Guidelines for Using the QuantiFERON®-TB Gold Test for Detecting Mycobacterium tuberculosis Infection, United States

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Summary

On May 2, 2005, a new in vitro test, QuantiFERON®-TB Gold (QFT-G, Cellestis Limited, Carnegie, Victoria, Australia), received final approval from the U.S. Food and Drug Administration as an aid for diagnosing Mycobacterium tuberculosis infection. This test detects the release of interferon-gamma (IFN-g) in fresh heparinized whole blood from sensitized persons when it is incubated with mixtures of synthetic peptides representing two proteins present in M. tuberculosis: early secretory antigenic target--6 (ESAT-6) and culture filtrate protein--10 (CFP-10). These antigens impart greater specificity than is possible with tests using protein derivative as the tuberculosis (TB) antigen. In direct comparisons, the sensitivity of QFT-G was statistically similar to that of the tuberculin skin test (TST) for detecting infection in persons with untreated culture-confirmed tuberculosis (TB). The performance of QFT-G in certain populations targeted by TB programs in the United States for finding latent TB infection is under study. Its ability to predict who will have TB disease has not been determined, and years of observational study of substantial population be needed to acquire this information. In July 2005, CDC convened a meeting of consultants and research expertise in the field to review scientific evidence and clinical experience with QFT-G. On the basis of that and discussion, CDC recommends that QFT-G may be used in all circumstances in which the TST is currently used, including contact investigations, evaluation of recent immigrants, and sequential-testing surveilla...
programs for infection control (e.g., those for health-care workers). This report provides specific caution interpreting negative QFT-G results in persons from selected populations. This report is aimed at public officials, health-care providers, and laboratory workers with responsibility for TB control activities in the United States.

Background

On May 2, 2005, a new in vitro test, QuantiFERON®-TB Gold (QFT-G, manufactured by Cellestis Lim Carnegie, Victoria, Australia), received final approval from the U.S. Food and Drug Administration (FDA) in diagnosing Mycobacterium tuberculosis infection, including both latent tuberculosis infection (LTBI) and tuberculosis (TB) disease. This enzyme-linked immunosorbent assay (ELISA) test detects the release of interferon-gamma (IFN-g) in fresh heparinized whole blood from sensitized persons when it is incubate mixtures of synthetic peptides simulating two proteins present in M. tuberculosis: early secretory antigen 6 (ESAT-6) and culture filtrate protein–10 (CFP-10). ESAT-6 and CFP-10 are secreted by all M. tuberculosis strains. Because these peptides are absent from all Bacille Calmette-Guérin (BCG) strains and from commonly encountered nontuberculous mycobacteria (NTM) except M. kansasii, M. scrofulaceum, and M. marinum, QFT-G is expected to be more specific for M. tuberculosis than tests that use tuberculin protein derivative (PPD) as the antigen.

QFT-G represents one type of IFN-g release assay (IGRA) (2). Tests such as QFT-G measure the IFN-g by sensitized white blood cells after whole blood is incubated with antigen. Tests such as ELISpot enun releasing IFN-g after mononuclear cells recovered from whole blood are incubated with similar antigen IGRAs have been approved by FDA for use in the United States: the original QuantiFERON®-TB test (the recently approved QFT-G. The two tests use different antigens to stimulate IFN-g release, different measurement, and different approaches to test interpretation. QFT was approved as an aid for diagnosing whereas QFT-G is approved as an aid for diagnosing both LTBI and TB disease. QFT is no longer com available.

Before QFT was approved in 2001, the tuberculin skin test (TST) was the only test available for detecting (3). QFT-G is intended to replace QFT. QFT-G results can be available <24 hours after testing without a second visit, whereas a TST requires a second encounter to read the result 48–72 hours after admin of the test. As a laboratory-based assay, QFT-G is not subject to biases and errors of TST placement and running and interpreting the assay decrease the accuracy of QFT-G. Related to the uncertainty in interpreting a test result, including that of when the test's measurement approaches a fixed cut-off point, the reproducibility of QFT-G is less when measured amount of IFN-g is near the test's cut-off point. Detection of substantial amounts of released IFN-g disallows arriving at a negative test result.

Each of the three tests (TST, QFT, and QFT-G) relies on a different immune response and differs in its measures of sensitivity and specificity. The TST assesses in vivo delayed-type hypersensitivity (Type I' QFT and QFT-G measure in vitro release of IFN-g. The TST and QFT measure response to PPD, a polyantigenic mixture, whereas QFT-G measures response to a mixture of synthetic peptides simulating two antigenic proteins that are present in PPD. The agreement between TST and QFT results in persons at increased risk for LTBI facilitated approval and acceptance of QFT (3,4). Results of similar studies using QFT-G in persons at increased risk have not been published, but less agreement between TST and QFT-G results is predictable because fewer and more specific antigens are used in QFT-G. QFT-G is not affected by prior vaccination (1) and is expected to be less influenced by previous infection with nontuberculous mycobacteria. TSTs are variably affected by these factors. QFT-G does not trigger an anamnestic response (i.e., boosting) because it does not expose persons to antigen. Injection of PPD for the TST can boost subsequent TST primarily in persons who have been infected with NTM or vaccinated with BCG. Compared with the TST.

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might be less affected by boosting from a previous TST.

Assessment of the accuracy of QFT-G and other indirect tests for *M. tuberculosis* infection (including T hampered by the lack of confirmatory tests to diagnose LTBI and culture-negative TB disease (6). This partially addressed by observing the proportion of negative tests among persons who are unlikely to have *tuberculosis* infection because they lack risks (this approach approximates specificity); by observing the proportion positive among persons with culture-confirmed TB disease (this approach approximates sens and by determining factors associated with discordance between a new test and the TST. One limitation approach is that certain persons who have no recognized risks might be infected with *M. tuberculosis*, v causes specificity to be underestimated. A broad limitation is that the TST and any newer tests might nc the same for detecting LTBI as they do for detecting *M. tuberculosis* infection during TB disease. For e reduction of in vitro IFN-g release has been attributed to suppressive cytokines associated with TB dise When comparing an IGRA with a TST, variations in methods also must be considered (e.g., use of different antigens or risk-stratified cut-off points for interpreting results).

Studies assessing QFT-G with these approximation methods have been published (5,8,9). A specificity was reported in 216 BCG-vaccinated Japanese nursing students who were entering their training and w low risk for *M. tuberculosis* infection, and a sensitivity of 89.0% was reported in 118 patients with cult confirmed TB (5). However, QFT-G results were derived slightly differently than the methods approve In another study (8), QFT-G was compared with TST by using two tuberculin units of RT-23 (8,10). In 99 healthy, BCG-vaccinated medical students in Korea, the specificity of QFT-G was 96%, compared v for the TST. Among 54 patients with pulmonary TB disease, the sensitivity of the QFT-G was 81%, cot with 78% for the TST (8). QFT-G and the TST were compared in an unselected population of 318 hosp patients (9). QFT-G had greater sensitivity for TB disease (67%) than did TST (33%), but indeterminate responses were common (21%) among patients with negative TST results, the majority of whom were t be immunocompromised or immunosuppressed.

The antigens or laboratory methods in other studies have varied (2). Although the findings are informat QFT-G will perform in the same circumstances is unknown. In an investigation of contacts in a high scl Denmark in which a student had infectious TB, the same ELISA used with QFT-G was employed, but recombinant ESAT-6 and CFP-10 antigens used rather than the mixtures of synthetic peptides used with (11). The IGRA used in that study agreed well with the TST in non-BCG--vaccinated contacts. BCG-v contacts were not skin tested, but their IGRA results closely paralleled those for the nonvaccinated cont suggested that BCG vaccination was not affecting the results of this IGRA.

**Methodology**

During July 11--12, 2005, CDC convened a meeting in Atlanta, Georgia, of consultants and researchers expertise in the field to review studies and assess experience with QFT-G. Unpublished data from studi G were considered in preparing these guidelines. Expert consultants (see Membership List), researchers control public health practitioners, and representatives of FDA, other federal agencies, and the manufac reviewed the evolving data on QFT-G. Data from ongoing studies evaluating QFT-G in U.S. Navy recr correctional facility inmates, persons with suspected TB disease, contacts of persons suspected to have ' and health care workers were reviewed. For developing these guidelines, CDC considered the scientific and the opinions of the consultants. Their opinions did not represent endorsement from their organizatio

This report provides interim guidance for use and interpretation of QFT-G. Confirming or excluding TE and assessing the probability of LTBI require a combination of epidemiologic, historic, physical, and di findings that should be considered when interpreting QFT-G results. This report is intended to assist pu officials, clinicians, and laboratorians in their efforts to understand the use of QFT-G for TB control.
Indications for QFT-G

FDA approved QFT-G as an in vitro diagnostic aid using peptide mixtures simulating ESAT-6 and CFP proteins to stimulate cells in heparinized whole blood. Detection of IFN-g by ELISA is used to identify responses to ESAT-6 and CFP-10 that are associated with *M. tuberculosis* infection (12). From a public health perspective, QFT-G testing is indicated for diagnosing infection with *M. tuberculosis*, including TB disease and LTBI. Whenever *M. tuberculosis* infection or disease is being diagnosed by any method, an optimal approach includes coordination with the local or regional public health TB control program.

How QFT-G Testing is Performed and Interpreted

Instructions for the QFT-G assay are in the package insert (13). Aliquots of heparinized whole blood are with the test antigens for 16–24 hours. The blood must be incubated with the test antigens ≤12 hours after collection. Test kits include two mixtures of synthetic peptides representing ESAT-6 and CFP-10 as test phytohemagglutinin (a mitogen used as a positive assay control), and saline (used as a nil sample to measure background level of IFN-g). After incubation, the concentration of IFN-g in the plasma is determined by using the reagents included in the test kit. The amount of IFN-g released is determined by subtracting the amount in the nil from the amount in the ESAT-6, CFP-10, or mitogen-stimulated plasma. QFT-G test results are calculated by using software provided by the manufacturer. This report provides guidelines for interpreting results (Table). Laboratory reports should include interpretation of QFT-G test results and indicate the concentration of IFN-g in each plasma sample.

Cautions and Limitations

Certain limitations of QFT-G are similar to those of the TST, but these limitations have not been studied extensively for QFT-G. Whereas the sensitivity of QFT-G for detecting *M. tuberculosis* infection in untreated culture-confirmed TB is approximately 80% in published studies (5,8), its sensitivity for particular groups of TB patients (e.g., young children and immunocompromised patients) has not been determined.

QFT-G sensitivity for LTBI might be less than that of the TST, although the lack of a confirmatory test makes it difficult to assess. Estimating the sensitivity of any indirect test for LTBI by testing patients who have TB might be inaccurate because of differences between these conditions. The ability of QFT-G to predict risk for LTBI progressing subsequently to TB disease has not been determined.

QFT-G, as with the TST, cannot differentiate infection associated with TB disease from LTBI. A diagnosis of LTBI requires that TB disease be excluded by medical evaluation, which should include checking for symptoms and signs, a chest radiograph, and, when indicated, examination of sputum or other clinical specimens for the presence of *M. tuberculosis*.

Similar to any other diagnostic test, the predictive value of QFT-G results depends on the prevalence of *tuberculosis* infection in the population being tested. Each QFT-G result and its interpretation should be considered in conjunction with other epidemiologic, historic, physical, and diagnostic findings.

As with a negative TST result, negative QFT-G results should not be used alone to exclude *M. tuberculosis* infection in persons with symptoms or signs suggestive of TB disease. The presence of symptoms or signs suggestive of TB disease increases the likelihood that *M. tuberculosis* infection is present, and these conditions decrease the predictive value of a negative QFT-G or TST result. Medical evaluation of such persons should include a history and physical examination, chest radiograph, bacteriologic studies, serology for human immunodeficiency virus (HIV), and, when indicated, other tests or studies.
The performance of QFT-G, in particular its sensitivity and its rate of indeterminate results, has not been determined in persons who, because of impaired immune function, are at increased risk for *M. tuberculosis* infection progressing to TB disease. Impaired immune function can be caused by HIV infection or acquired immunodeficiency syndrome (AIDS); current treatment with immunosuppressive drugs including high-corticosteroids, tumor necrosis factor-alpha (TNF-a) antagonists, and drugs used for managing organ transplantation; selected hematologic disorders (e.g., myeloproliferative disorders, leukemias, and lymph specific malignancies (e.g., carcinoma of the head, neck, or lung); diabetes; silicosis; and chronic renal failure. Each of these conditions or treatments is known or suspected to decrease responsiveness to the TST, and might decrease production of IFN-g in the QFT-G assay. Consequently, as with a negative TST result, a QFT-G result alone might not be sufficient to exclude *M. tuberculosis* infection in these persons.

Published data are relatively limited concerning the use of QFT-G among persons recently exposed to TB contacts and other populations at high risk for LTBI. No published data document the performance of QFT-G in children aged <17 years.

With any of the testing methods, persons who have a negative test result can still have LTBI. Those who have a negative result but who are likely to have LTBI and who are at greater risk for severe illness or poor outcome because of their HIV status, underlying disorders, or treatment with TNF-a antagonists (which increase the risk for progression from LTBI to TB disease) might need treatment or closer monitoring for disease (6). Potential examples include contacts who are aged <5 years, those who are immunocompromised because of HIV infection, or those who undergo treatment with TNF-a antagonists (which increase the risk for progression from LTBI to TB disease) (16).

QFT-G has practical limitations that include the need to draw blood and to ensure its receipt in a qualified laboratory in time for testing. The blood must be incubated with the test antigens ≤12 hours after collection because the lymphocytes are viable. After the blood is incubated with antigens for 16–24 hours, plasma must be carefully separated and immediately tested by ELISA. Collecting the required 5-mL blood sample from children might not be possible or acceptable.

**Additional Considerations and Recommendations in the Use of QFT-G in Testing Persons at High Risk for LTBI**

QFT-G can be used in all circumstances in which the TST is used, including contact investigations, evaluation for LTBI in recent immigrants who have had BCG vaccination, and TB screening of health-care workers and others in high-risk settings. QFT-G can usually be used in place of (and not in addition to) the TST.

A positive QFT-G result should prompt the same public health and medical interventions as a positive TST result. No reason exists to follow a positive QFT-G result with a TST. Persons who have a positive QFT-G result regardless of symptoms or signs, should be evaluated for TB disease before LTBI is diagnosed. At a minimum, a chest radiograph should be examined for abnormalities consistent with TB disease. Additional medical evaluation would depend on clinical judgment on the basis of findings from history (including exposure to infectious persons), physical examination, and chest radiography. HIV counseling, testing, and referral is recommended because infection increases the suspicion of TB and the urgency of treating LTBI. After TB has been excluded, LTBI should be considered (6).

The majority of healthy adults who have negative QFT-G results are unlikely to have *M. tuberculosis* infection and do not require further evaluation. However, for persons with recent contact with persons who have infection, negative QFT-G results should be confirmed with a repeat test performed 8–10 weeks after the end of exposure is recommended for a negative TST result. Studies to determine the best time to retest contacts with negative QFT-G results have not been reported. Until more information is available, the timing of QFT-G testing should be the same as that used for the TST (17,18).
When "window period" prophylaxis (i.e., treatment for presumed LTBI) is indicated for contacts aged < severely immunocompromised persons who are exposed to highly contagious TB, repeat testing for LT recommended 8--10 weeks after contact has ended (18). With either TST or QFT-G, negative results of the end of the window period should be interpreted by considering all available epidemiologic, historic, physical, and diagnostic information, including the findings for the other contacts in the investigation. A course of treatment should be considered even with a negative result from either test at the end of the w period when the rate of M. tuberculosis transmission to other contacts was high or when a false-negative suspected because of a medical condition (18).

A greater rate of positive results has been reported with TST than with QFT-G in persons with and with recognized risks for M. tuberculosis infection, except for patients who have culture-confirmed TB disease. This tendency might be explained by either greater specificity with QFT-G, greater sensitivity with TST. For this reason, all information must be considered when making treatment decisions for persons with risk for progression from LTBI to TB or in whom TB disease is associated with increased risk for severe poor outcomes.

An indeterminate QFT-G result does not provide useful information regarding the likelihood of M. tube infection. The optimal follow-up of persons with indeterminate QFT-G results has not been determined. Options are to repeat QFT-G with a newly obtained blood specimen, administer a TST, or do neither. For an increased likelihood of M. tuberculosis infection who have an indeterminate QFT-G result, add a second test, either QFT-G or TST, might be prudent. The potential for TST to cause boosting and two-step testing in settings conducting serial testing should be considered. For persons who are unlikely M. tuberculosis infection, no further tests are necessary after an indeterminate QFT-G result. Laboratories report the reason that the QFT-G result was indeterminate (e.g., high background levels of IFN-g in the or inadequate response to mitogen). In one report, inadequate response to mitogen was associated with immunosuppressive conditions (9).

As with the TST, if TB disease is suspected, additional diagnostic evaluations should be performed before the same time as the QFT-G and should not be delayed while awaiting QFT-G results. These evaluations should include chest radiography, bacteriologic studies, serology for HIV, and, as indicated by the illness, addi and studies. At present, as with the TST, the results of indirect tests for M. tuberculosis (e.g., QFT-G) would not influence the selection of additional tests and studies in such patients.

TB control programs can use QFT-G for investigating contacts of persons with potentially infectious TB. Because QFT-G does not require a second visit to complete, test results probably will be available from percentage of contacts than would be available using TST. Because of its greater specificity, QFT-G is expected to indicate a smaller proportion of contacts as infected than the TST would indicate. Public health resources, previously were devoted to completion of testing can instead be concentrated on full evaluation and corroborative care of contacts who have positive QFT-G results. In contrast to the TST, initial QFT-G testing of will not boost subsequent test results, which avoids uncertainty about interpreting follow-up results. However, QFT-G might be less sensitive for LTBI than the TST, and its ability to predict subsequent development of disease is undetermined.

QFT-G might represent a cost-effective alternative to the TST in testing programs which are part of the infection control program in institutions such as health care settings, correctional facilities, or homeless these settings, false-positive reactions to the TST pose a problem. This problem is compounded in setting BCG-vaccinated persons born in countries where TB is prevalent. Follow-up visits for reading the TST substantial operational challenges; the second visit for reading requires extra effort and leads to inefficiency.

Greater specificity of the QFT-G and the requirement for only one visit are compelling advantages. Guidelines recommendations on the use of QFT-G as part of the infection control program in health-care settings have included in the most recent revision of the TB infection control guidelines (19). In situations with serial
M. tuberculosis infection, initial two-step testing, which is necessary with the TST, is unnecessary with and is not recommended.

TB control programs or institutions that elect to use QFT-G should consult and collaborate with laboratory their system to ensure that specimens are properly obtained, handled, and processed prior to and after at laboratory. Information concerning the assay is in the package insert (13). Training of laboratory staff necessary. Certain facilities might elect to refer specimens for testing. The Clinical Laboratory Improve Amendments (CLIA) regulations for quality systems of all phases of the total testing process (pre-analytic, analytic, and post-analytic) and for general laboratory systems must be followed, including, but not limited requirements for test system, equipment, instruments, reagents, materials and supplies (42 CFR Part 493) and the establishment or verification of performance specifications (42 CFR Part 493.1253) (20). In addition under CLIA, documentation of all quality systems, including laboratory proficiency and staff competency is required.

**Future Research Needs**

Additional studies to assess the performance of the QFT-G test under program conditions should be conducted. Further research is needed regarding use of QFT-G in multiple clinical circumstances. Studies of test performance should assess specificity, sensitivity, reproducibility, and association of test results with risk for infection and progression to TB disease. Comparisons among different IGRA and TSTs are encouraged. Questions addressed include the following:

- performance of QFT-G in young children, especially those aged <5 years;
- performance of QFT-G in persons with impaired immune systems, including persons with HIV/AIDS who will be treated with TNF-alpha antagonists, and others;
- performance and practicality of use of QFT-G in substantial numbers of persons who undergo pre-screening;
- determination of the subsequent incidence of TB disease after LTBI has been either diagnosed or treated with QFT-G;
- length of time between exposure, establishment of infection, and emergence of a positive QFT-G test in LTBI;
- economic evaluation and decision analysis comparing QFT-G with TST;
- changes in QFT-G results during therapy for both LTBI and TB disease;
- ability of QFT-G to detect re-infection after treatment for both LTBI and TB disease; and
- performance of QFT-G in targeted testing programs (e.g., for recent immigrants from high-incidence countries) and contact investigations.

In collaboration with FDA and the manufacturer, CDC will establish mechanisms for postmarketing surveillance. Providers should use FDA's MedWatch (available at [http://www.accessdata.fda.gov/scripts/medwatch](http://www.accessdata.fda.gov/scripts/medwatch)) to report instances of a contact having all of the following criteria:

- a negative QFT-G or TST result ≥6 weeks after the end of exposure,
- culture-confirmed TB disease <2 years after the end of exposure, and
- an *M. tuberculosis* isolate that has a genotype identical to that of the presumed source case.

Certain instances consistent with these criteria might require further study of the circumstances. However, postmarketing surveillance is not a substitute for research targeted at the above-noted questions. Research on these areas and others should therefore be conducted through prospective studies.

The optimal methods for ensuring quality in laboratory implementation of QFT-G testing should be determined. Educational materials are needed that can be widely disseminated to educate physicians regarding the use of QFT-G.
QFT-G assay. CDC will work with partners and the manufacturer to ensure the development of such m:

Other IGRA tests and test formats might become available in the United States over the next several ye:

Users of any of these products should anticipate the need for periodic modifications in practice, with res:

improvements in utility of these testing technologies.

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Table

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### TABLE. Interpretation of QFT-G* results, from IFN-γ† concentrations in test samples

<table>
<thead>
<tr>
<th>ESAT-6-nil§ or CFP-10-nil¶ or both</th>
<th>Nil</th>
<th>Mitogen-nil**</th>
<th>QFT-G result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0.35 IU/mL†† and &gt;50% above nil</td>
<td>Any</td>
<td>Any</td>
<td>Positive</td>
<td><em>Mycobacterium tuberculosis</em> infection likely</td>
</tr>
<tr>
<td>&lt;0.35 IU/mL</td>
<td>≤0.7</td>
<td>≥0.5</td>
<td>Negative</td>
<td><em>M. tuberculosis</em> infection unlikely but cannot be excluded, especially when illness is consistent with tuberculosis disease, likelihood of progression to TB disease is increased</td>
</tr>
<tr>
<td>&lt;0.35 IU/mL</td>
<td>Any</td>
<td>&lt;0.5</td>
<td>Indeterminate</td>
<td>QFT-G results cannot be interpreted as a result of a positive skin test or a negative BCG vaccine reaction</td>
</tr>
<tr>
<td>≤50% above nil</td>
<td>&gt;0.7</td>
<td>Any</td>
<td>Indeterminate</td>
<td>QFT-G results cannot be interpreted as a result of a positive skin test or a negative BCG vaccine reaction</td>
</tr>
</tbody>
</table>

* QuantIFERON®-TB Gold test.
† Interferon-gamma.
§ The IFN-γ concentration in blood incubated with a mixture of synthetic peptides simulating early secretory antigenic target-6 (ESAT-6) in concentration in blood incubated with saline.
¶ The IFN-γ concentration in blood incubated with a mixture of synthetic peptides simulating culture filtrate protein-10 (CFP-10) minus the IFN-γ concentration in blood incubated with saline.
** IFN-γ concentration in blood incubated with mitogen minus the IFN-γ concentration in blood incubated with saline.
†† International units per mL.
§§ Tuberculosis.

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