low risk of TB infection.^[2] However, QFT-GIT has a drawback in that examinees are more likely to undergo a retest (based on the trend of our data) owing to the complex testing procedures involved even from the initial stage, such as blood sampling, which requires a special syringe for the test, a step that can affect the results.^[1]

Richeldi *et al.*^[25] found that T-SPOT improved specificity and sensitivity in the diagnosis of LTBI, particularly in those settings where the diagnosis is most needed.^[26] Another recent report found no significant difference between these two methods.^[2] In their study, Bae *et al.*^[27] noted that in active TB patients, QFT had lower sensitivity according to increasing age, but T-SPOT was not affected by age. However, our data from (LTBI) screening showed different results, suggesting that these two methods of TB or LTBI diagnosis may be related to or affected by patients' or examinees' age. Further prospective study needs to be performed for a definitive conclusion.

Regarding the cost issue of TST and IGRA, TST proved to be more cost effective (12.2%–17.9%) compared with IGRA.^[21,28,29] Moreover, in Japan, where a high percentage of the population has received BCG vaccination as mentioned above, IGRA is considered to be superior to TST, which was observed to have lower sensitivity and specificity (IGRA:sensitivity 89%, specificity 98% and TST:sensitivity 65.8%, specificity 35.4%).^[11] Based on our own comparison between QFT and T-SPOT, T-SPOT may be shown to be more cost effective.^[29] However, the combination of IGRA and TST demonstrated

Table 2: Latent tuberculosis infection tests

	Positive	Undetermined	Negative	Total	P
QFT-GIT	6	8	126	140	0.32
T-SPOT	8	3	129	140	

QFT-GIT: QuantiFERON-TB Gold-in-Tube, T-SPOT: T-SPOT-TB, TB: Tuberculosis

Table 3: Evaluation of age

Method	Age (years)	Positive	Undetermined	Negative	Total	P
QFT-GIT	≤29	4	5	87	96	0.914
	30-39	2	3	34	39	
	≥40	0	0	5	5	
T-SPOT	≤29	2	0	84	86	0.017
	30-39	3	2	32	37	
	≥40	3	1	13	17	

QFT-GIT: QuantiFERON-TB Gold-in-Tube, T-SPOT: T-SPOT-TB, TB: Tuberculosis

Table 4: Comparison of costs (in US dollars)

Category	QFT-GIT	T-SPOT	Difference
Tests	7711.86	6525.42	1186.44
Costs for retest (positive or undetermined results)	771.12	512.71	258.41
Total	8482.98	7038.13	1444.85

QFT-GIT: QuantiFERON-TB Gold-in-Tube, T-SPOT: T-SPOT-TB, TB: Tuberculosis

even further cost savings, a factor that should be carefully considered here in Japan owing to the reasons mentioned above.

We would like to emphasize the study limitations. First, the number of health-care worker examinees is not large enough to allow us to draw definitive conclusions. Next, our hospital did not generally treat TB infection patients, and the studies of T-SPOT from institutions where TB patients are treated need to be included for conclusive comparisons. Third, this study has retrospective nature, and cost comparison may have a bias and variation, and the examinee populations of these two groups were not the same. A study using the same people (healthy examinees) for two kinds of screenings seems impossible owing to the retrospective nature of this study. Finally, we lacked TST data; however, as mentioned above, this limitation may not be so serious because every examinee has a BCG vaccination history. These limitations need to be overcome in future studies.

CONCLUSION

T-SPOT is one of the available options for screening for LTBI partly owing to the viewpoint of cost-effectiveness, but QFT-GIT was not affected by age for LTBI diagnosis regarding similar tests - effectiveness requiring retests. Further prospective studies need to be considered for a definitive conclusion.

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Conflicts of interest

There are no conflicts of interest.

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