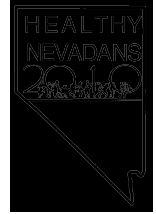




Nevada State Health Division Technical Bulletin



Topic: Using QuantiFERON and Tuberculin Skin Test to Screen for TB
Section/Program/Contact: Bureau of Community Health / Tuberculosis Program /
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TO: All Healthcare Providers

Tuberculosis Screening Tests

This report is intended to assist public health officials, clinicians, and laboratorians in their efforts to understand the use of QuantiFERON[®]-TB Gold test (QFT-G) and the Tuberculin Skin Test (TST) for TB control. Certain factors identify persons at high risk for TB infection and/or for progression to active TB disease (see table 1).

The diagnosis of Latent Tuberculosis Infection (LTBI), as well as TB Disease has traditionally been based upon results of TST however, the QuantiFERON[®]-TB Gold test (QFT-G), a whole-blood interferon gamma release assay (IGRA), has recently become an option for Nevada in detecting LTBI as well as active TB disease.

QFT-G or TST testing is indicated for the diagnosis of *M. tuberculosis* infections, including both TB active disease and LTBI (neither of these tests differentiate between TB disease and LTBI). Whenever *M. tuberculosis* infection or disease is being diagnosed by any method, the optimal approach includes coordination with the local or regional public health TB control program.

QFT-G may be used in contact investigations, evaluation of recent immigrants who have had BCG vaccination, and TB screening of health-care workers, as well as others undergoing serial evaluation for *M. tuberculosis* infection.

There are some practical limitations related to the QFT-G test that include the need to draw blood and to ensure its receipt in a qualified laboratory in time for testing. The blood specimen must be incubated with the test antigens within 12 hours post collection (while the lymphocytes are still viable). After the blood is incubated with antigens for 16-24 hours, plasma must be collected and either properly stored or promptly tested. Collecting the required 5-ml blood sample from younger children may be difficult requiring a very experienced phlebotomist.

In October 2007, the Food and Drug Administration (FDA) approved the QuantiFERON[®]-TB Gold In-Tube test. This blood assay offers some flexibility in transportation requirements. The QFT-G In-Tube blood samples may be either incubated immediately after the draw (for 16-24 hours) or shipped and then incubated

within 16 hours of the draw (for 16-24 hours). After the In-Tube samples have been processed through the incubation phase, they are stable at room temperature for 3 days allowing for more flexibility in transportation options. The QuantiFERON®-TB Gold In-Tube test is not currently available in Nevada. It is anticipated that the QuantiFERON®-TB Gold In-Tube test will be available by late 2008 or early 2009.

Table 1 Persons at **high risk** for Tuberculosis Infection and Progression to TB Disease

For Tuberculosis Infection	For Progression to Tuberculosis Disease
<ul style="list-style-type: none"> • High-priority contacts such as housemates or co-workers or contacts of persons (patients) who have smear-positive pulmonary or laryngeal tuberculosis (TB) • Infants, children, and adolescents exposed to adults in high-risk categories • Recent immigrants (<5 years) from countries with high incidence of TB. Asian, African, Latin American, and Eastern European countries have TB rates 5–30 times higher than U.S. rates, and an increasing percentage of all TB cases diagnosed in the U.S. is occurring among immigrants from those countries • Recent immigrants from Mexico • Migrant workers • Persons who have recently spent over 3 months in high-incidence countries (such as missionaries) • Native Americans • Persons with high rates of TB transmission: <ul style="list-style-type: none"> - Injection (IV) drug users - Homeless persons • Persons with Human Immunodeficiency Virus (HIV) infection • Persons living or working in institutions with individuals at risk for TB such as: <ul style="list-style-type: none"> - Hospitals, especially staff in nursing, emergency departments, and laboratories - Long-term care facilities - Homeless shelters - Residences for acquired Auto Immunodeficiency Syndrome (AIDS) patients - Correctional facilities 	<ul style="list-style-type: none"> • Persons with HIV infection • Infants and children aged <5 years • Persons infected with <i>Mycobacterium tuberculosis</i> within the previous 2 years • Persons with a history of untreated or inadequately treated TB disease • Persons with Chest x-ray findings consistent with previous TB disease • Persons who use alcohol or illegal drugs (such as injection drugs or crack cocaine) • Persons who have one or more of the following clinical or immunocompromising conditions: <ul style="list-style-type: none"> ○ Silicosis ○ Diabetes mellitus ○ End-Stage Renal Disease (ESRD), chronic renal failure, or patients on hemodialysis ○ Some hematologic disorders (e.g., leukemias and lymphomas) , and other malignancies (e.g., head, neck carcinoma, or lung cancer) ○ Body weight $\geq 10\%$ below ideal body weight ○ Prolonged corticosteroid use, and the use of other immunosuppressive treatments (e.g., prednisone or tumor necrosis factor-alpha [TNF- α] antagonists) ○ Organ transplantation ○ Gastrectomy, chronic malabsorption syndromes, and jejunio-ileal bypass

Source: Adapted from: CDC. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. *MMWR* 2005;54(No. RR-17):4–5; CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):7–9.

Interpreting QuantiFERON® TB Gold Results

Interferon gamma release assay (IGRA) results are interpreted based on this equation $[(\text{tuberculin-nil}) / (\text{mitogen-nil}) \times 100 = \text{percentage tuberculin response}]$ where the proportion of IFN-G released by the WBCs in response to tuberculin is compared with mitogen while accounting for the background IFN-G level in the nil control samples.

Indeterminate result

An IGRA result is considered indeterminate if the (mitogen-nil) IFN-G level ≤ 1.5 IU. An indeterminate QFT-G result must be followed with a thorough risk assessment for each individual patient. No further testing is required for those with low risk for *M. tuberculosis* infection. However, for those with an increased likelihood of *M. tuberculosis* infection, it would be prudent to repeat QFT-G with a newly obtained blood specimen, or administer a TST. It is also important to remember the potential for the TST to cause boosting and the need for two-step testing should be considered.

Laboratories should report the reason that a QFT-G result was indeterminate (e.g., high background levels of IFN-g in the nil sample or inadequate response to mitogen). Inadequate response to mitogen has been associated with immunosuppressive conditions (refer to Table 1).

Positive result

An IGRA result is considered positive if the following criteria were met: 1) (mitogen-nil) and (tuberculin-nil) are both ≥ 1.5 IU IFN-G or 2) percentage avian difference is ≤ 10 and the percent tuberculin response is $\geq 15\%$ (for persons at low risk for LTBI a percent tuberculin response of $\geq 30\%$ ^s). Persons with a positive QFT-G result or a positive TST result, regardless of symptoms and signs, should be evaluated for TB disease before LTBI is diagnosed. At a minimum, a chest X-ray should be examined for abnormalities consistent with TB disease.

Negative result

An IGRA result is considered negative if the (mitogen-nil) was ≥ 1.5 IU IFN-G and the percentage tuberculin response $\leq 15\%$. It is important to remember that regardless of the test results, conducting a thorough individual risk assessment is an essential component of every screening process.

QuantiFERON®-TB test (QFT) vs. Tuberculin Skin Test (TST)

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

Each of the screening tests (TST, and QFT-G) relies on a different immune response and differs in its relative measures of sensitivity and specificity. The TST assesses in vivo delayed-type hypersensitivity (Type IV), whereas QFT-G measures in vitro release of IFN-g. QFT-G is not affected by prior BCG vaccination and is expected to be less influenced by previous infection with Non-Tuberculous Mycobacteria (NTM), while, TST is variably affected by these two factors.

QFT-G does not trigger an anamnestic response (i.e., boosting) because it does not expose persons to an antigen. Injection of PPD for the TST can boost subsequent TST responses, primarily in persons who have been infected with NTM or vaccinated with BCG.

QFT-G results can be available <24 hours after testing without the need for a second visit, whereas a TST requires a second encounter to read the result 48-72 hours after administration of the test. However, as with other blood assays errors in collecting, transporting, analyzing, and interpreting blood samples may occur which could decrease the accuracy of the test. As a laboratory-based assay, QFT-G is not subject to administering errors and reading biases as is the case with the TST.

A positive QFT-G result should prompt the same public health and medical interventions as a positive TST result. There is no justification to follow-up on 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, and at a minimum, a chest X-ray (CXR) should be examined for abnormalities. Additional medical evaluation including proper history, exposure to infectious TB, and a thorough physical examination, is highly recommended, and, due to the increasing comorbidity of TB and HIV, it is imperative that all TB suspected cases be evaluated for HIV. After TB has been excluded, treatment of LTBI should be considered.

Negative QFT-G or TST results should not be used alone to exclude *M. tuberculosis* infection in persons with signs or symptoms or an abnormal CXR that is 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 circumstances decrease the predictive value of a negative QFT-G or TST result. Medical evaluation of such persons should include a history and physical examination, CXR, bacteriologic studies, serology for Human Immunodeficiency Virus (HIV), and, other tests or studies as indicated.

Cautions and Limitations

Similar to any other diagnostic test, the predictive value of QFT-G results depends on the prevalence of *M. 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.

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-dose

corticosteroids, tumor necrosis factor-alpha (TNF- α) antagonists, and drugs used for managing organ transplantation, selected hematologic disorders (e.g., myeloproliferative disorders, leukemias, and lymphomas), specific malignancies (e.g., carcinoma of the head, neck, or lung), diabetes, silicosis, and chronic renal failure. It is important to underline that each of these conditions or treatments is known or suspected to decrease responsiveness to the TST, and may also decrease the production of IFN- γ in the QFT-G assay, therefore, interpret test results in such conditions with caution.

Considerations and Recommendations

The majority of healthy adults who have negative QFT-G results are unlikely to have *M. tuberculosis* infection and do not require further evaluation except in the context of contact investigations. (See below)

A greater rate of positive results has been reported with TST than with QFT-G in persons with and without 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, or both. For the above mentioned reasons, all clinical and laboratory information must be considered when making treatment decisions.

Utilizing QFT-G, may provide additional information to guide treatment decision for LTBI among individuals with history of BCG vaccination, Also, QFT-G might represent a cost-effective alternative to the TST in testing programs which are part of the TB infection control program in institutions such as health care settings, correctional facilities, or homeless shelters. In these settings, false-positive reactions to the TST pose a problem. This problem is compounded in settings with BCG-vaccinated persons born in countries where TB is prevalent.

Contact Investigation

For persons that are recent contacts of an infectious TB case, negative QFT-G results should be confirmed with a repeat test performed 8-10 weeks after the end of exposure, as is recommended for a negative TST result in the same scenario. 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.

Contacts aged <5 years or severely immunocompromised persons who have been exposed to highly contagious TB should be started on prophylaxis treatment for a presumed LTBI during the “window period.” As in all contact investigations, repeat TB screening tests are performed 8-10 weeks after the contact has ended. Treatment options should be reevaluated after negative results (from either TST or QFT-G). All available epidemiologic, historic, clinical, physical, and diagnostic information, including the findings for other contacts in the investigation must be carefully evaluated. A full course of treatment should be considered when the rate of *M. tuberculosis* transmission to other contacts is high or when a false-negative result is suspected because of a medical condition.

TB control programs can use QFT-G for investigating contacts of persons with potentially infectious TB disease. Because QFT-G does not require a second visit to complete, test results will be available from a greater percentage of contacts than would have been 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 that previously were devoted to completion of TST testing can concentrate more on full evaluation and treatment compliance of contacts that have positive QFT-G results.

Laboratory Services

Nevada State Health Laboratory
1660 N. Virginia St., MS 225
Reno, NV 89557-0385
775-688-1335

Samples will be accepted at the NSHL Monday-Thursday 8 AM to 3 PM (no exceptions).

Quest Diagnostics
South West Medical Rancho PSC (on Rancho and Charleston)
Las Vegas, NV
702-733-7866

Cellestis Regional Sales Manager
William C. Schermer
28043 Smyth Drive
Valencia CA 91355
800-519-4627
wschermer@cellestis.com

Specimen Collection and Shipment for QuantiFERON®-TB Gold

7 ml lithium-heparin green top (no exceptions)

- Once drawn the specimen must remain at room temperature and transported STAT - if the sample is refrigerated for any length of time, the test will not be performed because the results would not be valid. The samples must be shipped to the laboratory **without** cold packs.

Unacceptable samples:

- Samples containing less than 5 ml of whole blood
- Transport delays of greater than 12 hours
- Refrigerated specimen
- Unlabeled or mislabeled blood tubes
- Tubes containing anticoagulant other than heparin

Follow-up Activities

If the person has signs or symptoms of TB, or if the TST or the QuantiFERON®-TB Gold Test result is positive, evaluate for TB disease.

Chest X-ray (CXR)

All individuals being considered for LTBI treatment should undergo a CXR to rule out pulmonary TB disease. A posterior-anterior x-ray of the chest is the standard view used for the detection and description of chest abnormalities in adults. In some instances, other views (e.g., lateral, lordotic) or additional studies (e.g., Computed Tomography [CT] scans) may be necessary. Children younger than 5 years of age should receive a posterior-anterior and lateral CXR.

For more information, contact:

Resources

Nevada State Health Division/Bureau of Community Health Susanne Paulson, TB Program Coordinator 775-684-5982	Nevada State Public Health Laboratory 775-688-1335
Southern Nevada Health District TB Prevention and Control Program 702-759-1369	Washoe County District Health Department TB Prevention and Control Program 775-785-4785
Centers for Disease Control and Prevention website: www.cdc.gov/tb	Cellestis Inc. www.cellestis.com

References

Francis J. Curry National TB Center, **Diagnosis of Latent Tuberculosis Infection**

<http://www.nationaltbcenter.edu/resources/07diagnosisltbi062007.doc>

Division of Tuberculosis Elimination, National Center for HIV,

STD, and TB Prevention G. Mazurek MD, J. Jereb MD, P. LoBue MD, M. Iademarco MD, B. Metchock PhD, A. Vernon, MD


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

<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5415a4.htm>

Corresponding address: CDC/National Center for HIV, STD, and TB

Prevention/Division of Tuberculosis Elimination; 1600 Clifton Road, NE, MS E-10, Atlanta, GA 30333. Telephone: 404-639-8120; Fax: 404-639-

8604; E-mail: mai9@cdc.gov. *Mycobacterium tuberculosis* I. Organism Information, HAEducational Info\iMycobacterium -iituberculosis-i.mht

Signed: 
Tracey Greer, MD, Acting State Health Officer
Nevada State Health Division

Date: 2/22/08

Signed: 
Richard Whitley, Administrator
Nevada State Health Division

Date: 2/19/08