Chapter 3
Testing for Tuberculosis Infection and Disease

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Chapter Objectives

After working through this chapter, you should be able to

- Describe why high-risk groups should be tested for *M. tuberculosis* infection;
- Identify appropriate testing methods for *M. tuberculosis* infection;
- Identify special considerations when using tuberculin skin tests (TSTs); and
- Discuss general recommendations for the use of interferon-gamma release assays (IGRAs).

Introduction

Targeted testing is a TB control strategy that is used to identify, evaluate, and treat persons who are at high risk for latent tuberculosis infection (LTBI) or at high risk for developing TB disease once infected with *M. tuberculosis*. Identifying persons with LTBI is important to the goal of TB control and elimination because treatment of LTBI can prevent infected persons from developing TB disease and stop the further spread of TB. All testing activities should be accompanied by a plan for appropriate follow-up medical evaluation and treatment. Necessary medical evaluation and treatment resources need to be identified before testing activities begin.

Targeted testing is a TB control strategy that is used to identify, evaluate, and treat persons who are at high risk for latent tuberculosis infection (LTBI) or at high risk for developing TB disease once infected with *M. tuberculosis*.

Study Question

3.1 Why is targeted testing conducted? (circle the one best answer)

G. To identify, evaluate, and treat persons who are at high risk for latent tuberculosis infection.

H. To identify, evaluate, and treat persons who are at high risk for developing TB disease once infected with *M. tuberculosis*.

I. To identify the strain of TB bacteria that a patient may have so the correct treatment regimen can be provided.

J. A, B, and C are all correct.

K. Only A and B are correct.

Identifying High-Risk Groups for *M. tuberculosis* Testing

As part of their routine evaluation, health-care providers should identify and test persons who are at high risk for acquiring TB infection or at high risk of progressing to TB disease if infected. In some select settings, active case finding may be more appropriate than testing for *M. tuberculosis* infection. Flexibility is needed in defining high-risk groups for testing. The changing epidemiology of TB indicates that the risk for TB disease or LTBI among groups currently considered high risk may decrease over time, and groups currently **not** identified as being at risk may subsequently be considered high risk (see Chapter 1, Overview of Tuberculosis Epidemiology in the United States).

Evaluation of Persons with Positive TB Test Results

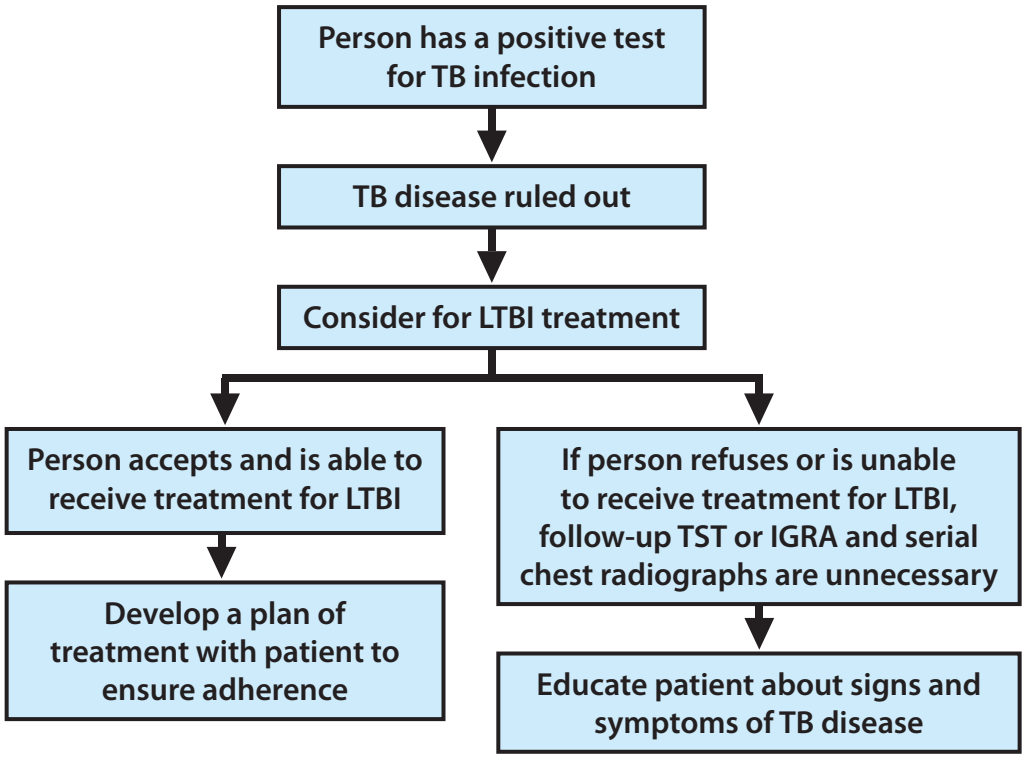
Health-care or other (e.g., correctional) facilities should consult with their local health department before starting a testing program, to ensure resources are available for the evaluation and treatment of

persons whose test results for LTBI or TB disease are positive. Persons with a positive test result for TB infection should be evaluated for TB disease and, if disease is ruled out, considered for treatment of LTBI (see Chapter 5, Treatment of Latent Tuberculosis Infection).

Health-care or other (e.g., correctional) facilities should consult with their local health department before starting a testing program to ensure there are resources available for the evaluation and treatment of persons whose test results for LTBI or TB disease are positive.

Follow-up TSTs or IGRAs and serial chest radiographs are unnecessary for persons who have a positive test result for TB infection and who have had TB disease ruled out or for persons who refuse or are unable to receive treatment for LTBI. These persons should be educated about the signs and symptoms of TB disease (Figure 3.1).

Figure 3.1
Evaluation of Persons with Positive TB Test Results



Study Question

3.2 Which of the following statements about evaluating persons with a positive TB test is true? (circle the one best answer)

A. Persons with a positive test for TB infection should be evaluated for TB disease and, if disease is ruled out, considered for treatment of LTBI.

B. If a person refuses or is unable to receive treatment for LTBI, follow-up TST or IGRA tests and serial chest radiographs are unnecessary.

C. All persons who have a positive test result for TB infection should receive LTBI treatment.

D. A, B, and C are all correct.

E. Only A and B are correct.

Testing Methods for TB Infection

Selection of the most suitable test(s) for detection of *M. tuberculosis* infection should be based on the reasons and the context for testing, test availability, and overall cost effectiveness of testing. Currently, there are two methods available for the detection of *M. tuberculosis* infection in the United States. The tests are:

- Mantoux tuberculin skin test (TST)
- Interferon-gamma release assays (IGRAs)
  - » QuantiFERON-TB Gold In-Tube test (QFT-GIT)
  - » T-SPOT.*TB* test

Currently, there are two methods available for the detection of *M. tuberculosis* infection in the United States. The tests are:
• Mantoux tuberculin skin test (TST)
• Interferon-gamma release assays (IGRAs)

These tests help clinicians differentiate infected from uninfected people. However, a negative reaction to any of the tests does **not** exclude the diagnosis of LTBI or TB disease. The decisions about medical or public health management should include epidemiological, historical, and other clinical information when using IGRA or TST results. Decisions should **not** be based on TST or IGRA results alone. Additional tests are needed to diagnose TB disease. A comparison of the TST and the IGRA is included in Table 3.1.

A negative reaction to a TST or IGRA does not exclude the diagnosis of LTBI or TB disease.

The decisions about medical or public health management should include epidemiological, historical, and other clinical information when using IGRA or TST results. Decisions should not be based on TST or IGRA results alone.

Table 3.1
TST vs IGRAs

TST	IGRA
Tuberculin is injected under the skin and produces a delayed-type hypersensitivity reaction if the person has been infected with *M. tuberculosis*	Blood is drawn for testing; test measures the immune response to the TB bacteria in whole blood
Requires two or more patient visits to conduct the test	Requires one patient visit to conduct the test
Results are available 48 to 72 hours later	Results can be available in 24 hours (depending on the batching of specimens by the laboratory and transport)
Can cause booster phenomenon	Does **not** cause booster phenomenon
Reading by HCW may be subjective	Laboratory test **not** affected by HCW perception or bias
BCG vaccination can cause false-positive result	BCG vaccination does **not** cause false-positive result and infection with most nontuberculous mycobacteria does **not** cause false-positive result
A negative reaction to the test does **not** exclude the diagnosis of LTBI or TB disease	A negative reaction to the test does **not** exclude the diagnosis of LTBI or TB disease

Mantoux Tuberculin Skin Test (TST)

The TST is used to determine if a person is infected with *M. tuberculosis*. In this test, a substance called purified protein derivative (PPD), which is derived from tuberculin, is injected under the skin. Typically PPD produces a T-cell mediated delayed-type hypersensitivity reaction if the person has been infected with *M. tuberculosis*. In most people who have TB infection, the immune system will recognize the PPD because it is extracted from the tubercle bacilli that caused the infection. It takes 2 to 8 weeks after initial infection with *M. tuberculosis* for the immune system to be able to react to PPD and for the infection to be detected by the TST.

The TST is used to determine if a person is infected with *M. tuberculosis*. In this test, a substance called PPD is injected under the skin.

It takes 2 to 8 weeks after initial infection with *M. tuberculosis* for the body's immune system to be able to react to PPD and for the infection to be detected by the TST.

In some people who are infected with *M. tuberculosis*, the ability to react to PPD may wane over the years. When these people receive a TST many years after infection, they may have an initial negative reaction. Subsequent TSTs may produce a positive reaction (see Boosted Reaction in this chapter).

Administering the TST

The TST is performed by intradermal injection of 0.1 ml of PPD containing 5 tuberculin units into the volar surface of the forearm. The injection should be made with a disposable 27-gauge tuberculin syringe, intradermally (just beneath the surface of the skin), with the needle bevel facing upward. This should produce a discrete, pale elevation of the skin (a wheal) 6 mm to 10 mm in diameter (Figure 3.2). Institutional guidelines regarding universal precautions for infection control (e.g., the use of gloves) should be followed (see Chapter 7, TB Infection Control).

The TST is performed by intradermal injection of 0.1 ml of PPD containing 5 tuberculin units into the volar surface of the forearm.

Reading the TST

The reaction to the TST should be assessed 48 to 72 hours after the injection by a health-care worker trained to read TST results. Reactions to PPD usually begin 5 to 6 hours after injection, reach a maximum at 48 to 72 hours, and subside over a period of a few days. However, positive reactions often persist for up to 1 week or longer. Health-care workers should **not** ask patients to read their own skin test.

The reaction to the TST should be assessed 48 to 72 hours after the injection by a health-care worker trained to read TST results.

The TST is read by palpating the site of injection to find an area of induration (firm swelling). The diameter of the indurated area should be measured across the forearm (Figure 3.3). Erythema (redness) should **not** be measured (Figure 3.4). Induration should be recorded in millimeters, even those classified as negative. If no induration is found, "0 mm" should be recorded.

The TST is read by palpating the site of injection to find an area of induration (firm swelling). The diameter of the indurated area should be measured across the forearm (Figure 3.3). Erythema (redness) should not be measured.

Figure 3.2
Administering the Mantoux TST

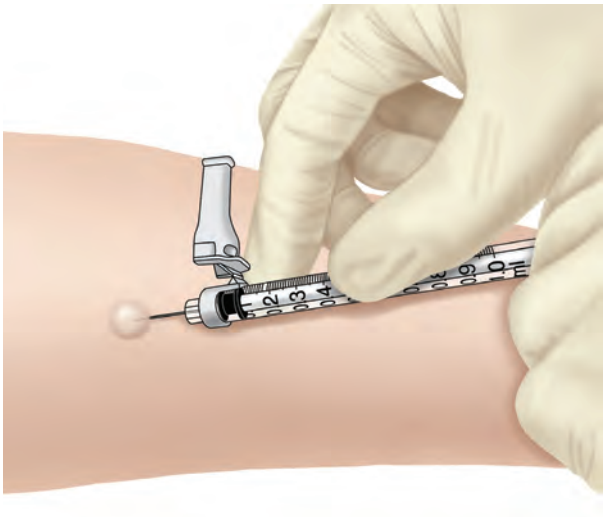


Figure 3.3
Reading the TST Correctly
Only the induration is being measured.
This is CORRECT.
The correct example below measures 10 mm.

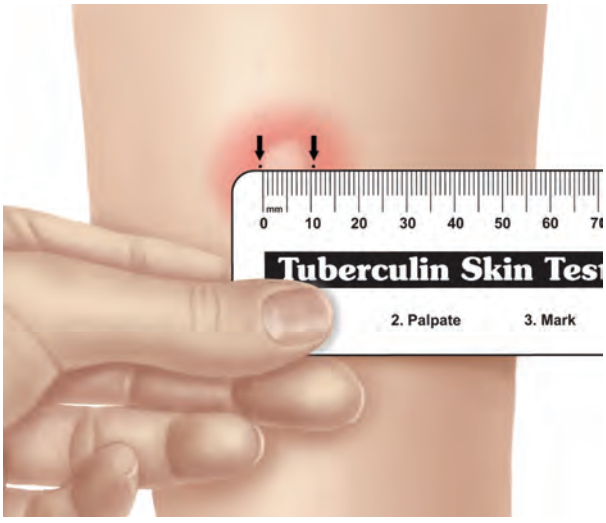
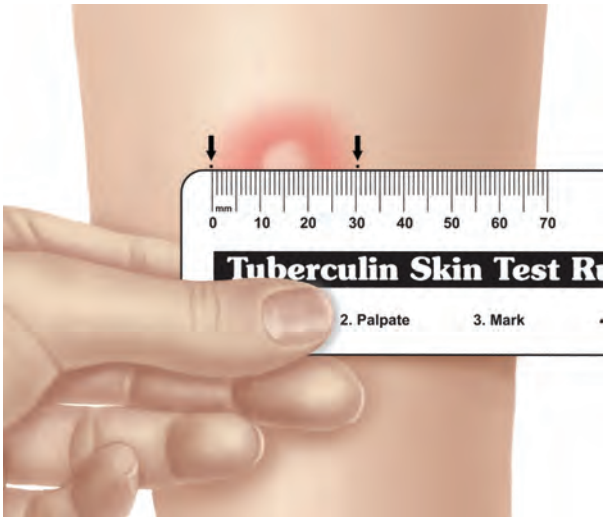


Figure 3.4
Reading the TST Incorrectly
The erythema is being measured.
This is INCORRECT.
The incorrect example below measures 30 mm.



Interpreting TST Reactions

Interpretation of TST reactions depends on the measurement (in millimeters) of induration and the person's risk of acquiring TB infection or the risk of progression to TB disease if infected (Table 3.2).

Induration of 5 or more millimeters is interpreted as a positive result in the following groups:

- HIV-infected persons;
- Recent contacts of persons with infectious TB disease;
- Persons with fibrotic changes on a chest radiograph consistent with prior TB; and
- Patients with organ transplants and other immunosuppressed patients (including patients receiving the equivalent of ≥ 15 mg/day of prednisone for ≥ 1 month).

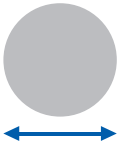
Induration of 10 millimeters or more is interpreted as a positive result in persons who do not meet the preceding criteria, but who have other risk factors for TB. These include the following:

- Recent arrivals to the United States (< 5 years) from high-prevalence areas (e.g., Africa, Asia, Eastern Europe, Latin America, and Russia);
- Injection drug users;
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, long-term care facilities, homeless shelters, and hospitals);
- Mycobacteriology laboratory personnel;
- Persons with medical conditions that increase the risk for progression to TB disease, including silicosis, diabetes mellitus, chronic renal failure, certain types of cancer (e.g., leukemia and lymphomas, or cancer of the head, neck, or lung), gastrectomy or jejunoileal bypass, and weight loss of at least 10% below ideal body weight;
- Children younger than 5 years of age; and
- Infants, children, and adolescents exposed to adults in high-risk categories.

An induration of 15 millimeters or greater is interpreted as a positive result in persons with no known risk factors for TB who, except for certain testing programs required by local law or regulation, would otherwise not be tested. Targeted testing programs should only be conducted among higher risk groups.

Interpretation of TST reactions depends on the measurement (in millimeters) of the induration and the person's risk of acquiring TB infection or the risk of progression to TB disease if infected.

Table 3.2
Interpreting the TST Reaction

		
5 or more millimeters	**10 or more millimeters**	**15 or more millimeters**
An induration of **5 or more millimeters** is considered positive for • HIV-infected persons • Recent contacts of persons with infectious TB • People who have fibrotic changes on a chest radiograph • Patients with organ transplants and other immunosuppressed patients (including patients taking a prolonged course of oral or intravenous corticosteroids or TNF-*α* antagonists)	An induration of **10 or more millimeters** is considered positive for • People who have come to the United States within the last 5 years from areas of the world where TB is common (for example, Asia, Africa, Eastern Europe, Russia, or Latin America) • Injection drug users • Mycobacteriology lab workers • People who live or work in high-risk congregate settings • People with certain medical conditions that place them at high risk for TB (silicosis, diabetes mellitus, severe kidney disease, certain types of cancer, and certain intestinal conditions) • Children younger than 5 years of age • Infants, children, and adolescents exposed to adults in high-risk categories	An induration of **15 or more millimeters** is considered positive for • People with no known risk factors for TB

TST False-Positive Reactions

The TST is a valuable tool, but it is **not** perfect. Several factors can lead to false-positive or false-negative skin test reactions (Table 3.3). Infection with nontuberculous mycobacteria can sometimes

cause a false-positive reaction to the TST. Another cause of a false-positive reaction is BCG (bacille Calmette-Guérin), a vaccine for TB disease that is rarely used in the United States. People who have been vaccinated with BCG may have a positive reaction to the TST even if they do **not** have TB infection (see BCG Vaccination in this chapter).

A false-positive reaction may also occur if an incorrect antigen is used or when the results are **not** measured or interpreted properly.

People who have been vaccinated with BCG may have a positive reaction to the TST even if they do not have TB infection.

TST False-Negative Reactions

Some people have a negative reaction to the TST even though they have been infected with *M. tuberculosis*. A false-negative reaction can be caused by many things (Table 3.3).

Some people have a negative reaction to the TST even though they have been infected with *M. tuberculosis*.

Anergy

A common cause of false-negative reactions is anergy. Anergy is the inability to react to a TST because of a weakened immune system. The absence of a reaction to a TST does **not** exclude a diagnosis of TB disease or infection with *M. tuberculosis*. Anergy may be caused by many factors, including advanced HIV infection, other acute or chronic bacterial, viral or fungal infections, sarcoidosis, poor nutrition, certain medications (e.g., TNF-alpha blockers or oral steroids), live virus vaccinations, TB disease itself, and other factors. HIV-infected persons may have a compromised ability to react to TST because of cutaneous anergy associated with progressive HIV immunosuppression; however, the usefulness of anergy testing in tuberculin-negative, HIV-infected persons who might benefit from treatment of LTBI has **not** been demonstrated.

Factors causing false-negative reactions may include, but are **not** limited to, the following:

- Concurrent viral infection (e.g., measles, mumps, chicken pox, HIV);
- Concurrent bacterial infection (e.g., typhoid fever, brucellosis, typhus, leprosy, pertussis);
- Concurrent fungal infection;
- Chronic renal failure;
- Low protein states (e.g., severe protein depletion, afibrinogenemia);
- Diseases affecting lymphoid organs (e.g., Hodgkin's disease, lymphoma, chronic leukemia, sarcoidosis);
- Immunosuppressive drugs (e.g., medical steroids);
- Children aged 6 months or less or elderly patients (i.e., immature or waning immunity);
- Stress (e.g., surgery, burns, mental illness, graft-versus-host reactions);

- Incorrect storage or handling of antigen or results that are **not** measured or interpreted properly;
- Vaccinations using live virus; or
- Recent TB infection.

Vaccinations

Vaccination with live viruses may interfere with TST reactivity and cause false-negative reactions; this includes measles, mumps, rubella, oral polio, varicella, yellow fever, BCG, and oral typhoid. For persons scheduled to receive TST and live virus vaccines, the testing should be done either on the same day as vaccination or at least 1 month after vaccination to minimize the potential for a false-negative TST reaction.

Infection occurs within 8 weeks of skin testing

False-negative TST reactions may occur if the TB infection occurred within 8 weeks of skin testing. For this reason, it is recommended that contacts of a person with infectious TB disease who have a negative reaction to the initial TST be retested at least 8 weeks after the last time they were in contact with the person who has infectious TB disease.

False-negative TST reactions may occur if the TB infection occurred within 8 weeks of skin testing.

Table 3.3
False-Positive and False-Negative Reactions to the TST

Type of Reaction	Possible Cause	People at Risk
False-positive	Nontuberculous mycobacteria (NTM)	People infected with NTM
	BCG vaccination	People vaccinated with BCG
	Administering of incorrect antigen	Any person being tested
	Incorrect interpretation of TST result	Any person being tested
False-negative	Anergy	HIV-infected people, other people with weakened immune systems, severe TB disease, and some viral illness (e.g., measles, mumps, and chicken pox) or bacterial infection (e.g., typhoid, etc.)
	Recent TB infection	People infected with *M. tuberculosis* within the past 8 weeks
	Concurrent viral infection	People injected with a live-virus vaccination
	Concurrent bacterial infection	People with typhoid fever, brucellosis, typhus, leprosy, pertussis
	Concurrent fungal infection	People with fungal infection
	Chronic renal failure	People with renal failure
	Low protein states	People with severe protein depletion or afibrinogenemia
	Diseases affecting lymphoid organs	People with Hodgkin's disease, lymphoma, chronic leukemia, sarcoidosis
	Immunosuppressive drugs	People taking medical steroids, TNF-alpha blockers or comparable drugs
	Very young or elderly persons	Newborns or elderly patients with immature or waning immunity
	Stress	People who have had surgery, burns, mental illness, graft-versus-host reactions
	Incorrect storage or handling of antigen, administering the TST, or results that are **not** measured or interpreted properly	Any person being tested

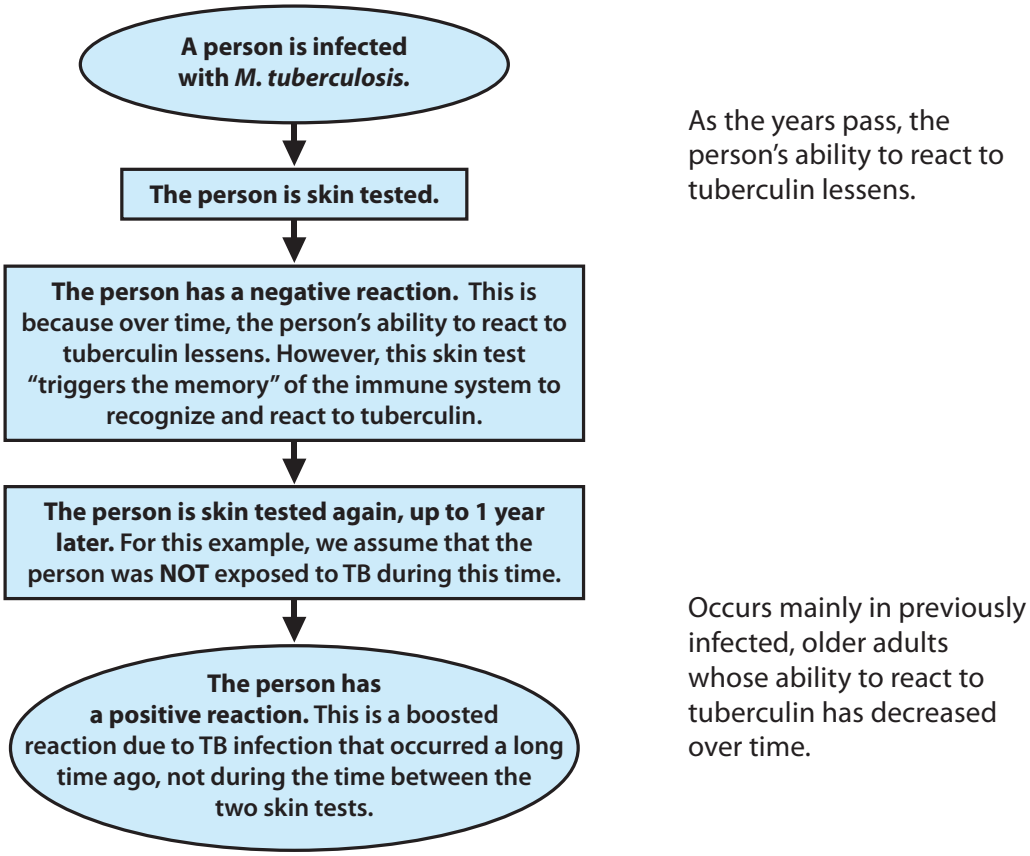
Special Considerations When Using TST

Boosted Reaction

The booster phenomenon occurs mainly in previously infected, older adults whose ability to react to tuberculin has waned over time (Figure 3.5). When these people are skin tested many years after they were infected with *M. tuberculosis*, they may have an initial negative reaction. However, if they are tested again within a year of the first test, they may have a positive reaction. This is because the first TST "triggered the memory" of the immune system, boosting its ability to react to the second TST. It may appear that these people were infected between the first and second tests (recent TB infection). The second, positive test reaction is actually a boosted reaction due to TB infection that occurred a long time ago. These people may still be considered for LTBI treatment if they fit into a high-risk category for progression to TB disease.

The booster phenomenon occurs mainly in previously infected, older adults whose ability to react to tuberculin has waned over time.

Figure 3.5
The TST Booster Phenomenon



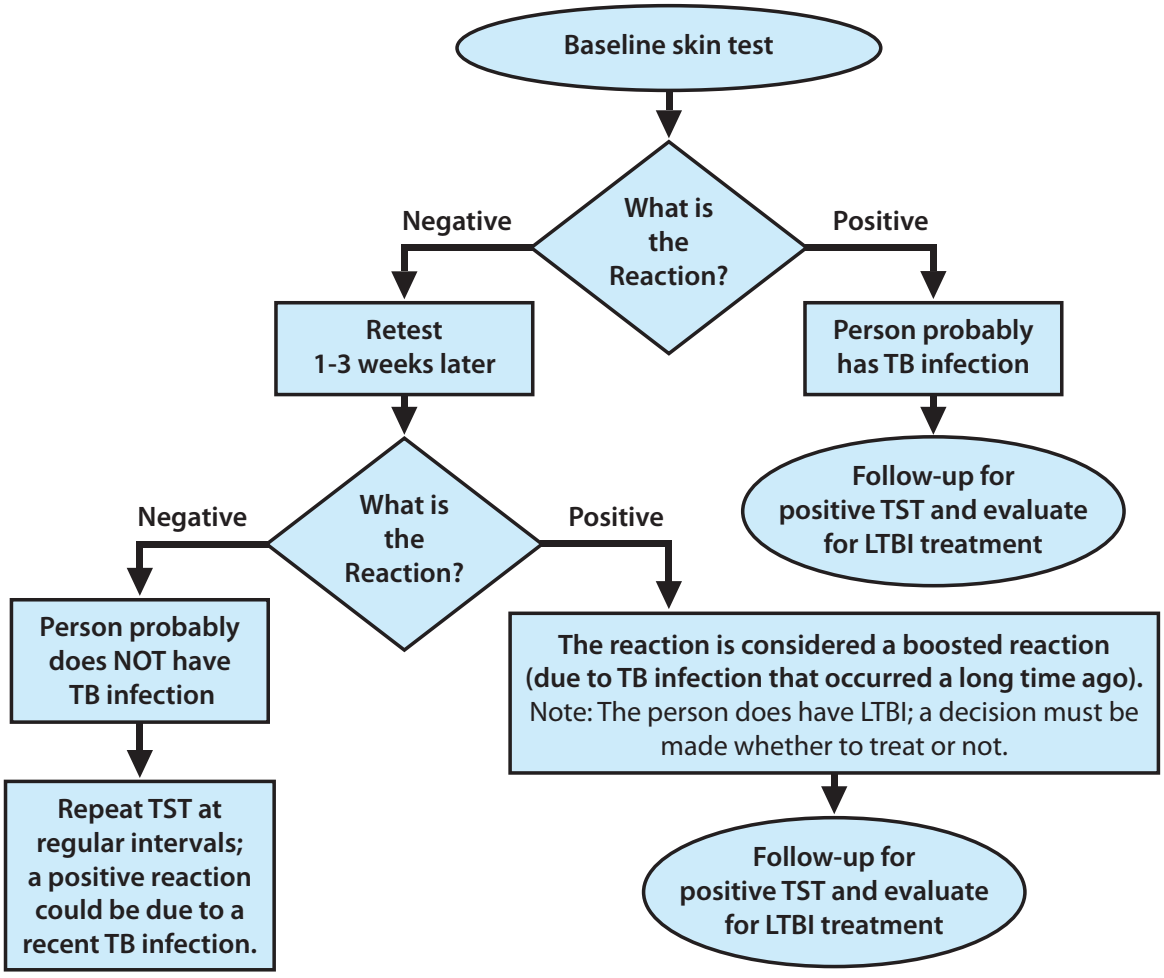
Two-step TST Testing

Two-step testing is a strategy used to reduce the likelihood that a boosted reaction will be misinterpreted as a recent infection (Figure 3.6). Two-step testing should be used for the initial skin testing of persons who will be retested periodically, such as health-care workers.

Two-step testing is a strategy used to reduce the likelihood that a boosted reaction will be misinterpreted as a recent infection.

If the reaction to the first test is classified as negative, a second test should be repeated 1 to 3 weeks later. A positive reaction to the second test probably represents a boosted reaction. On the basis of this second test result, the person should be classified as previously infected. This would **not** be considered a skin test conversion or a new TB infection; however, the patient may still be a candidate for LTBI treatment. If the second test result is also negative, the person should be classified as having a negative baseline TST result.

Figure 3.6
Two-Step TST Testing



Pregnant Women

TST is both safe and reliable throughout the course of pregnancy. Pregnant women should receive a TST if they have a specific risk factor for acquiring LTBI or for progression of LTBI to TB disease. No documented episodes of TST-related fetal harm have been reported since the test was developed, and no evidence exists that the TST has adverse effects on the pregnant mother.

TST is both safe and reliable throughout the course of pregnancy.

Occupational Exposure

Guidelines for interpreting TST reactions should also be applied to persons who may have occupational exposure to TB (e.g., health-care workers; staff of nursing homes, drug treatment centers, or correctional facilities). Thus, the appropriate cutoff for defining a positive reaction depends on the employee's individual risk factors for TB, including recent TB exposure and the prevalence of TB in the facility (based on facility risk assessment). In facilities where the risk of exposure is very low, 15 mm or greater induration may be an appropriate cut-off for employees with no other known risk factors.

Residents and employees of high-risk congregate facilities should be tested for TB with the two-step method upon employment or entry into the facility, and thereafter at intervals determined by the annual risk assessment in that facility (see Chapter 7, TB Infection Control).

Residents and employees of high-risk congregate facilities should be tested for TB with the two-step method upon employment or entry into the facility and thereafter at intervals determined by the annual risk assessment in that facility.

Study Questions

3.3 A negative reaction to a TST or IGRA does not exclude the diagnosis of LTBI or TB disease. (circle the one best answer)

A. True

B. False

3.4 After TB has been transmitted, how long does it take for the body's immune system to be able to react to tuberculin?
(circle the one best answer)

A. 48 to 72 hours

B. 7 to 10 days

C. 2 to 8 weeks

D. 6 months or more

What induration size is considered a positive TST reaction for the following people?
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Persons Who Received a TST		Size of Induration
____ **3.5**	Prieta lives in a homeless shelter in El Paso and has poor access to health care.	**A.** 5 or more millimeters **B.** 10 or more millimeters **C.** 15 or more millimeters
____ **3.6**	Gloria has no known risk factors for TB.	
____ **3.7**	Elwood has HIV infection.	

Match the factors associated with TST with the appropriate term.
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Factors Associated with TST	Terms
____ **3.8** Mainly occurs in previously infected, older adults whose ability to react to tuberculin has lessened over time.	**A.** False-positive skin test reaction
____ **3.9** May occur in people who have been vaccinated with BCG.	**B.** False-negative skin test reaction
____ **3.10** Should be used for initial skin testing of persons who will be retested periodically.	**C.** Anergy
____ **3.11** May occur in people who were recently infected with *M. tuberculosis.*	**D.** Boosted reaction
____ **3.12** Is the inability to react to a TST because of a weakened immune system.	**E.** Two-step testing

3.13 Is it safe for a pregnant woman to have a TST?
(choose the one best answer)

A. Yes

B. No

Case Study– Bret

Bret comes to the county health department for a TST. He believes that he has been exposed to TB, and he knows he is at high risk for TB disease because he is HIV infected. He is given a TST, and his reaction is read 48 hours later as 0 millimeters of induration.

3.14 Which of the following reasons is a possible interpretation for this result?
(circle the one best answer)

A. He may not have TB infection.

B. It may be less than 8 weeks since he was exposed to TB.

C. He may be anergic.

D. A, B, and C are all correct.

E. Only A and B are correct.

Interferon-Gamma Release Assays (IGRAs)

IGRAs detect the presence of *M. tuberculosis* infection by measuring the immune response to TB proteins in whole blood. IGRAs cannot differentiate between LTBI and active TB disease. As with the TST, additional tests are needed to diagnose or rule out TB disease. IGRAs may be used for surveillance purposes or to identify people who are likely to benefit from treatment, including people who are or will be at increased risk of progression to TB disease if infected with *M. tuberculosis*.

Two IGRAs are commercially available and approved by the U.S. Food and Drug Administration (FDA) as aids in diagnosing *M. tuberculosis* infection:

- QuantiFERON®-TB Gold In-Tube test (QFT-GIT); and
- T-Spot®.*TB* test.

IGRAs identify the presence of *M. tuberculosis* infection by measuring the immune response to the TB proteins in whole blood. IGRAs cannot differentiate between LTBI and active TB disease. As with the TST, additional tests are needed to diagnose or rule out TB disease.

IGRAs may be used for surveillance purposes or to identify people who are likely to benefit from treatment, including people who are or will be at increased risk of progression to TB disease if infected with *M. tuberculosis*.

General Recommendations for the Use of IGRAs

An IGRA may be used in place of (but **not** in addition to) a TST in all situations in which CDC recommends a TST as an aid in diagnosing *M. tuberculosis* infection, with the preferences and specific considerations noted below (Table 3.4).

- Preferred for testing persons from groups that historically have poor rates of return for TST reading.
- Preferred for testing persons who have received BCG (as a vaccine or for cancer therapy) (see BCG Vaccination in this chapter).
- Generally should not be used for testing children younger than 5 years of age unless used in conjunction with TST.
- May be used in place of TST to test recent contacts of persons with infectious TB disease with special considerations for follow-up testing:
  - » IGRAs offer the possibility of detecting *M. tuberculosis* infection with greater specificity than with a TST;
  - » Data on the ability of IGRAs to predict subsequent TB are limited;
  - » If IGRAs are to be used in contact investigations, negative results obtained prior to 8 weeks typically should be confirmed by repeating the test 8 to 10 weeks after the end of exposure;
  - » Use of the same test for repeat testing will minimize misclassification errors that occur due to test discordance.

- May be used in place of a TST for periodic screening that addresses occupational exposure to TB disease (e.g., surveillance programs for health-care workers).
- IGRAs do not boost subsequent test results and can be completed following a single patient visit.
- Routine testing with both a TST and an IGRA is **not** recommended; however, results from both tests may be useful in the following situations when the initial test is **negative**:
  - When the risk of infection, the risk of progression from infection to disease, and the risk of a poor outcome are high (e.g., HIV infection, children under 5 years of age who are exposed to persons with infectious TB); or
  - When there is clinical suspicion for TB disease (e.g., signs, symptoms, and/or radiographic evidence suggestive of TB disease) and confirmation of *M. tuberculosis* infection is desired.
- Routine testing with both a TST and an IGRA is **not** recommended; however, results from both tests may be useful in the following situations when the initial test is **positive**:
  - Additional evidence of infection is required to encourage compliance (e.g., foreign-born health-care workers who believe their positive TST is due to BCG); and
  - In healthy persons who have a low risk of both infection and progression from infection to TB disease.
- Repeating an IGRA or performing a TST may be useful when the initial IGRA result is indeterminate, borderline, or invalid, and a reason for testing persists.
- Each institution and TB control program should evaluate the availability, overall cost effectiveness, and benefits of the use of IGRAs.

An IGRA may be used in place of (but not in addition to) TST in all situations in which CDC recommends TST as an aid in diagnosing *M. tuberculosis* infection.

As with the TST, IGRAs generally should **not** be used for testing persons who have a low risk for both infection and disease attributable to *M. tuberculosis* (with exception of those who are likely to be at increased risk in the future) because screening such persons diverts resources from TB control activities of higher priority and increases the number of false-positive results.

Table 3.4
Recommendations for the Use of IGRAs

Category	Recommended	Not Recommended
Groups for use	• Preferred for groups that historically have poor rates of return for TST reading • Preferred for persons who have received BCG (as a vaccine or for cancer therapy)	• Children younger than 5 years of age unless it is used in conjunction with TST • Persons at low risk of infection • Persons at low risk of disease due to *M. tuberculosis* (except those who are likely to be at increased risk in the future)
In place of TST	• Recent contacts of persons with TB disease with special considerations for follow-up testing » If IGRAs are used in contact investigations, negative results obtained prior to 8 weeks typically should be confirmed by repeating the test 8 to 10 weeks after the end of exposure » Use of the same test for repeat testing will minimize misclassification errors that occur due to test discordance • Periodic screening that addresses occupational exposure to TB disease (e.g., surveillance programs for health workers)	
Testing with both TST and IGRA	Results from both tests may be useful when the initial test is **negative** • When the following risks are high » Risk of infection » Risk of progression from infection to disease » Risk of a poor outcome • When there is clinical suspicion for active TB and confirmation of *M. tuberculosis* infection is desired	Routine testing with both TST and IGRA

Category	Recommended	Not Recommended
Testing with both TST and IGRA	Results from both tests may be useful in the following situations when the initial test is **positive**: • Additional evidence of infection is required to encourage compliance (e.g., foreign-born health-care workers who believe their positive TST is due to BCG); and • In healthy persons who have a low risk of both infection and progression from infection to TB disease.	Routine testing with both TST and IGRA

Study Questions

Match the characteristic with the type of TB test.
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Characteristic	Type of TB Test
____ **3.15** Used to detect TB infection.	**A.** TST
____ **3.16** Blood is drawn for the test.	**B.** IGRA
____ **3.17** PPD is injected for the test.	**C.** Both TST and IGRA
____ **3.18** Requires two or more patient visits to conduct test.	
____ **3.19** Requires one patient visit to conduct test.	
____ **3.20** Results need to be read in 48–72 hours.	
____ **3.21** Results can be available in 24 hours.	
____ **3.22** BCG vaccination can cause false-positive result.	
____ **3.23** BCG vaccination does **not** cause false-positive result.	

BCG Vaccination

The bacille Calmette-Guérin (BCG) vaccine is a live, attenuated (weakened) vaccine derived from a strain of *Mycobacterium bovis* that was developed over several years by Calmette and Guérin at the Pasteur Institute in Lille, France. An early version of BCG was first administered to humans in 1921. Since that time, many different strains have been derived and used throughout the world. BCG vaccination is **not** generally recommended in the United States because of the low risk of infection with *M. tuberculosis*, the variable efficacy of the BCG vaccine against pulmonary TB, the low risk of severe disseminated TB disease in young children in the United States, and the vaccine's interference with the ability to determine TST reactivity. Many highly TB-prevalent countries vaccinate infants with BCG as part of their TB control effort to prevent children from contracting severe disseminated TB or TB meningitis.

BCG vaccination is not generally recommended in the United States because of the low risk of infection with *M. tuberculosis*, the variable efficacy of the BCG vaccine against pulmonary TB, the low risk of severe disseminated TB disease in young children in the United States and the vaccine's interference with the ability to determine TST reactivity.

Recommendations for the Use of BCG Vaccination in the United States

The BCG vaccine may be considered in limited circumstances for selected persons who meet specific criteria. The use of the BCG vaccine should be undertaken only after consultation with local health departments and experts in the management of TB.

Recent BCG vaccination may cause a subsequent false positive reaction to the TST. Thus, it may complicate decisions to prescribe treatment for LTBI for BCG-vaccinated persons who have a positive TST result. In such cases, an IGRA would be the test of choice for LTBI diagnosis.

Recent BCG vaccination may cause a subsequent false positive reaction to the TST. Thus, it may complicate decisions to prescribe treatment for LTBI for BCG-vaccinated persons who have a positive TST result.

Infants and Children

In the United States, BCG vaccination should only be considered for those children who have a negative TST or IGRA result and who are continually exposed to, and cannot be separated from, adults who:

- Are untreated or ineffectively treated for TB disease (if the child cannot be given long-term treatment for infection); or
- Have TB disease caused by strains resistant to isoniazid and rifampin.

The BCG vaccination is **contraindicated** in children infected with HIV.

BCG vaccination is contraindicated in children infected with HIV.

Health-Care Workers

BCG vaccination of health-care workers should be considered on an individual basis in settings in which:

- A high percentage of TB patients are infected with *M. tuberculosis* strains resistant to both isoniazid and rifampin;
- Transmission of such drug-resistant *M. tuberculosis* strains to health-care workers and subsequent infection are likely; and
- Comprehensive TB infection control precautions have been implemented and have **not** been successful.

BCG vaccination should **not** be required for employment or for assignment of health-care workers in specific work areas. Health-care workers considered for BCG vaccination should be counseled regarding the risks and benefits associated with both BCG vaccination and treatment of LTBI. BCG vaccination is **contraindicated** in health-care workers who are infected with HIV.

Contraindications to BCG Vaccination

BCG is contraindicated in persons who have an impaired immune system from the following:

- HIV infection;
- Congenital immunodeficiency;
- Leukemia;
- Lymphoma;
- Generalized malignancy;
- High-dose steroid therapy;
- Alkylation agents;
- Antimetabolites; or
- Radiation therapy.

It is also prudent to avoid giving BCG vaccination to pregnant women, although no harmful effects of BCG on the fetus have been observed.

BCG vaccination should not be given to pregnant women.

Interpretation of TB Testing Results in BCG-Vaccinated Persons

The TST or IGRA is **not** contraindicated for persons who have been vaccinated with BCG. The TST or IGRA results are used to support decisions about the diagnosis of infection with *M. tuberculosis*. TST in persons vaccinated with BCG should be interpreted using the same criteria for those **not** BCG vaccinated. The booster phenomenon may occur among persons who have had a prior BCG vaccination.

The TST or IGRA is not contraindicated for persons who have been vaccinated with BCG. The TST or IGRA results are used to support decisions about the diagnosis of infection with *M. tuberculosis*.

TST in persons vaccinated with BCG should be interpreted using the same criteria for those not BCG vaccinated. The booster phenomenon may occur among persons who have had a prior BCG vaccination.

Study Questions

3.24 Which of the following statements about recommendations for using BCG in the United States is true?
(choose the one best answer)

A. Should **NOT** be given to pregnant women.

B. Should be used for children infected with HIV.

C. Should be required for employment of all health-care workers.

D. A, B, and C are all correct.

E. Only A and B are correct.

Case Study–Anshuman

Anshuman recently immigrated from India. He is given a TST that results in an induration of 14 millimeters. He reports that he was vaccinated with BCG as a child. He also says that his wife was treated for pulmonary TB disease last year.

Are the following statements about how to interpret Anshuman's results true or false? (Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Statement	True or False
____ **3.25** He has a positive reaction to the TST.	**A.** True
____ **3.26** He is a contact of a person with pulmonary TB.	**B.** False
____ **3.27** There is no reliable way to distinguish a positive TST reaction caused by BCG or from a true TB infection.	
____ **3.28** Because he was vaccinated with BCG there is no need to evaluate him further.	
____ **3.29** He should be further evaluated for LTBI or TB disease.	

Which of the following factors make it more likely that Anshuman's positive reaction is due to TB infection? (Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Factor	Yes or No
____ **3.30** He is from an area of the world where TB is common, so he was probably exposed to TB in his native country.	**A.** Yes, a factor
____ **3.31** His wife has had pulmonary TB, which further increases the probability that he has been exposed to TB.	**B.** No, not a factor
____ **3.32** He had BCG as a child, not as an adult.	

Chapter Summary

Targeted testing is a TB control strategy that is used to identify, evaluate, and treat persons who are at high risk for LTBI or at high risk for developing TB disease once infected with *M. tuberculosis*. Identifying persons with LTBI is important to the goal of TB control and elimination because treatment of LTBI can prevent infected persons from developing TB disease and stop the further spread of TB. All testing activities should be accompanied by a plan for appropriate follow-up medical evaluation and treatment. Necessary medical evaluation and treatment resources need to be identified before testing activities begin.

As part of their routine evaluation, health-care providers should identify and test persons who are at high risk for acquiring TB infection or at high risk for progressing to TB disease if infected. In some select settings, active case finding may be more appropriate than testing for *M. tuberculosis* infection. Flexibility is needed in defining high-risk groups for testing. The changing epidemiology of TB indicates that the risk for TB disease or LTBI among groups currently considered high risk may decrease over time, and groups currently **not** identified as being at risk may subsequently be considered high risk.

Selection of the most suitable test(s) for detection of *M. tuberculosis* infection should be based on the reasons and the context for testing, test availability, and overall cost effectiveness of testing. Currently, there are two methods available for the detection of *M. tuberculosis* infection in the United States. The tests are:

- Mantoux tuberculin skin test (TST)
- Interferon-gamma release assays (IGRAs)
  - » QuantiFERON-TB Gold In-Tube test (QFT-GIT)
  - » T-Spot®.*TB* test

The TST is used to determine if a person is infected with *M. tuberculosis*. In this test, a substance called purified protein derivative (PPD), which is derived from tuberculin, is injected under the skin. Typically PPD produces a T-cell mediated delayed-type hypersensitivity reaction if the person has been infected with *M. tuberculosis*. In most people who have TB infection, the immune system will recognize the PPD because it is extracted from the tubercle bacilli that caused the infection. It takes 2 to 8 weeks after initial infection with *M. tuberculosis* for the body's immune system to be able to react to PPD and for the infection to be detected by the TST.

The booster phenomenon occurs mainly in previously infected, older adults whose ability to react to tuberculin has waned over time. When these people are skin tested many years after they were infected with *M. tuberculosis*, they may have an initial negative reaction. However, if they are tested again within a year of the first test, they may have a positive reaction. This is because the first TST "triggered the memory" of the immune system, boosting its ability to react to the second TST. It may appear that these people were infected between the first and second tests (recent TB infection). The second, positive test reaction is actually a boosted reaction due to TB infection that occurred a long time ago. These people may still be considered for LTBI treatment if they fit into a high-risk category for progression to TB disease.

IGRAs identify the presence of *M. tuberculosis* infection by measuring the immune response to the TB proteins in whole blood. These tests cannot differentiate between LTBI and active TB disease. As with the TST, additional tests are needed to diagnose or rule out TB disease. IGRAs may be used for surveillance purposes or to identify people who are likely to benefit from treatment, including people who are or will be at increased risk of progression to TB disease if infected with *M. tuberculosis*.

The bacille Calmette-Guérin (BCG) vaccine is a live, attenuated (weakened) vaccine derived from a strain of *Mycobacterium bovis* that was developed by Calmette and Guérin at the Pasteur Institute in Lille, France. An early version of BCG was first administered to humans in 1921. Since that time, many different strains have been derived and used throughout the world. BCG vaccination is **not** generally recommended in the United States because of the low risk of infection with *M. tuberculosis*, the variable efficacy of the BCG vaccine against pulmonary TB, the low risk of severe disseminated TB disease in young children in the United States, and the vaccine's interference with the ability to determine TST reactivity. Many highly TB-prevalent countries vaccinate infants with BCG as part of their TB control effort to prevent children from contracting severe disseminated TB or TB meningitis.

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