Science

QuantiFERON-TB Gold In-Tube Testing for Tuberculosis in Healthcare Professionals

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ABSTRACT

Objective: To assess the performance of the QuantiFERON-TB Gold in-tube (QFT-GIT) assay for tuberculosis (TB) screening using a convenience sample from among a population of healthcare provider (HCP) employees of a hospital.

Methods: For the individuals in our cohort, we reviewed occupational health records, including TB risk factors, and the results of QFT-GIT testing. We considered a QFT-GIT result of greater than 0.35 IU/mL to be positive; when we obtained a positive result from a specimen from a particular individual, we repeated testing on a fresh specimen from that individual.

Results: Of the 758 HCP employees whose specimens we screened, 439 had negative QFT-GIT results with negative TB risk factors and 268 had a negative QFT-GIT result but had positive TB risk factors. QFT-GIT results were positive in 47 subjects. Of the positive participants, 12 had a mean TB antigen value (antigen minus nil stimulated concentrations [Ag-Nil]) of 0.61 on initial testing and had a negative result on repeat testing, 22 had a TB Ag-Nil of 1.19 on initial testing and had a positive result on repeat testing (P = .01).

Conclusions: The QFT-GIT assay is useful for screening HCPs. However, false-positive results occur, particularly in a borderline zone of less than 1 IU/mL. Re-evaluation by repeat testing of fresh specimens from the same individual should be considered in subjects whose specimens test within the low-level positive cutoff.

Keywords: tuberculosis, screening, QuantiFERON, healthcare employee, children’s hospital

Tuberculosis (TB) is a communicable infection caused by Mycobacterium tuberculosis that is spread from individuals with contagious pulmonary or laryngeal disease via inhalation of droplet nuclei. TB continues to be one of the most common infectious diseases in the world; an estimated 20% to 45% of the worldwide population is infected.1 According to the most recent World Health Organization (WHO) global TB report released in 2012, there were almost 9 million new TB cases identified in 2011, equivalent to 125 new cases per 100,000 population.2 Additionally, according to the WHO report, there were 1.4 million deaths from TB, of which 990,000 were of patients who had tested negative for HIV.3 The majority of TB cases occurred in Asia (59%) and Africa (26%).2 Healthcare providers (HCPs) are at risk for infection with TB due to frequent, close contact with ill patients. HCPs with active TB may transmit the infection to their patients.

HCPs historically relied on the tuberculin skin test (TST), specifically the Mantoux method, for TB screening. A positive TST result may occur from infection with Mycobacterium tuberculosis; however, false-positive results can occur in patients who had previously been inoculated with Bacillus Calmette-Guérin (BCG) vaccine (an attenuated live-vaccine strain of Mycobacterium bovis), individuals who have been exposed to environmental...
nontuberculous mycobacteria, and occasionally in those with nonspecific reactions. A repeat visit is necessary for an experienced HCP to interpret the result of the test 48 to 72 hours after administration of the TST. The sensitivity and specificity of the TST is approximately 95%; however, when administered to subjects at low risk for TB infection, the positive predictive value may be as low as 15% due to many false-positive results. In 2005, the United States Food and Drug Administration (FDA) approved the use of interferon-γ release assays (IGRAs), which measure the in vitro interferon-γ released by antigen-stimulated lymphocytes sensitized to TB-associated antigens, for TB screening. This assay does not include antigens of the bacilli in the BCG vaccine strain; therefore, the screening test for TB is more specific. The Centers for Disease Control and Prevention (CDC) now recommends IGRAs for all adults in whom TB testing is indicated, including HCPs.

The objective of our study was to determine the clinical performance of the QuantiFERON-TB Gold in-tube (QFT-GIT; Quest Diagnostics Incorporated, Madison, NJ) test in employees of a children’s hospital in an area with a low incidence of TB. Secondly, we sought to determine the usefulness of repeat testing of healthcare employees whose initial specimens yielded a positive test result. Finally, we assessed TB risk factors based on self-reported risk factors provided by all new employees.

Materials and Methods

We performed a retrospective study using a convenience sample; the protocol was approved by the institutional review board of our hospital. We reviewed occupational health records, including TB screening forms, to evaluate the presence of TB risk factors including birth country, foreign travel, receipt of BCG vaccination, TB exposure, TB treatment, contact with high-risk persons (defined as individuals who were homeless, incarcerated, or known to have TB), and history of at least 1 positive TB test result. We obtained blood specimens from employees during their orientation period.

The QFT-GIT test is a commercial test for cell-mediated immune responses to peptide antigens that simulate mycobacterial proteins. The testing procedure was as follows: after incubation in 3 tubes of the blood of the patient, which contained no antigen (negative control), TB antigens (specific response), and mitogen (positive control), respectively, we tested the supernatant using an enzyme-linked immunoassay (EIA) for interferon γ, which is associated with a positive response. We considered QFT-GIT results to be positive for any specimen that yielded a result of greater than 0.35 IU/mL. When we obtained a positive QFT-GIT result, we repeated the test on a fresh specimen from the same donor.

Results

From October 2010 through September 2011, 758 employees of our hospital were screened for TB. A total of 707 (93.3%) employees had a negative QFT-GIT result, 2 (0.3%) had indeterminate results, and 47 (6.2%) had a positive result. Among the 47 patients with positive results, 13 (27.7%) underwent no follow-up testing; of the 34 individuals from whom specimens were collected for repeat testing, 22 (64.7%) were positive and 12 (35.3%) were negative on repeat testing. Of those specimens yielding a positive follow-up test result, the mean and median of the initial positive test were 1.19 and 0.92, respectively (range: 0.44-3.15). Among the specimens that yielded a negative follow-up test result, the mean and median values were 0.61 and 0.5, respectively (range: 0.43-1.02). The initial interferon gamma (IFN-γ) mean was lower for the employees with repeat-negative results compared to those with repeat-positive results ($P = .01$; Figure 1).

Among the 707 employees with a negative QFT-GIT result, 268 (37.9%) had risk factors for TB as the most frequently selected item on the screening tool. The most frequently selected items on the screening form were travel to a country in which TB is endemic (47.3%) and receipt of BCG vaccine (13.6%). We observed similar results among the 47 employees with a positive QFT-GIT result, of whom 17 (36.2%) reported a risk factor on the TB screening form. Of these, the most common response on the screening form were: 36.2% cited travel to a country in which TB is endemic, 8.5% reported having been inoculated with the BCG vaccine. Differences in risk factors reported by individuals whose specimens yielded negative results in repeat testing compared with those whose repeat-testing results had remained positive were not statistically significant ($P = .44$). More than half of the subjects (12 of 22) in the group with positive results in their follow-up specimen reported none of the risk factors on the TB screening form. The difference in risk factors between those who had positive or negative follow-up test results was not significant ($P = .86$) (Figure 2).
Discussion

In 2010 the CDC recommended using the QuantiFERON-TB test in individuals, including HCPs, in settings where the incidence of TB is low. Because we used this assay in our study, we were able to eliminate the diagnosis of latent tuberculosis infection (LTBI) in a significant number of our employees who previously had been inoculated with the BCG vaccine, which may have resulted in a positive TST, prompting chest radiography and possibly isoniazid therapy. Because none of the employees in our study had symptoms of active TB, the diagnosis of LTBI infection did not preclude them from working while retesting was being conducted.

Previous studies have recommended adopting a ‘new borderline zone’ for those with initial low-level positive results. In our study, 35.3% of employees whose initial specimens yielded a positive result produced a negative result with a freshly donated follow-up specimen. Although we observed a statistical difference ($P < .01$) in the initial positive test result values from individuals whose subsequent specimen yielded a positive result, versus individuals whose follow-up specimen yielded a negative result, there was overlap between quantitative results in these 2 groups, which minimizes the clinical utility of these values. Therefore, we cannot recommend changing the threshold value for a positive result. The FDA-approved package insert for the QFT-GIT assay does not include an equivocal zone; a single threshold of 0.35 IU/mL is suggested. Many assays with a cut off value for an interpretation of positive or negative have an equivocal zone which is interpreted as neither positive nor negative. This assay does not have an equivocal zone. Low positive results, which might have been in an equivocal zone if there was one, are read as positive. When the repeat testing is negative, the first result is interpreted as a false positive. If the quantitative threshold for a positive result is chosen for maximum sensitivity, which is ordinarily the case with screening tests, it is likely that false positive results will occur; some of these false positives may yield negative results on repeat testing. However, we performed a repeat blood draw after at least 4 weeks on individuals for whom the positive result of their initial test was less than 1.5. This delay in repeat testing might allow for minor infections or other T cell–activating conditions to resolve. This assay looks at lymphocyte secretion of gamma interferon by activated lymphocytes. We hypothesize that by delaying repeat testing for a period of time, other clinical conditions, such as minor infections or other T cell-activating condition may resolve.
Joshi et al reported results of QFT-GIT testing in more than 3000 employees of the Central Arkansas Veterans Healthcare System. The authors noted high numbers of positive test results and high reversion rates on repeat testing, which prompted them to suggest that the borderline zone between the interferon-γ values of 0.35 IU/mL and 2.0 IU/mL might need to be reconsidered. Also, a recent study by Thanassi et al reported a high reversion rate with a lower TB Ag-Nil value and found the separation point between repeat-positive and revision-to-negative results to be 1.11 IU per mL. Slater et al supported a higher cut-off to match historical TST conversion rates in a study of 9153 HCPs in which initial specimens from 1223 (13.4%) individuals yielded positive test results, whereas repeat specimens from 395 (32.3%) of the initially positive individuals reverted to negative results.

The cost of administering the QFT-GIT test was approximately $45 per employee, which included material, labor, and phlebotomy. The cost of a 9-month course of isoniazid for an adult averages $40. Although these costs are similar, the use of QFT-GIT can eliminate the diagnosis of LTBI; this would avoid exposing individuals to a potentially unnecessary course of medication that might result in adverse drug reactions.

We conclude that QFT-GIT testing in HCPs is feasible, practical, allows individuals to avoid the need for follow-up visits to interpret TST results, and reduces the rate of false positive results in individuals who had received the BCG vaccine. Although IGRA tests are correlated with occupational risk factors for TB exposure in settings with a low incidence of TB, we did not find that assessment of risk factors was predictive of positivity in our cohort. This was likely due to the fact that the TB screening form did not clarify the difference between exposure to latent and active TB. Similar to the results of other studies in adult institutions, we observed a false-positive rate in a borderline zone of less than 1 IU/mL; thus, we suggest that re-evaluation of the positive threshold, or retesting, zone should be considered. Clinical interpretation in individuals with low-level positivity is imperative before further evaluation, and we recommend that discussion be provided by an infectious disease expert who is knowledgeable about tuberculosis.

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Additional Information

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References