

Section X.
Testing for Latent
Tuberculosis Infection

Tuberculosis

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Note: The term “tuberculin skin testing” (TST) is no longer used, as it does not reflect the availability of blood-based tests for TB infection. A more general term, test for TB infection (TTBI), is used except in specific instances that reference the TST.

Despite the dramatic decline in the number of reported cases of TB in New York City (NYC), many New Yorkers remain at high risk for developing active TB disease once they have been infected with *M. tuberculosis* (*M. tb*) (i.e., have latent TB infection [LTBI]). Groups at especially high risk are those who have had contact with persons who have active TB, persons who are HIV infected, individuals with certain predisposing medical conditions and recent immigrants from countries with high rates of TB.

Candidates for Testing for Latent Tuberculosis Infection

TB screening should be focused on populations that are most at risk for recent infection, or, if already infected, are at increased risk for developing TB due to medical conditions. In general, populations at low risk for LTBI should not be tested since false positive reactions are common.

Currently, the tuberculin skin test (TST) performed by the Mantoux method using purified protein derivative (PPD) is the most commonly used test to diagnose LTBI. A TST is not necessary for individuals with a reliable history of, or a previously documented positive TST result.

Blood-based tests are increasingly becoming an alternative to the TST for identifying TB infection. The same target populations as listed above should be tested. See p. 183 for more detail.

Priorities for Testing

The following individuals should be screened for LTBI (see p.174 and 175, Tables XI-1 and XI-2):

- Contacts of persons who have pulmonary or laryngeal TB. (see p. 160, Table IX-2).
- Persons who have HIV infection.
- Persons who have immigrated to the United States within the past 5 years and who come from an area where TB rates are high (see p. 175, Table X-2).
- Injection drug users, whether or not they are HIV positive.
- Persons who have medical risk factors for TB disease, such as:
 - Diabetes mellitus
 - Silicosis
 - Cancers of the head, neck or lung
 - Hematologic and reticuloendothelial malignancies (e.g., leukemia and Hodgkin’s disease)
 - End-stage renal disease
 - Intestinal bypass or gastrectomy
 - Chronic malabsorption syndromes
 - Low body weight (10% or more below ideal)
 - Transplant recipient or currently on transplant lists
 - Receiving prolonged corticosteroid therapy (e.g., receiving the equivalent of more than 15 mg of prednisone for more than 1 month)
 - Receiving other immunosuppressive agents (e.g., chemotherapy, TNF-blockers)
- Persons with radiographic evidence of old, healed TB lesions.

- Employees or residents of congregate settings where TB exposure may be likely, such as:
 - Hospitals
 - Correctional facilities
 - Homeless shelters
 - Nursing homes
 - Drug treatment centers
- Children/adolescents exposed to adults in high-risk categories.
- Persons with a prolonged stay (more than 1 month) in areas with high TB rates (see p. 175, Table X-2).

In addition, the TTBI is valuable as a diagnostic tool in patients who have symptoms and/or clinical evidence, radiographic evidence or acid-fast bacilli smears suggestive of TB disease. In these patients, a positive TTBI reaction indicates TB infection and supports a diagnosis of active TB disease. A negative reaction usually, but not always, excludes TB as a cause. However, immunosuppression and other medical conditions, including severe TB disease itself, can cause a false-negative reaction to the TTBI.

TTBIs are not contraindicated for persons who have been vaccinated with Bacille Calmette-Guérin (BCG). A history of BCG vaccination should not be considered, either when deciding

Table X-1

Individuals Who Should be Tested for Latent Tuberculosis Infection

Individuals Who May Have Been Recently Infected	Individuals with Clinical Conditions Associated with Progression from LTBI to Active TB
<ul style="list-style-type: none"> • Persons who have had close contact with individuals with active TB. Retesting may be necessary 8 weeks after original test. • Persons who have immigrated to the United States within the past 5 years from areas with high TB rates* should be tested the first time they enter the health care system in the States. • Persons who have made prolonged stays (longer than 1 month) in areas with high TB rates.* • Persons who live or work in clinical or institutional settings where TB exposure may be likely (e.g., hospitals, prisons, homeless shelters, nursing homes, mycobacteriology labs); most CDC and local guidelines recommend testing annually. • Children/adolescents exposed to adults in high-risk categories. 	<ul style="list-style-type: none"> • Persons with HIV infection should be tested as soon as possible after diagnosis of HIV infection, and at least once a year afterward. • Injection drug users • Persons with evidence of old, healed TB lesions on chest X-ray • Underweight persons ($\geq 10\%$ under ideal body weight) • Persons with any of the following medical conditions or risk factors for TB disease: <ul style="list-style-type: none"> ◦ Diabetes mellitus ◦ Silicosis ◦ Cancer of the head, neck or lung ◦ Hematologic and reticuloendothelial malignancies (e.g., leukemia and Hodgkin's disease) ◦ End-stage renal disease ◦ Gastrectomy or jejunioileal bypass ◦ Chronic malabsorption syndromes ◦ Organ transplants or on transplant lists ◦ Receiving prolonged corticosteroid therapy or other immunosuppressive therapy (e.g., the equivalent of $\geq 15\text{mg}$ of prednisone for ≥ 1 month, TNF-α blockers or chemotherapy)

*See p. 175, Table X-2

Table X-2
Countries and Areas with an Estimated or Reported High Incidence of Tuberculosis, 2005¹

<p>Africa All countries except Seychelles</p> <p>Eastern Mediterranean Afghanistan Bahrain Djibouti Egypt Iraq Morocco Pakistan Qatar Somalia Sudan Yemen</p> <p>Europe Armenia Azerbaijan Belarus Bosnia and Herzegovina Estonia Georgia Kazakhstan Kyrgyzstan Latvia Lithuania Moldova (Republic of) Romania Russian Federation Tajikistan Turkmenistan Ukraine Uzbekistan</p>	<p>North, Central and South America Belize Bolivia Brazil Columbia Dominican Republic Ecuador El Salvador Guatemala Guyana Haiti Honduras Mexico² Nicaragua Panama Paraguay Peru Suriname</p> <p>Southeast Asia Bangladesh Bhutan India Indonesia North Korea (DPRK) Maldives Myanmar Nepal Sri Lanka Thailand Timor-Leste</p>	<p>Western Pacific Brunei Darussalam Cambodia China China (Hong Kong SAR) Guam Kiribati Lao PDR Macao (China) Malaysia Marshall Islands Micronesia Mongolia New Caledonia Northern Mariana Islands Palau Papua New Guinea Philippines Solomon Islands South Korea (ROK) Vanuatu Viet Nam</p>
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¹ Source: World Health Organization *Global Tuberculosis Control—Surveillance, Planning, Financing: WHO Report 2007* Geneva, World Health Organization (WHO/HTM/TB/2007.376) (www.who.int/tb/publications/global_report/2007/pdf/full_report.pdf). “High-incidence areas” are defined by the New York City Tuberculosis Control Program as areas with reported or estimated ≥ 20 new smear-positive cases per 100,000 persons.

² Has an estimated incidence of < 20 smear-positive cases per 100,000 persons; however, the Mexican community in NYC has a high burden of disease.

whether to test and/or when determining whether the test result is positive in high-risk individuals.

Although BCG vaccination can cause a false-positive cross-reaction to the TST (especially within the first 12 months after vaccination), sensitivity to tuberculin is highly variable and tends to decrease over time. There is no way to distinguish between a positive reaction due to

BCG-induced sensitivity and a positive reaction due to true LTBI. Therefore, a positive reaction to the TST in BCG-vaccinated persons should be interpreted as indicating infection with *M. tb* when the person tested is at increased risk of recent infection or when the person has a medical condition that increases the risk of progression to active TB disease.

Since the QuantiFERON®-TB Gold (QFT-G) blood-based test does not cross-react with BCG, this test is particularly useful for testing individuals with a history of BCG vaccination. (See p. 183.)

Testing for Pregnant Women

The TST is safe and reliable for pregnant women. No teratogenic effects have been documented. Routine TST screening for pregnant women is not indicated since pregnancy does not increase the risk for LTBI. However, pregnant women at high risk for LTBI or active TB disease should be tested. Specifically, pregnant women should be screened for LTBI if they have any of the high-risk conditions noted on p. 174, Table X-1.

Guidelines for Testing Specific High-Risk Groups

Close contacts of persons with active TB disease should receive a baseline TTBI immediately after exposure. Retesting is sometimes necessary, however, to determine whether or not infection resulted from the exposure. Since it can take up to 8 weeks after *M. tb* infection for the immune system to respond to a TTBI, tests may be falsely negative. Close contacts tested during the window period who had a negative result on the initial TTBI, should be retested 8 weeks from the contact's most recent exposure to active TB. (See p. 161.)

All individuals who are HIV-positive should receive a TTBI as soon as HIV infection is diagnosed. The test should be repeated at least every 12 months thereafter.

Recent immigrants (i.e., those who have been in the United States for less than 5 years), who have come from countries with high rates of TB should be tested for TB infection when they enter the medical care system in the States. They should also be tested any time after they return to their native country or after a prolonged (more than 1 month) stay abroad (see p. 175, Table X-2).

Individuals who have had a prolonged stay (more than 1 month) abroad in areas where TB rates are high should be evaluated immediately after return or at their next medical examination. (See p. 175, Table X-2.)

Individuals who live or work in institutional settings (e.g., prisons, hospitals, nursing homes, shelters) are under testing recommendations that vary according to risk of transmission based on local and Centers for Disease Control and Prevention guidelines (CDC). Most guidelines recommend annual testing. Individuals who will undergo serial testing should have either a 2-step TST or a single blood-based TTBI as part of their baseline evaluation.

Individuals with immunosuppressive conditions or who are being treated with immunosuppressive agents should be evaluated and treated for LTBI, either at the time that the condition is diagnosed or before starting treatment with immunosuppressive therapies such as prolonged corticosteroids and TNF-alpha antagonists (infliximab, etanercept and adalimumab). Patients awaiting transplant should be evaluated for LTBI and a TST result of greater than 5 mm should be considered indicative of TB infection in all such individuals. TST results in immunosuppressed individuals may be falsely negative, either due to the drug therapy or to the underlying medical condition causing anergy. The individual may still be infected with *M. tb* and some experts recommend 2-step testing as this may increase the yield of positive TSTs (blood-based tests have not yet been studied adequately in such cases).

Testing and treatment recommendations for children and adolescents were published in October 2004 by the Pediatric Tuberculosis Collaborative Group (for more information, visit: <http://pediatrics.aappublications.org/cgi/content/extract/114/4/S2/v>).

Targeted testing in children and adolescents should focus on pediatric populations at high risk for LTBI, and those at risk of progression to TB. Groups of children and adolescents who should be tested are high risk cases such as those who have had contact with an infected person, recent immigrants from high-TB-incidence countries and those at high risk of progression due to underlying conditions (See p. 174 and p. 175, Tables X-1 and X-2.) A risk-assessment questionnaire should be used to screen children and adolescents for risk factors for TB disease and LTBI. (See p. 177, Table X-3 for a sample questionnaire.)

Children should be tested only if one or more risk factor is present. Administrative or mandated tests for TB infection for entry to day care, school,

Table X-3

Sample Risk Assessment Questionnaire for Children*

Ask the following questions:

1. Was your child born outside the United States?

If yes, and the child was born in Africa, Asia, Latin America or Eastern Europe, a test for TB infection should be administered.

2. Has your child traveled outside the United States?

If yes, and the child stayed with friends or family members in Africa, Asia, Latin America or Eastern Europe for > 1 month cumulatively, a test for TB infection should be administered.

3. Has your child been exposed to anyone with TB disease?

If yes, and it has been confirmed that the child has been exposed to someone with suspected or known TB disease, a test for TB infection should be administered, and the Health Department should be notified.

4. Does your child have close contact with a person who had a positive test for TB infection?

If yes, proceed as in question 3 (above).

Risk assessment questionnaires can include the following questions, based on local epidemiology and priorities:

1. Does your child spend time with anyone who has been in jail (or prison), who is in a shelter, who uses illegal drugs or who has HIV?

2. Has your child consumed dairy products obtained from abroad such as raw milk or fresh cheese?

3. Does your child have a household member or caregiver who was born outside the United States?

4. Does your child have a household member or caregiver who has traveled outside the United States?

* Adapted from The Pediatric Tuberculosis Collaborative Group: Targeted tuberculin skin testing and treatment of latent tuberculosis infection in children and adolescents. *Pediatrics*, 2004;114(4):1175-1201

summer camp or college are discouraged in the absence of risk factors. However, in NYC, many children and adolescents will still need to be

tested for LTBI because of requirements based on the NYC Health Code and NY State regulations.

Administering the Tuberculin Skin Test

The TST should be administered by the Mantoux technique, in which PPD tuberculin is injected intradermally with a needle and syringe. Multiple-puncture tests (e.g., the Tine test) should not be used, even in infants and children, as this type of test is much less accurate than a properly administered Mantoux test.

TST by the Mantoux technique should be administered in the following manner:

Preparation

- Wash hands and put on gloves. If no water is available, use an appropriate skin-cleaning product (e.g., an antibacterial towelette).
- Check PPD vial's expiration/opening date.
- Place patient's arm on a flat surface, exposing the volar (inside) surface of the forearm.
- Locate site for the injection (2-4 inches below elbow, where no scars, bumps or veins are located).
- Clean the injection site with an alcohol swab.
- Wipe the top of the PPD vial with a second alcohol swab and place the vial on a flat surface.
- Use a short, disposable 26-gauge syringe needle.
- Prepare the syringe by inserting it into the vial. Inject 0.1 ml of air into the airspace in the vial. Do not inject air into the PPD solution.
- Invert the vial, keeping the needle tip below fluid level.
- Pull back on the plunger of the syringe and draw slightly more than 0.1 ml of PPD solution.
- Remove the syringe from the vial and tap the syringe lightly to dispel air bubbles. Hold the syringe point up and expel air and/or excess fluid, leaving exactly 0.1 ml of PPD solution in the syringe.
- Return the PPD vial to the refrigerator when not in use and place on a cooling pad when in use.

Injection

- Stretch the skin of the injection site with the thumb of the non-dominant hand (e.g., left hand for right-handed persons).
- Hold the syringe between the thumb and forefinger of the dominant hand, (e.g., right hand for right-handed persons) with the bevel of the needle pointing upward. Insert the needle intradermally (just under the top layer of skin) at a 5°-15° angle.
- Inject the PPD solution slowly. A firm resistance should be felt as the tuberculin solution enters the skin. Ensure that the entire needle bevel lies just under the skin.
- Release the stretched skin and remove the needle from the injection site (**DO NOT RECAP**). Discard the syringe immediately in a sharps container.
- Ensure that a discrete skin elevation (wheal), 6 to 10 mm in diameter, has been formed (measure wheal using a TST ruler). If the injection angle was too deep, no wheal will appear. If the angle was too shallow, fluid may leak. Be sure to check for leakage at the insertion site.
- Repeat injection 2 inches (5 cm) from site, or on opposite arm, if wheal is smaller than 6 mm or if less than 0.1 ml was injected (both tests need to be documented; [see below]). If, after a second injection, the wheal is still less than 6 mm or not enough fluid is injected, chest center staff should speak with a supervisor.

Post-Injection

- Educate the patient on the possible reactions to the TST, (e.g., mild itching, swelling, irritation).
- Instruct patient not to rub, scratch or put an adhesive bandage or lotion on the test site. The area may be washed and patted dry.
- Document the test in the patient's chart (including second test if done).
- Schedule reading date and explain the importance of the patient returning for reading in 48 to 72 hours.

Note: Vaccination with live attenuated viral vaccines such as measles, mumps and/or rubella (MMR) can cause a false-negative reaction to the TST. The TST can be administered on the same day as the live vaccine, because immunosuppression does not appear until after the first 48 hours post-vaccination. If a skin test is needed, and was not given in conjunction with the vaccination, wait 4-6 weeks before administering it.

Reading the Tuberculin Skin Test Reaction

The test result should be read only by a trained health care worker. Patients should never be allowed to read their own reaction. The following procedure should be used to read the reaction:

- Read the result 48 to 72 hours after administering the test.
- Inspect the injection site for raised areas.
- Palpate the arm for a hard, raised area known as an induration. Feel the edges of the induration with the index finger.
- Mark the 2 edges of the induration with a dot, using a black, watermark pen, if available.
- Measure the induration (not redness) at its widest point transversely, from 1 marked edge to the other, using a flexible TST ruler. If the reading is between 2 points, the lower value should be used. Swollen areas, if they feel hard, (but not red areas) should be palpated and included in the measurement.
- Record the size in millimeters and not simply as “positive” or “negative.” If there is no induration, record the result as “00 mm.”
- Interpret the reaction as positive or negative based on both the size of the induration and the individual’s risk factors (see p. 180, Table X-4).
- Explain the meaning of a positive or negative reaction to the individual and refer for follow-up evaluation, if needed. Provide appropriate literature.

If the patient fails to return for the scheduled reading but returns up to a week after the test, examine the test site and measure any induration present; if it is large enough to be classified as positive, record the result. No further testing is needed. If there is no reaction, or the induration is too small to be classified as positive, repeat the test. A repeat test can be given immediately.

Interpretation of the Tuberculin Skin Test Reaction

Whether a reaction to the TST is classified as positive depends on both the size of the induration and the person’s medical and epidemiologic risk factors for TB. (See p. 180, Table X-4.)

Patients who have a positive TST reaction should undergo clinical evaluation, including a chest X-ray (CXR) to rule out TB. (See p. 189.) If the initial CXR is normal, repeated ones are not indicated unless the individual develops signs or symptoms of TB. TST-positive individuals should be started on treatment for LTBI according to the guidelines in Section XI. (See also p. 181, Table X-5, for false-negative and false-positive reactions.)

An individual with either TB symptoms or an abnormal CXR should be appropriately evaluated using sputa and other tests as indicated. Active pulmonary or extra-pulmonary TB should be ruled out before treatment for LTBI is started.

Documentation of the results should be provided to the individual as repeat testing in the future is not necessary once a TST or blood-based test is determined to be positive.

Interpretation of the Tuberculin Skin Test in Bacille Calmette-Guérin-Vaccinated Individuals

BCG vaccine is used in many countries to protect children against some forms of TB disease. However, its efficacy in preventing TB in adults is variable and controversial. TST-positive persons from countries where TB is common are likely to be infected with TB and are at risk of developing active TB disease, even if they have been vaccinated with BCG.

Table X-4

Determination of a Positive Tuberculin Skin Test

The reaction to a TST is classified as positive based on the individual’s risk factor(s) and the following measurements of induration:

Test Result	Considered Positive In:
≥ 5 mm	<ul style="list-style-type: none"> • Persons with HIV infection • Recent contacts of persons with active tuberculosis (TB) • Persons with evidence of old, healed TB lesions on chest X-rays • Persons with organ transplants and other immunosuppressed persons, such as patients receiving prolonged corticosteroid therapy (the equivalent of more than 15 mg/d of prednisone for 1 month or more), TNF-α blockers and chemotherapy
≥ 10 mm	<ul style="list-style-type: none"> • Persons who have immigrated within the past 5 years from areas with high TB rates (see Table X-2). • Injection drug users • Persons who live or work in institutional settings where exposure to TB may be likely (e.g., hospitals, prisons, homeless shelters, single room occupancy units, nursing homes) • Mycobacteriology laboratory personnel • Persons with clinical conditions associated with increased risk of progression to active TB, including: <ul style="list-style-type: none"> • Silicosis • Chronic renal failure • Diabetes mellitus • Gastrectomy/jejunioileal bypass • Certain hematologic disorders, such as leukemias or lymphomas • Specific malignancies, such as carcinoma of the head, neck or lung • Body weight equal to or greater than 10% below ideal or BMI lower than 18.5 • Children less than 5 years of age or children/adolescents exposed to adults in high-risk categories • Persons with a prolonged stay (more than 1 month) in areas with high TB rates (see Table X-2)
≥ 15 mm	<ul style="list-style-type: none"> • Persons at low risk for TB disease, for whom testing is not generally indicated

Table X-5

Factors Associated with False-Negative or False-Positive Tuberculin Skin Test Reactions*

Factors	False-negative Reactions	False-positive Reactions
Infections	<ul style="list-style-type: none"> • Viral illnesses (HIV, measles, varicella) • Bacterial illnesses (typhoid fever, pertussis, brucellosis, typhus, leprosy) • Early TB infection (< 12 wks.) • Severe TB disease (meningitis, miliary) • Fungal disease 	Exposure to nontuberculous mycobacteria (e.g., <i>M. marinum</i> , <i>M. kansasii</i>)
Live virus vaccines	<ul style="list-style-type: none"> • Measles • Polio • Varicella • Smallpox 	Bacille Calmette-Guérin vaccine
Concomitant medical conditions	<ul style="list-style-type: none"> • Metabolic abnormalities • Chronic renal failure • Primary immunodeficiencies • Malignancies (e.g., Hodgkin's disease, lymphoma, leukemia) • Sarcoidosis • Poor nutrition • Newborns and children < 2 years of age • Low protein states 	Transfusion with whole blood from donors with known positive tuberculin skin test
Drugs and technical factors	<ul style="list-style-type: none"> • Corticosteroids or other immunosuppressive medications • Chemotherapy • Material—poor quality, inadequate dose (1 TU), improper storage (exposure to heat/light), expired • Administration—not injected intradermally; too long in syringe • Reading—inexperienced or biased reader; recording error, read too early/late 	Inexperienced or biased reader
Interpretative	Decreasing mm induration	Increasing mm induration

* Adapted from: The Pediatric Tuberculosis Collaborative Group: Targeted Tuberculin Skin Testing and Treatment of Latent Tuberculosis Infection in Children and Adolescents *Pediatrics*, 2004;114(4):1175-1201

BCG vaccination complicates the interpretation of TST results because it can produce a false-positive reaction to the TST, especially if BCG was given after age 1 year. There is no way to distinguish between a positive reaction due to BCG vaccination and a positive reaction due to LTBI. In BCG-vaccinated persons, however, sensitivity to tuberculin is highly variable, but the effect of BCG wanes with time. (BCG given only at birth does not appear to be a significant cause of false-positive TST reactions, especially after the age of 5 years.)

In general, a history of vaccination with BCG should not influence the need for tuberculin skin testing, the interpretation of the TST reaction or clinical decisions regarding the management of individuals who are TST positive. (Exceptions include cases where BCG was given within the last 12 months and where the patient is from a low-incidence country. [See p. 175, Table X-2.]

In BCG-vaccinated persons who did not receive the vaccine within the last 12 months, the TST reaction should be classified according to the guidelines described on p. 180, Table X-4. In particular:

- Patients who are close contacts of an individual with pulmonary or laryngeal TB disease are considered TST positive if they have a reaction greater than or equal to 5 mm, regardless of their BCG status. TST-positive contacts are candidates for treatment for LTBI (see p. 192).
- Patients who are from a high-incidence country (see p. 175, Table X-2) and who have no other risk factors are considered TST positive if they have a reaction of greater than or equal to 10 mm, regardless of their BCG status. (This is true even if the BCG was given within the last 12 months.)

Patients who are not from a high-incidence country (see p. 175, Table X-2) and who have no other risk factors are considered TST-positive if they have a reaction of greater than or equal to 15 mm, regardless of their BCG status.

Patients who were given BCG within the last 12 months and who are from countries where there is a low prevalence of TB should not be given a TST. If such a person is at risk for TB disease (e.g., a close contact), he/she should undergo a CXR and clinical examination to rule out active TB disease.

There may be patients who were given BCG within the last 12 months and who are from a low-prevalence country, but present at the center with a recent, documented TST reaction. If the induration is less than 15 mm, it should be considered negative if, after a clinical evaluation, it is determined the person has no medical or epidemiological risk factors for TB as listed in Table X-1 (see p. 174). If the TST is greater than or equal to 15 mm, the person should receive a CXR and medical evaluation. If both are normal, treatment is not indicated unless the person is either a recent contact of an active TB case or is infected with HIV.

Role of Anergy Testing

Anergy is the inability to mount a delayed-type, cutaneous, cellular immune response. Patients who are anergic may have a negative TST reaction, even if they have LTBI.

In the United States, anergy testing is no longer recommended as part of routine screening for TB infection among individuals infected with HIV. It also has no role in the evaluation of contacts. In general, TST-negative, HIV-infected close contacts of a person with pulmonary or laryngeal TB should receive treatment for LTBI, whether or not they are TST-negative. HIV-infected individuals who are not known to be contacts should be evaluated for treatment for LTBI according to their risk for TB exposure and infection.

Two-Step Tuberculin Skin Testing

Background

In some TB-infected individuals, the ability to react to a TST diminishes over time. Thus, infected individuals who are skin tested many years after infection may have a negative TST reaction. However, if they are retested within the next year, they may have a positive reaction. This phenomenon, called the “booster phenomenon,” occurs because the first TST “boosted” the immune response that had diminished over the years. Boosting is most common in persons age 55 and older and can also occur in BCG-vaccinated persons.

The booster phenomenon can complicate the interpretation of TST results in settings where testing is done repeatedly since a boosted reaction to a second TST may be mistaken for a recent conversion. Consequently, an infection acquired years ago may be interpreted as recent infection.

To eliminate boosted reactions as a cause of confusion, individuals who will be tuberculin skin tested repeatedly should undergo 2-step testing the first time that they are tested. With this type of testing, an initial TST is done. If the result is negative, a second TST is given 1 to 3 weeks later. The result of the second test is then used as the baseline. If it is positive, the patient is considered infected. If it is negative, the patient is considered uninfected.

Candidates and Procedure for 2-Step Testing

Two-step testing should be offered to individuals who cannot document a history of a negative TST reaction within the past year and who will be tested repeatedly. This would include health care workers and employees or residents of congregate settings. The procedure is as follows:

- If the reaction to the initial TST is negative, repeat the TST in 1 to 3 weeks using the same dose and strength of tuberculin. Inject the tuberculin on the other forearm or at least 5 cm away from the original test site.
- If the reaction to the second TST is negative (see p. 179), classify the individual as uninfected (TB Class 0 or TB Class I).
- If the reaction to the second TST is positive (see p. 179), obtain a CXR; if it is abnormal, classify the individual as Class V and evaluate for TB disease (see p. 26) or for another pulmonary disorder. If the CXR is normal, classify the individual as Class II and evaluate for treatment for LTBI (see p. 189).

Individuals who can provide documentation of a negative reaction to a TST given within the preceding year should be given an initial TST and should be classified on the basis of that result. A second TST is not necessary because the earlier test is, in effect, the first step of a 2-step test.

Blood-Based Tests for Tuberculosis Infection: The QuantiFERON®-Gold Test

QuantiFERON®-TB Gold (QFT-G) is a new FDA-approved blood test for detection of TB infection. As a modern alternative to the 100-year-old tuberculin skin test (TST), QFT-G may offer clinicians a simpler, more accurate, reliable and convenient TB diagnostic tool. QFT-G is highly specific, and a positive test result is strongly predictive of true infection with *M. tb*. The test is approved as an aid for diagnosing both active TB disease and LTBI; however, it cannot differentiate between them.

The QFT-G test is an indirect test for *M. tb* infection, based on measurement of a cell-mediated immune response in infected individuals. The

Like the TST, the QFT is a useful, but imperfect, diagnostic aide. It should not replace clinical judgment.

T lymphocytes of these individuals are sensitized to *M. tb*. When whole blood is incubated with *M. tb*-specific antigens used in the test, the T lymphocytes secrete interferon-gamma (IFN- γ), which is measured via a sensitive enzyme-linked immunosorbent assay (ELISA).

Advantages of the QFT-G Test

QFT-G specifically detects responses to 2 proteins, Early Secretory Antigenic Target-6 (ESAT-6), and Culture Filtrate Protein-10 (CFP-10), which are made by *M. tb*. These proteins are absent from all BCG vaccine preparations and from all environmental, i.e., nontuberculous mycobacteria (NTM), with the exception of *M.kansasii*, *M.marinum* and *M.szulgai*. As a result, the QFT-G test is completely unaffected both by the tested individual's BCG vaccination status and by the individual's sensitization to the majority of NTMs, thus providing a more accurate test of TB infection.

QFT-G	vs.	TST
<ul style="list-style-type: none"> • <i>In vitro</i>, controlled laboratory test with minimal inter-reader variability • <i>M. tb</i>-specific antigens used • No boosting; 2-step testing not needed • One patient visit possible • Unaffected by BCG or most environmental mycobacteria • Simple positive/negative result • Ability to predict the risk of LTBI progression to TB disease has not yet been determined in high-risk patients 		<ul style="list-style-type: none"> • <i>In vivo</i>, subject to errors during implantation and interpretation • Less specific PPD used • Boosting, with repeated testing • Two patient visits minimum • False-positive tests can occur after BCG and environmental mycobacteria exposure • Interpretation based on patient's risk of TB or development of disease

Abbreviations: LTBI = latent tuberculosis infection, PPD = purified protein derivative, QFT-G = QuantiFERON®-TB Gold test, TB = tuberculosis, TST = tuberculin skin test

Limitations of the QFT-G Test

At present, the major drawback to this test is that blood samples must be processed within 12 hours of the blood draw. In addition, the test has not been studied in many groups, including children, those with impaired immune function and with those with contacts to active TB cases. The ability of QFT-G to predict risk of LTBI progression to TB disease has not yet been determined. The risk of TB may be different from the risk in individuals with a positive TST.

Eligibility and Interpretation of the Results of the QFT-G Test

The QFT-G can be used to assess any patient for LTBI who is a candidate for a TST. It can also be used to aid in the diagnosis of active TB. However, it should **not** be used for patients

currently receiving anti-TB drugs for active TB, or for patients receiving treatment for LTBI. The test is reported as positive, negative and indeterminate, and the actual concentration level of IFN- γ is also reported.

Negative: A test is considered negative if the IFN- γ concentration is less than 0.35 IU/mL. A negative QFT-G result should be interpreted as a negative TST result: no further TB evaluation is needed unless indicated by clinical judgment.

Positive: A test is considered positive if the IFN- γ concentration is greater than 0.35 IU/mL. A positive QFT-G result should be interpreted as a positive TST result: medical evaluation and CXRs are still needed to exclude TB disease and to confirm LTBI.

Indeterminate: A test is considered indeterminate if the QFT-G results cannot be interpreted due to a response by the control groups. Repeat QFT-G or administer TST as diagnostic aide for TB or LTBI. QFT-G results may be indeterminate due to laboratory error or patient anergy. If 2 different specimens from a patient yield indeterminate results, do not repeat QFT-G for that person.

Costs and Benefits of the QFT-G Test

QFT-G can yield cost savings in terms of medical staff time—both by elimination of a second patient visit for test interpretation and by the elimination of common false-positive results, which typically involve both unnecessary follow-up testing and treatment for LTBI.

QFT-G can eliminate the need for the repeat 2-step testing that is required when TST is used for screening health care workers. That, in turn, may lower the administrative cost of maintaining testing compliance in health care facilities, which may offset the slightly higher cost of QFT-G, compared to TST.

Future Blood-Based Assays

Newer versions of the QuantiFERON® tests, which may address some of the limitations of the QFT-G, may be available in the near future. In addition, other blood-based tests are in development or under FDA review. TB diagnosis is a rapidly evolving field, and these guidelines may change as more data becomes available.

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