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Predictors for a positive QuantiFERON-TB-Gold test in BCG-vaccinated adults with a positive tuberculin skin test

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Summary
Background: Prevention of tuberculosis (TB) in the United States usually involves testing for latent tuberculosis infection (LTBI) with a tuberculin skin test (TST), followed by offering therapy to those who have a positive test result. QuantiFERON-TB Gold assay (QFT-G) is more specific for infection with *Mycobacterium tuberculosis* than the TST, especially among persons vaccinated with bacillus Calmette-Guérin, thereby reducing the number of false positive tests.
Methods: Adults referred to a pulmonary clinic for a positive TST result were tested with QFT-G. We assessed factors for having a positive QFT-G.
Results: Among 100 adults who were BCG-vaccinated and had a positive TST result, 30 (30%) had a positive result using QFT-G. Persons from high-incidence countries were 8.2 times more likely to have a positive QFT-G result compared with persons from low-incidence countries (46% versus 9%). Using logistic regression to assess QFT-G positivity, strong predictors included having an abnormal chest radiograph consistent with healed TB, a TST induration of $\geq$16 mm, and birth in a high-incidence country.
Conclusion: Use of QFT-G assay following a positive TST result further identifies persons who would most benefit from treatment for LTBI.

Introduction

An integral component of tuberculosis (TB) control in the United States is the identification and

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treatment of persons with latent tuberculosis infection (LTBI) [1]. Approximately 10% of persons infected with *Mycobacterium tuberculosis* (*M. tuberculosis*) develop TB disease. However, the risk of developing TB varies, and recently infected persons have an increased risk for TB disease [2,3]. One group for whom screening is recommended is persons recently arrived from areas of the world with a high incidence of TB, many of whom have been vaccinated with Bacillus Calmette-Guérin (BCG) [4].

LTBI has historically been diagnosed using the tuberculin skin test (TST). The interpretation of the TST requires knowledge of a person's medical and epidemiologic factors to determine the threshold at which the reaction is considered positive. Because the purified protein derivative used in the TST is a poorly defined mixture of antigens shared by the *M. tuberculosis* complex, including wild type *Mycobacterium bovis*, *M. bovis* var. BCG, and several other species of mycobacteria, it results in a specificity of approximately 60% in BCG-vaccinated populations [5]. The lack of specificity of the TST for *M. tuberculosis* has led to the inappropriate diagnosis of some patients with LTBI and to the development of alternative tests.

Interferon-γ release assays (IGRAs), including QuantiFERON-TB-Gold (QFT-G), represent a new class of tests that has been approved by the Federal Drug Administration for the diagnosis of LTBI. The QFT-G test uses an enzyme-linked immunosorbent assay to measure the concentration of interferon-γ released by activated T-lymphocytes after stimulation by antigens that are specific to the *M. tuberculosis* complex, are widely absent in nontuberculous mycobacteria, and more importantly, are not expressed in BCG [6]. Thus, IGRAs, such as QFT-G, might be particularly useful to test for LTBI in persons who have been vaccinated with BCG [7]. The higher specificity of QFT-G and other IGRAs compared with the TST can be used to eliminate the unnecessary treatment of persons with false-positive TSTs.

The aims of this study were (1) to determine the percentage of QFT-G positivity in persons with a history of BCG vaccination who had a positive TST result and (2) to identify patient characteristics that might predict a positive QFT test result.

Methods

Patients with a positive TST result were referred by local providers to the pulmonary clinic that serves as a referral center for the greater Hartford metropolitan area for medical evaluations to exclude TB disease. Patients aged $\geq$18 years with a documented positive TST result ($\geq$10 mm induration or $\geq$5 mm with a chest radiograph consistent with pulmonary TB) who presented to the clinic from June 2008 to December 2009 were included in this study. Patients were asked whether they had received a BCG vaccination, and those who did not know their vaccination status were visually inspected for a vaccination-related scar. A QFT-G test was performed at the time of this visit; testing was performed at a single large commercial laboratory. The QFT-G test results were interpreted according to the manufacturer's instructions [8]. Active TB disease was excluded using symptom review, physical examination, chest radiography, and, if necessary, sputum collection for acid-fast bacilli smear microscopy and mycobacterial culture.

Clinic providers reviewed the medical records and extracted data including age, gender, country of origin, length of residence in the United States, TST reaction size measured in millimeters of induration, chest radiograph findings, and risk factors for the development of TB disease. A high-incidence country was defined as a country with an incidence of $\geq$20 cases of acid-fast smear-positive pulmonary TB per 100,000 persons [9]. A step-wise logistic regression was used to determine the odds ratios (ORs) for demographic and clinical factors that were predictive of a positive QFT-G result. Age and TST induration were modeled as continuous variables. A P value of <0.05 was considered significant.

A review of the study determined that it entailed an assessment of routine public health practice and was not considered human subjects research. The Institutional Review Board of St. Francis Hospital and Medical Center (Hartford, CT) approved this retrospective cohort study.

Results

A total of 100 BCG-vaccinated adults who were referred to the pulmonary clinic because of a positive TST result were included in the study. The median patient age was 34 years, nearly half (46%) were male, and the study participants had been in the United States for a median duration of 4.5 years (range 0—44 years). The participants were from 42 different countries representing the Americas (47%), Europe (20%), Africa (18%), Southeast Asia (6%), the western Pacific (6%), and the eastern Mediterranean (3%). Their birth countries had a median TB incidence of 37 cases per 100,000

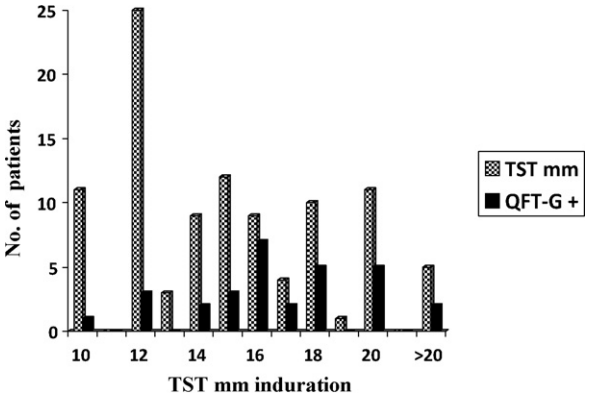

Figure 1 Distribution of positive TST (mm induration) and QuantiFERON-TB Gold.

population (range 2—312 cases); 57% were from countries with a high incidence of TB. The median TST induration was 15 mm.

Among the 100 persons with positive TST results, 30 (30%) also had a positive QFT-G result (Fig. 1). One QFT-G result was indeterminate, but a repeat test was negative. Twenty-six (46%) of the 57 adults from high-incidence countries were QFT-G positive (Table 1); in contrast, 4 of 43 adults (9%) from low-incidence countries were positive (OR = 8.2; 95% confidence interval (CI), 2.4—31.1). None had active TB disease.

A logistic regression was used to compare tuberculin reactivity. Persons with a TST induration $\geq$ 16 mm had a more than six fold greater likelihood of having a positive QFT-G result than persons with a smaller TST induration (Table 2). The combination of being from a high-incidence country and having a TST induration $\geq$ 16 mm also strongly predicted QFT-G positivity (Table 2). Eight persons, including seven from high-incidence countries, had chest radiographs consistent with a prior, healed TB infection and negative mycobacterial cultures; the seven patients from high-incidence countries also had a positive QFT-G result (OR = 21.0; 95% CI, 2.4—179.9). No patients were diagnosed with TB disease.

Table 1 Tuberculin skin test and QuantiFERON-TB-Gold results stratified by the tuberculosis incidence in the patient's country of origin.

	Low TB incidence (n = 43)	High TB incidence[a] (n = 57)
TST < 16 mm		
QFT-G negative	27	24
QFT-G positive	0	9
TST $\geq$ 16 mm		
QFT-G negative	12	7
QFT-G positive	4	17

TST, tuberculin skin test; QFT-G, QuantiFERON-TB Gold.
[a] High TB incidence defined as acid-fast smear positive pulmonary tuberculosis $\geq$ 20 cases/100,000 population.

Discussion

In this study of 100 BCG-vaccinated adults with positive TST results, 30% also had a positive QFT-G result. The strongest predictors of a positive QFT-G result were TST induration $\geq$ 16 mm, being from a high-incidence country, and having evidence of a previous, healed TB infection on a chest radiograph. These findings verify the results reported by a Canadian TB clinic, which used a similar approach that resulted in a significant reduction of the number of patients who were treated for LTBI [10]. In the Canadian study, researchers also observed that a positive QFT-G result was associated with the factors found in our study, in addition to increasing age. Additionally, our study showed that persons with a positive TST and a positive QFT result were more likely to have pulmonary abnormalities suggestive of previous TB disease. This is an important finding because these persons are at high risk for developing TB disease and are priority candidates for treatment for LTBI once TB disease is excluded. In BCG-vaccinated persons with a positive TST result observed at a TB clinic in Cleveland, OH, USA, male sex and a shorter time since arrival in the United States were also significantly associated with a positive IGRA result [11].

The advent of IGRAs and their increasing availability is having an important impact on setting priorities for the treatment of LTBI in an era of limited and decreasing resources [12]. Approaches to reducing the number of lower-risk persons who are started on treatment include using QFT-G as the test of choice for persons who have had BCG vaccination or using an IGRA to verify LTBI in those who have a positive TST result. Although the sensitivity of IGRA is similar to that of the TST in patients with culture-confirmed TB, proponents of doing two tests (a TST followed by an IGRA for those who have a positive TST result) highlight the specificity of IGRAs, which approaches $\geq$94% in BCG-vaccinated persons [5]. In contrast, the specificity of the TST is relatively low and is heterogeneous in BCG-vaccinated persons, ranging between 35% and 79%. These test parameters suggest that, in BCG-vaccinated persons, an IGRA should be the preferred test [13].

There is evidence suggesting that persons with a positive TST result and a negative QFT-G result are

Table 2 Factors predictive of a positive QuantiFERON-TB-Gold test result among 100 BCG-vaccinated adults with a positive tuberculin skin test result.

Characteristic	Persons with characteristic ($N = 100$)	Adjusted odds ratio for a positive QFT-G result (95%CI)	*P* value
TST $\geq$ 16 mm	40%	6.3 (2.2—18.0)	<0.001
High incidence area	57%	8.2 (2.4—34.1)	<0.001
High incidence and TST $\geq$ 16 mm	24%	11.8 (3.6—39.7)	<0.001
Abnormal chest X-ray	8%	21.0 (2.4—179.9)	<0.001

QFT-G, QuantiFERON-TB Gold; TST, tuberculin skin test.

at low risk for developing TB disease. In a German study of 954 close contacts of culture-confirmed pulmonary TB patients, treatment for LTBI was offered only to those who had a positive QFT-G result [14]. None of the treated patients developed TB disease. In contrast, among untreated contacts, only 3.1% of TST-positive [>5 mm] and QFT-G-negative contacts developed disease, while 12.9% of contacts with a positive QFT-G result developed TB disease.

Despite data that support the use of IGRAs among BCG-vaccinated persons, there continue to be several barriers to the widespread adoption of these tests. First, the national guidelines recommending the use of IGRAs to diagnose LTBI are not uniformly implemented in practice [15]. The most favored approach internationally, particularly among BCG-vaccinated populations, is to test with a TST followed by an IGRA if the TST result is positive. The two-test strategy stands in contrast to the one-test (preferably IGRA) approach for BCG-vaccinated persons advocated in the United States [13]. However, clinicians might see patients who had a TST performed in another setting. Faced with the unknown quality of a TST performed in another location, tests are often repeated. Second, the costs and logistics of testing are important limitations. In Connecticut, both major commercial laboratories offer QFT testing, as do some hospitals, but the cost of obtaining a QFT test can vary widely for patients who are uninsured. The Department of Public Health Laboratory offers QFT testing but restricts it to patients who are uninsured or underinsured or treated at a local health department clinic. Additionally, the requirements for specimen collection, delivery to the laboratory, and maintaining laboratory quality assurance can make obtaining an IGRA challenging. Although several studies have shown the cost effectiveness of IGRAs in testing for TB, these initial barriers to obtaining testing can make the realization of potential cost savings difficult [16—18].

The main limitation of this study is the low number of patients. However, our results are consistent with those from other settings, which suggests that these findings apply to our study population as well. The retrospective nature of this study means that we could not control for the quality of the TST among persons referred to the clinic. Nevertheless, the referring providers are accustomed to screening persons at risk for LTBI, so any biases are largely those inherent to the TST.

This study demonstrates the real-world experience of a referral pulmonary clinic in using the QFT-G test among a group of BCG-vaccinated adults. While IGRAs can be helpful in targeting certain patients for LTBI treatment, clinicians should also have a low threshold to start treatment for LTBI in persons from a country with a high incidence of TB and a positive TST result, particularly for those with indurations > 15 mm) [19].

Conflict of interest

The authors have no competing interests to declare.

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