Comparison of QuantiFERON-TB Gold In-Tube Test and Tuberculin Skin Test for Identification of Latent *Mycobacterium tuberculosis* Infection in Healthcare Staff and Association Between Positive Test Results and Known Risk Factors for Infection • Author(s): Paul Vinton, MBBS; Seema Mihrshahi, PhD; Paul Johnson, MBBS, PhD; Grant A. Jenkin, MBBS, PhD; Damien Jolley, MSc; Beverley-Ann Biggs MBBS, PhD 

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Comparison of QuantiFERON-TB Gold In-Tube Test and Tuberculin Skin Test for Identification of Latent *Mycobacterium tuberculosis* Infection in Healthcare Staff and Association Between Positive Test Results and Known Risk Factors for Infection

Paul Vinton, MBBS; Seema Mihrshahi, PhD; Paul Johnson, MBBS, PhD; Grant A. Jenkin, MBBS, PhD; Damien Jolley, MSc; Beverley-Ann Biggs MBBS, PhD

**Objective.** We compared a whole-blood interferon-γ release assay (QuantiFERON-TB Gold In-Tube test, hereafter “QFT–in tube test”) with a tuberculin skin test (TST) to determine which test more accurately identified latent *Mycobacterium tuberculosis* infection in healthcare staff.

**Methods.** A total of 481 hospital staff members were recruited from 5 hospitals in Melbourne, Australia. They provided information about demographic variables and tuberculosis (TB) risk factors (ie, birth or travel in a country with a high prevalence of TB, working in an occupation likely to involve contact with *M. tuberculosis* or individuals with TB, or being a household contact of an individual with a proven case of pulmonary TB). The QFT–in tube test and the TST were administered in accordance with standardized protocols. Concordance between the test results and positive risk factors was analyzed using the κ statistic, the McNemar test, and logistic regression.

**Results.** A total of 358 participants had both a TST result and a QFT–in tube test result available for comparison. There were fewer positive QFT–in tube test results than positive TST results (6.7% vs. 33.0%; *P* < .001). Agreement between the tests was poor (71%; κ = 0.16). A positive QFT–in tube test result was associated with birth in a country with a high prevalence of TB, the number of years an individual had lived in a country with a high prevalence of TB (ie, the effect of each additional year, treated as a continuous variable), and high-risk occupational contact. A positive TST result was associated with older age, receipt of bacille Calmette-Guérin (BCG) vaccination, and working in an occupation that involved patient contact. Receipt of BCG vaccination was most strongly associated with discordant results in instances in which the TST result was positive and the QFT–in tube test result was negative.

**Conclusion.** In a population of healthcare staff with a low prevalence of TB and a significant rate of BCG vaccination, a positive QFT–in tube test result was associated with the presence of known risk factors for TB exposure, whereas a positive TST result was more strongly associated with a prior history of BCG vaccination.
caused by previous BCG vaccination.\textsuperscript{13,14} The QUANTI-FERON-TB Gold In-Tube (Cellestis; hereafter “QFT–in tube”) is one such test; it has been shown to be comparable to the TST in terms of its sensitivity in detecting active disease and identifying infection among recent contacts of individuals with TB.\textsuperscript{14,15} Evidence is still accumulating regarding its suitability and sensitivity for occupational screening.\textsuperscript{16}

In this study, we evaluated the QFT–in tube test by comparing it with the TST as a method for screening healthcare staff for LTBI in metropolitan hospitals in Melbourne, Australia, where the percentage of individuals with positive TST results has previously been shown to be 20%.\textsuperscript{7} We used the correlation between the 2 test results and the presence or absence of known risk factors for TB exposure, as well as the extent of such exposure, to determine which of the tests more accurately detected latent infection.

\textbf{METHODOLOGY}

\textbf{Recruitment}

The study was conducted at 5 hospitals in the Southern Health Care Network (Melbourne, Australia) and was approved by the Human Research Ethics Committees of Melbourne Health and the Southern Health Care Network. All hospital staff (physicians, nurses, allied health staff, patient services assistants, and clerical staff) were invited to participate in the study; enrollment was encouraged by use of posters, public address system announcements, and ward visits, with the assistance of each hospital’s infection prevention and control unit. Staff members who were pregnant or who had previously experienced severe reaction or allergy to purified protein derivative were excluded from receiving the TST but were eligible to undergo the QFT–in tube test. Staff who had a previously documented positive TST result and did not wish to have another TST were also eligible to undergo the QFT–in tube test.

\textbf{Assessment of Previous Exposure and Risk Factors}

Information on age, sex, occupation, other illnesses, history of past TST results, country of birth, date of arrival in Australia, history and duration of overseas travel, and known exposure to TB was collected via interviews. BCG vaccination status was ascertained by self-reported vaccination history and/or the detection of a BCG vaccination scar on visual inspection by the interviewer; where possible, BCG vaccination status was confirmed with previous staff vaccination records. For each participant, the country of birth and the locations of overseas travel were divided into the following 3 groups on the basis of published TB prevalence rates: high-prevalence countries (\( \geq 100 \) cases of TB per 100,000 population), intermediate-prevalence countries (10-100 cases of TB per 100,000 population), and low-prevalence countries (<10 cases of TB per 100,000 population).\textsuperscript{17,18}

We also defined 5 groups that were at high risk for exposure to TB. In the absence of a “gold standard” diagnostic test for LTBI, we used the risk of exposure to TB (defined by these risk groups) as a proxy “gold standard” with which to compare the 2 tests. These groups were as follows: (1) those born in a high-prevalence country, (2) those with a lifetime history of travel to a high-prevalence country for more than 12 months, (3) those whose occupation included a high likelihood of TB contact (ie, work in a bronchoscopy suite, work as a respiratory or infectious diseases physician, work on a dedicated TB ward, microbiology or pathology work involving \textit{M. tuberculosis}, or performance of autopsies), (4) those with high-risk occupational contact (ie, more than 10 hours total contact with a patient known to have TB, without respiratory precautions), and (5) those who were household contacts of an individual with a proven case of pulmonary TB. An individual’s total number of risk factors and the duration of time that person had lived in a high-prevalence country were later used in our analysis as surrogate markers for the extent of exposure.

\textbf{TST}

A “one-step” tuberculin strategy was chosen because this was the strategy currently in use for TB screening in the Southern Health Care Network (Melbourne, Australia), where the percentage of individuals with positive TST results has previously been shown to be 20%.\textsuperscript{7} We used the correlation between the 2 test results and the presence or absence of known risk factors for TB exposure, as well as the extent of such exposure, to determine which of the tests more accurately detected latent infection.

\begin{table}[h]
\centering
\caption{Characteristics of Study Participants Who Underwent Tuberculosis Testing}
\begin{tabular}{ll}
\hline
Characteristic & Value \\
\hline
Age, median (range), years & 42 (20-66) \\
Sex & \\
\quad Female & 431 (89.6) \\
\quad Male & 50 (10.4) \\
Occupation & \\
\quad Nurse & 313 (65.1) \\
\quad Physician & 15 (3.1) \\
\quad Allied health staff & 47 (9.8) \\
\quad Clerical staff & 33 (6.9) \\
\quad Patient services assistant & 34 (7.1) \\
\quad Other & 39 (8.1) \\
BCG vaccination status & \\
\quad Vaccinated & 375 (78.0) \\
\quad Unvaccinated & 78 (16.2) \\
\quad Unknown & 28 (5.8) \\
Country of birth & \\
\quad Australia & 320 (66.5) \\
\quad Low-prevalence country & 64 (13.3) \\
\quad Intermediate-prevalence country & 39 (8.1) \\
\quad High-prevalence country & 58 (12.1) \\
Travel to a high-prevalence country & \\
\quad No & 383 (79.6) \\
\quad Yes & 98 (20.4) \\
High-risk occupational exposure & \\
\quad No & 420 (87.3) \\
\quad Yes & 61 (12.7) \\
Household contact of an individual with a proven case of pulmonary TB & \\
\quad No & 472 (98.1) \\
\quad Yes & 9 (1.9) \\
\hline
\end{tabular}
\end{table}

\textbf{NOTE}. Data are no. (% of participants, unless otherwise specified. See Methods for details about risk categories. BCG, bacille Calmette-Guérin; TB, tuberculosis.
Table 2. Results of QuantiFERON-TB Gold In-Tube Test (QFT–In Tube Test) and Tuberculin Skin Test (TST), According to Bacille Calmette-Guérin (BCG) Vaccination Status

<table>
<thead>
<tr>
<th></th>
<th>BCG vaccinated</th>
<th>Not BCG vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive QFT–in tube test result</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Negative QFT–in tube test result</td>
<td>94</td>
<td>164</td>
</tr>
</tbody>
</table>

Health Care Network. The TST was performed by use of the Mantoux method, in accordance with Australian guidelines,19 which recommend 10 IU of purified protein derivative (Commonwealth Serum Laboratories); the test result was interpreted 48-72 hours after administration by use of the palpation method. The test was performed by trained nursing staff who were blinded to the results of the QFT–in tube test and the questionnaire. A positive TST result was defined as induration of 10 mm or greater.20

QFT–In Tube Test

The QuantiFERON-TB Gold assay, also referred to as the “second-generation” QFT assay or QFT-2G, uses selected M. tuberculosis antigens or peptide-simulating antigens, including early secreted antigenic target 6 and culture filtrate protein 10. A newer version of this assay, known as the QuantiFERON-TB Gold In-Tube test or “third-generation” QFT assay, was used for this study. This test involves the collection of blood samples in tubes prefilled with antigen (typically a negative control tube, an M. tuberculosis–antigen tube, and an optional mitogen tube), which simplifies laboratory procedures.21 The QFT–in tube test was performed and results interpreted in accordance with the manufacturer’s guidelines.22 Kits were purchased from the manufacturer (Cellestis) and were processed at the Cellestis laboratory in Carnegie, Australia.

Statistical Analysis

Statistical analysis was performed using Stata, version 8.0 (Stata). Concordance between the TST results and the QFT–in tube test results was examined by use of the κ statistic; κ values of less than 0.4 indicate poor agreement, values of 0.4-0.75 indicate good agreement, and values greater than 0.75 indicate excellent agreement.23

We estimated the increase in the likelihood of a positive test result for each unit of exposure to the risk factors defined above and used matched-pair logistic regression to assess the significance of the difference in the associations between the tests. The McNemar test and multiple logistic regression analysis were used to determine which factors were significantly associated with a positive result. A multinomial logistic model was used to determine the factors associated with discordant test results (using concordant results as the comparator). Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs).

Results

A total of 481 hospital staff members participated in the study, all of whom had a QFT–in tube test performed. The characteristics of the study subjects are shown in Table 1. Of 481 participants, 32 (6.7%) had a positive QFT–in tube test result, 441 (91.7%) had a negative result, and 8 (1.6%) had an indeterminate result.

A total of 364 participants (75.7%) had a TST performed and interpreted during the study. Of these, 120 (33.0%) had a positive test result when a cutoff of 10 mm induration was used, 73 (20.0%) participants showed induration of 15 mm or greater, and 39 (10.7%) showed induration of 20 mm or greater. Four people had a severe reaction to purified protein derivative that involved ulceration or blistering, requiring treatment. One hundred seventeen (24.3%) of the participants did not have a TST result available; 61 (12.7%) had a previously documented positive TST result and declined to repeat the TST, 8 (1.7%) declined the TST on the basis of a previous severe reaction, and 47 (9.8%) failed to have the test result interpreted within 72 hours, despite repeated attempts to contact them (1 additional participant did not have a TST performed because of having recently received a measles-mumps-rubella vaccination, which can interfere with TST results).

Figure 1. Percentage of subjects with a positive QuantiFERON-TB Gold In-Tube (QFT–in tube) test result, according to size of tuberculin skin test (TST) induration.
Table 3. Multivariate Logistic Regression Comparing Positive QuantiFERON-TB Gold In-Tube Test (QFT–In Tube Test) and Tuberculin Skin Test (TST) Results With Risk Factors for Tuberculosis (TB)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Positive QFT–in tube test result</th>
<th>Positive TST result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Older age, per each additional year</td>
<td>1.03 (0.98-1.08)</td>
<td>.206</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.36 (0.09-1.43)</td>
<td>.149</td>
</tr>
<tr>
<td>Birth in a high-prevalence country</td>
<td>6.15 (2.00-18.9)</td>
<td>.002*</td>
</tr>
<tr>
<td>Residence in a high-prevalence country, per each year</td>
<td>1.04 (1.01-1.08)</td>
<td>.018*</td>
</tr>
<tr>
<td>Travel to a high-prevalence country</td>
<td>1.13 (0.59-2.15)</td>
<td>.702</td>
</tr>
<tr>
<td>&gt;12 months of travel in a high-prevalence country</td>
<td>1.01 (0.98-1.03)</td>
<td>.451</td>
</tr>
<tr>
<td>Receipt of BCG vaccination</td>
<td>1.29 (0.21-7.90)</td>
<td>.780</td>
</tr>
<tr>
<td>Receipt of prior TST</td>
<td>1.43 (0.29-6.88)</td>
<td>.657</td>
</tr>
<tr>
<td>Occupation involving patient contact</td>
<td>0.70 (0.22-2.16)</td>
<td>.534</td>
</tr>
<tr>
<td>High-risk occupation</td>
<td>1.15 (0.11-11.9)</td>
<td>.907</td>
</tr>
<tr>
<td>Duration of high-risk occupation, per each year</td>
<td>1.05 (0.89-1.23)</td>
<td>.552</td>
</tr>
<tr>
<td>High-risk occupational exposure</td>
<td>5.60 (1.42-22.0)</td>
<td>.014*</td>
</tr>
<tr>
<td>Household contact of an individual with pulmonary TB</td>
<td>3.26 (0.25-41.6)</td>
<td>.364</td>
</tr>
</tbody>
</table>

Note. See Methods for details about risk categories. BCG, bacille Calmette-Guerin; CI, confidence interval; OR, odds ratio.

* Statistically significant (P < .05).

Of the 364 participants who had TST results available, 6 had an indeterminate QFT–in tube test result; therefore, the final sample size for comparison of the tests was 358 participants. Table 2 shows the test results stratified by BCG vaccination status. The results analyzed below include only participants who had results available for both tests.

Agreement Between the Test Results

There were fewer positive QFT–in tube test results than positive TST results (6.7% versus 33.0%; OR, 19.6 [95% CI, 8.6-54.3]; P < .001). Five subjects with positive QFT–in tube test results had negative TST results. The agreement between the QFT–in tube test and the TST was generally poor (71% when a cutoff of 10 mm induration was used; $\kappa = 0.16$), but it improved slightly when higher cutoff points were used for the TST (82% for a cutoff of 15 mm induration [$\kappa = 0.23$] and 89% for a cutoff of 20 mm induration [$\kappa = 0.25$]). Agreement for tests of unvaccinated subjects was 92% when a cutoff of 10 mm induration was used ($\kappa = -0.03$), and 97% when a cutoff of 15 mm induration was used ($\kappa = -0.02$); agreement for tests of BCG-vaccinated subjects at the same cutoff points was 66% ($\kappa = 0.15$) and 79% ($\kappa = 0.22$), respectively. For each 5-mm increase in induration, an increasing proportion of subjects had a positive QFT–in tube test result (Figure 1).

Correlation with Risk Factors

Table 3 shows the odds ratio for a positive QFT–in tube test result relative to various exposures. The factors associated with a positive QFT–in tube test result were birth in a high-prevalence country, the number of years an individual had lived in a high-prevalence country, and high-risk occupational contact.

For the TST, receipt of BCG vaccination, an occupation involving patient contact (as opposed to hospital occupations that do not involve such contact, eg, clerical positions), and a greater number of years lived in a high-prevalence country were associated with a positive test result. Staff who reported having had a previous TST were more likely to have a positive result for the TST administered as part of this study (P < .001) and staff whose occupation involved patient contact were more likely to report a history of previous TST (P < .001).
TABLE 4. Results of Multinomial Logistic Regression for Discordant QuantiFERON-TB Gold In-Tube Test (QFT–in Tube Test) and Tuberculin Skin Test (TST) Results

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Positive QFT–in tube test result and negative TST result</th>
<th>Positive TST result and negative QFT–in tube test result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Older age, per each additional year</td>
<td>1.01 (0.90-1.14)</td>
<td>.813</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.21 (0.01-5.36)</td>
<td>.343</td>
</tr>
<tr>
<td>Birth in a high-prevalence country</td>
<td>22.5 (0.92-549)</td>
<td>.057</td>
</tr>
<tr>
<td>Residence in a high-prevalence country, per each additional year</td>
<td>1.01 (0.91-1.11)</td>
<td>.878</td>
</tr>
<tr>
<td>Travel to a high-prevalence country</td>
<td>1.44 (0.13-15.7)</td>
<td>.767</td>
</tr>
<tr>
<td>&gt;12 months of travel in a high-prevalence country</td>
<td>0.35 (0.03-4.09)</td>
<td>.402</td>
</tr>
<tr>
<td>Receipt of BCG vaccination</td>
<td>2.44 (0.06-105)</td>
<td>.641</td>
</tr>
<tr>
<td>Receipt of TST</td>
<td>0.56 (0.04-8.63)</td>
<td>.681</td>
</tr>
<tr>
<td>Occupation involving patient contact</td>
<td>0.97 (0.07-14.7)</td>
<td>.998</td>
</tr>
<tr>
<td>High-risk occupation</td>
<td>23.2 (0.26-2003)</td>
<td>.169</td>
</tr>
<tr>
<td>Duration of high-risk occupation, per each additional year</td>
<td>0.35 (0.03-4.01)</td>
<td>.400</td>
</tr>
<tr>
<td>High-risk occupational exposure</td>
<td>31.1 (1.30-746)</td>
<td>.034</td>
</tr>
<tr>
<td>Household contact of an individual with a proven case of pulmonary TB</td>
<td>3.66 (0.06-238)</td>
<td>.543</td>
</tr>
</tbody>
</table>

Note. See Methods for details about risk categories. BCG, bacille Calmette-Guérin; CI, confidence interval; OR, odds ratio; TB, tuberculosis.

* Statistically significant (P < .05).

The results of a multinomial logistic regression for discordant results are shown in Table 4. High-risk occupational contact and birth in a high-prevalence country showed the strongest association with discordant test results in instances in which the QFT–in tube test result was positive and the TST result was negative. Receipt of BCG vaccination and having an occupation that involved patient contact were most strongly associated with discordant results in instances in which the TST result was positive and the QFT–in tube test result was negative.

Correlation With Extent of Exposure

The relationship between positive results for each test and an individual’s total number of risk factors is shown in Figure 2, and the relationship between positive test results and the number of years participants had lived in a high-prevalence country is shown in Figure 3. A positive QFT–in tube test result correlated with increased exposure for both the number of years individuals lived in a high-prevalence country (OR, 1.5 [95% CI, 1.16-1.92]; P = .002) and their total number of risk factors (OR, 2.7 [95% CI, 1.49-4.71]; P = .001). Increased exposure as measured by duration of travel in a high-prevalence country or time worked in a high-risk occupation was not significantly associated with positive results for either test.

Discussion

To our knowledge, this is the largest study to date that compares the QFT–in tube test and the TST for screening healthcare staff in a developed country, and the first to correlate findings with the extent of exposure to known risk factors. The findings demonstrate that in a population with a low prevalence of TB but a significant rate of BCG vaccination, a positive QFT–in tube test result has a stronger degree of association with the presence of known risk factors for TB exposure than does a positive TST result, whereas a positive TST result has a strong association with a prior history of BCG vaccination (OR, 9.23) and some risk factors for TB. The findings support the hypothesis that BCG vaccination status may significantly affect the proportion of positive TST results and suggest that the QFT–in tube test may be more effective for identifying HCWs with LTBI in countries with...
a low prevalence of TB by eliminating the possibility of false-positive results caused by BCG vaccination.

Our results are consistent with those of a Korean study that showed the QFT–in tube test to be comparable with the TST in its ability to detect LTBI and showed QFT–in tube test results to be less affected by BCG vaccination status; our results are also consistent with those of a Japanese study in which HCWs in a community hospital were assigned a contact score on the basis of their contact time with an index patient with TB and the infectivity of the index patient. In that study, the QFT–in tube test result showed a better association with the contact score than did the TST result.

Our findings are contrary to those of a study conducted in India in which there was good agreement (k = 0.61) between the QFT–in tube test result and the TST result for HCWs. The differences between their findings and ours could be explained by the differing prevalence of exposure to TB in the 2 study populations. If both tests are of comparable sensitivity, the level of agreement between the tests is likely to increase as the TB prevalence (and therefore the number of true-positive results) in a population increases. Agreement would, therefore, be lower in low-prevalence populations with a comparable proportion of confounding factors, such as BCG vaccination, that might influence the result of one test (the TST) but not the other (the QFT–in tube test). The high level of agreement between the tests for Indian HCWs also provides indirect evidence that the QFT–in tube test may have a sensitivity similar to that of the TST.

Our findings are also contrary to those of a study of US military personnel that found discordant results to be associated with birth in a high-prevalence country. The authors of that study concluded that the QFT–in tube test was more specific than the TST when a cutoff of 10 mm induration is used, but also that it may not be as sensitive for the detection of TB as a properly performed TST. In our study, not only did a positive QFT–in tube test result show a stronger correlation than a positive TST result with birth in a high-prevalence country, but this factor was also associated with discordant results in instances in which the TST result was negative. The QFT–in tube test result also showed a stronger correlation with the number of years individuals had lived in a high-prevalence country when this was used as a marker for the extent of exposure. The odds of a positive TST result appeared to plateau after 20 years spent living in a high-prevalence country, whereas the odds of a positive QFT–in tube test result continued to rise after that point. This latter finding may be of relevance to the study by Mazurek et al., in which the mean age of participants was only 20 years.

A limitation of the present study was the high rate of loss to follow-up; 117 (24.3%) of the 481 participants originally recruited did not have a TST performed and/or a TST result interpreted, and a large proportion of these individuals had positive TST results in the past. Therefore, the possibility of selection bias cannot be excluded. Our study was further limited by the fact that some subcategories contained a small number of subjects, which may have prevented some relationships from becoming fully apparent in our analysis.

A number of different strategies have been suggested for LTBI screening of HCWs, including the use of a 2-stage testing strategy, in which an initial TST is followed by a QFT–in tube test for those with a positive TST result. Our findings suggest that this approach may fail to identify a significant proportion of individuals who may have a negative TST result but would have a positive QFT–in tube test result if tested. Although a strategy that combines the use of both the TST and the QFT–in tube test may be appropriate for patients at high risk for TB reactivation (such as immunosuppressed individuals), implementing this strategy for a low-risk group such as HCWs would result in increased cost without reducing any of the inherent problems of TST testing.

Our findings support the recent Centers for Disease Control and Prevention guidelines, which suggest that the QFT–in tube test is a viable alternative for a widespread HCW screening program. If this approach were used, it is likely that far fewer staff would require follow-up and treatment, which has significant implications for reducing the costs of a screening program, as well as for reducing the morbidity that results from adverse reactions to isoniazid therapy.

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Potential conflicts of interest: Cellestis is a listed Australian Security and supplied the QuantiFERON-TB Gold In-Tube test kits for the study. Cellestis personnel did not participate in study design, data analysis, or manuscript preparation. None of the authors are holders of Cellestis stock. G.A.J. and D.J. have received study support from Cellestis.

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