Core Curriculum on Tuberculosis: What the Clinician Should Know

SEVENTH EDITION  2021

Centers for Disease Control and Prevention
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
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Tuberculosis (TB)—a disease also historically known as consumption, wasting disease, and the white plague—has affected humans for centuries. TB is one of the most common infections in the world. Every year, about 10 million people develop TB disease, and 1.6 million people die of it. In fact, TB disease is one of the leading causes of death due to infectious disease in the world.

Since 1993, TB cases in the United States (U.S.) overall have been steadily declining. However, with every state in the country reporting cases, too many people in the U.S. still suffer from TB disease. We must continue to find and treat cases of active TB disease and test for and treat latent TB infection (LTBI) to prevent progression to disease and make TB elimination a reality. Even today, TB can be fatal if not treated in time.

TB is caused by a bacterium called *Mycobacterium tuberculosis* (*M. tuberculosis*). It is estimated that up to 13 million people in the U.S. have LTBI. Persons with LTBI are infected with *M. tuberculosis*, but they do not have TB disease. Persons with LTBI do not have signs and symptoms of TB disease, and they cannot spread *M. tuberculosis* to others. Treatment of LTBI is essential to controlling TB in the U.S. because it substantially reduces the risk that LTBI will progress to TB disease. While not everyone with LTBI will develop TB disease, about 5–10% will develop TB disease over their lifetimes if not treated. Progression from untreated LTBI to TB disease is estimated to account for approximately 80% of U.S. TB cases.

From 1995–2014, public health efforts prevented up to 319,000 cases of TB and averted up to $14.5 billion in costs. The U.S. has one of the lowest TB disease case rates in the world thanks to investments in domestic TB programs. Primary care providers play a key role in achieving the goal of TB elimination because of their access to populations at high risk for TB.
Current TB control measures, including early identification of TB disease, prompt and appropriate treatment for persons with TB disease, and ensuring that TB patients complete treatment, continue to be critical. Identifying and treating persons with LTBI is also paramount to TB elimination. Eliminating TB in the U.S. will require this dual approach which includes strengthening existing systems to track and stop transmission of infectious TB disease and expanding efforts to address LTBI. This strategy is consistent with the Centers for Disease Control and Prevention (CDC) recommendations as well as the recommendations from the U.S. Preventative Services Task Force (USPSTF).

**Purpose**

The *Core Curriculum on Tuberculosis: What the Clinician Should Know* presents information about TB for health care professionals. This document, produced by the CDC, Division of Tuberculosis Elimination (DTBE), updates the 2013 edition of the *Core Curriculum*.

This document is intended for use as a reference manual for clinicians caring for persons with or at high risk for TB disease or infection. It is **not** meant to provide detailed answers to all public health or clinical questions about TB, and it is **not** meant as a substitute for any specific guidelines. It is anticipated that new guidelines will be published in the future that will supersede information in this document, and these new guidelines will be posted on the DTBE website.

**Target Audience**

The audience for the *Core Curriculum on Tuberculosis: What the Clinician Should Know* includes clinicians who are caring for persons with or at high risk for TB disease or infection.

**Continuing Education**

To learn more about continuing education (CE) credit, please visit the [CDC CE website](https://www.cdc.gov/ce/). Search for CE opportunities, complete course evaluations and post-tests, receive your CE certificates, and manage your CE transcript.
**Key Tuberculosis Resources**

**State TB Control Program Offices**
Clinicians should immediately contact their state TB program office if they have a patient with presumed or confirmed TB disease. State TB programs can assist in providing guidance and overall public health management of patients and can answer questions on state-specific TB guidelines. A list of state TB program offices is provided on the DTBE website.

**CDC Division of TB Elimination**
For information on CDC TB guidelines and recommendations, visit the DTBE website.

**TB Centers of Excellence for Training, Education, and Medical Consultation**
DTBE funds four TB Centers of Excellence for Training, Education, and Medical Consultation (TB COEs) for the project period 2018–2022. The TB COEs are regionally assigned to cover all fifty states and the U.S. territories and support domestic TB control and prevention efforts with a focus on two major activities:
- Increasing knowledge, skills, and abilities for TB prevention and control through communication, education, and training activities.
- Improving sustainable evidence-based TB clinical practices and patient care through the provision of expert medical consultation.

Visit the TB COE website for contact information.

**TB Education and Training Resources**
For information on TB education and training resources, visit the following websites:
- DTBE Publications and Products
- Find TB Resources website
- TB COE product list

**Additional Information**
For additional information about TB guidelines and recommendations, visit the following websites:
- National TB Controllers Association (NTCA)
- American Lung Association
- American Thoracic Society
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Chapter Objectives
After working through this chapter, you should be able to

• Identify ways in which tuberculosis (TB) is spread.
• Describe the pathogenesis of TB.
• Identify conditions that increase the risk of TB infection progressing to TB disease.
• Define drug resistance.
• Describe the TB classification system.

Chapter Introduction

Tuberculosis (TB) is an airborne disease caused by the bacterium *Mycobacterium tuberculosis* (*M. tuberculosis*) (Figure 1.1). *M. tuberculosis* and seven very closely related mycobacterial species (*M. bovis, M. africanum, M. microti, M. caprae, M. pinnipedii, M. canetti, and M. mungi*) comprise what is known as the *M. tuberculosis* complex. Most—but not all—of these species have been found to cause disease in humans. In the United States, the majority of TB cases are caused by *M. tuberculosis*. *M. tuberculosis* organisms are also called tubercle bacilli.
Transmission of TB

*M. tuberculosis* is carried in airborne particles of 1-5 microns in diameter called droplet nuclei. Infectious droplet nuclei are generated when persons who have pulmonary or laryngeal TB disease cough, shout, or sing. Depending on the environment, these tiny particles can remain suspended in the air for several hours. *M. tuberculosis* is transmitted through the air, not by surface contact. Transmission occurs when a person inhales droplet nuclei containing *M. tuberculosis*, and the droplet nuclei traverse the mouth or nasal passages, upper respiratory tract, and bronchi to reach the alveoli of the lungs (Figure 1.2).

**Figure 1.2**
Transmission of TB

TB is spread from person to person through the air. The solid dots (red) in the figure to the right represent droplet nuclei containing tubercle bacilli.
Factors that Determine the Probability of\n*M. tuberculosis* Transmission

Not everyone who is exposed to a person with infectious TB becomes infected. There are four factors that determine the probability of transmission of *M. tuberculosis* (Table 1.1). The infectiousness of a person with TB disease is directly related to the number of tubercle bacilli that he or she expels into the air (Table 1.2). Persons who expel many tubercle bacilli are more contagious than those who expel few or no bacilli. There are also susceptibility, environmental, and exposure factors that can affect the transmission of TB (Tables 1.3 and 1.4).

Young children with pulmonary and laryngeal TB disease are less likely than adults to be infectious. There are two reasons for this: first, TB in young children is often paucibacillary, meaning that children are infected with fewer organisms compared to adolescents and older children. Second, young children do not often cough with enough force to expel organisms into the air. Nonetheless, transmission from children, especially older adolescents with features of adult disease (e.g., cavitary or sputum smear-positive disease), can occur. Therefore, children and adolescents with TB disease should be evaluated for infectiousness using the same criteria as adults. These criteria include presence of cough lasting 3 weeks or longer; cavitation on chest radiograph; or respiratory tract disease with involvement of lungs, airways, or larynx (see Chapter 2: Testing for Tuberculosis Infection).

### Table 1.1
Factors that Determine the Probability of Transmission of *M. tuberculosis*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptibility</td>
<td>Susceptibility (immune status) of the exposed individual</td>
</tr>
<tr>
<td>Infectiousness</td>
<td>Infectiousness of the person with TB disease, which is directly related to the number of tubercle bacilli that he or she expels into the air (Table 1.2; see also Chapter 6: TB Infection Control)</td>
</tr>
<tr>
<td>Environment</td>
<td>Environmental factors that affect the concentration of <em>M. tuberculosis</em> organisms (Table 1.3)</td>
</tr>
<tr>
<td>Exposure</td>
<td>Proximity, frequency, and duration of exposure (Table 1.4)</td>
</tr>
</tbody>
</table>
Table 1.2
Characteristics of a Patient with TB Disease that are Associated with Infectiousness

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Clinical**                  | • Presence of cough, especially lasting 3 weeks or longer  
• Respiratory tract disease, especially with involvement of the larynx (highly infectious)  
• Failure to cover the mouth and nose when coughing  
• Inappropriate or inadequate treatment (e.g., drugs, duration) |
| **Procedure**                 | Undergoing cough-inducing or aerosol-generating procedures (e.g., bronchoscopy, sputum induction, administration of aerosolized medications) |
| **Radiographic and laboratory** | • Cavitation on chest radiograph  
• Positive culture for *M. tuberculosis*  
• Positive acid-fast bacilli (AFB) sputum smear result |

Table 1.3
Environmental Factors that Enhance the Probability that *M. tuberculosis* Will Be Transmitted

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Concentration of infectious droplet nuclei</strong></td>
<td>The more droplet nuclei in the air, the more probable that <em>M. tuberculosis</em> will be transmitted</td>
</tr>
<tr>
<td><strong>Space</strong></td>
<td>Exposure in small, enclosed spaces</td>
</tr>
<tr>
<td><strong>Ventilation</strong></td>
<td>Inadequate local or general ventilation that results in insufficient dilution or removal of infectious droplet nuclei</td>
</tr>
<tr>
<td><strong>Air circulation</strong></td>
<td>Recirculation of air containing infectious droplet nuclei</td>
</tr>
<tr>
<td><strong>Specimen handling</strong></td>
<td>Improper specimen handling procedures that generate infectious droplet nuclei</td>
</tr>
<tr>
<td><strong>Air pressure</strong></td>
<td>Lack of negative air pressure in infectious patient’s room that causes <em>M. tuberculosis</em> organisms to flow to other areas</td>
</tr>
</tbody>
</table>
Table 1.4
Proximity and Exposure Factors that Can Affect Transmission of *M. tuberculosis*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of exposure to infectious person</td>
<td>The longer the duration of exposure, the higher the risk for transmission</td>
</tr>
<tr>
<td>Frequency of exposure to infectious person</td>
<td>The more frequent the exposure, the higher the risk for transmission</td>
</tr>
<tr>
<td>Physical proximity to infectious person</td>
<td>The closer the physical proximity, the higher the risk for transmission</td>
</tr>
</tbody>
</table>

Pathogenesis of TB

Infection occurs when a person inhales droplet nuclei containing tubercle bacilli that reach the alveoli of the lungs. These tubercle bacilli are ingested by alveolar macrophages. While most bacilli are destroyed or inhibited, a small number may multiply intracellularly and be released when the macrophages die. If alive, these bacilli may spread by way of lymphatic channels or through the bloodstream to more distant tissues and organs (including areas of the body in which TB disease is most likely to develop: regional lymph nodes, apex of the lung, kidneys, brain, and bone). This process of dissemination primes the immune system for a systemic response. Further details about pathogenesis of latent tuberculosis infection (LTBI) and TB disease are described in Figure 1.3.

Figure 1.3
Pathogenesis of LTBI and TB Disease

Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to the alveoli.
Tubercle bacilli multiply in the alveoli.

A small number of tubercle bacilli enter the bloodstream and spread throughout the body. The tubercle bacilli may reach any part of the body, including areas where TB disease is most likely to develop (such as the brain, larynx, lymph nodes, lungs, spine, bone, or kidneys).

Within 2 to 8 weeks, special immune cells called macrophages ingest and surround the tubercle bacilli. The cells form a barrier shell called a granuloma that keeps the bacilli contained and under control. (This is known as latent TB infection, or LTBI.)

If the immune system cannot keep the tubercle bacilli under control, the bacilli begin to multiply rapidly (TB disease). This process can occur in different areas in the body, such as the lungs, kidneys, brain, or bone (see diagram in box 3).
Latent Tuberculosis Infection (LTBI)

Persons with LTBI have *M. tuberculosis* in their bodies, but do not have TB disease and cannot spread the infection to other people. A person with LTBI is not a TB case. The process of LTBI begins when extracellular bacilli are ingested by macrophages and presented to other white blood cells. This triggers the immune response in which white blood cells kill or encapsulate most of the bacilli, leading to the formation of a granuloma. Once this happens, LTBI has been established. LTBI may be detected by using the interferon-gamma release assay (IGRA), also called a TB blood test, or tuberculin skin test (TST) (see Chapter 2: Testing for Tuberculosis Infection). It can take 2 to 8 weeks after the initial TB infection for the body’s immune system to be able to react to tuberculin and for the IGRA or TST to detect infection. Within weeks after infection, the immune system is usually able to halt the multiplication of the tubercle bacilli, preventing further progression.

TB Disease

In some people, the tubercle bacilli overcome the immune system and multiply, resulting in progression from LTBI to TB disease. Persons who have TB disease are usually infectious and may spread the bacteria to other people. The progression from LTBI to TB disease may occur at any time, but it is most common within the first two years of infection or in the context of certain medical conditions. Body fluid or tissue from the disease site should be collected for AFB smear and culture. Positive culture for *M. tuberculosis* confirms the diagnosis of TB disease (see Chapter 3: Diagnosis of Tuberculosis Disease). Table 1.5 indicates the differences between LTBI and TB disease.
Table 1.5
LTBI vs. TB Disease

<table>
<thead>
<tr>
<th>Person with LTBI</th>
<th>Person with TB Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has a small amount of TB bacteria in his/her body that are alive but <strong>inactive</strong></td>
<td>Has a large amount of <strong>active</strong> TB bacteria in his/her body</td>
</tr>
<tr>
<td><strong>Cannot</strong> spread TB bacteria to others</td>
<td>May spread TB bacteria to others</td>
</tr>
<tr>
<td>Does <strong>not</strong> feel sick, but may become sick if the bacteria in his/her body become active</td>
<td>May feel sick, and may have symptoms such as a cough, fever, and/or weight loss</td>
</tr>
<tr>
<td>Usually has a <strong>positive</strong> TB skin test or TB blood test result indicating TB infection</td>
<td>Usually has a <strong>positive</strong> TB skin test or TB blood test result indicating TB infection</td>
</tr>
<tr>
<td>Chest radiograph is typically <strong>normal</strong></td>
<td>Chest radiograph may be <strong>abnormal</strong></td>
</tr>
<tr>
<td>Sputum smears and cultures are <strong>negative</strong></td>
<td>Sputum smears and cultures may be <strong>positive</strong></td>
</tr>
<tr>
<td>Should consider treatment for LTBI to prevent TB disease</td>
<td>Needs treatment for TB disease</td>
</tr>
<tr>
<td>Does <strong>not</strong> require respiratory isolation</td>
<td>May require respiratory isolation</td>
</tr>
<tr>
<td><strong>Is not</strong> a TB case</td>
<td>Is a TB case</td>
</tr>
</tbody>
</table>

**Risk of Developing TB Disease over a Lifetime**

Without treatment, approximately 5% of persons who have been infected with *M. tuberculosis* will develop TB disease in the first two years after infection, and another 5% will develop TB disease sometime later in life. Thus, without treatment, approximately 10% of persons with normal immune systems who are infected with *M. tuberculosis* will develop TB disease at some point in their lives.

**Sites of TB Disease**

TB disease can occur in pulmonary and extrapulmonary sites.

**Pulmonary TB**

TB disease most commonly affects the lungs; this is referred to as pulmonary TB. Patients with pulmonary TB usually have a cough and an abnormal chest radiograph, and they may be infectious. Most TB cases reported in the United States are pulmonary.
Extrapulmonary TB

Extrapulmonary TB disease occurs in places other than the lungs, including the larynx, the lymph nodes, the pleura, the brain, the kidneys, or the bones and joints. TB can occur anywhere in the body. Persons with extrapulmonary TB disease usually are not infectious unless

- they have pulmonary disease in addition to extrapulmonary disease;
- extrapulmonary disease located in the oral cavity or the larynx; or
- extrapulmonary disease that includes an open abscess or lesion in which the concentration of organisms is high, especially if drainage from the abscess or lesion is extensive or drainage fluid is aerosolized.

Persons with TB pleural effusions may have underlying pulmonary TB that is masked on chest radiograph because the effusion fluid compresses the lung. These patients should be considered infectious until pulmonary TB disease is excluded. In HIV-infected persons, extrapulmonary TB disease is often accompanied by pulmonary TB.

Miliary TB

Miliary TB occurs when tubercle bacilli enter the bloodstream and disseminate to all parts of the body, where they grow and cause disease in multiple sites. This condition is rare but serious. “Miliary” refers to the radiograph appearance of millet seeds scattered throughout the lung (Figure 1.4). It is most common in infants and children younger than 5 years of age and in severely immunocompromised persons. Many TB endemic countries vaccinate infants with the bacille Calmette-Guérin (BCG) vaccine as part of their TB control efforts to prevent children from developing severe disseminated TB or TB meningitis.

Miliary TB may be detected in an individual organ, including the brain; in several organs; or throughout the whole body. The condition is characterized by a large amount of TB bacilli, although it may easily be missed; it is fatal if untreated. Up to 25% of patients with miliary TB may have meningeal involvement.
**TB Meningitis**

When TB occurs in the tissue surrounding the brain or spinal cord, it is called TB meningitis. TB meningitis is often seen at the base of the brain on imaging studies. Symptoms include headache, decreased level of consciousness, and neck stiffness. The duration of illness before diagnosis is variable and relates in part to the presence or absence of other sites of involvement. In many cases, patients with meningitis have abnormalities on a chest radiograph consistent with old or current TB, and they often have miliary TB.

**Risk of LTBI Progressing to TB Disease**

Anyone who has LTBI can develop TB disease, but some people are at higher risk than others (Table 1.6 and Box 1.1). Due to its effect on the immune system, HIV infection is the greatest risk factor for the development of TB disease in persons with LTBI. For those who are infected with both *M. tuberculosis* and HIV and who are not receiving highly active treatment for HIV, the risk of developing TB disease is **7% to 10% for each year of infection**. Those who have both diabetes and TB infection have about a 30% risk of developing TB disease over their lifetime.
**Table 1.6**

**Risk of Developing TB Disease**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Risk of Developing TB Disease</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB infection and no risk factors</td>
<td>About 10% over a lifetime</td>
<td>For people with TB infection, no risk factors, and no treatment, the risk is about 5% in the first 2 years after infection and about 10% over a lifetime.</td>
</tr>
<tr>
<td>TB infection and diabetes</td>
<td>About 30% over a lifetime</td>
<td>For people with TB infection, diabetes, and no LTBI treatment, the risk is about 30% over a lifetime (3 times as high as those with no risk factors).</td>
</tr>
<tr>
<td>TB infection and HIV infection</td>
<td>About 7% to 10% PER YEAR</td>
<td>For people with TB infection, untreated HIV infection and with no LTBI treatment, the risk is about 7% to 10% PER YEAR, a very high risk over a lifetime.</td>
</tr>
</tbody>
</table>

**Box 1.1**

**Persons at Increased Risk for Progression of LTBI to TB Disease**

- Persons infected with HIV
- Children younger than 5 years of age
- Persons who were recently infected with *M. tuberculosis* (within the past 2 years)
- Persons with a history of untreated or inadequately treated TB disease, including persons with fibrotic changes on chest radiograph consistent with prior TB disease
- Persons who are receiving immunosuppressive therapy such as tumor necrosis factor-alpha (TNF) antagonists, systemic corticosteroids equivalent to/greater than 15 mg of prednisone per day, or immunosuppressive drug therapy following organ transplantation
- Persons with diabetes mellitus
- Persons with silicosis; chronic renal failure; leukemia; or cancer of the head, neck, or lung
- Persons who have had a gastrectomy or jejunoileal bypass
- Persons who weigh less than 90% of their ideal body weight
- Cigarette smokers and persons who abuse drugs and/or alcohol
- Populations defined locally as having an increased incidence of disease due to *M. tuberculosis*, including medically underserved, low-income populations
Drug-Resistant TB

Drug-resistant TB is caused by *M. tuberculosis* organisms that are resistant to the drugs normally used to treat the disease. Drug-resistant TB is transmitted in the same way as drug-susceptible TB, and it is no more infectious than drug-susceptible TB. However, delay in the recognition of drug resistance or prolonged periods of infectiousness may facilitate increased transmission and further development of drug resistance.

**Multidrug-Resistant TB and Extensively Drug-Resistant TB**

Multidrug-resistant TB (MDR TB) is caused by organisms that are resistant to the most effective anti-TB drugs, isoniazid and rifampin. These drugs are considered first-line drugs and are used to treat most persons with TB disease (see Chapter 5: Treatment of Tuberculosis Disease).

Extensively drug-resistant TB (XDR TB) is a rare type of drug-resistant TB. XDR TB is resistant to isoniazid and rifampin, as well as any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin). Because XDR TB is resistant to both first-line and second-line drugs, patients are left with treatment options that are more toxic, more expensive, and much less effective.

Drug-resistant TB disease can develop in two different ways called primary and secondary resistance. Primary resistance is caused by person-to-person transmission of drug-resistant organisms. Secondary resistance, or acquired resistance, develops during TB therapy because the patient was not treated with an adequate regimen or did not take the medications as prescribed, or because of other conditions such as malabsorption or drug-drug interactions. Table 1.7 identifies reasons for each type of resistance.

Circumstances in which an exposed person is at an increased risk of infection with drug-resistant TB include the following:

- Exposure to a person who has known drug-resistant TB disease
- Exposure to a person with TB disease who has had prior treatment for TB (treatment failure or relapse) and whose susceptibility test results are unknown
• Exposure to a person with TB disease from an area in which there is a high prevalence of drug resistance, or travel to one of these areas (see the World Health Organization’s “Global Tuberculosis Report, 2020” for a list countries with highest prevalence of drug resistance)

• Exposure to a person who continues to have positive smear and cultures after 2 months of treatment

Table 1.7
Primary and Secondary Drug Resistance

<table>
<thead>
<tr>
<th>Primary Drug Resistance</th>
<th>Secondary Drug Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caused by person-to-person transmission of drug-resistant organisms</td>
<td>Develops during TB treatment</td>
</tr>
</tbody>
</table>

Circumstances that increase a person's risk of infection with drug-resistant TB:
• Exposure to a person who
  • Has known drug-resistant TB
  • Had prior treatment for TB (treatment failure or relapse) and whose susceptibility test results are unknown
  • Is from an area in which there is a high prevalence of drug resistance
  • Continues to have positive smears and cultures after 2 months of treatment
  • Travel in areas with a high prevalence of drug-resistant TB

Circumstances that lead to secondary drug resistance:
• Patient was not treated with the appropriate treatment regimen
• Patient did not follow the treatment regimen as prescribed
  • Took the drugs incorrectly
  • Took the drugs irregularly
• Malabsorption of drugs
• Drug-drug interactions causing low serum levels
TB Classification System

The current clinical classification system used for TB in the United States is based on the pathogenesis of the disease (Table 1.8). It is intended mainly as an operational framework for public health programs. This classification system provides clinicians the opportunity to track the development of TB in their patients. Health care providers should comply with state and local laws and regulations requiring the reporting of TB disease. All persons with Class 3 (clinically active) or Class 5 (TB suspected) TB should be reported promptly to the local or state health department. A patient should not have a Class 5 classification for more than 3 months.

Table 1.8

<table>
<thead>
<tr>
<th>Class</th>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
</table>
| 0     | No TB exposure—Not infected | • No history of TB exposure and no evidence of *M. tuberculosis* infection or disease  
• Negative reaction to TST or IGRA |
| 1     | TB exposure—No evidence of infection | • History of exposure to *M. tuberculosis*  
• Negative reaction to TST or IGRA (test given at least 8 to 10 weeks after exposure) |
| 2     | TB infection—No TB disease | • Positive reaction to TST or IGRA  
• Negative bacteriological studies (smear and cultures)  
• No clinical or radiographic evidence of active TB disease |
| 3     | TB disease clinically active | • Positive culture for *M. tuberculosis* OR  
• Positive reaction to TST or IGRA, plus clinical, bacteriological, or radiographic evidence of current active TB disease |
| 4     | Previous TB disease (not clinically active) | • May have past medical history of TB disease  
• Abnormal but stable radiographic findings  
• Positive reaction to the TST or IGRA  
• Negative bacteriologic studies (smear and cultures)  
• No clinical or radiographic evidence of current active TB disease |
| 5     | TB disease suspected | Signs and symptoms of active TB disease, but medical evaluation not complete |
Knowledge Check

Select the best answer for each question.

1. Tuberculosis (TB) is an airborne disease caused by the bacterium *Mycobacterium tuberculosis*.
   - A. True
   - B. False

2. Generally, what percentage of people in the United States who have TB infection and normal immune systems develop TB disease at some point in their lives?
   - A. 2%
   - B. 10%
   - C. 50%
   - D. 90%

3. HIV-positive persons are not at high risk for active TB disease after infection with *M. tuberculosis*.
   - A. True
   - B. False

4. When a person inhales droplet nuclei containing *M. tuberculosis*, transmission always occurs.
   - A. True
   - B. False

5. What is the difference between primary and secondary drug resistance?
   - A. Primary resistance is caused by person-to-person transmission of drug-resistant organisms.
   - B. Secondary resistance develops during TB treatment.
   - C. Secondary resistance can occur when the patient was not treated with the right TB drugs or the patient did not properly follow the prescribed treatment regimen.
   - D. All of the above

6. Multidrug-resistant TB is resistant to at least the drugs isoniazid and rifampin.
   - A. True
   - B. False

See page 195 for answer key.
Chapter 2 Contents

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Chapter Objectives

After working through this chapter, you should be able to

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

Chapter Introduction

Targeted testing for tuberculosis (TB) is a strategy to diagnose and treat latent TB infection (LTBI) among persons who are at high risk (or increased risk relative to the general U.S. population) for developing TB disease. Treating LTBI supports U.S. TB elimination goals through preventing infected persons from developing TB disease, thereby stopping the spread of TB to others.

All TB 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.
Identifying Persons at High Risk for *M. tuberculosis*

The CDC and the U.S. Preventive Services Task Force (USPSTF) recommend testing people who are at increased risk for TB infection. As part of routine patient evaluations, health care providers should identify persons who are at high risk for TB and test them for *M. tuberculosis* infection. Testing only populations at risk maximizes the positive predictive value of tests for TB infection (i.e., the proportion of persons with positive tests that have LTBI). People who are at low risk generally should not be tested because the positive predictive value in low-risk populations is lower. Testing low-risk populations therefore increases the number of false positive test results and can divert resources away from preventing TB among those most likely to develop it.

Flexibility is needed in defining groups for testing, as the epidemiology of TB can shift over time. For example, 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 might be considered high risk in the future. In general, however, groups at risk fall into two broad categories (Table 2.1):

- People who are at high risk for exposure to or infection with *M. tuberculosis*
- People who are at high risk for developing TB disease once infected with *M. tuberculosis*
### Table 2.1
**Groups at High Risk for TB Infection and TB Disease**

<table>
<thead>
<tr>
<th>People at High Risk for Exposure to or Infection with <em>M. tuberculosis</em></th>
<th>People at High Risk for Developing TB Disease after Infection with <em>M. tuberculosis</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Contacts of people known or presumed to have infectious TB disease</td>
<td>• People living with HIV</td>
</tr>
<tr>
<td>• People who were born in or who frequently travel to countries where TB disease is common, including Mexico, the Philippines, Vietnam, India, China, Haiti, Guatemala, or other countries with high rates of TB</td>
<td>• Children younger than 5 years of age</td>
</tr>
<tr>
<td>• People who currently live or used to live in large group settings where TB is more common, such as, homeless shelters, correctional facilities, or nursing homes</td>
<td>• People recently infected with <em>M. tuberculosis</em> (within the last 2 years)</td>
</tr>
<tr>
<td>• Employees of high-risk congregate settings</td>
<td>• People with a history of untreated or inadequately treated TB disease</td>
</tr>
<tr>
<td>• Health care workers who serve patients with TB disease</td>
<td>• Persons who are receiving immunosuppressive therapy such as tumor necrosis factor-alpha (TNF) antagonists, systemic corticosteroids equivalent to/greater than 15 mg of prednisone per day, or immunosuppressive drug therapy following organ transplantation</td>
</tr>
<tr>
<td>• Populations defined locally as having an increased incidence of LTBI or TB disease, possibly including medically underserved populations, low-income populations, or persons who abuse drugs or alcohol</td>
<td>• Persons with silicosis; chronic renal failure; leukemia; or cancer of the head, neck, or lung</td>
</tr>
<tr>
<td>• Infants, children, and adolescents exposed to adults who are at increased risk for LTBI or TB disease</td>
<td>• Persons with diabetes mellitus</td>
</tr>
<tr>
<td>• Persons who are receiving a gastrectomy or jejunooileal bypass</td>
<td>• Persons who have had a gastrectomy or jejunoileal bypass</td>
</tr>
<tr>
<td>• Persons with low body weight (&lt;90% of ideal body weight)</td>
<td>• Persons with low body weight (&lt;90% of ideal body weight)</td>
</tr>
<tr>
<td>• People who use substances (such as injection drug use)</td>
<td>• People who use substances (such as injection drug use)</td>
</tr>
<tr>
<td>• Populations defined locally as having an increased incidence of disease due to <em>M. tuberculosis</em>, including medically underserved and low-income populations</td>
<td>• Populations defined locally as having an increased incidence of disease due to <em>M. tuberculosis</em>, including medically underserved and low-income populations</td>
</tr>
</tbody>
</table>
Evaluation of Persons with Positive TB Test Results

As soon as possible, persons with positive tests for TB infection should be evaluated for TB disease. An evaluation for TB disease should include a medical history (to determine whether patients have signs or symptoms consistent with TB disease); chest radiography; and, in certain circumstances, sputum smear microscopy, culture, and nucleic acid amplification (NAA) testing (see Chapter 3: Diagnosis of Tuberculosis Disease). Additionally, clinicians should obtain information about any previous positive tests for TB infection or previous treatment for LTBI or TB disease.

Testing Methods for TB Infection

Selection of the most suitable test for detection of *M. tuberculosis* infection should be based on the reasons and context for testing, test availability, and overall cost effectiveness of testing. There are currently two methods available in the United States for the detection of *M. tuberculosis* infection:

- TB blood tests (interferon-gamma release assays [IGRAs])
  - QuantiFERON®-TB Gold Plus (QFT-Plus)
  - T-SPOT®.TB test (T-Spot)
- Mantoux tuberculin skin test (TST)

These tests help clinicians differentiate infected from uninfected people. However, a negative result from any of the tests does not exclude the diagnosis of LTBI or TB disease. Patient management decisions should include epidemiological, historical, and other clinical information. Decisions should not be based on TB blood test or TST results alone. Although both TB blood tests and TSTs provide evidence for infection with *M. tuberculosis*, they cannot distinguish LTBI from TB disease. A diagnosis of LTBI requires that TB disease be excluded by a medical evaluation.

Selecting a Test to Detect TB Infection

Health care providers are encouraged to use newer TB blood tests to screen for LTBI. There are a few preferences and special considerations when determining which test to use.
TB blood tests are the preferred method of testing for

- Groups of people who might be less likely to return for TST reading and interpretation (e.g., homeless persons or drug users).
- People who have received the bacille Calmette-Guérin (BCG) vaccine.
- People who are likely to be infected with *M. tuberculosis* and are at a low to intermediate risk of progression to TB disease.
- People who are unlikely to be infected with *M. tuberculosis* (note: persons who are unlikely to be infected generally should not be tested for TB; a confirmatory test is recommended if the initial test is positive in those unlikely to be infected).

Current U.S. guidelines suggest the TST as the recommended method of testing for children younger than 5 years of age while noting that some experts use TB blood tests in younger children. Clinicians may also choose to consult the American Academy of Pediatrics (AAP) guidance on the use of the TB blood test in children.

In general, using either a TB blood test or a TST is acceptable medical and public health practice. Routine testing using both a TB blood test and TST is not recommended. However, there are certain situations where results from both tests may be useful. When the initial test is negative, a second test may be performed when the risk of not identifying TB infection exceeds the risk from initiating inappropriate therapy. If the second test is positive and the person has a risk of infection, risk of progression to disease, or risk of poor outcome, the positive result enhances the ability to diagnose and treat TB disease or LTBI. If the second test is also negative, the lack of evidence of infection must be weighed along with other clinical factors as part of the evaluation for TB disease or LTBI.

When the initial test is positive, a second test may be performed if the person has a low risk of both infection and progression from infection to TB disease (e.g., populations being tested for administrative reasons rather than based on risk). In this case, a person at low risk should be considered positive only if both tests are positive. A second test may also be helpful if additional evidence of infection is required to encourage the patient’s acceptance and adherence to treatment. For example, when counseling a BCG-immunized person who has a positive TB skin test, a subsequent positive TB blood test (the results of which are not affected by BCG immunization) might be meaningful to the patient in accepting LTBI diagnosis and treatment.
In addition, a repeat TB blood test or a TST should be given when the initial test result is indeterminate, borderline, or invalid and a reason for testing persists.

A comparison of the TB blood tests and the TST is presented in Table 2.2.

**Table 2.2**  
**TB Blood Tests vs. TSTs**

<table>
<thead>
<tr>
<th>TB Blood Tests</th>
<th>TSTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood is drawn for testing; test measures the immune response to TB proteins in whole blood</td>
<td>Tuberculin is injected under the skin and produces a delayed-type hypersensitivity reaction if the person is infected with <em>M. tuberculosis</em></td>
</tr>
<tr>
<td>Requires one patient visit to conduct the test</td>
<td>Requires two or more patient visits to conduct the test</td>
</tr>
<tr>
<td>Results can be available in 24 hours (depending on availability of phlebotomy, batching of specimens by the laboratory, and transport)</td>
<td>Results are available 48 to 72 hours after TST administration</td>
</tr>
<tr>
<td>Does not cause booster phenomenon</td>
<td>Can cause booster phenomenon (see pg. 38)</td>
</tr>
<tr>
<td>BCG vaccination does not cause false-positive result</td>
<td>BCG vaccination can cause false-positive result</td>
</tr>
<tr>
<td>Infection with most nontuberculous mycobacteria does not cause false-positive result</td>
<td>Infection with nontuberculous mycobacteria can cause a false-positive result</td>
</tr>
<tr>
<td>Results are based on the amount of IFN-γ released or the number of IFN-γ producing cells (spots) produced</td>
<td>Results are based on millimeters (mm) of induration and the person’s risk of acquiring TB infection or progressing to TB disease</td>
</tr>
<tr>
<td>False negative and false positive tests can occur</td>
<td>False negative and false positive tests can occur</td>
</tr>
</tbody>
</table>
TB Blood Tests (Interferon-Gamma Release Assays [IGRAs])

TB blood tests (interferon-gamma release assays [IGRAs]) detect the presence of *M. tuberculosis* infection by measuring the immune response to TB proteins in whole blood. TB blood tests may be used to identify people who are likely to benefit from LTBI treatment, including people who are or will be at increased risk of progression to TB disease if infected with *M. tuberculosis*.

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

- QuantiFERON®-TB Gold Plus (QFT-Plus)
- T-Spot®.*TB test* (T-Spot)

A comparison of the QFT-Plus and the T-Spot is presented in Table 2.3.

**Conducting a TB Blood Test**

To conduct a TB blood test, a patient’s blood samples are mixed with antigens and controls. The major antigens used, ESAT-6 and CFP-10, are found in *M. tuberculosis* strains. If a person has *M. tuberculosis* infection, the blood cells in the sample will recognize the antigens and release IFN-γ in response. Control substances are used for comparison purposes to help verify test results and to determine a person’s background level of IFN-γ.

Health care workers should be properly trained on how to conduct a TB blood test. In general, health care workers should read the instructions from the manufacturer and follow the steps below:

- Confirm arrangements for testing in a qualified laboratory
- Arrange for delivery of the blood sample to the laboratory within the time the laboratory specifies to ensure testing of samples containing viable blood cells
- Draw a blood sample from the patient according to the test manufacturer’s instructions (Figure 2.1)
- Schedule a follow-up appointment for the patient to receive test results
- Provide follow-up evaluation and treatment as needed based on test results
Table 2.3
Comparison of the QFT-Plus and the T-Spot

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>QFT-Plus</th>
<th>T-Spot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Processing Time</td>
<td>Within 16 hours (whole blood)</td>
<td>Within 8 to 32 hours (blood cells)</td>
</tr>
<tr>
<td>M. tuberculosis Antigens</td>
<td>ESAT-6 and CFP-10</td>
<td>ESAT-6 and CFP-10</td>
</tr>
<tr>
<td>Measurement</td>
<td>IFN-γ concentration</td>
<td>Number of IFN-γ producing cells (spots)</td>
</tr>
<tr>
<td>Possible Results</td>
<td>Positive, negative, indeterminate</td>
<td>Positive, negative, invalid, borderline</td>
</tr>
</tbody>
</table>

Figure 2.1
Health Care Worker Collecting a Blood Sample for a TB Blood Test

Interpreting TB Blood Test Results

QFT-Plus results are based on the amount of IFN-γ that is released in response to the M. tuberculosis antigens and control substances. T-Spot results are based on the number of IFN-γ producing cells (spots) produced. Laboratories should report both the qualitative and quantitative test results. Qualitative results are reported as positive, negative, indeterminate, invalid, or borderline (Table 2.4). Quantitative results are reported as numerical values. Quantitative results may be useful for clinical decision making in combination with the patient’s risk factors (for in-depth information on interpretation of results, clinicians should refer to the package.
To calculate the test results, laboratories use software provided by the manufacturer. The laboratory conducting the analysis of the test will then submit a report of the results back to the health care provider who requested the test.

Health care workers should consider each TB blood test result and its interpretation along with other epidemiologic, historical, physical, and diagnostic findings. Regardless of test results, if a patient has signs and symptoms of TB disease or is at high risk for developing TB disease, the patient should receive further evaluation.

**Table 2.4**
**Interpretation of TB Blood Test Results**

<table>
<thead>
<tr>
<th>TB Blood Test Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td><em>M. tuberculosis</em> infection likely.</td>
</tr>
<tr>
<td>Negative</td>
<td><em>M. tuberculosis</em> infection unlikely, but cannot be excluded, especially if</td>
</tr>
<tr>
<td></td>
<td>• Patient has signs and symptoms of TB disease.</td>
</tr>
<tr>
<td></td>
<td>• Patient has a high risk medical condition for developing TB disease once infected with <em>M. tuberculosis</em> (e.g., HIV infection, immunosuppression).</td>
</tr>
<tr>
<td>Indeterminate (QFT-Plus only) or Invalid (T-Spot only)</td>
<td>The test did not provide useful information about the likelihood of <em>M. tuberculosis</em> infection. Repeating a TB blood test or performing a TST may be useful.</td>
</tr>
<tr>
<td>Borderline (T-Spot only)</td>
<td>Repeating a TB blood test or performing a TST may be useful.</td>
</tr>
</tbody>
</table>

**False-Positive TB Blood Test Results**

Errors in running and interpreting the test can decrease the accuracy of TB blood tests and lead to false-positive results. Therefore, it is important to perform the test according to the manufacturer’s instructions.
False-Negative TB Blood Test Results

Some people have a negative TB blood test result even though they are infected with *M. tuberculosis*. False-negative results can be caused by many things. For example, false-negative TB blood test results may occur if the TB infection occurred within 8 weeks of testing because it can take 2 to 8 weeks after being infected with *M. tuberculosis* for the body’s immune system to mount a response detectable by the test. Thus, negative TB blood test results for contacts of persons with infectious TB disease should be confirmed with a repeat test 8 to 10 weeks after their last exposure to TB. Patients with untreated, advanced HIV infection (or AIDS) or advanced immunosuppression, such as sepsis, can also have false-negative results.

The following are other factors that can cause a false-negative TB blood test result:

- Incorrect blood sample collection
- Incorrect handling of the blood collection tubes
- Incorrect performance of the assay

Advantages and Limitations of TB Blood Tests

There are both advantages and disadvantages to using TB blood tests for TB testing (Table 2.5).

**Table 2.5**

**Advantages and Limitations of TB Blood Tests**

<table>
<thead>
<tr>
<th>Advantages of TB Blood Tests</th>
<th>Disadvantages of TB Blood Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Requires only a single patient visit to conduct the test</td>
<td>• Blood samples must be processed within 8-32 hours of collection</td>
</tr>
<tr>
<td>• Results can be available within 24 hours</td>
<td>• Errors in collecting or transporting blood specimens or in running and interpreting the test can decrease accuracy of the test</td>
</tr>
<tr>
<td>• Does not cause the booster phenomenon</td>
<td>• Tests may be expensive</td>
</tr>
<tr>
<td>• BCG vaccination does not cause a false-positive result</td>
<td></td>
</tr>
</tbody>
</table>
Mantoux Tuberculin Skin Test (TST)

The TST is another test 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.

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 Booster Phenomenon under “Special Considerations When Using the TST” 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 intradermally (just beneath the surface of the skin) with a disposable 27-gauge tuberculin syringe 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 2.2). Institutional guidelines regarding universal precautions for infection control (e.g., the use of gloves) should be followed (see Chapter 6: Tuberculosis Infection Control).

Reading the TST

A health care worker trained to read TST results should assess the reaction 48 to 72 hours after the injection. 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 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 2.3). Erythema (redness) should not be measured (Figure 2.4). Induration, even those classified as negative, should be recorded in millimeters. If no induration is found, “0 mm” should be recorded.
Interpreting TST Reactions

Interpretation of TST reactions depends on the measurement of induration in millimeters and the person’s risk of TB infection or progression to TB disease if infected (Table 2.6).
Table 2.6
Interpreting the TST Reaction

<table>
<thead>
<tr>
<th>5 or more millimeters</th>
<th>10 or more millimeters</th>
<th>15 or more millimeters</th>
</tr>
</thead>
<tbody>
<tr>
<td>An induration of <strong>5 or more millimeters</strong> is considered positive for</td>
<td>An induration of <strong>10 or more millimeters</strong> is considered positive for</td>
<td>An induration of <strong>15 or more millimeters</strong> is considered positive for</td>
</tr>
<tr>
<td>• People living with HIV</td>
<td>• People born in countries where TB disease is common, including Mexico, the Philippines, Vietnam, India, China, Haiti, and Guatemala</td>
<td>• People with no known risk factors for TB</td>
</tr>
<tr>
<td>• Recent contacts of people with infectious TB disease</td>
<td>• People who abuse drugs or alcohol</td>
<td></td>
</tr>
<tr>
<td>• People who have fibrotic changes on a chest radiograph</td>
<td>• Mycobacteriology laboratory workers</td>
<td></td>
</tr>
<tr>
<td>• Patients with organ transplants</td>
<td>• People who live or work in high-risk congregate settings (e.g., nursing homes, homeless shelters, or correctional facilities)</td>
<td></td>
</tr>
<tr>
<td>• Other immunosuppressed patients (e.g., patients on prolonged therapy with corticosteroids equivalent to/greater than 15 mg per day of prednisone or those taking TNF-$$\alpha$$ antagonists)</td>
<td>• People with certain medical conditions that place them at high risk for TB (e.g., silicosis, diabetes mellitus, severe kidney disease, certain types of cancer, or certain intestinal conditions)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• People with a low body weight (&lt;90% of ideal body weight)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Children younger than 5 years of age</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Infants, children, and adolescents exposed to adults in high-risk categories</td>
<td></td>
</tr>
</tbody>
</table>
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 2.7). Infection with nontuberculous mycobacteria can sometimes cause a false-positive reaction to the TST. Another cause of a false-positive reaction is bacille Calmette-Guérin (BCG), 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 if the results are not measured or interpreted properly.

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

- Anergy
- 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)
- Very young age (younger than 6 months, i.e., immature immunity)
- Advanced age (i.e., 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
- Live-virus vaccinations
- Recent TB infection
**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; or other factors. HIV-infected persons may have a compromised ability to react to TST because of cutaneous anergy associated with progressive HIV immunosuppression.

**Live-Virus Vaccination**

Vaccination with live viruses might interfere with TST reactivity and cause false-negative reactions; live-virus vaccinations include measles, mumps, and rubella. For persons scheduled to receive both a TST and live virus vaccines, the TST should generally be administered 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.
Table 2.7
False-Positive and False-Negative Reactions to the TST

<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Possible Cause</th>
<th>People at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>False-positive</td>
<td>Nontuberculous mycobacteria (NTM)</td>
<td>People infected with NTM</td>
</tr>
<tr>
<td></td>
<td>BCG vaccination</td>
<td>People vaccinated with BCG</td>
</tr>
<tr>
<td></td>
<td>Administering incorrect antigen</td>
<td>Any person being tested</td>
</tr>
<tr>
<td></td>
<td>Incorrect interpretation of TST result</td>
<td>Any person being tested</td>
</tr>
<tr>
<td>False-negative</td>
<td>Anergy</td>
<td>People living with HIV, other people with weakened immune systems, severe TB disease, viral infections (e.g., measles, mumps, chicken pox), or bacterial infections (e.g., typhoid)</td>
</tr>
<tr>
<td></td>
<td>Recent TB infection</td>
<td>People infected with <em>M. tuberculosis</em> within the past 8 weeks</td>
</tr>
<tr>
<td></td>
<td>Recent live-virus vaccination</td>
<td>People who recently received a live-virus vaccination (e.g., mumps, measles, rubella)</td>
</tr>
<tr>
<td></td>
<td>Concurrent viral infection</td>
<td>People with current viral infection (e.g., HIV, measles, mumps, chickenpox)</td>
</tr>
<tr>
<td></td>
<td>Concurrent bacterial infection</td>
<td>People with current bacterial infection (e.g., typhoid fever, brucellosis, typhus, leprosy, pertussis)</td>
</tr>
<tr>
<td></td>
<td>Concurrent fungal infection</td>
<td>People with fungal infection</td>
</tr>
<tr>
<td></td>
<td>Chronic renal failure</td>
<td>People with chronic renal failure</td>
</tr>
<tr>
<td></td>
<td>Low protein states</td>
<td>People with severe protein depletion or afibrinogenemia</td>
</tr>
<tr>
<td></td>
<td>Diseases affecting lymphoid organs</td>
<td>People with Hodgkin's disease, lymphoma, chronic leukemia, or sarcoidosis</td>
</tr>
<tr>
<td></td>
<td>Immunosuppressive drugs</td>
<td>People taking medical steroids, TNF-alpha blockers, or comparable drugs</td>
</tr>
<tr>
<td></td>
<td>Very young age or advanced age (i.e., immature or waning immunity)</td>
<td>Children younger than 6 months of age or elderly patients</td>
</tr>
<tr>
<td></td>
<td>Stress</td>
<td>People who have had surgery, burns, mental illness, or graft-versus-host reactions</td>
</tr>
<tr>
<td></td>
<td>Incorrect storage or handling of antigen, incorrect administration of the TST, or improper measurement or interpretation of results</td>
<td>Any person being tested</td>
</tr>
</tbody>
</table>
Special Considerations When Using the TST

**Booster Phenomenon**

The booster phenomenon occurs mainly in previously infected older adults whose ability to react to tuberculin has waned over time (Figure 2.5). 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), but the second positive test reaction is actually a boosted reaction due to TB infection that occurred a long time ago. These people should still be considered for LTBI treatment after ruling out TB disease, particularly if they have risk factors for progression to disease.

TB blood tests do not boost subsequent test results because, unlike the TST, the patient is not exposed to the *M. tuberculosis* antigens. However, the TST can boost a subsequent TB blood test. Therefore, if a person will be tested with both the TST and a TB blood test, it is recommended to conduct the TB blood test either before or at the same time as the TST.

**Figure 2.5**

**The TST Booster Phenomenon**

As the years pass, the person’s ability to react to tuberculin lessens. Occurs mainly in previously infected older adults whose ability to react to tuberculin has decreased over time. These people should still be considered for LTBI treatment after ruling out TB disease, particularly if they have risk factors for progression to disease.
**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 2.6). Two-step testing should be used for the initial skin testing of persons who will be retested periodically.

If the reaction to the first TST is classified as negative, a second TST should be repeated 1 to 3 weeks later. A positive reaction to the second TST likely represents a boosted reaction. Based on 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 skin test result is also negative, the person should be classified as having a negative baseline TST result.

**Figure 2.6**

**Two-Step TST Testing**

- **Baseline Skin Test**
  - **Reaction**
    - **NEGATIVE**
      - Retest 1-2 weeks later
    - **POSITIVE**
      - Person likely has TB infection
  - **Follow-up for positive TST and evaluate for LTBI treatment**
  - **NEGATIVE**
    - Person likely does NOT have TB Infection
  - **POSITIVE**
    - The reaction is considered a boosted reaction (due to TB infection that occurred a long time ago)
  - Retesting not necessary. Person likely has TB infection.
**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.

**Interpreting TST Reactions for Occupational Exposure**

For people who may be exposed to TB on the job (such as health care workers and staff at nursing homes or correctional facilities), the interpretation of the TST reaction depends on the employee’s individual risk factors for TB and the risk for exposure to TB on the job. For more information on testing health care workers, please refer to *Tuberculosis Screening, Testing, and Treatment of U.S. Health Care Personnel: Recommendations from the National Tuberculosis Controllers Association and CDC, 2019*, available on the CDC TB website.

**Advantages and Disadvantages of the TST**

As with TB blood tests, there are both advantages and disadvantages to using the TST to test for TB infection (Table 2.8)

**Table 2.8**

**Advantages and Disadvantages of the TST**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Simple to perform (e.g., no laboratory equipment required)</td>
<td>• Requires trained personnel to administer and interpret</td>
</tr>
<tr>
<td>• Low cost</td>
<td>• Requires 2 or more patient visits</td>
</tr>
<tr>
<td>• No need for phlebotomy</td>
<td>• False-positive results can occur due to previous BCG vaccination</td>
</tr>
<tr>
<td>• Well-established definitions of TST conversions</td>
<td>• False-positive results can occur due to nontuberculous mycobacteria</td>
</tr>
<tr>
<td></td>
<td>• False-negative results can occur due to concurrent infections</td>
</tr>
<tr>
<td></td>
<td>• Rare adverse effects</td>
</tr>
<tr>
<td></td>
<td>• Can cause the booster phenomenon</td>
</tr>
<tr>
<td></td>
<td>• May be subject to biases and errors with TST placement and reading</td>
</tr>
</tbody>
</table>
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. The primary benefit of BCG is its effectiveness in preventing 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 severe disseminated TB disease in young children in the United States;
- the variable efficacy of the BCG vaccine against pulmonary TB;
- the low overall risk of infection with *M. tuberculosis* in the United States; and
- the vaccine’s interference with the interpretation of the TST.

Outside of the United States, many countries with a high prevalence of TB vaccinate infants with BCG as part of their pediatric TB control efforts.

The BCG vaccine may be considered in limited circumstances for select 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.

As discussed previously, BCG vaccination may cause a subsequent false-positive reaction to the TST. If a decision is made to use the TST for a person who has been vaccinated with BCG, the reaction should be interpreted using the same criteria for those not vaccinated with BCG.

TB blood tests use *M. tuberculosis* specific antigens that do not cross react with the BCG vaccine, and therefore do not cause false positive reactions in BCG vaccine recipients. TB blood tests are the preferred test for people who have received the BCG vaccine.
Knowledge Check

Select the best answer for each question.

1. The Mantoux tuberculin skin test (TST) is performed by placing an intradermal injection of 0.1 ml of purified protein derivative (PPD) containing 5 tuberculin units (TU) into the volar surface of the forearm.
   A. True
   B. False

2. Which of the following groups are more likely to be exposed to or infected with *M. tuberculosis*?
   1. Contacts of people known or presumed to have infectious TB
   2. People who live in, or have lived in, high-risk congregate settings (for example, homeless shelters or correctional facilities)
   3. Health care workers who serve patients with TB disease
   4. People born in or who frequently travel to countries where TB disease is common, including Mexico, the Philippines, Vietnam, India, China, Haiti, and Guatemala
   A. 1, 2, and 3 are correct
   B. 1 and 3 are correct
   C. 2 and 3 are correct
   D. Only 4 is correct
   E. All are correct

3. For the following groups, what induration size is considered a positive reaction to the tuberculin skin test? (Choose only 1 answer for all 3 groups.)
   - Recent contacts of a TB case
   - HIV-positive persons
   - Persons with fibrotic changes on a chest radiograph consistent with prior TB
   A. 5 millimeters or greater
   B. 10 millimeters or greater
   C. 15 millimeters or greater

4. Both the TB blood test (interferon-gamma release assay [IGRA] test) and TST are contraindicated for persons who have been vaccinated with BCG.
   A. True
   B. False
5. The only approved TB blood tests for detection of *M. tuberculosis* are interferon-gamma release assays (IGRAs).
   A. True
   B. False

6. Which of the following is NOT true about a TB blood test?
   A. Routine testing using both a TB blood test and TST is not recommended.
   B. TB blood test results can be available in 24 hours.
   C. TB blood test can cause booster phenomenon.
   D. BCG vaccine does not cause false-positive result.
   E. Results are based on the amount of interferon-gamma (IFN-γ) released or the number of IFN-γ producing cells (spots) produced.

7. Which of the following is true about two-step testing?
   A. Two-step testing should be used for the initial skin testing of adults who will be retested periodically.
   B. Two-step testing should be used on all children.
   C. Two-step testing should be used on all adults.
   D. A negative reaction to the second test probably represents a boosted reaction.

8. TB blood tests are the preferred method of testing for (select all that apply)
   A. Homeless persons or drug users.
   B. People who have received the BCG vaccine.
   C. Children younger than 5 years of age.
   D. A and B
   E. All of the above

9. The presence of erythema (redness) at the site of the skin test injection indicates that a person has TB infection
   A. True
   B. False

10. After TB has been transmitted, how long does it take for the body’s immune system to mount a response detectable by a TST or IGRA?
    A. 6 months or more
    B. 7 to 10 days
    C. 2 to 8 weeks
    D. 24 hours
11. What are IGRA results based on?
   A. Amount of heparin in the sample
   B. The size of the induration at the site of the injection
   C. Amount of interferon-gamma (IFN-γ) released in response to the antigens and control substances
   D. Number of acid-fast bacilli present

See page 195 for answer key.
Chapter 3 Contents

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Chapter Objectives

After working through this chapter, you should be able to

• Describe the five components of a TB medical evaluation.
• Identify the major components of TB diagnostic microbiology.
• List at least five symptoms of pulmonary TB disease.
• Explain the purpose and significance of bacteriologic examination of clinical specimens.
• Explain the purpose and significance of genotyping.

Chapter Introduction

Tuberculosis (TB) is not as common in the United States as it was many years ago; consequently, clinicians do not always consider the possibility of TB disease when evaluating patients who have symptoms. As a result, the diagnosis of TB disease may be delayed or even overlooked, and the patient may remain ill and possibly infectious for a prolonged period.

Not everyone with TB disease has symptoms. However, most individuals with TB disease have one or more symptoms that lead them to seek medical care. All persons with symptoms of TB disease, a positive TB blood test (interferon-gamma release assay [IGRA]), or a positive tuberculin skin test (TST) result indicative of M. tuberculosis infection should be medically evaluated to exclude TB disease.
Medical Evaluation

A complete medical evaluation for TB disease includes the following five components:

1. Medical history
2. Physical examination
3. Test for *M. tuberculosis* infection
4. Chest radiograph
5. Bacteriologic examination

**1. Medical History**

When conducting a medical history, the clinician should ask if any symptoms of TB disease are present; if so, for how long; and if there is known exposure to a person with infectious TB disease. Equally important is obtaining information on whether or not the person has been diagnosed with and/or treated for latent tuberculosis infection (LTBI) or TB disease in the past. Clinicians may also contact the local health department for information on whether a patient has a past history of LTBI or TB disease. If the previous treatment regimen for TB disease was inadequate or if the patient did not adhere to therapy, TB disease may recur and possibly be drug resistant. It is important to consider demographic factors (e.g., country of origin, travel to a country where TB is common, age, ethnicity, occupation, or race) that may increase the patient’s risk for being exposed to TB infection (see Chapter 1: Transmission and Pathogenesis of Tuberculosis). Clinicians should determine if the patient has underlying medical conditions, especially human immunodeficiency virus (HIV) infection, other immunocompromising conditions, or diabetes, which increase the risk for progression from LTBI to TB disease.

As discussed in Chapter 1: Transmission and Pathogenesis of Tuberculosis, TB disease most commonly affects the lungs; this is referred to as pulmonary TB disease. Pulmonary TB disease usually causes one or more of the symptoms indicated in Table 3.1.

Extrapulmonary TB disease, which affects organs in addition to or instead of the lungs, may cause symptoms related to the part of the body that is affected (Table 3.1). For example, TB of the spine may cause back pain, TB of the kidney may cause blood in the urine, and TB meningitis may cause headache or confusion.
Extrapulmonary TB disease should be considered in the differential diagnosis of ill persons who have systemic symptoms and who are at high risk for TB disease.

Symptoms associated with pulmonary and extrapulmonary TB disease can be caused by other diseases; however, these symptoms should prompt the clinician to consider TB disease.

**Table 3.1**

**Symptoms of Pulmonary and Extrapulmonary TB Disease**

<table>
<thead>
<tr>
<th>Symptoms of Pulmonary TB Disease</th>
<th>Symptoms of Possible Extrapulmonary TB Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cough (especially lasting for 3 weeks or longer)</td>
<td>• Blood in the urine (may indicate TB of the kidney)</td>
</tr>
<tr>
<td>• Coughing up sputum or blood (hemoptysis)</td>
<td>• Headache or confusion (may indicate TB meningitis)</td>
</tr>
<tr>
<td>• Chest pain</td>
<td>• Back pain (may indicate TB of the spine)</td>
</tr>
<tr>
<td>• Loss of appetite</td>
<td>• Hoarseness (may indicate TB of the larynx)</td>
</tr>
<tr>
<td>• Unexplained weight loss</td>
<td>• Loss of appetite</td>
</tr>
<tr>
<td>• Night sweats</td>
<td>• Unexplained weight loss</td>
</tr>
<tr>
<td>• Fever</td>
<td>• Night sweats</td>
</tr>
<tr>
<td>• Fatigue</td>
<td>• Fever</td>
</tr>
</tbody>
</table>

**2. Physical Examination**

A physical examination is an essential part of any patient evaluation. It cannot be used to confirm or rule out TB disease, but it can provide valuable information about the patient’s overall condition, inform the method of diagnosis, and reveal other factors that may affect TB disease treatment in the event of a diagnosis.

**3. Test for M. tuberculosis Infection**

Selection of the most suitable tests 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:

- TB blood tests (Interferon-gamma release assays [IGRA]) *(Figure 3.1)*
- Mantoux tuberculin skin test (TST) *(Figure 3.2)*
Figure 3.1
TB Blood Tests

QuantiFERON®-TB Gold Plus (QFT-Plus)
Photo courtesy of Tennessee Public Health Laboratory

T-SPOT®.TB test (T-Spot)
Photo courtesy of San Antonio Metro Health District Laboratory

Figure 3.2
Mantoux Tuberculin Skin Test

These tests help clinicians differentiate people infected with *M. tuberculosis* from those uninfected. However, a negative test result does not exclude the diagnosis of TB disease or LTBI (see Chapter 2: Testing for Tuberculosis Infection).

4. Chest Radiograph

With pulmonary TB being the most common form of TB, the chest radiograph (x-ray) is useful for diagnosis of TB disease. Chest abnormalities can suggest pulmonary TB disease (Figure 3.3). A posterior-anterior radiograph of the chest is the standard view used for the detection of TB-related chest abnormalities. In some cases, a lateral or lordotic view may be helpful, especially in children.
In some instances, a computerized tomography (CT) scan may provide additional information. A CT scan provides more detailed images of parts of the upper body that cannot easily be seen on a standard chest radiograph; however, CT scans can be difficult to obtain due to reasons such as cost and access.

In pulmonary TB disease, radiographic abnormalities are often seen in the apical and posterior segments of the upper lobe or in the superior segments of the lower lobe. However, lesions may appear anywhere in the lungs and may differ in size, shape, density, and cavitation, especially in HIV-infected and other immunosuppressed persons. Radiographic abnormalities in children tend to be minimal with a greater likelihood of lymphadenopathy, more easily diagnosed on the lateral film.

Mixed nodular and fibrotic lesions may contain slowly multiplying tubercle bacilli and have the potential for progression to TB disease. Individuals with lesions consistent with findings of “old” TB disease on a chest radiograph who also have a positive TST reaction or a positive TB blood test result should be considered high-priority candidates for treatment of LTBI (see Chapter 4: Treatment for Latent Tuberculosis Infection). Before treating for LTBI, TB disease must be excluded by obtaining three specimens for acid-fast bacilli (AFB) smear and culture, because “old” TB cannot be differentiated from active TB disease based on radiographic appearance alone. Conversely, fully calcified, discrete nodular lesions without fibrosis likely represent granulomas and pose a lower risk for future progression to TB disease.
In HIV-infected persons, pulmonary TB disease may present with atypical findings or with no lesions seen on the chest radiograph. The radiographic appearance of pulmonary TB disease in persons infected with HIV might be typical; however, cavitary disease is less common among such patients. More common chest radiograph findings for HIV-infected persons include infiltrates in any lung zone, mediastinal or hilar adenopathy, or occasionally a normal chest radiograph. Typical cavitary lesions are usually observed in patients with higher CD4 counts, and more atypical patterns are observed in patients with lower CD4 counts, because cavitation is thought to occur as a result of the immune response to TB bacteria. In HIV-infected persons, almost any abnormality on a chest radiograph may be indicative of TB disease.

Abnormalities seen on chest radiographs may be suggestive of TB disease, but they are not by themselves diagnostic of TB disease. Chest radiographs may be used to exclude pulmonary TB disease in a person who has a positive TST reaction or TB blood test and who has no symptoms or signs of TB disease.

In patients with symptoms and signs of TB disease, a negative chest radiograph result does not exclude TB disease.

5. Bacteriologic Examination of Clinical Specimens
Examinations of clinical specimens (e.g., sputum, urine, or cerebrospinal fluid) are of critical diagnostic importance. The specimens should be examined and cultured in a laboratory that specializes in testing for *M. tuberculosis*. Optimal bacteriologic examination has five parts:

- Specimen collection, transport, and processing
- AFB smear classification
- Direct detection of *M. tuberculosis* in clinical specimens using nucleic acid amplification (NAA) and, as applicable, molecular detection of resistance
- Specimen culture and identification of *M. tuberculosis*
- Drug susceptibility testing using growth-based and molecular methods

**Specimen Collection, Transport, and Processing**
For diagnostic purposes, any person presumed to have TB disease at any anatomical site, even individuals without respiratory symptoms, should have sputum specimens collected for an AFB smear and culture. At least three
consecutive sputum specimens are needed, each collected in 8- to 24-hour intervals, with at least one being an early morning specimen. If possible, specimens should be obtained in an airborne infection isolation (AI) room (Figure 3.4); a sputum collection booth; or another isolated, well-ventilated area (e.g., outdoors). Meticulous attention to detail during the collection and subsequent laboratory processing of the specimen can improve yield.

Figure 3.4
TB Patient Coughing Up Sputum in AI Room

During specimen collection, patients produce an aerosol that may be hazardous to health care personnel or other patients in close proximity. For this reason, precautionary measures for infection control must be followed during sputum collection, induction, bronchoscopy, and other common diagnostic procedures (see Chapter 6: TB Infection Control).

Specimen Collection Methods for Pulmonary TB Disease
Respiratory specimen collection methods for pulmonary TB disease (Table 3.2) include

- Spontaneous sputum sample (coughing)
- Sputum induction
- Bronchoscopy
- Gastric aspiration
Spontaneous sputum sample (coughing)

Coughing is the most common method for spontaneous sputum collection. Coughing should be supervised to ensure that the sputum is collected correctly. A health care worker wearing the recommended personal protective equipment should coach and directly supervise the patient when sputum is collected (Figure 3.5). Patients should be informed that sputum is the material brought up from the lungs, and that mucus from the nose or throat and saliva are not good specimens. Unsupervised patients are less likely to provide a specimen that is adequate in quality (i.e., thick material that contains mucus and pus) or quantity (ideally 3–5 ml) for assessment. Specimen quality is assessed by the laboratory, and collection of additional specimens or an alternate collection method may be necessary if poor-quality specimens are obtained. Some laboratories may also reject specimens not meeting their submission criteria.

Figure 3.5
Patient Coughing Up Sputum Under Supervision

Sputum Induction

For patients unable to cough up sputum spontaneously, deep sputum-producing coughing may be induced by inhalation of an aerosol of warm, sterile, hypertonic saline (3–5%). Because induced sputum is very watery and resembles saliva, it should be labeled “induced” to ensure that laboratory staff do not discard it for unacceptable quality (e.g., thin and watery). It is of note that diagnostic yield of induced sputum increases with multiple specimens, with 99–100% yield when three or more specimens are obtained.
**Bronchoscopy with Bronchioalveolar Lavage (BAL)**

A bronchoscopy (Figure 3.6) is a medical procedure that allows visualization of the inside of a person’s airways. The airways are called the bronchial tubes or bronchi. The bronchi may be washed, or lavaged (bronchioloalveolar lavage [BAL]), to obtain a specimen.

Bronchoscopy might be needed for specimen collection if previous spontaneous or induced sputum results have been nondiagnostic and doubt exists as to the diagnosis. In this case, bronchoscopy should always be performed with proper infection control measures and, when possible, should be the last procedure of the day (see Chapter 6: TB Infection Control). Bronchoscopy might be necessary if TB is among several diagnoses being considered. In this case, three spontaneous or induced sputa should ideally be collected first to assess for a diagnosis of TB disease before bronchoscopy. Bronchial washings, brushings, and transbronchial lung biopsy specimens may be obtained, depending on bronchoscopy findings. Sputum collected after a bronchoscopy may also be useful for a diagnosis. Bronchoscopy for diagnosis of TB should not be performed prior to spontaneous or induced sputum collection, but rather used as an additional diagnostic procedure as needed.

Figure 3.6
Performing a Bronchoscopy

Whenever feasible, bronchoscopy should be performed in a room that meets the ventilation requirements for an All room. At a minimum, health care workers should wear N95 respirators during a bronchoscopy procedure on a patient with presumed or confirmed infectious TB disease (see Chapter 6: TB Infection Control).
Gastric Aspiration

Gastric aspiration is a procedure sometimes used to obtain a specimen for culture when a patient cannot cough up adequate sputum. A tube is inserted through the mouth or nose and into the stomach to recover sputum that was coughed into the throat and then swallowed. This procedure is particularly useful for diagnosis in children, who are often unable to cough up sputum (Figure 3.7). Gastric aspiration often requires hospitalization and should be performed in the morning before the patient gets out of bed or eats, as morning is the optimal time to collect swallowed respiratory secretions from the stomach. Specimens obtained by gastric aspiration should be transported to the laboratory immediately for neutralization or neutralized immediately at the site of collection.
### Table 3.2
Methods of Obtaining a Respiratory Specimen

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spontaneous Sputum Sample</strong></td>
<td>Patient coughs up sputum into a sterile container</td>
<td>• Inexpensive • Easy to do</td>
<td>• Patient may not be able to cough up sputum without assistance or may spit up saliva instead of sputum • Health care provider must coach and supervise the patient when collecting sputum</td>
</tr>
<tr>
<td><strong>Sputum Induction</strong></td>
<td>Patient inhales a saline mist which can cause a deep cough</td>
<td>• Easy to do • Used to obtain sputum when coughing sputum is not productive</td>
<td>• Specimens may be watery and may be confused with saliva (should be labeled “induced specimen”) • Requires special equipment • May cause bronchospasm</td>
</tr>
<tr>
<td><strong>Bronchoscopy with Lavage</strong></td>
<td>Bronchoscope is passed through the mouth or nose directly into the diseased portion of the lung, which is lavaged (bronchoalveolar lavage [BAL]) to obtain specimen.</td>
<td>• Used to obtain specimen when coughing or inducing sputum is not productive or other diagnoses are being considered • Brushings and transbronchial biopsy may also be performed</td>
<td>• Most expensive and invasive procedure • Requires special equipment • Must be performed by a specialist in a hospital or clinic • Requires anesthesia</td>
</tr>
<tr>
<td><strong>Gastric Aspiration</strong></td>
<td>Tube is inserted through the patient’s mouth or nose and passed into the stomach to get a sample of gastric secretions that contain sputum that has been coughed into the throat and then swallowed.</td>
<td>Used to obtain samples in children who are not able to produce sputum when they cough</td>
<td>• Must be performed as soon as the patient wakes up in the morning • Patient may be required to stay in the hospital • Can cause discomfort for the patient.</td>
</tr>
</tbody>
</table>
**Specimen Collection Methods for Extrapulmonary TB**

TB disease can occur in almost any anatomical site; thus, a variety of clinical specimens other than sputum (e.g., urine, cerebrospinal fluid, pleural fluid, pus, or biopsy specimens) may be submitted for examination in the case of presumptive extrapulmonary TB disease. Procedures for the expeditious and recommended handling of the specimen must be in place or assured before the specialist performs an invasive procedure to obtain the specimen. It is especially important to ensure rapid transportation of specimens to the laboratory according to the laboratory’s instructions. It is important to note that a portion of any biopsy specimen should be sent to the laboratory specifically for culture, and a separate second portion of the biopsy should be placed in formalin for histologic examination. Once in formalin, tissue cannot be used for culture.

**AFB Smear Classification and Results**

Microscopic detection of AFB in smears may provide the initial bacteriologic evidence of the presence of mycobacteria in a clinical specimen. Smear microscopy is the quickest and easiest procedure that can be performed. There are two procedures commonly used for acid-fast staining:

- Carbolfuchsin methods (including the Ziehl-Neelsen and Kinyoun methods)
- Fluorochrome methods using auramine-O or auramine-rhodamine dyes (fluorescent microscopy) (Figure 3.8)
Studies have shown that 5,000–10,000 bacilli per milliliter of specimen must be present to allow the detection of bacteria in stained smears. In contrast, 10–100 bacilli are needed for a positive culture. Smear examination is a quick procedure; results should be available within 24 hours of specimen collection when specimens are delivered to the laboratory promptly. However, smear examination permits only the presumptive diagnosis of TB disease because the AFB in a smear may be acid-fast organisms other than *M. tuberculosis*. Many TB patients also have negative AFB smears with a subsequent positive culture. Negative smears do not exclude TB disease.

When AFB are seen in a smear, they are counted; there is a system for reporting the number of AFB that are seen at a certain magnification. According to the number of AFB seen, the smears may be classified as 4+, 3+, 2+, or 1+. Some laboratories use different grading scales (e.g., many, moderate, few, rare). The greater the number, the more infectious the patient (Table 3.3).

<table>
<thead>
<tr>
<th>What you see (250X)</th>
<th>What you see (450X)</th>
<th>What to report</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 AFB/ smear</td>
<td>0 AFB/ smear</td>
<td>No AFB seen</td>
</tr>
<tr>
<td>1-2/ 30 fields</td>
<td>1-2/ 70 fields</td>
<td>Report exact count; order repeat specimen</td>
</tr>
<tr>
<td>1-9/ 10 fields</td>
<td>2-18/ 50 fields</td>
<td>1+</td>
</tr>
<tr>
<td>1-9/ field</td>
<td>4-36/ 10 fields</td>
<td>2+</td>
</tr>
<tr>
<td>10-90/ field</td>
<td>4-36/ field</td>
<td>3+</td>
</tr>
<tr>
<td>&gt;90/ field</td>
<td>&gt;36/ field</td>
<td>4+</td>
</tr>
</tbody>
</table>


**Direct Detection of *M. tuberculosis* in Clinical Specimen Using NAA**

Nucleic acid amplification (NAA) tests are used to amplify DNA and RNA segments to rapidly identify the microorganisms in a specimen. NAA testing can reliably detect *M. tuberculosis* DNA in specimens in just hours, compared to a week or more for detection of *M. tuberculosis* organisms in culture (Figure 3.9).
Possible benefits of using NAA tests include

- Earlier laboratory confirmation of TB disease.
- Earlier treatment initiation.
- Improved patient outcomes.
- Interruption of transmission by early diagnosis, respiratory isolation, and appropriate treatment.
- Earlier, more efficient use of respiratory isolation (i.e., informed decisions about starting and stopping respiratory isolation).
- Earlier initiation of contact investigation.
- More effective public health interventions.
- Earlier detection of drug resistance when certain NAAs are used (e.g., Gene Xpert).

CDC recommends that NAA testing be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities, such as contact investigations.

Figure 3.9
NAA Test Being Performed

Photo courtesy of the Association of Public Health Laboratories

Photo courtesy of Orange County Public Health Laboratory
Clinicians should interpret all laboratory results in the context of the clinical situation. A single negative NAA test result should **not** be used as a definitive result to exclude TB disease, especially when the clinical suspicion of TB disease is moderate to high. Rather, the negative NAA test result should be used as additional information in making clinical decisions, to expedite testing for an alternative diagnosis, or to prevent unnecessary TB disease treatment. Interpretation of NAA test results should take AFB smear results into account. Culture remains the gold standard for laboratory confirmation of TB disease, and growing bacteria are required to perform drug susceptibility testing and genotyping. In accordance with current recommendations, sufficient numbers and portions of specimens should always be reserved for culture. It is important to note that NAA tests do not distinguish between live and dead organisms, so a sample with a positive NAA test result can be negative in culture. Nonetheless, NAA testing should be performed as standard practice for patients presumed to have TB, and **all** clinicians and public health TB programs should have access to NAA testing for TB to shorten time to diagnosis (**Table 3.4**).
<table>
<thead>
<tr>
<th>Company</th>
<th>N/A (platforms include Bruker Biotyper or bioMerieux Vitek MS)</th>
<th>Hologic</th>
<th>Hologic</th>
<th>Cepheid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleic Acid Amplification?</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Identification of <em>Mycobacterium tuberculosis</em> complex (MTBC) from culture isolates</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Sometimes, if validated for that purpose by an individual laboratory</td>
</tr>
<tr>
<td>Detection of MTBC in clinical specimen</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Detection of mutations associated with drug resistance</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Matrix-assisted laser desorption/ionization time of flight which uses mass spectrometry based on analysis of proteins depicted as mass spectra with patterns of characteristic peaks which is compared to a known database.</td>
<td>DNA probe hybridizes to a specific ribosomal RNA target.</td>
<td>Transcription Mediated Amplification (TMA) to amplify the ribosomal RNA target followed by DNA probe hybridization to detect the amplified target.</td>
<td>Real time polymerase chain reaction (PCR) to simultaneously amplify and detect MTBC and the presence of mutations in the <em>rpoB</em> gene.</td>
</tr>
<tr>
<td>FDA approved</td>
<td>No</td>
<td>Yes (cleared)</td>
<td>Yes</td>
<td>Yes (market-authorized)</td>
</tr>
<tr>
<td>Turnaround time from specimen receipt in laboratory</td>
<td>Requires growth in culture</td>
<td>Requires growth in culture</td>
<td>24-48 hrs.</td>
<td>24-48 hrs.</td>
</tr>
</tbody>
</table>
Xpert MTB/RIF Assay

The Xpert MTB/RIF assay is an NAA test that simultaneously detects *M. tuberculosis* complex and resistance to rifampin (RIF), one of the most effective drugs used to treat TB.

To conduct the Xpert MTB/RIF assay, a sputum sample is mixed with a sterilizing reagent provided with the assay, and a cartridge containing the mixture is placed in the GeneXpert machine.

Results that are positive for *M. tuberculosis* complex and RIF resistance indicate that the bacteria have a high probability of resistance to RIF. This result should be confirmed by DNA sequencing as applicable to identify the specific mutation present. If RIF resistance is confirmed, rapid molecular testing for drug resistance to both first-line and second-line drugs should be performed so that an effective treatment regimen can be selected. Growth-based drug susceptibility testing should be performed as well. Growth-based susceptibility testing is discussed in more detail later in this chapter.

Results that are positive for *M. tuberculosis* complex but negative for RIF resistance mean that the bacteria are probably susceptible to RIF. However, all tests that are positive for *M. tuberculosis* complex should have growth-based drug susceptibility testing to first-line TB drugs.

Results that are positive for *M. tuberculosis* complex and indeterminate for RIF resistance mean that the test could not accurately determine if the bacteria are resistant.

As with other NAA tests, the Xpert MTB/RIF assay should be interpreted along with clinical, radiographic, and other laboratory findings. The Xpert MTB/RIF assay does not replace the need for AFB smear microscopy or culture for mycobacteria, growth-based drug susceptibility testing, and genotyping. Providers and laboratories need to ensure that patient specimens are available for all recommended mycobacterial testing.

Specimen Culture and Identification

Positive cultures for *M. tuberculosis* confirm the diagnosis of TB disease; however, in the absence of a positive culture, TB disease may also be diagnosed on the basis of clinical signs and symptoms alone. Culture examinations should be performed on all diagnostic specimens, regardless of AFB smear or NAA results. The commercially available broth culture systems (e.g., MGIT, VersaTREK, or MB/BacT) allow detection of most mycobacterial growth in 4-14 days compared to
3–6 weeks for solid media (Figure 3.10). Laboratories performing TB cultures should routinely use a broth-based system. The differences between using AFB smears or cultures to test for *M. tuberculosis* are compared in Table 3.5.

**Figure 3.10**  
Colonies of *M. tuberculosis* Grown on Solid Media

**Table 3.5**  
Differences Between AFB Smears and Cultures

<table>
<thead>
<tr>
<th>Feature</th>
<th>AFB Smears</th>
<th>Cultures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equipment and supplies needed</td>
<td>• Microscope</td>
<td>• Incubators, including method-specific instruments</td>
</tr>
<tr>
<td></td>
<td>• Glass slides</td>
<td>• Biological safety cabinet</td>
</tr>
<tr>
<td></td>
<td>• Special dyes</td>
<td>• Specific instruments</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Culture media and identification methods</td>
</tr>
<tr>
<td>Anticipated turnaround time for lab</td>
<td>One day after laboratory receipt</td>
<td>Four days to eight weeks after laboratory report (depending on method used and how quickly the organism grows)</td>
</tr>
<tr>
<td>report</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basis of procedure</td>
<td>Looking for AFB on slide under microscope</td>
<td>Growth and identification of tubercle bacilli or other mycobacteria in culture media</td>
</tr>
<tr>
<td>Significance of a negative report</td>
<td>• Patient is probably not infectious</td>
<td>• Negative result indicates no live tubercle bacilli found in specimen</td>
</tr>
<tr>
<td></td>
<td>• Does not rule out TB disease</td>
<td>• Does not rule out TB disease (live tubercle bacilli may be in other specimens and/or body sites)</td>
</tr>
<tr>
<td></td>
<td>(culture may be positive)</td>
<td></td>
</tr>
<tr>
<td>Significance of a positive report</td>
<td>• Patient is more likely to be infectious</td>
<td>Confirms diagnosis of TB disease with <em>M. tuberculosis</em> identification</td>
</tr>
<tr>
<td></td>
<td>(if AFB are tubercle bacilli)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• AFB could be nontuberculous mycobacteria—NAA testing and culture needed</td>
<td></td>
</tr>
</tbody>
</table>
**Follow-up Bacteriologic Examination**

Follow-up bacteriologic examinations are important for assessing the patient’s infectiousness and response to therapy. Culture conversion is the most important objective measure of response to treatment. Specimens should be obtained at monthly intervals until two consecutive specimens sent for culture are reported as negative. Conversion is documented by the first negative culture in a series of previously positive cultures with all subsequent culture results negative.

**Reporting Results**

Laboratories should report initial positive smears, positive *M. tuberculosis* cultures, and positive NAA results within 24 hours (either by phone or electronically) to the primary health care provider and health department as required by statute or regulation. Out-of-state laboratories that receive referral specimens must contact the **health care provider and health department** in the patient’s state of origin. Follow-up results should be reported. It is the responsibility of the primary health care provider to report all presumed or confirmed cases of TB disease promptly to the state or local health department unless state laws indicate otherwise. Submitters should follow up with laboratories if anticipated results are not received within expected time frames. Prompt reporting to health authorities ensures that the person with TB disease can be adequately treated, interrupting the potential for ongoing transmission. It also ensures that contact investigations can be initiated quickly to find contacts of the patient who may have LTBI or TB disease.

**Drug Susceptibility Testing**

**Molecular Detection of Drug Resistance (MDDR)**

For patients with risk factors for drug-resistant TB, AFB smear positive and/or NAA test positive respiratory specimens should be sent for molecular drug resistance testing immediately.

There are different laboratory tests that can detect mutations associated with drug resistance (**Table 3.6**). Some of these assays can be performed directly on patient specimens prior to cultures turning positive; others currently require an isolate cultured from patient specimens. CDC’s MDDR service is available nationally, and it is free of charge through [state public health laboratories](#). Other services for molecular detection are available through some public health, clinical, or commercial laboratories.
These assays allow rapid detection of drug resistance through the detection of genetic mutations associated with resistance, and results provide guidance for clinical decision making in devising an effective course of therapy. Many state and local public health laboratories, as well as larger clinical and commercial laboratories, are exploring increased use of molecular testing for drug resistance.

Molecular detection of drug resistance should be considered for patients with the following characteristics:

- High risk of rifampin resistance, including multidrug-resistant TB (MDR TB) (e.g., previously treated TB, contact with someone with MDR TB, or being from a country with high rate of RIF resistance)
- First-line drug susceptibility results are available and show resistance to RIF
- Infectiousness poses a risk to vulnerable contacts (e.g., daycare worker, nurse)
- Contraindications to essential first-line medications (e.g., RIF allergy)
- Challenges encountered in the laboratory in performing growth-based drug susceptibility testing, such as contamination or no growth in subculture

Although many high confidence mutations have been identified for both first- and second-line drugs, there remain some limitations of molecular testing for drug resistance in that the clinical relevance of some mutations remains unknown. Depending on the limit of detection for the assay used and the specific genetic regions evaluated, the absence of mutations may indicate susceptibility, especially for first-line drugs. However, the absence of mutations cannot always completely rule out resistance, and care should be taken to understand the limitations of the test performed. In addition, limitations and knowledge base differ by drug. Results from conventional growth-based drug susceptibility tests can be used in conjunction with molecular results when both are available.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GeneXpert® MTB/RIF</th>
<th>GenoType® MTBDRplus</th>
<th>HAIN GenoType® MTBDRplus</th>
<th>Sanger Sequencing</th>
<th>Pyrosequencing</th>
<th>Next Generation Sequencing (NGS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Company</td>
<td>Cepheid</td>
<td>HAIN Lifescience/ Bruker</td>
<td>HAIN Lifescience/ Bruker</td>
<td>N/A— (laboratory developed test)</td>
<td>N/A— (laboratory developed test)</td>
<td>N/A— (laboratory developed test)</td>
</tr>
<tr>
<td>Genetic loci</td>
<td>rpoB (for RIF)</td>
<td>rpoB (RIF), katG (INH), and inhA (INH)</td>
<td>gyrA (FQ), rrs (injectables), and embB (EMB)</td>
<td>Varies but can commonly include rpoB, inhA, katG, aphC, embB (EMB), pncA (PZA), gyrA (FQ), and rrs (injectables)</td>
<td>Varies but can commonly include rpoB, inhA, katG, aphC, gyrA, and rrs</td>
<td>Whole Genome Sequencing (WGS) - any locus can be analyzed. Targeted NGS varies but can include rpoB, inhA, katG, aphC, gyrA, and rrs</td>
</tr>
<tr>
<td>Format</td>
<td>Semi-automated real-time PCR</td>
<td>Line probe assay</td>
<td>Line probe assay</td>
<td>DNA sequencing</td>
<td>DNA sequencing</td>
<td>DNA sequencing</td>
</tr>
<tr>
<td>FDA approved</td>
<td>Yes (market-authorized)</td>
<td>No</td>
<td>No</td>
<td>N/A— (laboratory developed test)</td>
<td>N/A— (laboratory developed test)</td>
<td>N/A— (laboratory developed test)</td>
</tr>
</tbody>
</table>

N/A = Not applicable
**Growth-based Drug Susceptibility Testing**

The initial *M. tuberculosis* isolate from a patient should be tested for resistance to the first-line anti-TB drugs: isoniazid, rifampin, ethambutol, and pyrazinamide (Figure 3.11). The results of both growth-based and molecular drug susceptibility tests should inform the clinicians’ choices of the appropriate drugs for treating each patient. Patients with TB disease who are treated with drugs to which their strain of TB is resistant may **not** be successfully cured. In fact, their strain of TB may become resistant to additional drugs.

**Figure 3.11**

Culture plates reveal results of a drug susceptibility test on *M. tuberculosis* bacteria

Growth-based drug susceptibility tests include broth-based and agar proportion tests (Table 3.7). Rapid, broth-based systems should be used to identify drug resistance to first-line drugs as early as possible in order to ensure appropriate treatment. Broth-based systems will yield results more quickly than agar-based methods. Susceptibility results from laboratories should be promptly forwarded to the physician and health department. Drug susceptibility tests using a recent specimen should be repeated for patients who do **not** respond to treatment as expected or who have positive culture results despite three months of adequate treatment.
Second-line drug susceptibility testing should be performed only in reference laboratories and should generally be limited to specimens from patients who have the following characteristics:

- Prior TB disease treatment
- Difficulty with tolerating first-line treatment
- Contact with a patient with known anti-TB drug resistance
- Demonstrated resistance to first-line anti-TB drugs
- Positive cultures after more than three months of treatment

A patient is diagnosed with MDR TB disease if the organisms are resistant to at least isoniazid (INH) and RIF, the two most potent first-line anti-TB drugs. A patient is diagnosed with extensively drug-resistant TB (XDR TB) disease if the TB isolate is resistant to INH and RIF, any fluoroquinolone, and at least one of three injectable second-line drugs (amikacin, kanamycin, or capreomycin).
### Table 3.7
Culture-Based (Phenotypic) Laboratory Tests for Drug Susceptibility Testing

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Method</th>
<th>MGIT 320 or 960</th>
<th>VersaTrek</th>
<th>Indirect Agar Proportion</th>
<th>Trek Sensititre</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Company</strong></td>
<td>Becton Dickinson</td>
<td>Thermo Scientific</td>
<td>N/A</td>
<td>Thermo Scientific</td>
<td></td>
</tr>
<tr>
<td><strong>Media</strong></td>
<td>Liquid broth</td>
<td>Liquid broth</td>
<td>Solid</td>
<td>Liquid broth</td>
<td></td>
</tr>
<tr>
<td><strong>Results:</strong> Susceptible/Resistant or Minimum Inhibitory Concentration (MIC)**</td>
<td>Usually Susceptible/Resistant; few labs might report MIC for some drugs</td>
<td>Usually Susceptible/Resistant</td>
<td>Usually Susceptible/Resistant; few labs might report MIC for some drugs</td>
<td>Laboratory might provide interpretive criteria of Susceptible/Resistant for some drugs or report MIC value</td>
<td></td>
</tr>
<tr>
<td><strong>Drugs</strong></td>
<td>FDA cleared for INH, RIF, PZA, EMB, STR; some labs might not test STR or PZA. Some reference laboratories have validated for use of other drugs</td>
<td>FDA cleared for INH, RIF, PZA, EMB</td>
<td>Varies depending on lab but can include first-line (except PZA), second-line, and new/repurposed drugs</td>
<td>Research Use Only (RUO) plate available with INH, RIF, EMB, STR, Rifabutin, Ethionamide, Amikacin, Kanamycin, Ofloxacin, Moxifloxacin, Cycloserine, Para-Amino Salicylic Acid. Custom plates can be ordered.</td>
<td></td>
</tr>
<tr>
<td><strong>Concentrations tested</strong></td>
<td>Generally, one critical concentration for each drug with exception of INH (2 concentrations)</td>
<td>Generally, one critical concentration for each drug with exception of INH (2 concentrations)</td>
<td>Generally, one critical concentration for each drug with exception of INH and some second-line drugs (e.g., moxifloxacin)</td>
<td>6–8 different concentrations of each drug for determining MIC</td>
<td></td>
</tr>
<tr>
<td><strong>FDA approved</strong></td>
<td>Yes (cleared)</td>
<td>Yes (cleared)</td>
<td>No (laboratory developed test)</td>
<td>No (RUO)</td>
<td></td>
</tr>
<tr>
<td><strong>Expected turnaround time (TAT)</strong></td>
<td>Typically, within 5 weeks of specimen receipt</td>
<td>Typically, within 5 weeks of specimen receipt</td>
<td>Longer TAT than broth-based methods</td>
<td>Within 10–21 days of incubation after isolation on solid culture</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** EMB, ethambutol; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin; STR, streptomycin.
Genotyping

TB genotyping is a laboratory-based approach used to analyze the genetic material (i.e., DNA) of *M. tuberculosis*. The total genetic content is referred to as the genome. Specific sections of the *M. tuberculosis* genome form distinct genetic patterns that help distinguish different strains of *M. tuberculosis*. *M. tuberculosis* genotyping is based on polymorphisms in the number and genomic location of mycobacterial repetitive elements. *M. tuberculosis* isolates with identical genotypes suggest that there may have been recent TB transmission among the persons from whom they were isolated. The main purpose of genotyping is to add to TB controllers’ understanding of TB transmission in their community.

When coupled with traditional epidemiologic investigations, analyses of the genotype of *M. tuberculosis* strains can detect or confirm transmission of *M. tuberculosis*. These analyses have also identified risk factors for recent infection with rapid progression to TB disease, demonstrated re-infection with different strains, identified weaknesses in conventional contact investigations, documented the existence of laboratory cross-contamination, and identified outbreaks of TB that were not previously recognized (Box 3.1). Genotyping has become an increasingly useful tool for studying the pathogenesis, epidemiology, and transmission of TB.

**Box 3.1**

Use of Genotyping Analyses

- When coupled with traditional epidemiologic investigations, can detect or confirm transmission of *M. tuberculosis*
- Identified risk factors for recent infection with rapid progression to TB disease
- Demonstrated re-infection with different strains
- Identified weaknesses in conventional contact investigations
- Documented the existence of laboratory cross-contamination
- Identified outbreaks of TB that were not previously recognized
Knowledge Check

Select the best answer for each question.

1. Culture examinations should be done on all specimens, regardless of AFB smear results.
   A. True
   B. False

2. Gastric aspiration is the best way to obtain specimens from infants and young children if they cannot produce sputum.
   A. True
   B. False

3. Which of the following statements are true?
   A. Genotyping is a laboratory-based approach used to analyze the genetic material (e.g., DNA) of *M. tuberculosis*.
   B. When coupled with traditional epidemiologic investigations, analyses of the genotype of *M. tuberculosis* strains can detect or confirm transmission of *M. tuberculosis*.
   C. Specific sections of the *M. tuberculosis* genome form distinct genetic patterns that help distinguish different strains of *M. tuberculosis*.
   D. All of the above

4. Which of the following is NOT a component for conducting a complete medical evaluation for diagnosing TB disease?
   A. Medical history
   B. Genotyping
   C. Test for TB infection
   D. Chest x-ray
   E. Bacteriologic examination

For question 5 check all that apply. There may be more than one answer to the question.

5. Which of the following may be a symptom of TB disease?
   A. Fever
   B. Weight loss
   C. Fatigue
   D. Runny nose
6. Which of the following confirms the diagnosis of TB?
   A. Chest x-ray
   B. Detection of acid-fast bacilli in smear examination
   C. Positive tuberculin skin test
   D. Positive culture of *M. tuberculosis*

7. What part of a patient’s medical history should lead a clinician to suspect the possibility of TB disease?
   1. Exposure to a person who has TB disease
   2. Symptoms of TB disease
   3. Previous TB infection or TB disease
   4. Risk factors for developing TB disease
      A. 1, 2, and 3 are correct
      B. 1 and 3 are correct
      C. 2 and 4 are correct
      D. Only 4 is correct
      E. All are correct

8. Second-line drug susceptibility testing should be performed only in reference laboratories.
   A. True
   B. False

See page 195 for answer key.
Chapter Objectives

After working through this chapter, you should be able to

- Identify groups who should be given high priority for latent tuberculosis infection (LTBI) treatment.
- Describe LTBI treatment regimens.
- Describe special considerations for LTBI treatment.
- Identify components of patient monitoring.

Chapter Introduction

It is estimated that up to 13 million people in the United States have latent tuberculosis infection (LTBI). Although not everyone with LTBI will develop tuberculosis (TB) disease, approximately 5%–10% of those infected will progress to TB disease if untreated.
Treatment for LTBI is essential for controlling and eliminating TB disease in the United States. Progression from untreated LTBI to TB disease accounts for approximately 80% of U.S. TB cases. Treatment substantially reduces the risk that a person infected with *Mycobacterium tuberculosis* (*M. tuberculosis*) will progress to TB disease.

There are several regimens available for the treatment of LTBI. In 2020, the Centers for Disease and Control and Prevention (CDC) and the National Tuberculosis Controllers Association (NTCA) released updated guidelines on the treatment of LTBI. While all the regimens are effective, short-course, rifamycin-based 3-or 4-month regimens are preferred. Short-course LTBI treatment regimens are effective, are safe, and have higher completion rates than longer 6–9-month regimens of isoniazid (INH) monotherapy. If short-course treatment is not an option, 6 or 9 months of daily INH are alternative LTBI treatment regimens.

## Candidates for LTBI Treatment

Certain groups are at higher risk for developing TB disease after becoming infected. Targeted testing programs should be designed to help identify persons who are at high risk for LTBI and TB disease and who would benefit from treatment (see Chapter 2: Testing for Tuberculosis Infection).

### Persons with a Positive Blood Test Result or a TST Reaction of ≥5 mm of Induration

Persons in the following groups at high risk should be treated for LTBI if they have a positive blood test result or if their reaction to the TST is ≥5 mm of induration (Table 4.1):

- People living with HIV
- Recent contacts of people with infectious TB disease
- People who have fibrotic changes on chest radiograph
- People with organ transplants
- Other immunosuppressed patients (e.g., patients on prolonged therapy with corticosteroids equivalent to/greater than 15 mg per day of prednisone or those taking TNF-α antagonists)
Persons with a Positive Blood Test Result or a TST Reaction of $\geq 10$ mm of Induration

Persons in the following groups at high risk should be treated for LTBI if they have a positive blood test result or if their reaction to the TST is $\geq 10$ mm of induration (Table 4.1):

- People who were born in countries where TB disease is common, including Mexico, the Philippines, Vietnam, India, China, Haiti, and Guatemala, or other countries with high rates of TB
- People who abuse drugs
- Mycobacteriology laboratory workers
- People who currently (or used to) live or work in high-risk congregate settings (e.g., nursing homes, homeless shelters, or correctional facilities)
- People with certain medical conditions that place them at high risk for TB (e.g., silicosis, diabetes mellitus, severe kidney disease, certain types of cancer, and certain intestinal conditions)
- People with a low body weight ($<90\%$ of ideal body weight)
- Children younger than 5 years of age
- Infants, children, and adolescents exposed to adults in high-risk categories (see Chapter 2: Testing for Tuberculosis Infection)

Persons with No Known Risk Factors Who Have a Positive Blood Test Result or a TST Reaction of $\geq 15$ mm of Induration

Typically, persons with no known risk factors should not be tested for TB infection. Testing should be targeted for groups at high risk for LTBI and TB disease. However, if a person without any risk factors is tested and has a positive blood test result or a TST reaction that is $\geq 15$ mm of induration, he or she should be evaluated for LTBI treatment after TB disease has been excluded. Please see a summary of the evaluation of persons with positive TB test results (Figure 4.1).
CHAPTER 4: TREATMENT FOR LATENT TUBERCULOSIS INFECTION

Figure 4.1
Evaluation of Persons with Positive TB Test Results

- Person has a positive test for TB infection
- TB disease ruled out
- Consider LTBI treatment
- Person accepts and is able to receive treatment for LTBI
- Develop a treatment plan with the patient to ensure adherence
- If person refuses or is unable to receive LTBI treatment, follow-up blood test or TST is unnecessary. Follow-up chest radiographs are unnecessary unless the patient develops signs or symptoms of TB disease or wishes to begin LTBI treatment at a future time.
- Educate patient about signs and symptoms of TB disease

Table 4.1
Groups Who Should Be Given High Priority for LTBI Treatment

<table>
<thead>
<tr>
<th>Persons Who Have a Positive Blood Test Result or a TST Reaction of ≥5 mm of Induration</th>
<th>Persons Who Have a Positive Blood Test Result or a TST Reaction of ≥10 mm of Induration</th>
</tr>
</thead>
<tbody>
<tr>
<td>• People living with HIV</td>
<td>• People who were born in countries where TB disease is common, including Mexico, the Philippines, Vietnam, India, China, Haiti, and Guatemala, or other countries with high rates of TB</td>
</tr>
<tr>
<td>• Recent contacts of people with infectious TB disease</td>
<td>• People who abuse drugs</td>
</tr>
<tr>
<td>• People who have fibrotic changes on a chest radiograph</td>
<td>• Mycobacteriology laboratory workers</td>
</tr>
<tr>
<td>• People with organ transplants</td>
<td>• People who live or work in high-risk congregate settings (e.g., nursing homes, homeless shelters, or correctional facilities)</td>
</tr>
<tr>
<td>• Other immunosuppressed patients (e.g., patients on prolonged therapy with corticosteroids equivalent to/greater than 15 mg per day of prednisone or those taking TNF-α antagonists)</td>
<td>• People with certain medical conditions that place them at high risk for TB (e.g., silicosis, diabetes mellitus, severe kidney disease, certain types of cancer, and certain intestinal conditions)</td>
</tr>
<tr>
<td></td>
<td>• People with a low body weight (&lt;90% of ideal body weight)</td>
</tr>
<tr>
<td></td>
<td>• Children younger than 5 years of age</td>
</tr>
<tr>
<td></td>
<td>• Infants, children, and adolescents exposed to adults in high-risk categories</td>
</tr>
</tbody>
</table>
Contacts at High Risk for Rapid Development of TB Disease

Certain contacts who have a negative blood test or TST result should be evaluated for LTBI treatment after TB disease has been excluded including

- Immunocompromised persons of all ages, including those who are HIV infected.
- Children younger than 5 years of age.

Expert consultation should be sought to determine if contacts with immunocompromised states other than HIV infection (e.g., those taking immunosuppressive therapies or those with diabetes) could benefit from treatment even if they have a negative blood test or TST result. Treatment for presumed *M. tuberculosis* infection may be considered if the likelihood of infection is high based on the circumstances of the exposure and prevalence of TB infection among other contacts.

Contacts who have a negative blood test or TST result should be retested 8–10 weeks after they were last exposed to a person with infectious TB disease, because the body’s immune system needs 2–8 weeks after infection to mount a response detectable by the tests. If the result of the repeat test is positive and TB disease is excluded, the contact should be classified as recently infected and followed up and treated appropriately. Any contact who is to be treated for LTBI should have a chest radiograph to exclude pulmonary TB disease before starting treatment.

**HIV-Infected Contacts**

After TB disease has been excluded, contacts who have HIV infection should be started on LTBI treatment regardless of their blood test or TST result. LTBI treatment can be discontinued if the second blood test or TST result is negative and 8–10 weeks have passed since the last exposure to someone with infectious TB disease.

However, HIV-infected persons might be anergic (i.e., there is impairment in cell-mediated immune responsiveness to stimulation by an antigen) and thus unable to manifest a positive blood test or TST result even if infected. In these instances, medical providers might decide to prescribe a complete course of LTBI treatment, even if the second blood test or TST result is negative, particularly if the exposure to TB is substantial (e.g., prolonged, frequent exposure to a patient with highly infectious TB disease).
Infants and Young Children

Because of their age, infants and young children with LTBI are known to have been infected recently and thus are at high risk for progressing to TB disease (Table 4.2). Infants and young children are also more likely than older children and adults to experience life-threatening forms of TB disease, especially meningeal and disseminated disease, because they do not have fully developed immune systems.

Window Prophylaxis

Children aged <5 years who are contacts of an adult with infectious TB disease should receive treatment for LTBI even if the initial TST or blood test result is negative and less than 8-10 weeks have passed since their last exposure to infectious TB; this is called window prophylaxis. As discussed in Chapter 2: Testing for Tuberculosis Infection, current U.S. guidelines suggest the TST as the recommended method of testing for children younger than 5 years of age, while noting that some experts use TB blood tests in younger children. Before starting window prophylaxis, TB disease should be excluded by chest radiograph and symptom review (see Table 3.1 in Chapter 3: Diagnosis of Tuberculosis Disease). Similar to HIV-infected persons, infants aged ≤6 months can be anergic and thus unable to manifest a positive TST result if infected.

A second TST or blood test should be administered 8-10 weeks after the last exposure to someone with infectious TB disease. If testing is repeated, the same type of test (TB blood test or TST) should be used. If the repeat test result is positive, treatment should be continued. If the repeat test result is negative, treatment can usually be discontinued. Window prophylaxis can be discontinued if all of the following conditions are met:

- Infant is aged ≥6 months.
- Second TST or blood test result is also negative.
- Second TST or blood test was performed ≥8 weeks after the child was last exposed to an adult with infectious TB disease.

In certain instances, medical providers might decide to prescribe a complete course of LTBI treatment even if the second TST or blood test is negative, particularly if the exposure to someone with TB disease is substantial.
### Table 4.2

**LTBI Among Infants and Young Children**

<table>
<thead>
<tr>
<th>Characteristics of Infants and Young Children with LTBI</th>
<th>Treating Children Aged &lt;5 Years Who Are Contacts</th>
</tr>
</thead>
</table>
| • Known to have been infected recently because of their young age  
• More likely than older children and adults to experience life-threatening forms of TB disease (e.g., disseminated TB or TB meningitis) | • Provide LTBI treatment even if initial TST or blood test result is negative after TB disease has been excluded  
• Administer a second TST or blood test 8–10 weeks after the last exposure to someone with infectious TB disease  
• Can discontinue window prophylaxis if **all** of the following conditions are met:  
  • Infant is aged ≥6 months  
  • Second TST or blood test result is also negative  
  • Second TST or blood test was performed ≥8 weeks after the child was last exposed to someone with infectious TB disease |
Medical Evaluation Before Starting LTBI Treatment

All persons being considered for LTBI treatment should receive a medical evaluation. The purposes of the medical evaluation are to

• Exclude the possibility of TB disease.

• Determine if the patient has a history of prior treatment for LTBI or TB disease.

• Determine if the patient has any coexisting medical conditions that are a contraindication to LTBI treatment or are associated with an increased risk for adverse effects from treatment.

• Obtain information about current and previous drug therapy, including any previous or current adverse reactions to drugs considered for LTBI treatment.

Health care providers should also recommend HIV testing for all TB and LTBI patients, unless the patient declines (opts out).

As part of the medical evaluation, a chest radiograph should be performed. LTBI treatment should only be prescribed if the chest radiograph is normal (i.e., no findings consistent with TB disease). If any abnormalities consistent with TB disease are identified or if the patient is symptomatic, the patient should have 3 sputum specimens collected for acid-fast bacilli (AFB) smear and culture. LTBI treatment should only be administered after all 3 cultures are negative. Treating TB disease with an LTBI regimen can lead to drug resistance. Therefore, persons presumed to have TB disease should receive the recommended multidrug regimen for TB disease treatment until the diagnosis is confirmed or excluded (See Chapter 5: Treatment for TB Disease).

Conducting a medical evaluation also provides an opportunity for establishing rapport with the patient and for highlighting important aspects of treatment, such as

• Treatment benefits.

• The importance of adherence to the treatment regimen.

• The regimen’s possible adverse effects.

• Establishment of an optimal follow-up plan.
LTBI Treatment Regimens

Several LTBI treatment regimens are available (Table 4.3). Health care providers should choose the best regimen for each patient on the basis of

- Drug-susceptibility results of the presumed source patient, if known.
- Coexisting medical conditions.
- Potential for drug-drug interactions.

While all the regimens are effective, the CDC and NTCA preferentially recommend short-course rifamycin-based 3- or 4-month treatment regimens for LTBI. Short-course LTBI treatment regimens are effective, are safe, and have higher completion rates than longer 6- to 9-month regimens of isoniazid (INH) monotherapy. If short-course treatment is not an option, 6 or 9 months of daily INH are recommended as alternative LTBI treatment regimens. For more information, please see Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020, available from the CDC TB website.

LTBI treatment can be administered by directly observed therapy (DOT) or by self-administered therapy (SAT). The health care provider should choose the mode of administration (DOT versus SAT) based on local practice, individual patient attributes and preferences, and other considerations, including risk for progression to severe forms of TB disease.

DOT should be considered for persons who are at high risk for TB disease and for whom there may be difficulty adhering to a treatment regimen. DOT must be used for patients who are administered an intermittent isoniazid monotherapy dosing regimen (e.g., twice-weekly INH). DOT might be more readily implemented if the person in need of LTBI treatment lives in a household with someone who is on DOT for TB disease, or if that person lives in an institution or facility where treatment for LTBI can be observed by staff.
## Table 4.3
Drug Regimens for LTBI Treatment

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Duration</th>
<th>Dose and Age Group</th>
<th>Frequency</th>
<th>Total Doses</th>
</tr>
</thead>
</table>
| **Isoniazid (INH)* and Rifapentine (RPT)†** | 3 months | Adults and children aged >12 years  
**INH**: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum  
**RPT**:  
10.0–14.0 kg, 300 mg  
14.1–25.0 kg, 450 mg  
25.1–32.0 kg, 600 mg  
32.1–49.9 kg, 750 mg  
≥50.0 kg, 900 mg maximum  
Children aged 2–11 years:  
**INH**: 25 mg/kg; 900 mg maximum  
**RPT**: as above | Once weekly | 12 |
| **Rifampin (RIF)***              | 4 months | Adults: 10 mg/kg  
Children: 15–20 mg/kg**  
Maximum dose: 600 mg | Daily | 120 |
| **Isoniazid (INH)* and Rifampin (RIF)*** | 3 months | Adults  
**INH**: 5 mg/kg; 300 mg maximum  
**RIF**: 10 mg/kg; 600 mg maximum  
Children  
**INH**: 10-20 mg/kg††; 300 mg maximum  
**RIF**: 15-20 mg/kg; 600 mg maximum | Daily | 90 |
| **Isoniazid (INH)***             | 6 months | Adults: 5 mg/kg  
Children: 10–20 mg/kg**  
Maximum dose: 300 mg | Daily | 180 |
|                                  |          | Adults: 15 mg/kg  
Children: 20–40 mg/kg**  
Maximum dose: 900 mg | Twice weekly§ | 52 |
| **Isoniazid (INH)***             | 9 months | Adults: 5 mg/kg  
Children: 10-20 mg/kg**  
Maximum dose: 300 mg | Daily | 270 |
|                                  |          | Adults: 15 mg/kg  
Children: 20–40 mg**  
Maximum dose: 900 mg | Twice weekly§ | 76 |

* Isoniazid is formulated as 100-mg and 300-mg tablets.  
† Rifapentine is formulated as 150-mg tablets in blister packs that should be kept sealed until use.  
§ Intermittent regimens must be provided via directly observed therapy (i.e., a health care worker observes the ingestion of medication). DOT or self-administered therapy (SAT) may be used for the 3-month regimen of INH and RPT.  
¶ Rifampin (rifampicin) is formulated as 150-mg and 300-mg capsules.  
†† The American Academy of Pediatrics recommends an isoniazid dosage of 10–15 mg/kg for the daily regimen and 20–30 mg/kg for the twice-weekly regimen.
Isoniazid (INH) and Rifapentine (RPT) Regimen (3HP)

Once-weekly INH and RPT for 3 months (3HP) is administered by DOT or SAT.

The 3HP regimen is recommended for people older than 2 years of age, including people with HIV/AIDS who are taking antiretroviral therapy (ART) that has acceptable drug-drug interactions with RPT, such as efavirenz and raltegravir.

The 3HP regimen is not recommended for

- Children younger than 2 years of age.
- People with HIV/AIDS who are taking antiretroviral medications with clinically significant or unknown drug interactions with RPT.
- Patients with presumed INH- or RIF-resistant *M. tuberculosis*.
- Pregnant women or women expecting to become pregnant within the treatment period.

RPT can reduce the effectiveness of hormonal contraceptives; therefore, women who use hormonal birth control should be advised to add or switch to a barrier method when taking 3HP.

It is important for clinicians and pharmacists to know the difference between rifampin (RIF) and rifapentine (RPT). RIF and RPT are not interchangeable, and clinicians and pharmacists should ensure that patients receive the correct medication for the prescribed treatment regimen.

Rifampin (RIF) Regimen (4R)

A 4-month regimen of RIF (4R) is recommended for HIV-negative adults and children of all ages. The 4R regimen is especially recommended for persons who cannot tolerate INH or who have INH-resistant *M. tuberculosis*. LTBI treatment with RIF should be given daily for 4 months.

RIF should not be used for women on oral contraceptives. As with RPT, RIF can reduce the effectiveness of hormonal contraceptives; therefore, women who use hormonal birth control should be advised to add or switch to a barrier method when taking 4R because of substantial drug-drug interactions. Additionally, RIF should not be used for HIV-infected persons being treated with certain combinations of ART. In situations where RIF cannot be used, sometimes another drug, rifabutin (RBT), may be substituted.
Isoniazid (INH) and Rifampin (RIF) Regimen (3HR)
The 3-month regimen of INH and RIF (3HR) is given daily. 3HR is one of the three preferentially recommended short-course, rifamycin-based regimens for adults and children of all ages, including HIV-negative and HIV-positive patients as drug interactions allow.

Isoniazid (INH) Regimens (6H or 9H)
If short-course treatment is not an option (e.g., due to drug interactions with rifamycins), CDC and NTCA recommend regimens of 6 or 9 months of daily INH as alternative treatment regimens. Six months of daily INH (6H) is strongly recommended for HIV-negative adults and children of all ages and is also a treatment option for HIV-positive adults and children of all ages. Nine months of daily INH (9H) is another treatment option for adults and children of all ages, both HIV-negative and HIV-positive. Patients can be treated daily or twice weekly with INH. Patients being treated twice weekly should receive DOT.

It is important to note that although efficacious, treatment regimens of 6 or 9 months of daily INH have higher toxicity risk and lower treatment completion rates as compared to short-course rifamycin-based treatment regimens.

Recommendation Against Using a Rifampin (RIF) and Pyrazinamide (PZA) Treatment Regimen
Previous recommendations for using a daily or a twice-weekly 2-month regimen of rifampin (RIF) with pyrazinamide (PZA) for LTBI treatment have changed based on associated severe liver injury. On the basis of high rates of hospitalization and death from liver injury among patients treated with RIF and PZA for LTBI, the American Thoracic Society and CDC now recommend that this regimen NOT be offered to persons with LTBI. However, RIF and PZA should still continue to be administered in multidrug regimens for treating persons with TB disease. For more information, please see Update: Adverse Event Data and Revised American Thoracic Society/CDC Recommendations Against the Use of Rifampin and Pyrazinamide for Treatment of Latent Tuberculosis Infection—United States, 2003, available from the CDC TB website.
Adverse Drug Reactions

Some health care providers have concerns about treating patients for LTBI. These concerns have traditionally been related to the length of treatment and the potential side effects of medications. As with any treatment, the health care provider must weigh the risks and benefits for each individual. Obtaining a detailed and accurate medical history and updating information at frequent intervals will identify persons who require close monitoring; this will aid in determining the most appropriate course of action. CDC guidelines, drug package inserts, and other authoritative medical sources should also be consulted whenever there is a question about side effects or drug-drug interactions. For patients without drug intolerability or drug-drug interactions, short-course (3–4 months) rifamycin-based treatment regimens are preferred over the longer-course (6–9 months) INH monotherapy for treatment of LTBI. Shorter, rifamycin-based treatment regimens generally have a lower risk of hepatotoxicity than longer 6- to 9-month regimens of INH monotherapy.

Patients on LTBI treatment should be instructed to report any signs and symptoms of adverse drug reactions to their health care provider, including

- Unexplained anorexia, nausea or vomiting, dark urine, or icterus (jaundice).
- Persistent paresthesia of hands or feet.
- Persistent weakness, fatigue, fever, or unexplained or persistent abdominal pain.
- Easy bruising or bleeding.

Adverse Reactions to Rifampin (RIF) and Rifapentine (RPT)

Below are potential adverse reactions to RIF and RPT:

- **Hepatotoxicity:** Shorter, rifamycin-based treatment regimens generally have a lower risk of hepatotoxicity than longer 6-9-month regimens of INH monotherapy. Evidenced by transient asymptomatic hyperbilirubinemia, hepatotoxicity may occur in 0.6% of persons taking RIF.

- **Cutaneous reactions:** Pruritus/itching (with or without a rash), or other cutaneous reactions, may occur in some persons taking RIF. The reactions are generally self-limited and may not be a true hypersensitivity; continued treatment may be possible.
• **Hypersensitivity reactions:** Rarely, rifamycins can be associated with hypersensitivity reactions, including hypotension, anaphylaxis, nephritis or thrombocytopenia, and manifested by symptoms such as fever, headache, dizziness/lightheadedness, musculoskeletal pain, petechiae, and pruritus.

• **Gastrointestinal symptoms:** Symptoms such as nausea, anorexia, and abdominal pain are rarely severe enough to discontinue treatment.

• **Discoloration of body fluids:** Orange-red discoloration of body fluids, such as urine and breast milk, is expected and harmless, but patients should be advised beforehand. Soft contact lenses and dentures may be permanently stained.

• **Drug-drug interactions:** RIF and RPT have drug-drug interactions with numerous medications. They are known to reduce concentrations of methadone, warfarin, hormonal contraceptives, tricyclic antidepressants, haloperidol, diazepam, phenytoin, and blood pressure medicines (beta blockers and calcium channel blockers). For a full list of clinically significant drug-drug interactions, see Table 8 in the *Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis*. Dose adjustment of the companion medication may be necessary. Women using hormonal contraceptives should be advised to consider an alternative method of contraception (e.g., a barrier method).

• **Contraindication with certain antiretroviral therapy (ART) medications:** Rifampin (RIF) should not be used in HIV-infected individuals being treated with certain antiretroviral medications, such as protease inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors, or the CCR5 antagonist maraviroc. Substitution of rifabutin (RBT) for RIF in the 4-month regimen may be considered for such patients. Rifapentine (RPT) should not be used in HIV-infected persons taking antiretroviral medications that have clinically significant or unknown drug interactions with RPT. For the most current recommendations for TB treatment for persons with HIV infection and LTBI, clinicians should refer to the AIDSinfo guidelines, *Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV.*
Adverse Reactions to Isoniazid (INH)

- **Peripheral neuropathy:** Peripheral neuropathy is associated with using INH (Table 4.4). Persons with risk factors for neuropathy (e.g. pregnant women; breastfeeding infants; persons infected with HIV; patients with diabetes, alcoholism, malnutrition, or chronic renal failure; or those who are of advanced age) are given pyridoxine (vitamin B6). To prevent neuropathy, vitamin B6 can be administered at 25–50 mg/day with 6H, 9H, or 3HR and at 50 mg/week with 3HP.

- **Clinical hepatitis:** Clinical hepatitis occurs in fewer than 1% of people taking INH and is more common when INH is combined with other hepatotoxic agents. Factors that may increase either of these rates or the severity of hepatitis include daily alcohol consumption, underlying liver disease or risks for liver disease, and the concurrent use of other medications that are metabolized in the liver. Symptomatic hepatitis is rare, but severe and fatal cases have been reported.

  - Limited evidence indicates that pregnant women are at increased risk for fatal hepatitis associated with INH, and this risk might also increase during the immediate postpartum period. Therefore, pregnant women should be monitored closely for adverse reactions throughout the treatment course.

- **Elevated liver enzymes:** Approximately 10%–20% of persons taking INH will have some mild asymptomatic elevation of liver enzymes (alanine aminotransferase or aspartate aminotransferase). These abnormalities tend to resolve even if INH is continued. For this reason, routine monitoring of liver enzymes is not recommended for all patients receiving INH. For persons who experience symptoms consistent with liver injury and who have liver disease or risk factors for liver disease (e.g., coinfection with hepatitis B or C virus or heavy alcohol use), liver enzymes should be measured to evaluate for hepatotoxicity.

  - If any of the liver enzymes exceed 3 times the normal limit with symptoms present or 5 times the upper limit of normal with no symptoms, INH should typically be withheld.

  - For liver enzyme elevations <3 times the upper limit of normal in a symptomatic patient, at a minimum, close clinical and laboratory monitoring should be instituted if treatment is to be continued.
### Table 4.4
**Adverse Drug Reactions to INH**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Comment</th>
</tr>
</thead>
</table>
| Peripheral neuropathy | • This condition is uncommon at doses of 5 mg/kg body weight  
  • Pyridoxine (vitamin B6) might also be administered to persons at high risk, including  
  • pregnant women  
  • breastfeeding infants  
  • persons with HIV  
  • patients with diabetes, alcoholism, malnutrition, or chronic renal failure  
  • patients with advanced age |
| Clinical hepatitis | • Pregnant women are at increased risk  
  • Postpartum women are at increased risk, especially during the initial 3-month postpartum period |
| Elevated liver enzymes | • 10%–20% of persons taking INH will have some mild elevation of liver enzymes; these tend to resolve even if INH is continued  
  • Discontinue INH if any of the following occurs:  
    • measurements exceed 3 times the normal limit in a symptomatic person  
    • measurements exceed 5 times the upper limit of normal in an asymptomatic person  
  • Provide close clinical and laboratory monitoring if any signs or symptoms of hepatotoxicity occur or if liver function test elevations are less than the levels listed previously |
Special Considerations for LTBI Treatment

HIV-Infected Persons

LTBI treatment for HIV-infected persons should be provided in consultation with an expert in the management of HIV and TB coinfection. When treating HIV-infected persons for LTBI, it is important to be aware of potential drug-drug interactions with ART medications. For information about drug-drug interactions between specific anti-mycobacterial agents, including rifamycins (rifampin [RIF], rifabutin [RBT], and rifapentine [RPT]), and antiretroviral agents, refer to *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV*. Additionally, please refer to the TB section of the AIDSinfo guidelines, *Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV*, as they are regularly updated and address LTBI treatment in HIV/AIDS patients.

Isoniazid (INH) and Rifapentine (RPT) Regimen (3HP)

Once-weekly INH and RPT for 3 months (3HP) is a 12-dose regimen recommended for HIV-infected persons with LTBI who are taking ART medications with acceptable drug-drug interactions with RPT, such as efavirenz or raltegravir. This regimen offers the added benefit of a shorter treatment duration. RPT should not be used in HIV-infected persons taking antiretroviral medications that have clinically significant or unknown drug interactions with RPT.

Rifampin (RIF) Regimen (4R)

For HIV-infected patients who cannot tolerate INH or who have been exposed to INH-resistant *M. tuberculosis*, a 120-dose treatment regimen of 4 months of daily rifampin (RIF) is a treatment option. However, RIF should not be used for HIV-infected persons being treated with certain combinations of ART. RIF should not be used in HIV-infected individuals being treated with certain antiretroviral medications, such as protease inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors, or the CCR5 antagonist maraviroc. In situations where RIF cannot be used, sometimes another drug, rifabutin (RBT), may be substituted. RBT should not be used in HIV-infected persons taking antiretroviral medications that have clinically significant or unknown drug interactions with RBT.
Given the theoretical risks of rifamycin monotherapy in undiagnosed early-stage TB disease and the relatively poor performance of symptom screens alone in HIV-infected patients on ART, clinicians may consider performing a sputum culture before starting the 4R treatment regimen for LTBI. Chest radiography should be evaluated to ensure no radiographic evidence of abnormalities that could be consistent with TB disease.

**Isoniazid (INH) and Rifampin (RIF) Regimen (3HR)**

The 90-dose daily 3HR regimen is also recommended for adults and children of all ages living with HIV, as drug interactions allow.

**Isoniazid (INH) Regimens (6H or 9H)**

The 6- or 9-month regimens of daily INH are treatment options for HIV-infected adults and children with LTBI. For HIV-infected persons, INH can be administered together with nucleoside reverse transcriptase inhibitors, protease inhibitors, or nonnucleoside reverse transcriptase inhibitors. Children and adolescents who are HIV-infected or have nutritional deficiencies should receive pyridoxine (vitamin B6) supplements.

**Persons with Fibrotic Lesions**

Persons who have a chest radiograph indicative of old fibrotic lesions thought to represent previous TB disease should be treated for LTBI if they have all of the following:

- A positive blood test result or TST of ≥5 mm of induration
- No symptoms of TB disease
- No history of treatment for TB disease

These persons should be evaluated by using 3 sputum specimens for acid-fast bacilli smear and culture, and they should only be treated for LTBI after these specimens are negative by culture. Persons with evidence indicative of healed, primary TB disease (i.e., calcified solitary pulmonary nodules, calcified hilar lymph nodes, or apical pleural capping) are not at increased risk for TB disease. Their risk for TB disease and the need for LTBI treatment should be determined by consideration of other risk factors.
Contacts of Persons with INH-Resistant TB
If a person is a contact of a patient with INH-resistant but RIF-susceptible TB, a 4-month regimen of daily RIF may be recommended.

Contacts of Persons with Multidrug-Resistant TB (MDR TB)
Based on the drug-susceptibility test results of the source-case isolate, contacts presumed to have been infected with MDR TB should be treated for 6–12 months with a later-generation fluoroquinolone alone or with a second drug. Pyrazinamide (PZA) should not be routinely used as the second drug due to concerns with toxicity, adverse events, and discontinuations. Depending on the drug resistance profile, the benefit of LTBI treatment versus the risks from medication may need to be considered. Treatment of multidrug-resistant LTBI should be prescribed in consultation with an MDR TB expert.

Pregnancy and Breastfeeding

Pregnancy
For most pregnant women, LTBI treatment can be delayed until 2–3 months postpartum to avoid administering unnecessary medication during pregnancy. There is potential for an increased risk of hepatotoxicity during pregnancy and in the first 2–3 months of the postpartum period.

For women who are at high risk for progression from LTBI to TB disease, especially those who are a recent contact of someone with infectious TB disease, LTBI treatment should not be delayed on the basis of pregnancy alone, even during the first trimester. Before starting LTBI treatment, TB disease must be excluded through a symptom review and chest radiograph (see Table 3.1 in Chapter 3: Diagnosis of Tuberculosis Disease). For pregnant women at high risk for progression to TB disease, careful clinical monitoring or laboratory monitoring should be conducted.

Pregnant women can take any of the following regimens for the treatment of LTBI:

- 4-month daily regimen of RIF (4R)
- 3-month daily regimen of INH and RIF (3HR)
- 6- or 9-month daily regimen of INH (6H or 9H)
Pregnant women taking INH should also take pyridoxine (vitamin B6) supplementation to ameliorate possible adverse effects of the drug.

The 3HP regimen is **not** recommended for pregnant women or women expecting to become pregnant during the treatment period because its safety during pregnancy has not been studied.

### Breastfeeding
Breastfeeding is not contraindicated when a mother is undergoing LTBI treatment with INH or RIF separately. The amount of INH or RIF in the mother’s breast milk is inadequate to either harm or benefit an infant. Breastfed infants of mothers who take INH should receive supplemental pyridoxine (vitamin B6). Women taking RIF should be advised that they may notice a normal orange discoloration of body fluids, including breast milk. Currently, there are not enough data to indicate whether 3HP is safe for women to take while breastfeeding.

### Renal Disease
Renal insufficiency can complicate LTBI management because certain anti-TB drugs are cleared by the kidneys. For patients with end-stage renal disease requiring hemodialysis, TB medication might need to be administered after dialysis and sometimes might need to be consolidated to higher doses administered three times weekly to conform with a dialysis schedule. Consultation with the patient’s nephrologist is advised.

### Liver Disease
LTBI treatment for patients with unstable or advanced liver disease might be problematic because

- The likelihood of drug-induced hepatitis is greater.
- The implications of drug-induced hepatitis for patients with marginal hepatic reserve are potentially serious, even life-threatening.
- Fluctuations in the indicators of liver function related to the preexisting liver disease can confound monitoring for drug-induced hepatitis.

Clinicians might consider watchful waiting instead of LTBI treatment for patients with advanced or unstable liver disease. Expert consultation is advised when treating such patients.
Children

Although all of the LTBI regimens are effective, health care providers should prescribe the more convenient shorter treatment regimens when possible. The following regimens are recommended for the treatment of LTBI in children:

- 3-month once-weekly regimen of INH and RPT (3HP)
- 4-month daily regimen of RIF (4R)
- 3-month daily regimen of INH and RIF (3HR)
- 6- or 9-month daily regimen of INH (6H or 9H)

3HP is recommended for children older than 2 years of age and may be given via DOT or SAT. LTBI treatment regimens that are recommended for children of any age include 4R and 3HR. Regimens of 6 or 9 months of daily INH are alternative recommended treatment regimens for children of any age.

DOT for LTBI treatment should be considered for persons who are at especially high risk for TB disease (e.g., young children) and who are either taking an intermittent regimen or who may have difficulty with treatment adherence. Because of the importance of each dose, DOT must be used for patients on INH regimens given twice weekly. Risk of INH-related hepatitis in infants, children, and adolescents is minimal. Routine monitoring of serum liver enzymes is not necessary unless the child has risk factors for hepatotoxicity.
Patient Monitoring

The components of patient monitoring for LTBI treatment include

- Baseline laboratory testing, when indicated.
- Monthly medical evaluation.
- Routine laboratory monitoring.
- Treatment follow up.

Baseline Laboratory Testing

Baseline laboratory testing is not routinely indicated for all patients at the start of LTBI treatment. Baseline hepatic measurements of serum aspartate aminotransferase (serum glutamic-oxaloacetic transaminase) or alanine aminotransferase (serum glutamic pyruvic transaminase) and bilirubin are indicated for patients who have a history of chronic liver disease (e.g., hepatitis B or C virus infection, alcoholic hepatitis, or cirrhosis), persons who use alcohol regularly, and others who are at risk for chronic liver disease. Baseline testing is also indicated for

- Patients with HIV infection.
- Women who are pregnant or in the immediate postpartum period (within 3 months after delivery).

Baseline laboratory testing is not routinely indicated for older persons. However, testing might be considered on an individual basis, particularly for patients who are taking other medications for chronic medical conditions. Active hepatitis and end-stage liver disease are relative contraindications to the use of INH, RIF, or RPT for LTBI treatment. Use of these drugs for such patients must be undertaken with caution. Patients with baseline abnormal liver function tests should be monitored at regular intervals with clinical and laboratory evaluations.

Monthly Medical Evaluation

At least once a month, the patient should be evaluated for

- Adherence to the prescribed regimen.
- Signs and symptoms of TB disease.
- Signs and symptoms of adverse effects, especially hepatitis (e.g., jaundice, loss of appetite, fatigue, or muscle and joint aches).
Routine Laboratory Monitoring
Routine laboratory monitoring during LTBI treatment is recommended only for those whose baseline liver function tests are abnormal or for others with a risk for hepatic disease. Clinicians should order laboratory testing (e.g., liver function studies) for patients with symptoms compatible with hepatotoxicity to evaluate possible adverse reactions that occur during the treatment regimen. If any of the liver enzymes exceed 3 times the normal limit with symptoms present or 5 times the upper limit of normal in an asymptomatic person, it is recommended that LTBI treatment be withheld. For liver enzyme elevations less than 3 times the upper limit of normal in a symptomatic patient, close clinical and laboratory monitoring should be instituted at a minimum if treatment is to be continued.

Treatment Follow-Up
Patients should receive documentation of blood test or TST results, medication(s) taken, treatment duration, and treatment completion dates. They should be told to present this documentation whenever they are required to be tested for TB in the future. Patients should also be reminded about the signs and symptoms of TB disease and advised to seek medical attention if any of these signs or symptoms occur. They should be advised that treatment greatly reduces the risk for progression to TB disease but does not eliminate it.
Knowledge Check

Select the best answer for each question.

1. Which of the following groups should be given high priority for treatment of latent TB infection?
   A. Patients with organ transplants and other immunosuppressed patients
   B. HIV-positive persons
   C. Recent contacts of persons with infectious TB disease
   D. Persons with fibrotic changes consistent with prior TB
   E. All of the above

2. Which of the following LTBI treatment regimens is an alternative to rifampin for HIV-positive persons who are receiving protease inhibitors or nonnucleoside reverse transcriptase inhibitors?
   A. Streptomycin
   B. Rifampin
   C. Ethambutol
   D. Rifabutin

3. Which of the following describes directly observed therapy (DOT)?
   A. A public health worker gives the patient a bottle of pills monthly.
   B. A designated individual watches the patient swallow every dose of the prescribed medication.
   C. A public health worker counts the remaining pills in the medication bottles.
   D. All of the above.

4. Which statement is true about the purpose of treatment for latent TB infection?
   A. It is given to people who have latent TB infection to prevent them from testing positive on future tests for TB infection.
   B. It is given to people who have latent TB infection to prevent them from developing TB disease.
   C. It is given to people who have TB disease to prevent the disease from getting worse.
   D. It is given to people who have TB disease to prevent them from becoming infectious.
5. Your patient is a 67-year-old man with latent TB infection. According to the guidelines from the National Tuberculosis Controllers Association (NTCA) and Centers for Disease Control and Prevention (CDC), which of the following statements about preferred regimens for treatment of latent TB infection among U.S. residents is correct?

A. For patients without drug intolerability or drug-drug interactions, long-course (6- to 9-month) isoniazid is preferred over short-course (3- to 4-month) rifamycin-based treatment regimens.

B. Preferred treatment regimens include 3 short-course, rifamycin-based treatment regimens: 3 months of once-weekly isoniazid plus rifapentine; 4 months of daily rifampin; or 3 months of daily isoniazid plus rifampin.

C. 3 months of once-weekly isoniazid plus rifapentine is less expensive than most alternative regimens.

D. 4 months of daily rifampin is preferred for HIV-positive persons.

6. The daily or twice-weekly 2-month regimen of rifampin (RIF) with pyrazinamide (PZA) is recommended for LTBI treatment.

A. True

B. False

7. Which of the following is not a preferred LTBI treatment regimen?

A. 9H-INH given daily (270 doses) for 9 months

B. 3HP- INH and RPT given once weekly (12 doses) for 3 months

C. 3HR-INH and RIF given daily (90 doses of each drug) for 3 months

D. 4R- RIF given daily (120 doses) for 4 months

8. A health care provider may use rifampin and rifapentine interchangeably when treating LTBI.

A. True

B. False

See page 195 for answer key.
Chapter Objectives

After working through this chapter, you should be able to

- Describe treatment regimens for TB disease.
- Describe methods for monitoring patients for adverse reactions.
- Describe TB disease treatment adherence strategies.

Chapter Introduction

The major goals of tuberculosis (TB) disease treatment are to

- Cure the patient.
- Minimize risk for death and disability.
- Reduce transmission of *Mycobacterium tuberculosis* to other persons.
- Prevent acquisition of drug resistance during treatment.
To ensure that these goals are met, TB disease is generally treated for 6 months, and in some cases even longer. The majority of the bacteria are killed during the first 8 weeks of treatment; however, persistent organisms require longer treatment. If treatment is not continued for a long enough duration, surviving bacteria can cause the patient to become ill and the disease to become infectious again; there is also potential for drug-resistant disease to develop. Drug-resistant TB occurs when the TB bacteria that the person is infected with will not respond to at least 1 of the 4 main TB treatment drugs, which include isoniazid (INH), rifampin (RIF), ethambutol (EMB), and pyrazinamide (PZA) (Table 5.1).

Multiple options for daily and intermittent therapy are available. The goal of treatment for TB disease should be to provide the safest and most effective therapy for the shortest period. Given adequate treatment, almost all patients will recover and be cured. To help patients adhere to treatment, in-person directly observed therapy (DOT) or electronic directly observed therapy (eDOT) should be used.

Regimens for treating TB disease must contain multiple drugs to which the bacteria are susceptible. The standard of care for initiating treatment of TB disease is 4-drug therapy. This initial 4-drug therapy is referred to as the intensive phase of treatment. Treatment with a single drug can lead to development of a bacterial population resistant to that drug. Likewise, the addition of a single drug to a failing anti-TB treatment regimen can lead to additional resistance. When 2 or more drugs to which in vitro susceptibility has been demonstrated are administered together, each helps prevent the emergence of tubercle bacilli that are resistant to the other drug.

**Treatment and Monitoring Plan**

For each patient with newly diagnosed TB disease, a specific treatment and monitoring plan should be developed in collaboration with the local TB control program within 1 week of the presumptive diagnosis. The plan should include

- A description of the TB treatment regimen.
- The methods that will be used for assessing and ensuring adherence to the TB treatment regimen.
- How coordination of social services and patient support will be conducted.
- The methods that will be used for monitoring for adverse reactions.
- The methods that will be used for evaluating treatment response.
TB Disease Treatment Regimens

Anti-TB Drugs

Several drugs are used for treating TB disease. INH, RIF, EMB, and PZA are considered first-line anti-TB drugs and form the core of standard treatment regimens (Table 5.1; Figure 5.1). Rifabutin (RBT) and rifapentine (RPT) may also be considered first-line drugs under certain circumstances. RBT is typically reserved for patients for whom drug-drug interactions preclude the use of RIF (e.g., persons taking certain antiretroviral therapy [ART] drugs). Streptomycin (SM) was formerly considered to be a first-line drug and, in certain instances, is still used during the intensive phase of treatment. However, an increasing prevalence of resistance to SM in many parts of the world has decreased its overall usefulness. Bedaquiline, cycloserine, and ethionamide are reserved for special situations (e.g., drug intolerance or resistance).

The fluoroquinolones—levofloxacin and moxifloxacin—are commonly used to treat TB disease caused by drug-resistant organisms or for patients who are intolerant of certain first-line drugs. Amikacin is an aminoglycoside drug that can be used to treat patients with TB disease caused by drug-resistant organisms.

Figure 5.1
First-Line Anti-TB Drugs

From left to right: Isoniazid, rifampin, pyrazinamide, and ethambutol, the 4-drug regimen that forms the core of the intensive phase of treatment for TB disease.
### Table 5.1
First- and Second-Line Drugs Used for Treating TB Disease in the United States

<table>
<thead>
<tr>
<th>Line of Drugs</th>
<th>Anti-TB Drugs</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line</td>
<td>Isoniazid (INH)</td>
<td>INH, RIF, PZA, and EMB form the core of the intensive phase of treatment.</td>
</tr>
<tr>
<td></td>
<td>Rifampin (RIF)</td>
<td>RBT may be substituted for RIF in certain situations where concern exists for drug-drug interactions, RIF intolerance, or similar situations.</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide (PZA)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ethambutol (EMB)</td>
<td>RPT is currently used for latent tuberculosis infection (LTBI); its role in the management of drug-susceptible tuberculosis will depend on the results of ongoing randomized clinical trials.</td>
</tr>
<tr>
<td></td>
<td>Rifabutin (RBT)*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rifapentine (RPT)</td>
<td></td>
</tr>
<tr>
<td>Second-line</td>
<td>Streptomycin (SM)</td>
<td>• SM was formerly considered to be a first-line drug and, in certain instances, is still used during the intensive phase of treatment.</td>
</tr>
<tr>
<td></td>
<td>Bedaquiline</td>
<td>• Increasing prevalence of resistance to SM in many parts of the world has decreased its overall usefulness.</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin*</td>
<td>These second-line drugs are reserved for special situations (e.g., drug intolerance or resistance).</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clofazimine*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cycloserine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amikacin*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carbapenems w/ clavulanic acid*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Delamanid**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ethionamide/ Prothionamid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ρ-Aminosalicylic acid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pretomanid***</td>
<td></td>
</tr>
</tbody>
</table>

*Not approved by the U.S. Food and Drug Administration for use in the treatment of tuberculosis.
**Delamanid is not approved by the FDA and can only be obtained through a compassionate use program.
***Pretomanid is FDA-approved in the treatment of tuberculosis only as part of the BPal regimen (comprised of bedaquiline, pretomanid, and linezolid).
Fixed-Dose Combination Drugs

Clinical trials demonstrate that no substantial difference exists between fixed-dose combination (FDC) and single-drug combinations for treatment outcomes. Use of FDC capsules or tablets facilitates DOT administration because fewer tablets are used, minimizing the chance for error. Use of FDCs might reduce the risk for acquired drug resistance because one medication cannot be taken selectively. FDCs can also simplify prescription writing and drug supply management processes for clinicians. In the United States, the FDA has approved FDCs of INH and RIF (Rifamate®; Sanofi US, Bridgewater, New Jersey) and INH, RIF, and PZA (Rifater®; Sanofi US, Bridgewater, New Jersey). Clinicians should become familiar with the names of these different drug combinations and TB disease management when using FDC drugs.

TB Treatment Phases

The recommended treatment regimens are based on evidence that was appraised using Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Methodology. There are four basic treatment regimens recommended for treating adults with TB disease caused by organisms that are known or presumed to be susceptible to INH, RIF, PZA, and EMB (Tables 5.2, 5.3, and 5.4). Each treatment regimen consists of an intensive 2-month treatment phase, followed by a continuation phase of either 4 or 7 months. The 4-month continuation phase is used for the majority of patients.

Intensive Phase

The intensive phase is used to kill active growing TB bacilli. This phase of treatment is crucial for preventing emergence of drug resistance and determining the ultimate regimen outcome. Four drugs—INH, RIF, PZA, and EMB—should be included during the intensive phase until the results of drug-susceptibility tests are available. Each of the drugs in the intensive phase plays a key role. INH and RIF are bactericidal against *M. tuberculosis*, PZA has potent sterilizing activity, and EMB helps to prevent emergence of RIF resistance when primary INH resistance is present. If drug-susceptibility test results are known and the organisms are fully susceptible, EMB need not be included. Because EMB carries a risk for ocular toxicity, EMB may be excluded from the intensive phase for patients whose clarity or sharpness of vision cannot be monitored (e.g., infants), except when the risk for drug resistance is high or in more severe forms of TB disease.
Continuation Phase

The continuation phase is designed to eliminate remaining TB bacilli and to reduce treatment failure and relapse. This phase of treatment is administered for either 4 or 7 months. The 4-month continuation phase should be used in the majority of patients. Extension of the continuation phase to 7 months is recommended for select patients, particularly including those who meet any of the following criteria:

- Patients with cavitary pulmonary TB caused by drug-susceptible organisms and whose sputum culture obtained at the time of completion of 2 months of treatment continues to be positive
- Patients whose intensive phase of treatment did not include PZA
- Patients with HIV infection who are not receiving ART during TB treatment
### Table 5.2
TB Treatment Phases for Drug-Susceptible Pulmonary TB Disease

<table>
<thead>
<tr>
<th>Phase</th>
<th>Purpose</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intensive</strong></td>
<td>• Kills the majority of the tubercle bacilli during the first 8 weeks of treatment, but some bacilli can survive longer • Prevents emergence of drug resistance • Determines the ultimate outcome of the regimen</td>
<td>Intensive 2-month treatment regimen • Includes 4 drugs (usually INH, RIF, PZA, and EMB) • Each of the 4 drugs plays a key role • Multiple drugs are needed for preventing development of drug-resistant TB disease • EMB may be discontinued if drug susceptibility test results are known and the organisms are fully susceptible</td>
</tr>
<tr>
<td><strong>Continuation</strong></td>
<td>• Kills remaining persistent tubercle bacilli (after intensive phase) • If treatment is not continued long enough, the surviving bacilli can cause TB disease in the patient at a later time</td>
<td>An addition of either 4 or 7 months of treatment through the end of the continuation phase • Treatment includes 2 drugs (usually INH and RIF) • 4 months is used for the majority of patients • 7 months is recommended for patients • with cavitary pulmonary TB caused by drug-susceptible organisms and whose sputum culture obtained at the time of completion of 2 months of treatment is positive • whose intensive phase of treatment did not include PZA • with HIV infection who are not receiving ART during TB treatment</td>
</tr>
</tbody>
</table>

**Abbreviations:** EMB, ethambutol; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin.

*Note: Use of once-weekly therapy with INH 900 mg and rifapentine 600 mg in the continuation phase is not generally recommended. In uncommon situations where more than once-weekly DOT is difficult to achieve, once-weekly continuation phase therapy with INH 900 mg plus rifapentine 600 mg may be considered for use only in HIV uninfected persons without cavitation on chest radiography.*
### Table 5.3
Drug Regimens for Adults with Pulmonary TB Caused by Drug-Susceptible Organisms*

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Intensive Phase</th>
<th>Continuation Phase</th>
<th>Range of Total Doses (Days)</th>
<th>Commentsc,d</th>
<th>Regimen Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>INH RIF PZA EMB</td>
<td>7 days/week for 56 doses (8 weeks) or 5 days/week for 40 doses (8 weeks)</td>
<td>INH RIF</td>
<td>7 days/week for 126 doses (18 weeks) or 5 days/week for 90 doses (18 weeks)</td>
<td>182-130</td>
</tr>
<tr>
<td>2</td>
<td>INH RIF PZA EMB</td>
<td>7 days/week for 56 doses (8 weeks) or 5 days/week for 40 doses (8 weeks)</td>
<td>INH RIF</td>
<td>3 times weekly for 54 doses (18 weeks)</td>
<td>110-94</td>
</tr>
<tr>
<td>3</td>
<td>INH RIF PZA EMB</td>
<td>3 times weekly for 24 doses (8 weeks)</td>
<td>INH RIF</td>
<td>3 times weekly for 54 doses (18 weeks)</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>INH RIF PZA EMB</td>
<td>7 days/week for 14 doses, then twice weekly for 12 doses</td>
<td>INH RIF</td>
<td>2 times weekly for 36 doses (18 weeks)</td>
<td>62</td>
</tr>
</tbody>
</table>


**Abbreviations:** DOT, directly observed therapy; EMB, ethambutol; HIV, human immunodeficiency virus; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin; RPT, rifapentine.

**Note:** Use of once-weekly therapy with INH 900 mg and RPT 600 mg during the continuation phase usually is not recommended. In uncommon situations where more than once-weekly DOT is difficult to achieve, once-weekly continuation phase therapy with INH 900 mg plus RPT 600 mg might be considered for use only in HIV-uninfected persons without cavitary on chest radiograph.


*Based on expert opinion, patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31-week) continuation phase.

*Pyridoxine (vitamin B6), 25–50 mg/day, is administered with INH to all persons at risk for neuropathy (e.g., pregnant women; breastfeeding infants; persons with HIV infection; patients with diabetes, alcoholism, malnutrition, or chronic renal failure; or patients with advanced age). For patients with peripheral neuropathy, experts recommend increasing the pyridoxine dose to 100 mg/day.

*Alternatively, some US TB control programs have administered intensive-phase regimens 5 days/week for 15 doses (3 weeks), then twice weekly for 12 doses.

**CHAPTER 5: TREATMENT OF TUBERCULOSIS DISEASE**

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### Table 5.4
Doses, mg/kg Body Weight, a of Anti-TB Drugs for Adults and Children*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adults/Children</th>
<th>Daily</th>
<th>1 Time/Week</th>
<th>2 Times/Week</th>
<th>3 Times/Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>Adults</td>
<td>5 mg/kg (typically 300 mg)</td>
<td>15 mg/kg (typically 900 mg)</td>
<td>15 mg/kg (typically 900 mg)</td>
<td>15 mg/kg (typically 900 mg)</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>10–15 mg/kg</td>
<td>—</td>
<td>20–30 mg/kg</td>
<td>—b</td>
</tr>
<tr>
<td>RIF</td>
<td>Adults</td>
<td>10 mg/kg (typically 600 mg)</td>
<td>—</td>
<td>10 mg/kg (typically 600 mg)</td>
<td>10 mg/kg (typically 600 mg)</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>10–20 mg/kg</td>
<td>—</td>
<td>10–20 mg/kg</td>
<td>—b</td>
</tr>
<tr>
<td>RBT</td>
<td>Adults</td>
<td>5 mg/kg (typically 300 mg)</td>
<td>—</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>Optimal dosing for children is unknown but is estimated at 5 mg/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPT</td>
<td>Adults</td>
<td>—</td>
<td>10–20 mg/kg*</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>Active TB disease: For children aged ≥12 years, same dosing as for adults, administered once weekly; RPT is not FDA-approved for treatment of active TB disease for children aged &lt;12 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PZA</td>
<td>Adults</td>
<td>40–55 kg 18.2–25 mg/kg (1000 mg)</td>
<td>—</td>
<td>36.4–50 mg/kg (2000 mg)</td>
<td>27.3–37.5 mg/kg (1500 mg)</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>56–75 kg 20–26.8 mg/kg (1500 mg)</td>
<td>—</td>
<td>40–53.6 mg/kg (3000 mg)</td>
<td>33.3–44.6 mg/kg (2500 mg)</td>
</tr>
<tr>
<td>EMB</td>
<td>Adults</td>
<td>76–90 kg 22.2–26.3 mg/kg (2000 mg)</td>
<td>—</td>
<td>44.4–52.6 mg/kg (4000 mg)</td>
<td>33.3–39.5 mg/kg (3000 mg)</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>35 (30–40) mg/kg</td>
<td>—</td>
<td>50 mg/kg</td>
<td>—b</td>
</tr>
</tbody>
</table>


**Abbreviations**: EMB, ethambutol; FDA, Food and Drug Administration (US); INH, isoniazid; RBT, rifabutin; RIF, rifampin; RPT, rifapentine; PZA, pyrazinamide.

a Dosing that is based on actual body weight is acceptable for patients who are not obese. For obese patients (>20% above ideal body weight [IBW]), dosing that is based on IBW might be preferred for intensive doses. Some clinicians prefer a modified IBW (IBW + (0.40 x (actual weight - IBW)) as is done for initial aminoglycoside doses. Because TB drug dosing for obese patients has not been established, therapeutic drug monitoring might be considered for such patients.

b For purposes of this curriculum, adult dosing begins at age 15 years or at a weight of >40 kg for younger children. The optimal doses for thrice-weekly therapy for children and adolescents have not been established. Some experts recommend for adolescents the same doses as recommended for adults, and for younger children, the same doses as recommended for twice-weekly therapy.

c Higher doses of RIF, currently as high as 35 mg/kg body weight, are being studied in clinical trials.

2D) RBT dose might need to be adjusted when concomitantly using protease inhibitors or nonnucleoside reverse-transcriptase inhibitors.

The Tuberculosis Trials Consortium (TBTC) Study 22 team used RPT dosages of 10 mg/kg body weight in the continuation phase of treatment for active disease; however, the RIFAQUIN and PREVENT TB trial teams safely used higher dosages of RPT, administered once weekly. Daily doses of 1200 mg RPT are being studied in clinical trials for active TB disease.

With normal renal function.

4Based on estimated lean body weight; optimal doses for obese patients have not been established.

5Numbers in parentheses are calculated as mg/kg doses for patients at the highest and lowest body weights in the weight range.

6As an approach to avoiding EMB ocular toxicity, some clinicians use a 3-drug regimen (INH, RIF, and PZA) during the intensive 2 months of treatment for children who are HIV-uninfected, have no prior TB treatment history, are living in an area of low prevalence of drug-resistant TB, and have no exposure to a persons from an area of high prevalence of drug-resistant TB. However, because the prevalence of and risk for drug-resistant TB can be difficult to ascertain, the American Academy of Pediatrics and the majority of experts include EMB as part of the intensive-phase regimen for children with TB disease.
Treatment Interruptions

Interruptions during TB disease treatment are common. Health care providers are responsible for deciding whether to restart a complete course of treatment or to continue as intended. These decisions should be based on when the interruption occurred and the interruption duration.

Treatment Interruption During Intensive Phase

If the interruption occurs during the intensive phase, the following guidelines apply (see Figure 5.2):

- If lapse is $\geq 14$ days—restart treatment from the beginning.
- If lapse is $<14$ days—continue treatment to complete planned total number of doses, as long as all doses are completed within 3 months.

Figure 5.2
Algorithm for Management of Intensive-Phase Treatment Interruptions
Treatment Interruption During Continuation Phase

If the interruption occurs during the continuation phase, the following guidelines apply (see Figure 5.3):

If the patient received

- ≥80% of doses and sputum was acid-fast bacilli (AFB) smear negative on initial testing—further therapy might not be necessary.
- ≥80% of doses and sputum was AFB smear positive on initial testing—continue therapy until all doses are complete.
- <80% of doses and accumulative lapse is <3 months in duration—continue therapy until all doses are complete. If there is a consecutive lapse of >2 months; if treatment cannot be completed within the required time frame, restart treatment from the beginning of the intensive phase.
- <80% of doses and the lapse is ≥3 months in duration—restart therapy from the beginning of the intensive phase.

Figure 5.3
Algorithm for Management of Continuation Phase Treatment Interruptions

**Abbreviation:** AFB, acid-fast bacilli.
TB Disease Treatment Regimens for Specific Situations

TB disease treatment regimens for specific situations require special management and should be administered in consultation with a TB expert. Specific situations include the following, and each situation is discussed in the next section:

- Pregnancy
- Breastfeeding
- Infants and children
- HIV infection
- Renal insufficiency or end-stage renal disease
- Hepatic disease
- Extrapulmonary TB disease
- Drug-resistant TB disease
- Culture-negative TB disease
- Advanced age

Pregnancy

Untreated TB disease represents a greater hazard to a pregnant woman and her fetus than does TB treatment. Because of the risk of untreated TB to a pregnant woman and her fetus, TB treatment for pregnant women should be initiated when the probability of maternal disease is moderate to high. The intensive phase of treatment should include at least INH, RIF, and EMB. Although all of these drugs cross the placenta, they do not appear to have teratogenic effects. SM is the only anti-TB drug documented to have harmful effects on the human fetus (e.g., congenital deafness), and SM should not be used for TB treatment of pregnant women. In the United States, adding PZA to the treatment regimen for pregnant women is controversial; therefore, expert consultation should be sought to evaluate the risks and benefits of prescribing it on a case-by-case basis. If PZA is not included in the regimen, total treatment should last for at least 9 months (i.e., 2-month intensive phase, 7-month continuation phase).

For pregnant women with multidrug-resistant TB (MDR TB), treatment should only be administered in consultation with an MDR TB expert. Many of the medications currently used for treatment of MDR TB might be harmful to the fetus.
Breastfeeding

Breastfeeding should not be discouraged for women who are deemed noninfectious and are being treated with first-line anti-TB drugs. This is because the small concentrations of TB drugs in breast milk do not produce toxicity in the nursing newborn. Conversely, drugs in breast milk should not be considered an effective treatment for TB disease or latent TB infection (LTBI) in a nursing infant. A 25-mg/day vitamin supplement of pyridoxine (vitamin B6) is recommended for all pregnant or breastfeeding women taking INH. The amount of pyridoxine in multivitamins is variable, but it is typically less than the needed amount.

Infants and Children

In the United States, 5% of reported TB cases occur among children aged 0–14 years. Children with TB disease can be treated with the preferred 4-drug regimen (INH, RIF, PZA, and EMB) for 2 months followed by a 2-drug (INH and RIF) regimen for 4 months. Children receiving EMB should be monitored for vision changes. Some clinicians use a 3-drug regimen (INH, RIF, and PZA) in the intensive phase for children who are too young to have their vision monitored, are not infected with HIV, have no prior TB treatment history, and are not at risk for having drug-resistant TB.

Among infants, TB is much more likely to disseminate (i.e., spread from the lungs to other parts of the body); therefore, treatment should be started as soon as a TB diagnosis is presumed. Children commonly experience primary TB disease, which typically affects the middle and lower lung. Most forms of extrapulmonary TB among children can be treated with the same regimens as pulmonary disease. Exceptions are disseminated TB and TB meningitis, for which 9–12 months of treatment is recommended. For children with TB meningitis, experts sometimes advocate replacement of EMB with ethionamide or an aminoglycoside for 2 months, followed by 7–10 months of INH and RIF. For more information on treating TB disease among infants and children, see the Tuberculosis section of the Red Book 2018 Report of the Committee on Infectious Diseases. DOT should be used for all children and adolescents with TB disease.
**HIV Infection**

Management of HIV and TB coinfection is complex, and the clinical and public health consequences associated with treatment failure and other negative outcomes are serious. Patients with HIV infection might be on multiple medications, some of which interact with anti-TB drugs. Therefore, CDC strongly recommends consulting experts in treating HIV-related TB.

For HIV-infected TB patients receiving ART, the recommended treatment for drug-susceptible TB disease is a 6-month daily regimen consisting of both

- An intensive phase of INH, RIF, PZA, and EMB for 2 months.
- A continuation phase of INH and RIF for 4 months.

The use of intermittent TB treatment regimens has been associated with relapse and the development of drug resistance, and it is therefore recommended that TB treatment be given daily in both the intensive and continuation phases for HIV-infected TB patients. Additionally, DOT and other strategies should be used to promote adherence in all HIV-infected TB patients.

**Initiating ART for HIV-infected patients**

To improve treatment outcomes, all patients with HIV and active TB who are not on antiretroviral therapy (ART) should be started on ART. For patients with CD4+ cell counts of <50/mm³, ART should ideally be initiated within the first 2 weeks of TB treatment. For patients with CD4+ cell counts of ≥50/mm³, ART should ideally be initiated by week 8–12 of TB treatment. However, for HIV-infected patients with TB meningitis or TB involving the central nervous system, ART should not be initiated during the first 8 weeks of TB treatment because of increased risks for TB immune reconstitution inflammatory syndrome.

**Drug interactions involving RIF and ART medications**

A major concern in treating TB disease among HIV-infected patients is the interaction of RIF with certain ART medications (some protease inhibitors and nonnucleoside reverse-transcriptase inhibitors). However, a rifamycin-based regimen should be used for the entire course of therapy for coinfected patients, unless the isolate is resistant to the rifamycins or the patient has a severe side effect that is clearly caused by the rifamycins. RIF can be used for treating TB with certain combinations of ART agents. RBT, which has fewer drug-drug interactions because of its decreased induction of the cytochrome P450 system, can also be
used in place of RIF and appears to be equally effective, although the doses of the RBT and ART agents might require adjustments and should be administered with expert consultation.

As new ART agents and more pharmacokinetic data become available, these recommendations might be modified. For more information, see Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis and Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV.

**TB treatment duration for HIV-infected persons**

Six months is considered the minimum duration of TB treatment for HIV-infected adults, even for patients with culture-negative TB disease. If evidence exists of a slow or suboptimal response (e.g., cultures are still positive after 2 months of therapy), the continuation phase should be prolonged to 7 months (for a total of 9 months of treatment). In the uncommon situation in which HIV-infected patients do not receive ART during TB treatment, the continuation phase should also be extended to 7 months (for a total of 9 months of treatment).

**TB treatment for HIV-infected pregnant women**

Multiple challenges complicate the treatment of HIV-infected pregnant women with TB disease. Pregnancy alters the distribution and metabolism of certain drugs, including ART drugs; however, information is limited regarding whether pregnancy alters the metabolism of anti-TB drugs. Notably, the serum concentrations of protease inhibitors are decreased during the latter stages of pregnancy. No published data are available regarding drug-drug interactions between anti-TB and ART drugs among pregnant women. However, the effects of RIF on protease inhibitors are probably exacerbated during pregnancy.

**TB treatment for HIV-infected children**

HIV-infected children with TB disease are at greater risk for severe, life-threatening manifestations (e.g., disseminated disease or TB meningitis). Data are limited regarding the absorption, metabolism, and elimination of anti-TB drugs among children, particularly among very young children (those aged <2 years). For more information on treating TB in children, see Treating Children with HIV-Associated Tuberculosis and the Tuberculosis section of the Red Book 2018 Report of the Committee on Infectious Diseases. Consultation with a pediatric TB expert is recommended.
Renal Insufficiency or End-Stage Renal Disease

Renal insufficiency complicates management of TB disease because certain anti-TB drugs are cleared by the kidneys. Alteration in dosing of anti-TB drugs is commonly necessary among patients with renal insufficiency or end-stage renal disease requiring hemodialysis. The dosage of anti-TB drugs should not be decreased because the peak serum concentrations can be low and smaller doses might decrease drug efficacy. Instead, the dosing interval of anti-TB drugs should be increased. On the basis of creatinine clearance, the majority of anti-TB drugs can be administered thrice weekly immediately after hemodialysis. Consultation with the patient’s nephrologist is advised.

Hepatic Disease

TB treatment among patients with unstable or advanced liver disease is problematic due to the following:

- The likelihood of drug-induced hepatitis is greater.
- The implications of drug-induced hepatitis for patients with marginal hepatic reserve are potentially serious, even life-threatening.
- Fluctuations in the indicators of liver function related to the preexisting liver disease can confound monitoring for drug-induced hepatitis.

Thus, clinicians might consider regimens with fewer potentially hepatotoxic agents for patients with advanced or unstable liver disease. Expert consultation is advisable when treating such patients. Of note, TB disease itself can involve the liver, causing abnormal liver function; therefore, not all abnormalities in liver function tests noted at baseline should be attributed to causes other than TB disease. The hepatic abnormalities caused by TB disease will improve with effective treatment.

Extrapulmonary TB Disease

Overall, the principles used for treating pulmonary TB disease also apply to extrapulmonary forms of the disease. A 6- to 9-month treatment regimen is recommended for the majority of extrapulmonary TB disease sites. The exception to these recommendations is TB meningitis. The optimal length of therapy for TB meningitis has not been established; however, experts usually recommend 12 months of treatment. The majority of experts also recommend that corticosteroids be used as additional therapy for patients with TB meningitis; consultation with a TB expert is recommended.
Drug-Resistant TB Disease

Drug-resistant TB disease can occur in two ways, either primary or secondary resistance. Primary resistance occurs among persons who have been intensively exposed to and infected with resistant organisms. Secondary (or acquired) resistance develops during TB therapy because the patient was treated with an inadequate regimen, or the patient did not take the prescribed regimen as directed, or because of other conditions (e.g., drug malabsorption or drug-drug interactions leading to low serum levels) (see Chapter 1: Transmission and Pathogenesis of Tuberculosis).

Drug resistance in a patient with newly diagnosed TB disease might be presumed on the basis of previous treatment, contact with a known TB patient with drug resistance, or time spent in a geographic region in which drug resistance is common. Drug resistance can be confirmed only by drug-susceptibility testing (see Chapter 3: Diagnosis of Tuberculosis Disease).

Patients with strains of *M. tuberculosis* resistant to both INH and RIF (i.e., multidrug-resistant or MDR TB) are at high risk for

- Treatment failure.
- Relapse.
- Further acquired resistance.
- Death.

These patients must be referred immediately to an expert in the management of drug-resistant TB disease. Because of their legal responsibilities for TB control, state and local health departments should be the primary point of contact when medical consultation is needed. Consultation can also be obtained from a TB Center of Excellence for Training, Education, and Medical Consultation. Contact information for state TB programs and the TB Centers of Excellence for Training, Education, and Medical Consultation can be found on the [CDC Division of TB Elimination website](https://www.cdc.gov/tb/).

**Treatment of MDR TB Disease**

Table 5.5 presents a clinical strategy that can be used to develop a treatment regimen for MDR TB disease. At least 5 drugs should be used in the intensive phase of treatment, and at least 4 drugs should be used in the continuation phase. The intensive phase of treatment should last 5 to 7 months after culture
conversion, and the total duration of treatment (i.e., intensive and continuation phases combined) should last 15 to 21 months after culture conversion. The final treatment duration will depend on the clinical context, extent of disease, response to treatment, and other factors.

It is important to note that a patient’s final treatment regimen should be based on many factors, including patient preferences, harms and benefits associated with the drugs, the ability to appropriately monitor for significant adverse effects, drug-drug interactions, comorbidities, and drug availability. A patient’s treatment regimen may therefore differ substantially from the approach outlined in Table 5.5. As stated previously, drug-resistant TB should always be treated in consultation with an expert in the treatment and management of drug-resistant TB. DOT should be used for patients with MDR TB disease.

MDR TB treatment regimens should only include drugs to which the patient’s \textit{M. tuberculosis} isolate is susceptible. Drugs that are known to be ineffective based on growth-based or molecular drug susceptibility testing should NOT be used. In children with TB disease who are contacts of infectious MDR TB patients, the source case’s drug susceptibility test results should be used if an isolate cannot be obtained from the child.

In 2019, the FDA approved pretomanid in combination with bedaquiline and linezolid to treat a limited and specific population of adult patients with extensively drug-resistant, treatment-intolerant, or nonresponsive MDR pulmonary TB.

For more information on the treatment of drug-resistant TB disease, please refer to the \textit{Treatment of Drug-Resistant Tuberculosis} guidelines, available on the CDC website.
Table 5.5
Clinical Strategy to Build an Individualized Treatment Regimen for MDR TB


<table>
<thead>
<tr>
<th>Instructions</th>
<th>Drugs</th>
</tr>
</thead>
</table>
| **Step 1:** Choose one later-generation fluoroquinolone | • Levofloxacin  
|  | • Moxifloxacin |
| **Step 2:** Choose both of these prioritized drugs | • Bedaquiline  
|  | • Linezolid |
| **Step 3:** Choose both of these prioritized drugs | • Clofazimine  
|  | • Cycloserine/terizidone |
| **Step 4:** If a regimen cannot be assembled with 5 effective oral drugs and the isolate is susceptible, use one of these injectable agents* | • Amikacin  
|  | • Streptomycin |
| **Step 5:** If needed or if oral agents preferred over injectable agents in Step 4, use the following drugs† | • Delamanid‡  
|  | • Pyrazinamide  
|  | • Ethambutol |
| **Step 6:** If limited options and cannot assemble a regimen of five effective drugs, consider use of the following drugs | • Ethionamide or prothionamide§  
|  | • Imipenem–cilastatin/clavulanate or meropenem/clavulanate‖  
|  | • ρ-Aminosalicylic acid¶  
|  | • High-dose isoniazid** |

The following drugs are not recommended for inclusion in MDR TB regimens:

- Capreomycin and kanamycin  
- Amoxicillin/clavulanate (when used without a carbapenem)  
- Azithromycin and clarithromycin

**Definition of abbreviations:** DST = drug susceptibility testing; INH = isoniazid; IPDMA = individual patient data meta-analyses; MDR = multidrug-resistant; PS = propensity score; TB = tuberculosis.

* Amikacin and streptomycin should be used only when the patient’s isolate is susceptible to these drugs. Because of their toxicity, these drugs should be reserved for when more-effective or less-toxic therapies cannot be assembled to achieve a total of 5 effective drugs.

† Patient preferences in terms of the harms and benefits associated with injectables (the use of which is no longer obligatory), the capacity to appropriately monitor for significant adverse effects, consideration of drug–drug interactions, and patient comorbidities should be considered in selecting Step 5 agents over injectables. Ethambutol and pyrazinamide had mixed/marginal performance on outcomes assessed in our PS-matched IPDMA; however, some experts may prefer these drugs over injectable agents to build a regimen of at least five effective oral drugs. Use pyrazinamide and ethambutol only when the isolate is documented as susceptible.

‡ Data on dosing and safety of delamanid are available in children ≥ 3 years of age.

§ Mutations in the inhA region of the *Mycobacterium tuberculosis* genome can confer resistance to ethionamide/prothionamide as well as to INH. In this situation, ethionamide/prothionamide may not be a good choice unless the isolate is shown to be susceptible with *in vitro* testing.

‖ Divided daily intravenous dosing limits feasibility. Optimal duration of use not defined.

¶ Fair/poor tolerability and low performance. Adverse effects reported to be less common in children.

** Data not reviewed in PS-matched IPDMA, but high-dose isoniazid can be considered despite low-level isoniazid resistance but not with high-level INH resistance.
Treatment of INH-Resistant TB

Patients with INH-resistant TB disease should be treated with a 6-month daily regimen of RIF, EMB, PZA, and a later-generation fluoroquinolone. In certain situations, the duration of PZA can be shortened to 2 months. Expert consultation should be sought for the treatment of patients with INH-resistant TB.

Cross-Resistance

- Resistance to RIF is associated in approximately all instances with cross-resistance to RPT and often to RBT.
- No cross-resistance occurs between SM and the other injectable agents, amikacin, kanamycin, and capreomycin (although resistance to each can occur as independent events); cross-resistance between amikacin and kanamycin is not universal but is frequently seen.
- Resistance to PZA is uncommon in the absence of resistance to other first-line drugs; if monoresistance to PZA is observed, consideration must be given to the possibility that the disease is caused by Mycobacterium bovis.
- Cross-resistance is substantial among the fluoroquinolone (FQ) agents. Resistance to any FQ drug suggests that no drug in the class can reliably be used for TB treatment.

Culture-Negative TB Disease

Decision to Treat Culture-Negative TB Disease

Failure to isolate *M. tuberculosis* from correctly collected specimens among persons who are presumed to have pulmonary TB disease on the basis of clinical or radiographic findings does not exclude a diagnosis of TB disease. Failure to isolate organisms might be due to recent use of antibiotics with bactericidal activity against *M. tuberculosis* (e.g., fluoroquinolones), low bacillary populations, inadequate sputum specimens for accurate testing, temporal variations in the number of bacilli being expelled, overgrowth of cultures with other microorganisms, or errors in specimen processing. Alternative diagnoses must be carefully considered and recommended diagnostic studies undertaken for patients who have what appears to be culture-negative TB disease. As part of the diagnostic evaluation, patients being evaluated for pulmonary TB disease should have a minimum of three sputum specimens collected for AFB smear and culture or for rapid molecular testing. Depending on the clinical features and differential diagnosis, other diagnostic testing (e.g., bronchoscopy with bronchoalveolar lavage and biopsy or nucleic acid amplification tests) are considered before
making a presumptive diagnosis of culture-negative TB disease. Similarly, for patients being evaluated for extrapulmonary TB disease, tissue or fluid from affected organs should also be submitted when feasible for diagnostic testing in assessing a presumptive diagnosis of culture-negative TB disease.

**Treatment of Smear-Negative, Culture-Negative TB Disease**

Patients who are thought to have a high likelihood of pulmonary TB disease on the basis of careful clinical and radiographic evaluation should have treatment initiated with INH, RIF, PZA, and EMB, even when the initial sputum smears are negative. If *M. tuberculosis* is isolated in culture or a rapid molecular test is positive, treatment for TB disease should be continued for a full standard 6-month course. Patients who have negative cultures but who are still presumed to have pulmonary TB disease should have a thorough follow-up clinical and radiographic evaluation as soon as 2 months of therapy has been completed. This is to determine whether a response attributable to anti-TB treatment has occurred. If either clinical or radiographic improvement has occurred and no other etiology is identified, treatment for TB disease should be continued. For HIV-negative patients, the total duration of therapy for smear-negative, culture-negative TB disease may be reduced to 4 months. HIV-infected patients should receive a minimum of 6 months of treatment, even with culture-negative TB disease.

**Treatment of Smear-Positive, Culture-Negative TB Disease**

Occasionally, patients will have positive AFB smears, but negative cultures. The approach taken in such cases should be individualized on the basis of clinical and radiographic findings. If likelihood of TB disease is high and the patient has positive AFB smears and negative cultures, the patient should be treated as if the culture were positive by using one of the recommended treatment regimens (Table 5.3).

**Figure 5.4** provides an algorithm for treatment of smear-negative, culture-negative TB disease.
Figure 5.4
Algorithm for Guiding Treatment of Smear-Negative TB Disease

Advanced Age

Advanced age can increase the risk for drug-induced hepatitis and other serious adverse effects. This is attributable to less efficient drug elimination caused by reduced renal and hepatic clearance. Because PZA is the most common cause of drug-induced hepatitis, the risk for serious adverse effects might outweigh the benefits of including PZA in the initial regimen for patients >75 years of age. In such cases, some experts use an initial regimen of INH, RIF, and EMB only. When PZA is not used during the intensive phase, the total duration of TB treatment should be extended to 9 months.
Monitoring Patients

Baseline Monitoring

Before starting treatment, adult patients should have certain baseline blood and vision tests to help detect any underlying problems that can complicate treatment. For children, only vision tests are necessary unless other medical conditions exist that might complicate treatment. Recommended examinations for baseline monitoring are included in Table 5.6.

Table 5.6
Recommended Tests for Baseline Monitoring for TB Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Recommended Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>Measure aminotransferases (i.e., AST or ALT), bilirubin, alkaline phosphatase, and serum creatinine and a platelet count, HIV serology, and HbA1c</td>
</tr>
<tr>
<td>Patients at risk for hepatitis B or C (e.g., injection drug users, those born in Asia or Africa, or HIV-infected patients)</td>
<td>Conduct serologic tests</td>
</tr>
<tr>
<td>Patients who are taking EMB</td>
<td>Test visual acuity (Snellen chart) and color vision (Ishihara)</td>
</tr>
<tr>
<td>HIV-infected patients</td>
<td>Obtain CD4+ lymphocyte count</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; EMB, ethambutol; HbA1c, glycated hemoglobin.

Monitoring During Treatment

Patients being treated for TB disease should have clinical evaluations at least monthly to assess medication adherence (Table 5.7) and to identify possible adverse reactions to medications (Table 5.8).

Routinely monitoring liver or renal function or platelet counts for patients being treated with first-line anti-TB drugs is unnecessary, unless abnormalities are detected at baseline or clinical reasons exist for obtaining measurements. Patients who have stable abnormalities of hepatic or renal function at baseline should have repeat measurements early in the treatment course, then less frequently to ensure conditions have not worsened.
Monthly repeat testing of visual acuity (Snellen) and color vision (Ishihara) is recommended for patients receiving an EMB dose exceeding 15–20 mg/kg body weight (the recommended range) and for patients receiving EMB for >2 months. Patients receiving EMB should be questioned at monthly intervals regarding visual disturbances. Patients should be educated regarding the possible visual side effects of EMB and instructed to immediately report vision changes to their health care provider.

The 2019 *Treatment of Drug-Resistant Tuberculosis: An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline* recommends the Curry International TB Center’s guides *Drug Resistant TB: Clinician’s Survival Guide* and *Nursing Guide for Managing Side Effects to Drug-Resistant TB Treatment*, in addition to the World Health Organization (WHO) companion handbook for the programmatic management of drug-resistant TB, as good resources to assist in evaluation and monitoring of patients with drug-resistant TB.

**Table 5.7**  
**Recommended Tests for Monitoring Patients During TB Treatment**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Recommended Test</th>
</tr>
</thead>
</table>
| All patients                   | Repeat at least monthly clinical evaluations to  
• Assess adherence to TB medication regimen  
• Identify possible adverse reactions to medications                                                                                   |
| Patients who are taking EMB    | • Ask patients monthly regarding visual disturbances  
• Repeat monthly testing for visual acuity (Snellen chart) and color vision (Ishihara) for patients whose dose exceeds 15–20 mg/kg body weight and those who have been receiving EMB for >2 months |
| Patients who have extrapulmonary TB disease | Evaluation depends on  
• Sites involved  
• Ease with which a test specimen can be obtained |

**Abbreviation:** EMB, ethambutol.
Evaluating the Patient’s Response to Treatment

Clinicians should evaluate a patient’s response to treatment to determine the efficacy of the treatment and to identify any adverse reactions by using the following 3 methods:

1. Clinical evaluation
2. Bacteriologic examination
3. Chest radiograph

**Clinical Evaluation**

Patients should have clinical evaluations at least monthly to

- Identify possible adverse reactions to medications.
- Assess adherence.
- Determine treatment efficacy.

Although each patient responds to treatment at a different pace, all TB signs (e.g., weight loss) and symptoms should gradually improve and eventually resolve. If a patient’s symptoms do not improve during the first 2 months of treatment, or if symptoms worsen after initial improvement, the patient should be evaluated for nonadherence to, or malabsorption of, the treatment regimen; development of drug resistance; or symptoms consistent with immune reconstitution.

**Adverse Reactions to Anti-TB Drugs**

In addition to bacteriologic evaluations, patients should have clinical evaluations for identifying possible adverse effects of the anti-TB drugs (Table 5.8). Monitoring for adverse reactions must be individualized. The type and frequency of monitoring depends on the drugs used and the patient’s risk for adverse reactions (e.g., age or alcohol use). At a minimum, patients should be examined monthly during therapy and questioned by health care providers concerning adverse reactions, even if problems are not apparent.

Adverse reactions to anti-TB drugs are relatively rare, but for certain patients, they can be severe. Mild adverse effects can usually be managed by adjusting the timing of the medications, by taking the medications with food, or by symptomatic
therapy. However, the medications must be discontinued if more severe effects occur. Importantly, first-line drugs should not be stopped without adequate justification. If a drug is discontinued, a replacement drug is typically included in the regimen. Consult a TB medical expert to assist in managing serious adverse reactions.

Patients should be specifically instructed to look for symptoms associated with the most common reactions to the medications they are taking. They should also be instructed to seek medical attention immediately if these symptoms occur. All patients receiving INH, RIF, or PZA should immediately report any symptoms indicative of hepatitis (i.e., nausea, loss of appetite, vomiting, persistently dark urine, yellowish skin or eyes, malaise, unexplained fever for ≥3 days, or abdominal tenderness). If the symptoms indicate adverse reactions, the patient should be instructed to stop the medication, and relevant laboratory testing should be performed.
### Table 5.8
Adverse Reactions to Anti-TB Drugs

<table>
<thead>
<tr>
<th>Caused by</th>
<th>Adverse Reaction</th>
<th>Signs and Symptoms</th>
<th>Significance of Reaction&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any drug</td>
<td>Allergic</td>
<td>Skin rash</td>
<td>Might be serious or minor</td>
</tr>
<tr>
<td>EMB</td>
<td>Eye damage</td>
<td>• Blurred or changed vision&lt;br&gt;• Changed color vision</td>
<td>Serious</td>
</tr>
<tr>
<td>INH</td>
<td>Hepatic toxicity</td>
<td>• Abdominal pain&lt;br&gt;• Abnormal liver function test results&lt;br&gt;• Brown urine or light-colored stool&lt;br&gt;• Fatigue&lt;br&gt;• Fever for ≥3 days&lt;br&gt;• Flu-like symptoms&lt;br&gt;• Lack of appetite&lt;br&gt;• Nausea&lt;br&gt;• Vomiting&lt;br&gt;• Yellowish skin or eyes</td>
<td>Serious</td>
</tr>
<tr>
<td>PZA</td>
<td></td>
<td>erekinal toxicity</td>
<td>Seri</td>
</tr>
<tr>
<td>RIF</td>
<td></td>
<td>erekinal toxicity</td>
<td>Seri</td>
</tr>
<tr>
<td>INH</td>
<td>Nervous system damage</td>
<td>• Dizziness&lt;br&gt;• Tingling or numbness around the mouth</td>
<td>Serious</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Tingling sensation in hands and feet</td>
<td></td>
<td>Serious</td>
</tr>
<tr>
<td>PZA</td>
<td>Stomach upset</td>
<td>• Stomach upset&lt;br&gt;• Vomiting&lt;br&gt;• Lack of appetite</td>
<td>Might be serious or minor</td>
</tr>
<tr>
<td>Gout</td>
<td></td>
<td>• Abnormal uric acid level&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt;• Joint aches</td>
<td>Serious</td>
</tr>
<tr>
<td>RIF</td>
<td>Bleeding problems</td>
<td>• Easy bruising&lt;br&gt;• Slow blood clotting</td>
<td>Serious</td>
</tr>
<tr>
<td>Discoloration of body fluids</td>
<td>Orange urine, sweat, or tears&lt;br&gt;• Permanently stained soft contact lenses</td>
<td></td>
<td>Minor</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Interferes with certain medications (e.g., birth control pills, birth control implants, certain ART medications, or methadone treatment)</td>
<td>Might be serious or minor</td>
<td></td>
</tr>
<tr>
<td>Sensitivity to the sun</td>
<td>Frequent sunburn</td>
<td></td>
<td>Minor</td>
</tr>
</tbody>
</table>

Abbreviations: EMB, ethambutol; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin.

<sup>a</sup>Patients should stop taking the medication and consult a clinician immediately if serious adverse reactions occur. Patients can continue taking medication if they have minor adverse reactions.

<sup>b</sup>Asymptomatic elevated uric acid levels are expected with PZA treatment. Acute gouty arthritis, which is rare without preexisting gout, is a contraindication for PZA use.
Common Adverse Reactions to TB Disease Treatment

The following are common adverse reactions to TB treatment:

- Gastrointestinal problems
- Hepatitis
- Rash
- Drug fever

Gastrointestinal Problems

Gastrointestinal reactions to anti-TB drugs are common, particularly in the first few weeks of therapy; reactions can include the following:

- Upset stomach
- Nausea
- Poor appetite
- Abdominal pain

In the presence of gastrointestinal symptoms, the clinician should measure serum aminotransferases (i.e., AST, ALT) and bilirubin.

Hepatotoxicity

Drug-induced hepatitis is the most frequent serious adverse reaction to the first-line TB drugs INH, RIF, and PZA. Drug-induced liver injury is indicated by ALT levels ≥3 times the upper limit of normal in the presence of hepatitis symptoms, or ≥5 times the upper limit of normal in the absence of hepatitis symptoms. An ALT level <5 times the upper limit of normal indicates mild toxicity; an ALT level of 5–10 times normal defines moderate toxicity; and an ALT level >10 times normal is severe toxicity. In addition to elevation of ALT, disproportionate increases in bilirubin and alkaline phosphatase occasionally occur; these conditions are associated with RIF hepatotoxicity that should be evaluated promptly. Before diagnosing drug-induced hepatitis, other causes of abnormal liver tests should be excluded. If ALT levels are consistent with hepatotoxicity, drugs must be stopped until ALT concentration returns to <2 times the upper limit of normal, and anti-TB drugs should be restarted one drug at a time.
Rash
All drugs used in treating TB disease can cause a rash, but the response to a patient with a rash depends upon the severity of the rash. The rash might be minor, affecting a limited area or manifesting predominantly as itching. In this case, antihistamines should be administered for symptomatic relief, but all TB disease medications can be continued.

Drug Fever
Recurrence of fever in a patient who has been receiving therapy for several weeks might indicate drug fever, especially if the patient’s tests are revealing microbiologic and radiographic improvement. Note, however, that fever from TB can persist for as long as 2 months after therapy has been initiated.

Bacteriologic Examination
Crucial treatment decisions concerning the continuation phase regimen are based on the patient’s bacteriologic status at the end of the intensive treatment phase. Patients whose cultures have not converted to negative after 2 months of therapy should be reevaluated for potential drug-resistant disease or potential nonadherence to the regimen. Patients who have positive cultures after 4 months of treatment should be considered as having failed treatment and managed accordingly.

For patients with extrapulmonary tuberculosis, the frequency and kinds of evaluations will depend on the sites involved and the ease with which specimens can be obtained.

Positive Sputum Cultures Before Treatment
For patients whose sputum culture is positive before treatment, the best way to measure the efficacy of therapy is to obtain specimens for culture at least monthly until 2 consecutive specimens are negative on culture (Table 5.9). Patients with MDR TB should have sputum AFB smears and cultures performed monthly throughout the entire treatment course.

Negative Sputum Cultures Before Treatment
For patients with negative sputum cultures before treatment for pulmonary disease, the major indicators of response to therapy are the chest radiograph and the clinical evaluation (Table 5.9). The intervals at which chest radiography should be repeated depend on the clinical circumstances and the differential diagnosis
that is being considered. If the radiograph does not improve after the patient has received 2 months of treatment, the abnormality might be the result of either previous, not current TB disease or another reason.

**Chest Radiograph**

For patients with positive cultures at diagnosis, a repeat chest radiograph can be useful upon completion of 2 months of treatment, but it is not essential. For patients with culture-positive TB, a chest radiograph at completion of treatment provides a baseline for comparison with any future films. For patients with cultures that are initially negative, a chest radiograph is necessary after 2 months of treatment, and a radiograph at completion of treatment is desirable. Follow up after completion of therapy is usually unnecessary.

**Table 5.9**

**Response to Treatment for Pulmonary TB Disease**

<table>
<thead>
<tr>
<th>Bacteriologic Status</th>
<th>Recommendations for Response to Treatment</th>
</tr>
</thead>
</table>
| Positive sputum cultures before treatment         | • Obtain specimens for culture at least monthly until 2 consecutive specimens are negative on culture  
• Perform monthly sputum AFB smears and cultures on MDR TB patients throughout entire treatment course  
• A repeat chest radiograph after 2 months of treatment can be useful but is not essential |
| Negative sputum cultures before treatment         | • Repeat chest radiograph at intervals based on clinical circumstances and differential diagnosis  
• If radiograph does not improve after patient has received 2 months of treatment, abnormality might be caused by  
  • Previous, not current, TB disease  
  • Another reason |
| Cultures have not converted to negative after 3 months of therapy | Reevaluate for  
  • Potential drug-resistant disease  
  • Potential nonadherence to the regimen |
| Cultures are still positive after 4 months of treatment | Consider treatment to have failed and manage accordingly in consultation with an expert |
**Treatment Completion**

Treatment completion is defined primarily as the ingestion of the total number of doses prescribed within the specified time frame. The duration of therapy depends on the drugs used, drug-susceptibility test results of the isolate, and the patient’s response to therapy (see Chapter 3: Diagnosis of Tuberculosis Disease). The majority of patients with TB disease can be treated with either a 6- or 9-month regimen, although the 6-month regimen is primarily used. All 6-month regimens must contain INH, RIF, and, initially, PZA. The goal is to complete all doses within 1 year.

**Follow-Up After Treatment**

Routine follow up after treatment completion is unnecessary for patients who have had a satisfactory response to a 6- or 9-month regimen. Patients whose organisms were fully susceptible to the drugs being used should be instructed to promptly report any symptoms, particularly prolonged cough, fever, or weight loss. Patients with MDR TB should be monitored for 2 years after treatment completion. For patients with organisms resistant to either INH or RIF (but not both), follow-up evaluation must be individualized.

**Adherence Strategies**

To treat TB disease and prevent the patient from acquiring drug resistance, clinicians must ensure that their patients with TB disease follow the recommended treatment course. However, ensuring that patients adhere to treatment can be difficult because they are often unable or reluctant to take multiple medications for long periods. Nonadherence to treatment is a major problem in TB prevention and control, because inadequate treatment can lead to

- Treatment failure.
- Relapse.
- Ongoing transmission to others.
- Development of drug resistance.
The responsibility for successful TB treatment is placed primarily on the provider or program initiating therapy rather than on the patient. Provider responsibility is a central concept in treating patients with TB disease, regardless of the source of their care. Health care professionals should consult their health department’s TB control program to ensure that TB patients are able to adhere to a prescribed treatment regimen. The TB control program should assist the health care professional in evaluating patient barriers to adherence. The TB control program should also recommend the use of DOT, incentives, and enablers that can assist the patient in completing the recommended therapy.

If these efforts are unsuccessful, the TB control program should take more restrictive action. For example, the program should consider court-ordered DOT or, after all other measures fail, the involuntary isolation of a patient who is unwilling or unable to complete treatment. This action is necessary to protect the public from patients who have infectious TB disease or who have disease that might become infectious; nonadherent patients might also be at risk for experiencing drug-resistant TB. A patient can be involuntarily isolated, but the patient cannot be forced to swallow anti-TB drugs. Linking the patient to social services might prevent involuntary isolation if the patient is able to resolve the barriers that are preventing treatment completion. Involuntary isolation should be pursued only as a last resort after all less restrictive measures have failed.

**Patient Education**

Educating patients about TB disease helps ensure successful therapy completion. Health care providers should take time to explain clearly to patients what medication they should take, how much, how often, and when. Patients should be informed about possible adverse reactions to the medications they are taking and when it is necessary to seek medical attention. It is imperative to provide patients with the knowledge they need regarding the consequences of not taking their medications correctly. Additionally, patients should be educated about infection control measures and the potential need for isolation (Box 5.1).

HIV testing and counseling is recommended for all patients with TB disease in all health care settings. The patient must first be notified that testing will be performed. The patient has the right to decline HIV testing and counseling (i.e., to opt out of screening).
Box 5.1
Topics That Should Be Included in Patient Education

When providing patient education, include information regarding
- Expected clinical outcomes and duration of therapy
- General principles about infectiousness before and during therapy
- What medications to take, how much, how often, and when
- Possible adverse reactions to the medications
- When it is necessary to seek medical attention
- Consequences of not taking medications as prescribed
- TB infection control measures and potential need for isolation
- Treatment reminders
- Availability of TB program staff support
- Directly observed therapy

For more information regarding available TB educational resources, see CDC’s Patient and General Public Materials, Find TB Resources, and the TB Centers of Excellence for Training, Education, and Medical Consultation.

Case Management

Case management is a strategy health departments use to manage patient care and help ensure patients successfully complete treatment.

Case managers are health department employees, including nurses or other public health professionals, who are assigned primary responsibility for managing a specific patient’s care. Case managers are held accountable for educating each patient about TB disease and its treatment, ensuring that therapy is continuous and complete, and confirming that all contacts are evaluated according to CDC/National Tuberculosis Controllers Association contact investigation guidelines. Some specific responsibilities might be assigned to other professionals (e.g., clinic supervisors, outreach workers, health educators, social workers, or human service workers). Case management is a patient-centered strategy. Whenever possible, case managers should be assigned to patients with whom they share similar culture and language.
**Directly Observed Therapy (DOT)**

DOT is a component of case management that helps ensure patients adhere to therapy. It is the method whereby a trained health care worker or another trained designated person watches a patient swallow each dose of anti-TB drugs and documents that treatment, either in person or by video. DOT is the preferred core management strategy recommended by CDC for TB disease treatment and, if resources allow, for LTBI treatment. DOT can reduce drug resistance development, treatment failure, or relapse after the end of treatment. Ideal case management, which includes establishing a relationship with the patient and addressing barriers to adherence, facilitates successful DOT.

During the continuation phase of treatment, nearly all treatment regimens for drug-susceptible TB disease can be administered intermittently if they are directly observed. When clinically appropriate, using intermittent regimens reduces the total number of doses a patient must take and the total number of encounters with the health care provider or outreach worker, making these regimens more cost-effective. Drug-resistant TB disease should always be treated with a daily regimen under direct observation. Intermittent regimens should not be used for treating MDR TB. If anti-TB drugs for treating MDR TB need to be administered twice daily, DOT should also be provided twice daily. DOT should be used for HIV-infected patients as well as all children and adolescents with TB disease.

It is important that DOT be carried out at times and in locations that are as convenient as possible for the individual patient (Figures 5.5 and 5.6). In certain situations, staff of correctional facilities or drug treatment programs, home health care workers, maternal and child health staff, or designated community members may provide DOT. In contrast, family members should not provide DOT. Therapy might be directly observed in a medical office or clinic setting, but it can also be observed by an outreach worker in the field (e.g., at the patient’s home, place of employment, school, or other mutually agreeable place).

Because DOT is time- and resource-intensive, some TB programs are now using electronic methods of delivering DOT for both TB disease and LTBI. Electronic DOT (eDOT) is an alternative to in-person DOT in which a patient is remotely observed (e.g., over a smartphone or other video-enhanced electronic device) while taking TB medication (Figure 5.7). For more information on eDOT, see Implementing an Electronic Directly Observed Therapy (eDOT) Program: A Toolkit for Tuberculosis (TB) Programs.
Figure 5.5
Conducting DOT in a Clinic Setting

Figure 5.6
Conducting DOT in a Location Convenient for the Patient

Figure 5.7
Conducting eDOT
Incentives and Enablers

Incentives and enablers can be used to ensure adherence to therapy (Figure 5.8). Incentives are inexpensive rewards given to patients to encourage them to take their medications or to keep DOT or clinic appointments. Enablers are things that help the patient receive treatment (e.g., bus fare for getting to the clinic). Incentives and enablers should be chosen according to each patient’s needs and are frequently offered along with DOT.

Self-Administered Therapy

Patients on self-administered therapy should be asked about adherence at all follow-up visits. Pill counts should be performed consistently, and urine or blood tests can be used periodically to check for the presence of urine drug metabolites or adequate blood serum levels of the medications. Additionally, a patient’s response to treatment should be monitored closely. If culture results have not converted to negative after 2 months of treatment, the patient should be reevaluated and DOT should be considered for the remainder of treatment.
Knowledge Check

Select the best answer for each question.

1. Patients with HIV-related TB disease should be treated with a regimen including a rifamycin for the full course of TB disease treatment, unless the isolate is resistant to the rifamycins or the patient has a severe side effect that is clearly due to the rifamycins.
   A. True
   B. False

2. TB patients should have clinical evaluations yearly to identify possible adverse reactions to medications and to assess adherence.
   A. True
   B. False

3. The recommended regimen for the initial phase of a 6-month regimen for TB disease in HIV-negative individuals is
   A. Isoniazid, ethambutol, pyrazinamide, streptomycin.
   B. Isoniazid, rifampin, pyrazinamide, ethambutol.
   C. Isoniazid, rifabutin, ethambutol, pyrazinamide.
   D. Isoniazid, rifabutin, streptomycin, ethionamide.

4. Which TB medication(s) can be associated with hepatitis?
   A. Ethambutol only
   B. Isoniazid, pyrazinamide, and rifampin
   C. Streptomycin only
   D. Rifampin only

5. What should be included in each patient’s treatment plan?
   1. A description of the treatment regimen
   2. Methods of monitoring for adverse reactions
   3. Methods of assessing and ensuring adherence to the treatment
   4. Methods for evaluating treatment response
      A. 1, 2, and 3 are correct
      B. 1 and 3 are correct
      C. 2 and 4 are correct
      D. Only 4 is correct
      E. All are correct
6. Patients receiving treatment for TB disease should be carefully reevaluated if

1. Their culture results have not become negative after 2 months of treatment.
2. Their symptoms worsen after improving initially.
3. Their culture results become positive after being negative.
4. Their tuberculin skin test reaction does not become negative.

   A. 1, 2, and 3 are correct
   B. 1 and 3 are correct
   C. 2 and 4 are correct
   D. Only 4 is correct
   E. All are correct

See page 195 for answer key.
Chapter Objectives

After working through this chapter, you should be able to

- Describe the factors that determine the infectiousness of a tuberculosis (TB) patient.
- Explain the main goals of a TB infection control program.
- Discuss the three levels of an effective TB infection control program.
- Explain the purpose and the characteristics of a TB airborne infection isolation room.
- Describe the circumstances when respirators and surgical masks should be used.

Chapter Introduction

*M. tuberculosis* can be transmitted in virtually any setting. Transmission has been documented in health care settings with inadequate implementation of infection control measures where health care personnel (HCP), patients, and visitors
encounter persons with infectious TB disease who have not yet received adequate or appropriate treatment.

Health care settings include, but are not limited to, inpatient settings, outpatient settings, laboratories, emergency medical services, medical settings in correctional facilities, home-based health care and outreach settings, long-term care facilities, homeless shelter clinics and many other settings where health care is provided. Given that infectious TB patients or their clinical specimens may be in any of these settings, it is essential to have a TB infection control plan designed to ensure early and prompt

- Detection of TB disease.
- Implementation of airborne infection isolation precautions.
- Treatment of persons with confirmed or presumptive TB disease.

Many of the recommendations included in this chapter are based on the Guidelines for Preventing the Transmission of TB in Health Care Settings, 2005, and Tuberculosis Screening, Testing, and Treatment of U.S. Health Care Personnel: Recommendations from the National Tuberculosis Controllers Association and CDC, 2019. These resources are available from the CDC TB website.

## Infectiousness

The infectiousness of a TB patient is directly related to the amount of droplet nuclei carrying *M. tuberculosis* (tubercle bacilli) that the patient expels into the air. Depending on the environment, these tiny particles can remain suspended in the air for long periods of time, up to several hours. *M. tuberculosis* is transmitted through the air, not by surface contact. Infection occurs when a person inhales droplet nuclei containing *M. tuberculosis*, and the droplet nuclei traverse the mouth or nasal passages, upper respiratory tract, and bronchi to reach the alveoli of the lungs.

Persons with extrapulmonary TB disease may have concurrent pulmonary or laryngeal TB disease. Except for laryngeal TB disease, extrapulmonary TB disease is rarely infectious; however, transmission from extrapulmonary sites has been reported to occur during aerosol-producing procedures such as autopsies and tissue irrigation. The characteristics of a patient with TB disease that are associated with infectiousness include, but are not limited to, those listed in Table 6.1.
Table 6.1
Factors Associated with Infectiousness*

<table>
<thead>
<tr>
<th>Factors Associated with Less Infectiousness</th>
<th>Factors Associated with More Infectiousness</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cough</td>
<td>Presence of a cough</td>
</tr>
<tr>
<td>No cavity in the lung</td>
<td>Cavity in the lung</td>
</tr>
<tr>
<td>No acid-fast bacilli (AFB) on sputum smear</td>
<td>Acid-fast bacilli (AFB) on sputum smear</td>
</tr>
<tr>
<td>Most extrapulmonary (non-pulmonary) TB disease</td>
<td>TB disease of the lungs, airway, or larynx</td>
</tr>
<tr>
<td>Receiving adequate treatment for 2 weeks or longer</td>
<td>Not receiving adequate treatment</td>
</tr>
<tr>
<td>Not undergoing cough-inducing procedures</td>
<td>Undergoing cough-inducing procedures (e.g., bronchoscopy, sputum induction, and administration of aerosolized medications)</td>
</tr>
<tr>
<td>Negative sputum cultures</td>
<td>Positive sputum cultures</td>
</tr>
</tbody>
</table>

*Infectiousness depends on a variety of factors. Clinicians should consider all these factors when determining whether a person with TB should be considered infectious.

In general, young children with pulmonary TB disease are less likely than adults to be infectious. There are two reasons for this. First, TB in young children is often paucibacillary, meaning that children are infected with fewer organisms compared to adolescents and older children. Second, young children do not often cough with enough force to expel organisms into the air. Nonetheless, transmission from children, especially older adolescents with features of adult disease (e.g., cavitary, sputum smear-positive disease), can occur.

For most patients, infectiousness appears to decline rapidly after adequate and appropriate treatment is started; however, the rate of decline varies from person to person. Some patients with unrecognized or inadequately treated drug-resistant TB disease might remain infectious for weeks or even months. Patients with drug-resistant TB disease might not respond to the initial drug regimen, might acquire further drug resistance, or might remain infectious until they receive adequate treatment.

Persons with extrapulmonary TB disease usually are not infectious unless they also have pulmonary TB disease, TB disease located in the oral cavity or the larynx, or extrapulmonary TB disease that includes an open abscess or lesion in which the
concentration of organisms is high. Pulmonary TB should always be ruled out when there is a diagnosis of extrapulmonary TB disease. Box 6.1 indicates the criteria for patients to be considered noninfectious. State and local TB regulations supersede the criteria in Box 6.1. The criteria for a patient to be considered noninfectious may also vary based on access to nucleic acid amplification testing.

**Box 6.1**

Criteria for TB Patients to Be Considered Noninfectious

TB patients can be considered noninfectious when they meet all of the following three criteria:

1. They have three consecutive negative AFB sputum smears collected in 8- to 24-hour intervals (at least one being an early morning specimen).
2. Their symptoms have improved clinically (e.g., decreased frequency of cough, resolution of fever, weight gain, etc.).
3. They have received adequate treatment for two weeks or longer.

It is important to consider the environmental factors that enhance the probability that *M. tuberculosis* will be transmitted (Table 6.2).

**Table 6.2**

Environmental Factors that Enhance the Probability that *M. tuberculosis* Will Be Transmitted

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration of infectious droplet nuclei</td>
<td>More droplet nuclei in the air, the more probable that <em>M. tuberculosis</em> will be transmitted</td>
</tr>
<tr>
<td>Space</td>
<td>Exposure in small, enclosed spaces</td>
</tr>
<tr>
<td>Ventilation</td>
<td>Inadequate local or general ventilation that results in insufficient dilution or removal of infectious droplet nuclei</td>
</tr>
<tr>
<td>Air circulation</td>
<td>Recirculation of air containing infectious droplet nuclei</td>
</tr>
<tr>
<td>Specimen handling</td>
<td>Improper specimen handling procedures that generate infectious droplet nuclei</td>
</tr>
<tr>
<td>Air pressure</td>
<td>Lack of negative air pressure in infectious patient’s room that allows <em>M. tuberculosis</em> organisms to flow to other areas</td>
</tr>
</tbody>
</table>
**TB Infection Control Measures**

TB infection control measures should be based on an assessment of risk for transmission of TB in the facility or setting. The main goals of TB infection control programs are to ensure early and prompt

- Detection of TB disease.
- Implementation of airborne infection isolation precautions (e.g., isolation of people with confirmed or presumptive TB disease).
- Treatment of people who have confirmed or presumptive TB disease.

Thus, within health care settings, laboratories, and non-traditional facility-based settings, protocols should be implemented and enforced to promptly identify, isolate, and transfer or manage persons who have confirmed or presumptive TB disease.

**Detection of TB Disease**

In communities where TB is common, health care facility staff should be alert for TB. Staff at public health clinics, community clinics, emergency rooms, and hospitals should be especially aware of TB signs and symptoms, as patients who are at high risk for TB often receive care at these settings prior to diagnosis or treatment.

Personnel who admit patients to facilities should be trained to ask appropriate questions to help detect patients who have signs or symptoms of TB. Staff at homeless shelters, nursing homes, and correctional facilities should also be aware of TB signs and symptoms to detect TB among their residents or personnel.

Clinicians and other HCP should consider TB disease in people who have any symptoms of TB and isolate them until TB is excluded. Symptoms of pulmonary TB include the following:

- Persistent cough (3 weeks or longer)
- Chest pain
- Hemoptysis (coughing up blood)
- Unexplained weight loss
- Loss of appetite
- Fever
- Chills
- Night sweats
- Malaise
- Fatigue

People who have any of these symptoms should be given a diagnostic evaluation as soon as possible (see Chapter 3, Diagnosis of Tuberculosis Disease).
Airborne Precautions

TB airborne precautions should be initiated for any patient who has signs or symptoms of TB disease, or who has documented infectious TB disease and remains infectious despite treatment.

People who have or are thought to have infectious pulmonary TB disease should be placed in an area away from other patients, preferably in an airborne infection isolation (All) room. An All room is a single-occupancy patient-care room in which environmental factors are controlled to minimize transmission of infectious agents. If a facility does not have an All room, patients should be asked to wear a surgical mask and then placed in a room (with the door closed) that has been designated for isolation of persons with confirmed or presumptive infectious TB disease; if possible, the patient should be referred to a facility with an All room. When people with confirmed or presumptive infectious TB disease are in the TB clinic and not in an All room, they should wear a surgical mask at all times and be placed in an area away from other people (Figure 6.1).

Patients should be instructed to observe strict respiratory hygiene and cough etiquette procedures. To help prevent the spread of germs, patients should cover their mouth with a tissue when they cough (Figure 6.2). They should throw their used tissues in the trash and then wash their hands. If a tissue is not available, patients may cough or sneeze into their elbow, not their hands. “Cover your Cough” is an example of a poster that may be displayed in a medical setting to remind patients of best practices (Figure 6.3).

Figure 6.1
Person with Infectious TB in Waiting Room Wearing a Surgical Mask
Figure 6.2
Cough Etiquette

Figure 6.3
Cover your Cough Poster

Cover your mouth and nose with a tissue when you cough or sneeze. Put your used tissue in the waste basket.

If you don’t have a tissue, cough or sneeze into your upper sleeve or elbow, not your hands.

You may be asked to put on a face mask to protect others.

Wash hands often with soap and warm water for 20 seconds. If soap and water are not available, use an alcohol-based hand rub.
Health care settings, such as TB public health clinics, community clinics, emergency rooms, and hospitals, in which patients with confirmed or presumptive TB disease are expected to be encountered, should also implement a respiratory protection program. In these settings, health care personnel who enter All rooms, visit areas in which persons with confirmed or presumptive TB disease are located, or transport patients with confirmed or presumptive TB disease in vehicles should be included in the respiratory protection program.

For settings other than TB clinics, patients with presumptive TB disease should be promptly referred so that they can receive a medical evaluation. These patients should not stay in the setting any longer than the time it takes to arrange a referral or transfer to an All room.

All cough-inducing and aerosol-generating procedures should be performed using environmental controls (e.g., specimen collection in a sputum induction booth or an All room). Patients should be left in the booth or All room until coughing subsides. Another patient or HCP should not be allowed to enter the booth or the All room until enough time has passed for adequate removal of air contaminated with *M. tuberculosis*. Because of the increased risk for *M. tuberculosis* transmission during the performance of aerosol-generating procedures, such as bronchoscopy, a higher level of respiratory protection than an N95 filtering facepiece respirator (e.g., an elastomeric full-facepiece respirator or a powered air-purifying respirator [PAPR]) should be considered during aerosol-generating procedures on patients with presumptive or confirmed TB disease.

For more information on the number of air changes required per hour for adequate removal of airborne contaminants, refer to the CDC Guidelines for Environmental Infection Control in Health-Care Facilities, 2019, Table B-1, available from the CDC Infection Control website.

**Discontinuation of Airborne Isolation for Patients with Presumptive TB Disease**

For patients with presumptive or confirmed TB disease, airborne precautions may be discontinued when infectious TB disease is considered unlikely, and either another diagnosis is made, or the patient has three consecutive negative sputum smear results and symptoms have improved. Each of the three sputum specimens should be collected in 8- to 24-hour intervals (at least one being an early morning specimen). When a person with TB has met those conditions and received adequate TB treatment for two weeks or longer, they may be released from All.
Results from a nucleic acid amplification (NAA) test, such as the Xpert MTB/RIF assay (see Chapter 3, Diagnosis of TB Disease), may also aid in making decisions regarding the discontinuation of airborne isolation. Patients with two negative Xpert MTB/RIF assay test results, considered in the context of the AFB smear results, may be able to be released from airborne isolation. However, Xpert MTB/RIF assay results should not be the sole basis for infection control practices. Decisions regarding whether to remove a patient from isolation should always be based on all the clinical and epidemiologic information available about the patient. The Xpert MTB/RIF assay does not replace the need for AFB smear microscopy, culture for mycobacteria, molecular or growth-based drug susceptibility testing, and genotyping. Personnel and laboratories need to ensure that patient specimens are available for all recommended mycobacterial testing. For more information on the Xpert MTB/RIF assay, refer to the CDC guidelines, *Availability of an Assay for Detecting Mycobacterium tuberculosis, Including Rifampin-Resistant Strains, and Considerations for Its Use — United States, 2013*, available from the CDC TB website. State and local TB control programs can provide additional guidance. An additional resource on using Xpert MTB/RIF assay to discontinue AII is the National Tuberculosis Controllers Association (NTCA)/Association of Public Health Laboratories (APHL) *Consensus Statement on the Use of Cepheid Xpert MTB/RIF Assay in Making Decisions to Discontinue Airborne Infection Isolation in Healthcare Settings*.

**Treatment**

Patients who have confirmed TB disease or who are considered highly likely to have TB disease should promptly start appropriate treatment (see Chapter 5, Treatment of Tuberculosis Disease). It is also important to identify and treat people diagnosed with latent tuberculosis infection (LTBI) as a consequence of exposure to infectious TB.
TB Infection Control Programs

A comprehensive TB infection control program should include the following three elements:

1. **Administrative controls**, which reduce risk of exposure to TB.

2. **Environmental controls (also known as “engineering controls”),** which prevent the spread and reduce the concentration of droplet nuclei.

3. **Respiratory protection controls**, which further reduce risk of exposure to droplet nuclei in special areas and circumstances.

**Administrative Controls**

The first and most important level of a TB infection control program is the use of administrative measures to reduce the risk of exposure to persons who might have TB disease. Administrative controls consist of implementing the following activities:

- Assigning someone the responsibility and authority for TB infection control in the health care setting.
- Conducting a TB risk assessment of the setting.
- Developing and instituting a written, local, specific TB infection control plan to ensure prompt detection, isolation, and treatment or transfer of persons who have confirmed or presumptive TB disease.
- Conducting training based on the infection control plan and associated risk assessment.
- Ensuring the availability of recommended laboratory processing, testing, and reporting of results.
- Ensuring adequate supply of appropriate TB medications.
- Implementing effective work practices for managing patients who may have TB disease.
- Ensuring proper cleaning, sterilization, and/or disinfection of equipment that might be contaminated (e.g., endoscopes).
- Educating, training, and counseling HCP about LTBI and TB disease.
- Screening, testing, and treating HCP for LTBI and TB disease.
- Applying epidemiology-based prevention principles, including the use of setting-related TB infection control data.
• Using posters and signs to remind patients and staff of proper cough etiquette (i.e., covering mouth when coughing) and respiratory hygiene.

• Developing referral processes to relevant partners.

• Coordinating efforts between local health department and high-risk health care and congregate settings.

**TB Risk Assessment**

Every health care and congregate setting should conduct initial and ongoing evaluations of the risk for transmission of *M. tuberculosis*. The TB risk assessment determines the types of administrative, environmental (i.e., engineering), and respiratory protection controls needed for a setting. It also serves as an ongoing monitoring and evaluation tool of the infection control program. The TB risk assessment examines a number of factors that help determine the level of risk and what mitigation strategies might be implemented, including

- Number of patients with TB disease seen in the setting in the past 12 months.

- Promptness of detection, isolation, and evaluation of patients with confirmed or presumptive TB disease.

- Evidence of *M. tuberculosis* transmission in the setting through identification of LTBI or TB disease among contacts of patients with TB disease.

- Number of All rooms or other areas to meet the needs of the patient population (e.g., negative pressure rooms, sputum collection booths, separate sitting areas for those with a cough).

- Types of procedures that might be performed (e.g., collecting naturally expectorated sputum, inducing for collection, bronchoalveolar lavage [BAL], autopsy).

- Community rate of TB disease.

For more detailed information on how to conduct a TB risk assessment, please refer to the CDC *Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Settings, 2005*, available from the [CDC TB website](https://www.cdc.gov/tb/). Additional infection control tools for healthcare settings can be found at the [CDC Infection Control Tools website](https://www.cdc.gov/infectioncontrol/).
Risk Classification

The risk classification, or risk level, will vary from setting to setting. There are three TB risk classifications (Table 6.3):

- Low risk
- Medium risk
- Potential ongoing transmission

Table 6.3
TB Risk Classifications

<table>
<thead>
<tr>
<th>Risk Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>• Should be used for settings in which persons with TB disease are not expected to be encountered.</td>
</tr>
<tr>
<td></td>
<td>• Exposure to <em>M. tuberculosis</em> in these settings is unlikely.</td>
</tr>
<tr>
<td>Medium risk</td>
<td>• Should be used for facilities or settings in which the risk assessment has determined that HCP will possibly be exposed to persons with TB disease.</td>
</tr>
<tr>
<td></td>
<td>• Medium risk classification can also be used for settings in which health care or lab personnel will be working with or collecting clinical specimens and potentially come in contact with specimens that may contain <em>M. tuberculosis</em>.</td>
</tr>
<tr>
<td>Potential ongoing transmission</td>
<td>Should be temporarily assigned to any setting where there is evidence of person-to-person transmission of <em>M. tuberculosis</em> in the past year.</td>
</tr>
</tbody>
</table>

TB Screening Program

TB screening and testing of HCP is recommended as part of a TB infection control plan and might be required by state regulations. For TB regulations in your area, please contact your state or local TB control program. Contact information can be located at the [CDC TB Control Offices website](https://www.cdc.gov/tb/).
TB screening programs should include anyone working or volunteering in health care settings, including

- Inpatient settings.
- Outpatient settings.
- Laboratories.
- Emergency medical services.
- Medical settings in correctional facilities.
- Home-based health care and outreach settings.
- Long-term care facilities.
- Clinics in homeless shelters.

All U.S. HCP should be screened for TB upon hire (i.e., pre-placement). The local health department should be notified immediately if TB disease is considered a possibility. Serial TB testing of HCP is not recommended unless there is a known exposure or ongoing transmission. Serial TB testing might be considered for those with increased occupational risk or if the individual HCP has risk factors for TB outside of the health care setting. Treatment is strongly encouraged for HCP diagnosed with LTBI upon hire or post-exposure. There are several regimens available for the treatment of LTBI. While all the regimens are effective, short-course, rifamycin-based 3- or 4-month regimens are preferred. Short-course LTBI treatment regimens are effective, are safe, and have higher completion rates than longer 6- to 9-month regimens of isoniazid (INH) monotherapy. If short-course treatment is not an option, 6 or 9 months of daily INH are alternative LTBI treatment regimens (see Chapter 4, Treatment of LTBI).

In 2019, CDC and NTCA released updated recommendations for TB screening, testing, and treatment of U.S. HCP (Table 6.4), available on the CDC TB website. These recommendations update the HCP screening and testing section of the CDC Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Settings, 2005, available on the CDC TB website. Another helpful resource is the guidance statement Tuberculosis Screening, Testing, and Treatment of US Healthcare Personnel developed by the American College of Occupational and Environmental Medicine (ACOEM) and NTCA.
### Table 6.4
Summary of Updates to TB Screening, Testing, and Treatment Recommendations for U.S. Health Care Personnel

<table>
<thead>
<tr>
<th></th>
<th>2005 Recommendations</th>
<th>2019 Recommendations — Key Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening</strong></td>
<td>• Recommended for all health care personnel pre-placement/upon hire*</td>
<td>• Individual baseline TB risk assessment added</td>
</tr>
<tr>
<td></td>
<td>• Annual screening may be recommended based on risk assessment of health care facility and setting</td>
<td>• Annual TB screening no longer routinely recommended for most health care personnel unless occupational risk or ongoing exposure</td>
</tr>
<tr>
<td><strong>Post-exposure testing</strong></td>
<td>• Recommended IGRA or TST test for all health care personnel when an exposure is recognized*</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td>• If that test is negative, do another test 8-10 weeks after last exposure*</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment of positive TB test</strong></td>
<td>Referral to determine whether latent TB infection (LTBI) treatment is indicated</td>
<td>• Treatment is encouraged for all health care personnel with untreated LTBI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Shorter course (3 to 4 month) treatments encouraged over the longer (6 or 9 month) regimens because they are easier to complete</td>
</tr>
<tr>
<td><strong>TB education</strong></td>
<td>Recommended annually for all health care personnel*</td>
<td>Annual education should include information about TB risk factors, the signs and symptoms of TB disease, and TB infection control policies and procedures</td>
</tr>
</tbody>
</table>

* No change in the 2019 recommendations

Table adapted from *Tuberculosis Screening, Testing, and Treatment of U.S. Health Care Personnel: Recommendations from the National Tuberculosis Controllers Association and CDC, 2019*
Baseline TB Screening and Testing

All HCP should be screened for TB upon hire/pre-placement. This screening should include

- A baseline individual TB risk assessment.
- TB symptom screen.
- A TB test (e.g., a TB blood test [IGRA] or a TST).
- Additional evaluation for TB disease as needed.

All HCP should have a baseline TB screening, including an individual risk assessment. The Health Care Personnel Baseline Individual TB Risk Assessment is a tool to help interpret the results of a blood test or a TST given upon hire/pre-placement (Figure 6.4). If HCP answer yes to any of the statements in the risk assessment tool, they may be at increased risk for TB.

A positive TB test result only tells that a person may have been infected with TB bacteria. A negative TB test result does not exclude the diagnosis of LTBI or TB disease. Patient management decisions should include epidemiological, historical, and other clinical information. Decisions should not be based on TB blood test or TST results alone.

HCP with a newly positive TB test result should receive a symptom evaluation and a chest x-ray to evaluate for TB disease. Additional evaluation may be needed based on those results.

HCP who have a documented history of a prior positive TB test should receive a baseline individual TB risk assessment and a TB symptom screen upon hire/preplacement. They do not require a repeat TB test. HCP with a prior positive TB test who have not received treatment or who have TB symptoms should undergo a chest x-ray for further evaluation of TB disease or provide documentation of a recent normal chest x-ray.

HCP with untreated LTBI should receive an annual symptom screen to detect early evidence of TB disease and to reevaluate the benefits of LTBI treatment. Repeat chest x-rays are not required unless they are part of the repeat evaluation prior to starting LTBI treatment or HCP are symptomatic.
**Figure 6.4**
Sample Baseline Individual TB Risk Assessment for Health Care Personnel

**Health Care Personnel (HCP)**
Baseline Individual TB Risk Assessment

HCP should be considered at increased risk for TB if any of the following statements are marked “Yes”:

- Temporary or permanent residence of ≥1 month in a country with a high TB rate
  - Any country other than the United States, Canada, Australia, New Zealand, and those in Northern Europe or Western Europe

  **YES □**
  **NO □**

  **OR**

- Current or planned immunosuppression, including human immunodeficiency virus (HIV) infection, organ transplant recipient, treatment with a TNF-alpha antagonist (e.g., infliximab, etanercept, or other), chronic steroids (equivalent of prednisone ≥15 mg/day for ≥1 month) or other immunosuppressive medication

  **YES □**
  **NO □**

  **OR**

- Close contact with someone who has had infectious TB disease since the last TB test

  **YES □**
  **NO □**

Abbreviations: HCP, health-care personnel; TB, tuberculosis; TNF, tumor necrosis factor.


Risk factors for TB include

- Temporary or permanent residence of ≥1 month in a country with a high TB rate. (Any country other than the United States, Canada, Australia, New Zealand, and those in Northern Europe or Western Europe.)

- Current or planned immune system suppression (e.g., HIV infection or taking medication that suppresses the immune system).

- Close contact with someone who has had infectious TB disease since the last TB test.
Annual TB Screening and Testing

Annual TB testing of HCP is not recommended unless there is a known exposure or ongoing transmission at a health care facility. Health care facilities might consider using annual TB screening for certain groups at increased occupational risk for TB exposure or in certain settings where transmission has occurred in the past. Facilities should work with their state and local health departments to help make these decisions.

HCP with untreated LTBI should receive an annual TB symptom screen. Symptoms for TB disease include any of the following: a cough lasting longer than three weeks, hemoptysis, unexplained weight loss, night sweats, fever, malaise, fatigue, and loss of appetite. If HCP report symptoms, a physical examination and chest x-ray are used to evaluate for TB disease.

Post-Exposure Screening and Testing

All HCP with a known exposure to TB disease should receive a TB symptom screen, timely testing, and treatment if indicated.

HCP with a previous negative TB test result (TST or IGRA) should be tested immediately if they have been exposed to TB disease. Those with an initial negative test result should be retested 8 to 10 weeks after their last known exposure to TB disease. This is because it can take 2 to 8 weeks after being infected with *M. tuberculosis* for the body’s immune system to mount a response detectable by the tests.

HCP with a documented history of a positive TB test result do not need to be retested after exposure to TB. They should receive a TB symptom screen, and if they have symptoms of TB, they should receive further evaluation for TB disease, including a physical examination and chest x-ray. HCP with LTBI are strongly encouraged to be treated for LTBI if they have not previously been treated.

For more information, please refer to the *Tuberculosis Screening, Testing, and Treatment of U.S. Health Care Personnel: Recommendations from the National Tuberculosis Controllers Association and CDC, 2019*, available from the CDC TB website.
Health Care Personnel Education and Training

Education and training for HCP is an essential part of a TB infection control program and can increase adherence to TB infection control measures. All HCP should receive annual TB education. TB education should include information on TB risk factors, the signs and symptoms of TB disease, and TB infection control policies and procedures. Resources for TB education and training can be found on the following websites:

- CDC Division of TB Elimination (DTBE)
- Find TB Resources
- TB Centers of Excellence for Training, Education, and Medical Consultation

Environmental Controls

The second element of a comprehensive TB infection control program is the use of environmental controls (Box 6.2). Environmental controls (also known as “engineering controls”) use engineering technology to control potential exposures in the workplace. They are designed to either remove the hazard at the source before it comes in contact with the worker or, when direct-source control is not possible, to quickly dilute room air contaminants and/or prevent their migration into other parts of the facility. Well-designed environmental controls can be highly effective in protecting workers and will typically be independent of worker interactions to provide a high level of protection. Environmental controls prevent the spread of droplet nuclei and reduce the concentration of droplet nuclei by

- controlling the source of infection by capturing and removing contamination near the point of generation, or
- controlling potential contaminants that have been released into a space and cleaning the air through enhanced dilution, directional airflows, negative room pressurization, and single-pass airflow and/or high-efficiency filtration.
**Box 6.2**

**Summary of Environmental Control Methods**

- Use increased enclosure of source and/or exhaust hood systems that capture the contaminant before it has an opportunity to disperse throughout the room.
- Control the room pressure and airflow to prevent air contamination from escaping the room (All room).
- Use high ventilation airflow rates to quickly dilute airborne contaminants (All room).
- Clean the air by using high-efficiency particulate air (HEPA) filtration and/or ultraviolet germicidal irradiation (UVGI).
- Use natural ventilation (sometimes useful for non-traditional facility-based and congregate settings that do not have a central ventilation system).

**Environmental Control Approaches**

**Ventilation**

Ventilation is the movement and replacement of air in a building with air from outside or with clean, recirculated air. When fresh air enters a room, it dilutes the concentration of particles, such as droplet nuclei, in the existing room air. There are two types of ventilation:

- Natural ventilation
- Mechanical ventilation

**Natural Ventilation**

Natural ventilation relies on the use of open doors, louvers, and windows to bring in fresh air from outside and allow for the escape of contaminated room air. Natural ventilation can be useful for non-traditional facility-based and congregate settings that do not have a central ventilation system. In these settings, waiting rooms, shelter dormitories, or other rooms in which people congregate should have multiple operable windows, doors, or skylights that are kept open as often as possible. Note that a single opening to the outdoors is dramatically less effective than multiple openings, preferably distributed among different room surfaces.

Fans can be used to help establish airflow (Figure 6.5). If the direction of room airflow is unknown, staff should sit near the fresh air source and clients should sit near the exhaust location (Figure 6.6). This can help protect staff from inhaling...
droplet nuclei expelled by patients with undiagnosed infectious TB disease. In addition to these environmental measures, cough etiquette and respiratory hygiene should be encouraged to further reduce risk.

**Figure 6.5**  
Fan Used To Assist Naturally-ventilated Room

**Figure 6.6**  
Fan-assisted Natural Ventilation in TB Exam or Counseling Room
**Mechanical Ventilation**

Mechanical ventilation refers to the use of equipment to circulate, move, and sometimes clean the air in a building. Mechanical ventilation should be used by hospitals, TB clinics, and other health care and congregate settings expecting to see TB patients. Mechanical ventilation consists of

- Local exhaust ventilation.
- General ventilation.

Local exhaust ventilation stops airborne contaminants before they spread into the general environment. Local exhaust ventilation includes the use of

- External hoods.
- Enclosing hoods.
- Booths.
- Tents.

Local exhaust ventilation should be used for cough-inducing and aerosol-generating procedures (Figure 6.7). If local exhaust ventilation cannot be used, cough-inducing and aerosol-generating procedures should be performed in an AII room. If an AII room is not available, the procedures should be performed outdoors and at least 25 feet away from people, windows, and air intakes.

**Figure 6.7**
Local Exhaust in Sputum Collection Booth

![Local Exhaust in Sputum Collection Booth](image)
**General ventilation systems** maintain air quality in health care settings by

- Diluting contaminated air.
- Removing contaminated air.
- Cleaning (filtering) contaminated air.
- Controlling airflow patterns in the patient’s procedure room or setting (e.g., clean to less-clean directional airflow in AII rooms).
- Establishing static pressure relationships between areas to control contaminant dissemination (e.g., negative pressure in AII rooms).

TB AII rooms are designed to contain and quickly dilute droplet nuclei expelled by a patient with TB disease while preventing spread to the remainder of the facility. In TB clinics, hospitals, and other inpatient settings, patients with known or presumptive TB disease should be placed in a TB AII room immediately (**Figure 6.8**).

**Figure 6.8**

*Airborne Infection Isolation (AII) Room*
One characteristic of AII rooms is their negative pressure of at least \( \geq 0.01 \) inches of water relative to other parts of the facility. Negative pressure causes air to flow from the corridors into the AII room. The air from the AII room cannot escape to other parts of the health care setting when the door is closed and the ventilation system is operating properly. Windows in AII rooms should remain closed whenever the room is occupied. The doors of AII rooms must be kept closed as much as possible, especially when the room is occupied, in order to maintain negative pressure; the pressure difference should be checked daily with smoke tubes, other visual indicators, or electronic monitors. If the AII room is not being used for patients who have confirmed or presumptive TB but could potentially be used for such patients, the negative pressure should be checked monthly.

Air from the AII room can be exhausted directly to the outdoors, where the droplet nuclei will be diluted in the outdoor air, or passed through a high efficiency particulate air (HEPA) filter that removes most (>99.97%) of the droplet nuclei before air is returned to the ventilation system. If a HEPA filter is not used, the air should be exhausted directly to the outside at least 25 feet away from air-intake vents, people, and animals in accordance with applicable federal, state, and local regulations.

All rooms built or renovated since 1995 should have a total airflow of twelve or more air changes per hour (ACH). Any AII rooms which have not been renovated since 1995 should have airflow of at least six ACH. When feasible, the airflow in pre-1995 health care setting AII rooms should be increased to twelve ACH by

- Adjusting or modifying the ventilation system; or
- Using air-cleaning methods: room-air recirculation units containing HEPA filters or ultraviolet germicidal irradiation (UVGI) systems that increase the equivalent ACH.

As part of the total ACH requirement, a minimum of two ACH of outdoor air should be provided to AII rooms and other negative-pressure rooms.

It is important that AII rooms be single-patient rooms with a private bathroom. Visitor and HCP entry should be restricted and monitored to minimize the transmission of \( M. \) *tuberculosis*. All HCP who enter an AII room should wear an N95 or higher disposable filtering facepiece respirator (see Respiratory Protection Controls). An N95 or higher filtering facepiece respirator should be fitted correctly before using. Visitors should be offered and encouraged to use respiratory protection (e.g., N95 filtering facepiece respirator) and instructed by HCP on how
to use it. Health care settings with All rooms should observe the policies and practices indicated in Box 6.3.

**Box 6.3**  
**Policies and Practices for Airborne Infectious Isolation (All) Rooms in Health Care Settings**

- Maintain an adequate number of All rooms.
- Keep doors and windows closed as much as possible, especially when the room is occupied.
- Check negative pressure by monitoring and recording the direction of airflow on a daily basis.
- Perform diagnostic and treatment procedures in the All room.
- Ensure patients adhere to All precautions.
- Group All rooms in one part of the health care setting.
- Schedule procedures for patients with presumptive and confirmed infectious TB disease when few HCP and no other patients are present.
- Provide a surgical mask for patients with presumptive or confirmed infectious TB disease whenever they are out of an All room, during transport, in waiting areas, and when others are present.
- Review environmental control maintenance procedures and logs to determine if maintenance is being conducted properly and regularly.

Auxiliary environmental controls can be used to supplement natural or mechanical ventilation to increase protective directional airflows, pressure relationships, and effective air exchange rates. Examples include portable HEPA filtration systems (Figure 6.9) that remove most (>99.97%) of the droplet nuclei, or UVGI (Figure 6.10). UVGI (also known as germicidal ultraviolet, or GUV) is an air-cleaning technology that consists of the use of special lamps that emit germicidal ultraviolet irradiation (wavelength=220-280 nm). Ultraviolet energy at these wavelengths is effective at inactivating the tubercle bacilli contained in the droplet nuclei by damaging the DNA to the point that the bacilli can no longer replicate and cause disease. Overexposure to ultraviolet light can be harmful to the skin and eyes; lamps must be installed in the upper part of rooms or corridors or placed inside air-handling systems. Regular, appropriate maintenance is essential to ensure UVGI lamps are operating correctly, and maintenance staff should be trained in the safety precautions appropriate for working around such systems.
Respiratory Protection Controls

Respiratory protection control is the third element of a comprehensive TB infection control program and consists of the use of personal protective equipment (PPE) in situations that pose a high risk for exposure to TB disease (Figure 6.11). Respiratory protection may also be thought of as a component within a larger category of PPE that includes items such as gloves, goggles, face shields, or other splatter guards. Use of respiratory protection can further reduce risk for exposure to droplet nuclei expelled into the air. The following measures can be taken to reduce risk for exposure:

- Implement a respiratory protection program.
- Train HCP on respiratory protection.
- Provide respirator fit testing for HCP.
- Educate patients on respiratory hygiene and the importance of cough etiquette.
All health care settings that use respiratory protection controls are required by the Occupational Safety and Health Administration (OSHA) to develop, implement, and maintain a respiratory protection program.

Administrative and environmental controls minimize the number of areas in which exposure to *M. tuberculosis* might occur and therefore minimize the number of persons exposed. These control measures also reduce, but do not eliminate, the risk for exposure in limited areas. In these settings, respiratory protection should be used by HCP and offered to visitors. These settings include:

- TB All rooms.
- Rooms where cough-inducing or aerosol-generating procedures are done.
- Ambulances and other vehicles transporting patients with infectious TB disease.
- Homes or other residential settings of patients with infectious TB disease (this applies to HCP; others should not visit the homes of persons with infectious TB).

The effectiveness of a respiratory protection program requires the development of written standard operating procedures. Standard procedures should include information and guidance for the proper selection, use, and care of respirators. Settings where HCP use respiratory protection to prevent transmission of *M. tuberculosis* should develop, implement, and maintain a respiratory protection program. The program should provide HCP with annual training on TB control, TB infection control, and respiratory protection, including fit testing.
The minimum respiratory protection is a filtering facepiece respirator (FFR) and must be selected from those approved by CDC/National Institute for Occupational Safety and Health (NIOSH) under Title 42 CFR, Part 84. It must meet one of the following specifications:

- Non-powered air-purifying respirators (N95, N99, N100, R95, R99, R100, P95, P99, and P100), including disposables
- Powered air-purifying respirators (PAPRs) with high-efficiency filters
- Supplied-air respirators

Filtering facepiece respirators are divided into classes based on their filtration capabilities. “N95” refers to the N95 filtration class, which removes at least 95% of airborne particles. The FFR classes include N (not resistant to oil), R (somewhat resistant to oil), and P (strongly resistant to oil) series, which are available at the 95, 99, and 100 filtration efficiency levels.

Inhaled air can leak around the outside of a filtering facepiece respirator instead of passing through the respirator’s filter. It is important that respirators fit different face sizes and features properly. It is also important to understand the difference between respirators and surgical masks.

Respirators are designed to protect HCP and other individuals from inhaling droplet nuclei (Figure 6.12). Surgical masks are designed to reduce the number of droplets being exhaled into the air by persons with infectious TB disease when they cough, sneeze, shout, or sing (Figure 6.13). Persons with presumptive or confirmed infectious TB disease should be given a surgical mask and encouraged to use it to minimize the risk of expelling droplet nuclei into the air.

Filtering facepiece respirators are generally used in the context of a respiratory protection program (including medical clearance, fit testing, and education and training in using a respirator properly).
Filtering Facepiece Respirators

- Designed to filter out droplet nuclei from being inhaled by HCP and other individuals.
- Should be used in context of a respiratory protection program.
- Should be properly fit-tested for different face sizes and features.
- Should be worn by HCP, not TB patients.

Surgical Masks

- Designed to stop droplets from being spread (in exhaled breath) by the patient.
- Should be worn by persons with presumptive or confirmed TB when others are around.
- Should not be worn by HCP caring for patients with TB disease.
Box 6.4

Elements of a comprehensive TB infection control program

Administrative Controls

• Assigning someone the responsibility and authority for TB infection control in the health care setting.
• Conducting a TB risk assessment of the setting.
• Developing and instituting a written, local, specific TB infection control plan to ensure prompt detection, isolation, and treatment or transfer of persons who have confirmed or presumptive TB disease.
• Conducting training based on the infection control plan and associated risk assessment.
• Ensuring the availability of recommended laboratory processing, testing, and reporting of results.
• Ensuring adequate supply of appropriate TB medications.
• Implementing effective work practices for managing patients who may have TB disease.
• Ensuring proper cleaning, sterilization, and/or disinfection of equipment that might be contaminated (e.g., endoscopes).
• Educating, training, and counseling HCP about LTBI and TB disease.
• Screening, testing, and treating HCP for LTBI and TB disease.
• Applying epidemiology-based prevention principles, including the use of setting-related TB infection control data.
• Using posters and signs to remind patients and staff of proper cough etiquette (i.e., covering mouth when coughing) and respiratory hygiene.
• Developing referral processes to relevant partners.

Environmental Controls

• Reduce concentration of infectious droplet nuclei through the application of both primary and secondary environmental controls that use the following technologies:
  • Ventilation technologies, including
    • Natural ventilation
    • Mechanical ventilation (and filtration)
    • Local exhaust ventilation
    • High-efficiency particulate air (HEPA) filtration
    • Ultraviolet germicidal irradiation (UVGI)

Respiratory Protection Controls

• Implement a respiratory protection program
• Train HCP on respiratory protection
• Provide fit testing for HCP
• Educate patients on respiratory hygiene and the importance of covering their cough
TB Infection Control Programs in Non-traditional Facility-based Settings

All facility-based settings where patients with possible TB disease receive care and services should establish and follow a TB infection control program (Table 6.5). These settings include, but are not limited to

- Correctional facilities.
- Homeless shelters.
- Long-term care facilities.
- Home-based health care and outreach settings.
- Emergency medical services (EMS).

**Correctional Facilities**

TB disease can be a substantial health concern in correctional facilities. TB outbreaks in correctional facilities can lead to transmission within the correctional facility and in surrounding communities. Health care and medical settings in correctional facilities should be classified as at least medium risk based on the possibility of exposure to persons with TB disease.

Administrative controls at a medical setting in a correctional facility include the following:

- Assigning responsibilities for TB infection control to a point-person at each facility.

- Developing a written TB infection control plan for each facility:
  - This plan should include procedures for systematically evaluating inmates/detainees, staff, and volunteers for TB disease and infection. In addition to screening at intake, long-term inmates and correctional facility staff should receive routine screening at least annually. In addition, HCP in the correctional facility should receive annual TB education.

  - Facilities should follow federal, state, or local regulations requiring TB diagnostic evaluations for inmates/detainees in jails, prisons, or other detention centers to help ensure all inmates have been evaluated and treated, if necessary.
• Maintaining bed maps and tracking bed assignments, ideally in a searchable format to facilitate contact investigations if a TB case is reported.

• Providing ongoing TB education to staff, volunteers, and clients.

Environmental controls at a medical setting in a correctional facility work in conjunction with administrative controls, such as isolation of inmates with presumptive TB disease detected through screening. Some environmental controls are designed to capture and remove potential infectious contaminants at the source before they are encountered by other room occupants. An example at a correctional facility might be a sputum induction booth with HEPA-filtered exhaust airflow. Other environmental controls regulate the room/area airflow and pressure relationships to prevent the migration of contaminated air into areas adjacent to the source (e.g., All rooms). Environmental controls can also dilute the airborne contaminant concentration within the source room and may use portable HEPA filtration or UVGI to increase the number of equivalent ACH.

Incremental improvements in environmental controls (e.g. increasing the removal efficiency of an existing filtration system in any area) are likely to lessen the potential for TB transmission from persons with unsuspected or undiagnosed TB. To be most effective, environmental controls should be installed, operated, and maintained correctly. Ongoing maintenance should be part of any written TB infection control plan. The plan should outline the responsibility and authority for maintenance and address staff training needs.

A respiratory protection program should be implemented with at least one All room available where inmates with presumptive or confirmed TB disease can be isolated immediately. Inmates with presumptive or confirmed TB disease who must be transported should wear a surgical mask during transport. Drivers, HCP, and other staff transporting patients with presumptive or confirmed TB should wear an N95 or higher filtering facepiece respirator. Correctional facilities should maintain a tracking system for inmate TB testing and treatment and establish a mechanism for sharing this information with state and local health departments and other correctional facilities.

For more information, please refer to Screening for Tuberculosis and Tuberculosis Infection in High-Risk Populations Recommendations of the Advisory Council for the Elimination of Tuberculosis, 1995, and Prevention and Control of Tuberculosis in Correctional and Detention Facilities: Recommendations from CDC, 2006, both available from CDC TB website.
Homeless Shelters

TB disease is more common in the homeless population than in the general population. Several factors in the homeless shelter environment can influence the likelihood of *M. tuberculosis* transmission, including crowding and the state of the ventilation system. The number and population density of persons sharing the same breathing space is important. If all other factors are constant, the size of the shelter population is directly proportional to the likelihood that someone with infectious TB disease will be present and that clients, staff, volunteers, and/or frequent visitors will be exposed and may become infected. Accordingly, the smaller the population and less crowded the shelter, the lower the risk.

Of the three types of infection control measures, administrative controls are the most fundamental. Administrative controls work particularly well when homeless facilities in a community collaborate with a TB control program to implement certain core measures, including the following:

• Assigning responsibilities for TB infection control to a point person at each facility.

• Conducting TB risk assessments for these facilities.

• Developing a written TB infection control plan for each facility:
  • This plan should include procedures for systematically evaluating clients, staff, and volunteers for TB disease and infection based on state and local regulations.
  • TB diagnostic evaluations should be required for clients who stay longer than a defined period of time (e.g., after staying 1 day, 3 days, or 1 week) to help ensure all clients have been evaluated and treated, if necessary.
  • Staff and regular volunteers in homeless facilities should be screened for TB prior to working in the facility. HCP should receive annual TB education.
  • Maintaining bed maps and tracking bed assignments, ideally in a searchable format to facilitate contact investigations if a TB case is reported.
  • Maintaining as much space as possible between beds and positioning beds head to toe to reduce the possibility of transmission.
  • Posting signs and informational posters for client awareness and cough monitoring.
  • Considering use of a cough log to document which persons are coughing, particularly at night, so that they can be referred for medical evaluation.
• Separating clients with TB symptoms from others until a medical evaluation for TB disease has been performed. Clients should remain separated until TB disease has been excluded or the patient is not infectious.

• Evaluating residents for signs and symptoms of TB disease for early detection and treatment.

• Providing ongoing education to staff, volunteers, and clients.

Homeless shelters should implement a bed-tracking system for clients and establish a mechanism for sharing this information with state and local health departments for identifying and following up with persons who test positive for LTBI or TB disease.

When used in conjunction with administrative and respiratory protection controls, environmental controls can help reduce TB transmission. Environmental strategies include

• Ensuring optimal ventilation of congregate spaces, either mechanically or naturally (e.g., increasing natural air flow).

• Increasing the filtration efficiency and/or portion of outdoor air in the mechanically-ventilated air supply (Note that changes to filtration or outdoor air must be compatible with existing HVAC system operation).

• Installing air-cleaning methods (e.g., UVGI or HEPA filters). These systems must be correctly installed and maintained and adequately sized for the intended space.

• Using partial air recirculation systems; however, it is important to note that if the air is not filtered (UVGI or HEPA), contaminated air will be recirculated.

Respiratory controls reduce TB transmission from symptomatic persons until medical evaluations can be completed. Strategies include

• Encouraging all homeless shelter staff, volunteers, or clients who are coughing to wear a surgical mask.

• Providing disposable paper or cloth surgical masks to any symptomatic person.

• Separating those coughing until they can be medically evaluated and found to be free of TB disease or no longer infectious.

• Encouraging staff and volunteers who are coughing to stay home until they are no longer coughing.
For more information, please refer to *Workshop on Tuberculosis and Homelessness: Infection Control Measures in Homeless Shelters and Other Overnight Facilities That Provide Shelter: Summary of the Workshop Held September 28–29, 2015* and *Screening for Tuberculosis and Tuberculosis Infection in High-Risk Populations Recommendations of the Advisory Council for the Elimination of Tuberculosis, 1995*, both available from CDC TB website.

**Long-term Care Facilities**

TB disease poses a health risk in long-term care facilities (LTCFs) such as hospice and skilled nursing facilities. Transmission of *M. tuberculosis* has occurred in LTCFs and TB disease has been documented in HIV-infected patients and other immunocompromised patients residing in hospices. The risk of TB infection and disease among staff and residents in a LTCF varies by geographic location and community of people receiving care and working in the facility. Therefore, LTCFs should conduct an annual evaluation of the risk for transmission of TB in the facility to determine the types of administrative, environmental, and respiratory protection controls that should be in place. LTCFs should work with their state or local health department TB programs for assistance in performing the risk assessment.

LTCFs must have adequate administrative and environmental infection controls if they accept patients with presumptive or confirmed infectious TB disease. These include airborne precaution capabilities and a respiratory protection program. People most at risk in LTCFs include

- Patients (residents).
- HCP.
- Visitors.
- Volunteers.

Patients/residents and HCP should be screened for TB on admission or initial employment. Decisions regarding the need for testing upon admission and/or ongoing symptom screening or testing of residents should be made in consultation with the health department; certain state and local regulations may require TB testing for LTCF residents. Regardless of testing decisions and frequency, facility staff should be trained on how to screen for and recognize TB symptoms. Given the challenges with TB detection and management in LTCFs, education is critical to ensure staff, residents, and families understand the importance of TB testing and how to recognize and respond to presumptive TB disease.
LTCFs must have adequate administrative, environmental, and respiratory protection controls that include

- Airborne precaution capabilities.
- A respiratory protection program.

Patients with presumptive or confirmed infectious TB disease should avoid staying in LTCFs unless adequate administrative, environmental, and respiratory protection controls are in place. Facilities without adequate controls like AII rooms to prevent spread of TB are not equipped to care for a resident with infectious TB disease. Such facilities should work with the health department to move the resident to a health care facility with the capacity to care for them. A resident with known or presumptive TB disease should be placed in a single-person room with the door closed. Facilities should minimize the number of individuals allowed to enter the room and minimize interactions with a resident awaiting transfer for further evaluation for presumptive TB. The ill resident should also wear a surgical mask, if tolerated. This may help decrease the dissemination of TB particles while the resident is awaiting transfer or being moved to another health care facility. Residents should not be asked to wear respirators.

For more information, refer to the *Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Settings, 2005*, the *Screening for Tuberculosis and Tuberculosis Infection in High-Risk Populations Recommendations of the Advisory Council for the Elimination of Tuberculosis, 1995* (both available from the CDC TB website) and the *Nursing Home Infection Preventionist Training Course, Module 12B: Tuberculosis Prevention*.

**Home-based Health Care and Outreach Settings**

People most at risk in home-based health care and outreach settings include

- Patients.
- HCP.
- Others in the home.

All home-based health care and outreach staff should be screened for TB upon hire and should receive TB education annually.
Transmission of *M. tuberculosis* has been documented in home-based health care and outreach settings. HCP in these settings should be able to

- Educate patients and staff on the importance of reporting symptoms and signs of TB disease.
- Conduct home health care visits outdoors when patient, environmental, privacy and safety conditions allow.
- Wear an N95 or higher filtering facepiece respirator when entering homes of persons with presumptive or confirmed infectious TB disease or when transporting such persons in an enclosed vehicle.

For more information, refer to *Tuberculosis Screening, Testing, and Treatment of U.S. Health Care Personnel: Recommendations from the National Tuberculosis Controllers Association and CDC, 2019* and the *Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Settings, 2005*, both available from CDC TB website.

**Emergency Medical Services (EMS)**

Although the overall risk is low, transmission of *M. tuberculosis* in EMS occupational settings has been documented. All EMS employees should be screened for TB upon hire and should receive annual TB education on the importance of reporting signs and symptoms of TB disease. EMS personnel should be included in

- Comprehensive training, education, and testing programs for TB infection.
- Follow-up testing as indicated by the risk classification of the setting.

Drivers, HCP, and other staff transporting patients with presumptive or confirmed TB should wear an N95 or higher filtering facepiece respirator, and the patients should wear a surgical mask.

In addition, ambulances should allow for the maximum amount of outdoor air to be circulated in the vehicle. Some ambulances have built-in capacity for HEPA filtration of their HVAC system and, when available, these ambulances should be prioritized for use when transferring patients with potential/known infectious TB.

For more information, refer to *Tuberculosis Screening, Testing, and Treatment of U.S. Health Care Personnel: Recommendations from the National Tuberculosis Controllers Association and CDC, 2019* and the *Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Settings, 2005*, both available from CDC TB website.
### Table 6.5
TB Infection Control for Non-traditional Settings

<table>
<thead>
<tr>
<th>Setting</th>
<th>Transmission of <em>M. tuberculosis</em></th>
<th>Screening/testing</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| **Correctional Facilities** (jails, prisons, detention centers)\(^{a,b}\) | • TB outbreaks in these settings can lead to transmission within the facility and to surrounding communities.  
• Health care settings in these facilities are at least medium risk. | • In addition to screening at intake, long-term inmates and correctional facility staff (e.g., custody and medical) should receive routine (i.e., at least annual) screening.  
HCP should receive annual TB education.  
• Facilities should follow federal, state, or local regulations requiring TB diagnostic evaluations for inmates/detainees in jails, prisons, or other detention centers to help ensure all individuals have been evaluated and treated, if necessary. | • Coordinate with TB control programs to establish systems for identifying and following up with persons who test positive for LTBI or TB disease.  
• Implement a respiratory protection program with at least one AII room or have a transfer policy.  
• Immediately isolate inmates with presumptive or confirmed TB disease and require that they wear a surgical mask when being transported outside of an AII room.  
• Maintain a tracking system for sharing information with state and local health departments and other correctional facilities.  
• Educate staff on importance of reporting signs and symptoms of TB disease. |
| **Homeless Shelters**\(^{a,c}\) | • Transmission is more common in homeless shelters than in general population.  
• Clients, staff, volunteers, and frequent visitors are at risk of exposure. | • All clients, staff, and volunteers should be systematically evaluated for TB based on state and local regulations.  
• Staff and regular volunteers in shelters for the homeless should be screened on admission or initial employment.  
• HCP should receive annual TB education. | • Coordinate with TB control programs to establish systems, such as bed-tracking, for identifying and following up with persons who test positive for LTBI or TB disease.  
• Separate clients with TB symptoms from others until a medical evaluation for TB disease has been performed. Clients should remain separated until TB disease has been excluded or the patient is not infectious.  
• Evaluate residents for signs and symptoms of TB disease for early detection and treatment.  
• Educate staff on importance of reporting signs and symptoms of TB disease.  
• Implement relevant administrative, environmental, and respiratory protection control policies. |
<table>
<thead>
<tr>
<th>Setting</th>
<th>Transmission of <em>M. tuberculosis</em></th>
<th>Screening/testing</th>
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<tbody>
<tr>
<td>Long-term Care Facilities(^a)</td>
<td>Patients, HCP, visitors, and volunteers are at risk of exposure.</td>
<td>• Clients and HCP should be screened for TB on admission or initial employment.</td>
<td>• Provide adequate administrative, environmental, and respiratory protection controls that include</td>
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<td>• HCP should receive annual TB education.</td>
<td>• Airborne precaution capabilities.</td>
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<td></td>
<td>• A respiratory protection program.</td>
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<td>• Patients with presumptive or confirmed infectious TB disease should avoid staying in LTCFs unless adequate</td>
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<td></td>
<td>administrative and environmental controls are in place.</td>
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<td></td>
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<td></td>
<td>• Educate staff on importance of reporting signs and symptoms of TB disease.</td>
</tr>
<tr>
<td>Home-based Health Care and Outreach Settings(^d)</td>
<td>Patients, HCP, and others in the home are at risk of exposure.</td>
<td>All home-based health care and outreach staff should be screened for TB upon hire and</td>
<td>• Evaluate the patient for signs and symptoms of TB disease for early detection and treatment.</td>
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<td></td>
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<td>should receive annual TB education.</td>
<td>• Educate patients and staff on importance of reporting signs and symptoms of TB disease.</td>
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<td></td>
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<td></td>
<td>• Wear an N95 or higher filtering facepiece respirator when entering homes of persons with presumptive</td>
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<td>infectious TB disease.</td>
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<tr>
<td>Emergency Medical Services(^d)</td>
<td>Patients and HCP are at risk of exposure.</td>
<td>All EMS employees should be screened for TB upon hire and should receive annual TB education.</td>
<td>• Require drivers, health care personnel, and other staff to wear an N95 or higher filtering facepiece</td>
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<td></td>
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<td>respirator around a person with presumptive or confirmed TB disease.</td>
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<td></td>
<td>• Require persons with presumptive TB disease who are transported in an ambulance to wear a surgical mask.</td>
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<td></td>
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<td></td>
<td>• Educate staff on importance of reporting signs and symptoms of TB disease.</td>
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</table>

\(^a\) Screening for Tuberculosis and Tuberculosis Infection in High-Risk Populations Recommendations of the Advisory Council for the Elimination of Tuberculosis [https://www.cdc.gov/mmwr/preview/mmwrhtml/00038873.htm](https://www.cdc.gov/mmwr/preview/mmwrhtml/00038873.htm)

\(^b\) Prevention and Control of Tuberculosis in Correctional and Detention Facilities: Recommendations from CDC [https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5509a1.htm](https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5509a1.htm)


TB Infection Control in the Home

Patients with presumptive or confirmed TB disease are frequently requested to isolate at home after starting treatment if there are no other vulnerable housemates. They are instructed to remain isolated and stay away from others while they undergo treatment and until they are no longer considered to have infectious TB. Patients with TB disease can be discharged home, even if they do not have three negative sputum smears, if all of the following criteria are met:

- There are no infants or children less than 5 years of age or persons with immunocompromising conditions in the household.
- A follow-up plan has been made with the local TB program.
- The patient is on standard TB treatment and directly observed therapy (DOT) has been arranged.
- The patient is willing to remain isolated in the home except for health care-associated visits until the patient has negative sputum smear results.

Patients who have presumptive or confirmed pulmonary TB disease may have already transmitted TB infection to members of their household before their TB disease was diagnosed and treatment was started. TB patients and members of their household should take steps to prevent the further spread of TB infection after they return home (Table 6.6). Patients with TB disease should

- Be instructed to cover their mouth and nose when coughing or sneezing.
- Sleep alone and not in a room with other household members.
- Avoid having visitors in the home until they are noninfectious.

HCP who visit TB patients in their homes should take the following precautions to protect themselves from exposure to *M. tuberculosis* (Table 6.6):

- Instruct patients who are potentially infectious to cover their mouth and nose with a tissue when coughing or sneezing.
- Wear an N95 or higher filtering facepiece respirator when visiting the home of a patient with infectious TB disease or when transporting a patient with infectious TB disease in a vehicle.
- Collect specimens away from other people in a well-ventilated area or outdoors.
In addition, HCP whose responsibilities include working with potentially infectious TB patients should participate in an annual TB testing and/or screening program because this group may be at a higher occupational risk for TB.

**Table 6.6**

**TB Infection Control in the Home**

<table>
<thead>
<tr>
<th>Steps that Patients Can Take to Prevent the Further Transmission of TB in the Home</th>
<th>Precautions for Health Care Personnel to Take to Protect Themselves from Exposure to <em>M. tuberculosis</em></th>
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</thead>
</table>
| • Cover their mouth and nose when coughing or sneezing.  
• Sleep alone and not in a room with other household members.  
• Avoid having visitors in the home until the patient is not infectious. | • Instruct patients to cover their mouth and nose with a tissue when coughing or sneezing.  
• Meet the patient outside when possible.  
• Wear an N95 or higher filtering facepiece respirator when visiting the home of a patient with infectious TB disease or when transporting a patient with infectious TB disease in a vehicle.  
• Collect specimens away from other people in a well-ventilated area. |
Knowledge Check

Select the best answer for each question.

1. One characteristic of TB airborne infection isolation (AII) rooms is the positive pressure relative to other parts of a facility.
   A. True
   B. False

2. When can a TB patient be considered noninfectious?
   A. When they are on adequate therapy for two weeks or longer
   B. When their symptoms have improved
   C. When they have had 3 consecutive negative sputum smear results from specimens collected in 8- to 24-hour intervals (one being an early morning specimen)
   D. When all of the above are true

3. What should be done when a health care worker thinks that a patient has TB?
   1. The patient should be isolated and placed in an AII room right away, if available.
   2. The patient should be given a surgical mask and instructed to keep it on.
   3. The patient should be given a diagnostic evaluation.
   4. The patient should be tested for lung capacity.
      A. 1, 2, and 3 are correct
      B. 1 and 3 are correct
      C. 2 and 4 are correct
      D. Only 4 is correct
      E. All are correct

4. You are advising a large health care organization about preventing tuberculosis (TB) transmission in healthcare settings. According to the updated National Tuberculosis Controllers Association (NTCA) and Centers for Disease Control and Prevention (CDC) recommendations, which of the following statements about baseline and post-exposure TB screening and testing for US health care personnel (HCP) is correct?
   A. HCP should undergo TB screening and testing with an individual risk assessment and symptom evaluation upon hire.
   B. HCP are considered to be at increased risk for TB only if they have close contact with someone who has had infectious TB disease since the last TB test.
C. Every HCP with a single positive baseline screening test should be considered infected with *Mycobacterium tuberculosis*.

D. HCP with documented prior latent tuberculosis infection (LTBI) or TB disease should have another TB test after known exposure (without adequate personal protection) to a person with potentially infectious TB disease.

5. According to the updated NTCA and CDC recommendations, which of the following statements about serial screening and testing for HCP without LTBI is correct?

   A. HCP who care for patients with respiratory infections should have routine serial TB screening annually.
   
   B. The decision to perform TB testing after baseline should be based on the HCP's risk for TB exposure at work or elsewhere since that person's last test.
   
   C. All HCP, regardless of occupational risk, should have serial TB screening.
   
   D. All of the above

6. Which of the statements about respirators and surgical masks are correct?

   1. A user seal check is done each time a respirator is put on to ensure that the respirator is properly sealed.
   
   2. Respirators are designed to protect a person by reducing the droplet nuclei breathed in (inhaled).
   
   3. Surgical masks are designed to reduce droplets from being spread (exhaled) into the air by the person wearing them.
   
   4. Healthcare workers working with persons with suspected or confirmed infectious TB should be given a surgical mask to wear to reduce the droplet nuclei breathed in (inhaled).
   
      A. 1, 2, and 3 are correct
   
      B. 1 and 3 are correct
   
      C. 2 and 4 are correct
   
      D. Only 4 is correct
   
      E. All are correct

7. What are the three types of controls in an infection control program?

   A. Administrative, environmental, respiratory protection
   
   B. Environmental, respiratory protection, HEPA filters
   
   C. Environmental, ventilation systems, HEPA filters
   
   D. Ventilation systems, respiratory protection, HEPA filters
8. In places where administrative and environmental controls may not fully protect HCP from droplet nuclei, health care settings should establish respiratory protection controls.
   A. True
   B. False

9. What precautions should a health care worker take when visiting the home of a TB patient who may be infectious?
   1. Instruct the patient to cover their mouth and nose with a tissue when coughing or sneezing.
   2. Wear a N95 filtering facepiece when visiting the home of an infectious TB patient or when transporting an infectious TB patient in a vehicle.
   3. When it is necessary to collect a sputum specimen in the home, collect the specimen in a well-ventilated area, away from other household members; if possible, the specimen should be collected outdoors.
   4. Wear surgical scrubs, gloves, and goggles.
      A. 1, 2, and 3 are correct
      B. 1 and 3 are correct
      C. 2 and 4 are correct
      D. Only 4 is correct
      E. All are correct

10. Annual TB testing of all health care personnel is recommended.
    A. True
    B. False

See page 195 for answer key.
### Chapter 7 Contents

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### Chapter Objectives

After working through this chapter, you should be able to

- Describe the roles and responsibilities for tuberculosis (TB) control and prevention in the public health sector.
- Describe the roles and responsibilities for TB control and prevention in the private health sector.

### Chapter Introduction

TB control and prevention is a complex undertaking that requires the collaborative efforts of a broad range of persons, organizations, and institutions in both the public and private health sectors. Individuals and organizations in both of these sectors have a role in

- Curing the patient.
- Minimizing risk for death or disability.
- Reducing transmission of *Mycobacterium tuberculosis* to others.
- Preventing the acquisition of drug resistance during treatment.
Roles and Responsibilities of the Public Health Sector

State and local health departments have the primary responsibility for preventing and controlling TB. This includes the essential role of planning, coordinating, and evaluating program activities, including

- Planning and policy development.
- Contact investigation.
- Clinical and diagnostic services for TB patients and their contacts.
- Training and education.
- Surveillance data and information management.
- Monitoring and evaluation.

Planning and Policy Development

A written TB control plan should include the policies pertinent to respective TB programs. The plan should be developed in collaboration with community stakeholders and experts in medical and nonmedical aspects of TB. Laboratory directors and professional organizations are also key partners to collaborate with when developing TB control policies.

The TB control plan should be based on an understanding of local epidemiology and on available clinical and support services for clients. Available funding for TB control also determines the plan’s scope and direction, as well as ongoing indicators of program performance. Policies and procedures should reflect national, state, and local standards of care and should offer guidance in the management of latent TB infection (LTBI) and TB disease.

A written TB control plan should be updated and distributed to all partners on a regular basis and should

- Assign specific roles and responsibilities.
- Define essential pathways of communication between all stakeholders.
- Assign sufficient human and financial resources to ensure its implementation, including a responsible case manager for each presumptive or confirmed case of TB disease.
• Provide information for accessing expert consultation.
• Provide special guidance to local laboratories that process TB specimens.
• Assist local authorities in conducting contact and/or outbreak investigations and directly observed therapy (DOT).
• Provide resources for culturally appropriate information to be distributed to patients, persons at risk, and the community.

Current TB legal statutes are important to include and should be reviewed periodically and updated as necessary to ensure consistency with current clinical and public health practice. Current clinical and public health practice includes mandatory reporting laws, institutional infection control procedures, hospital and correctional system discharge planning, and involuntary confinement laws.

Contact Investigation

The health department is legally responsible for ensuring that a complete and timely contact investigation is conducted for any TB cases reported in its jurisdiction. Health departments should work closely with providers in the private health sector to ensure that contacts are located and promptly treated. Providers should understand the public health aspects of TB, including the role of jurisdictional health agencies in case management and the need to report presumptive cases promptly.

Federal agencies should take the lead in resolving interstate TB control issues, including movement of TB patients across state lines and multistate TB outbreaks.

Clinical and Diagnostic Services for Patients with TB Disease and Their Contacts

TB programs should ensure that patients with confirmed or presumptive TB disease have ready access to diagnostic and treatment services that meet national standards. Clinical facilities should provide screening, diagnostics, and monitoring tests. Radiology services are critical, and clinics should have functioning radiograph equipment, a trained radiograph technician, and radiograph interpretation by a qualified person. Radiograph findings and reports should be available within 24 hours.

These clinical and diagnostic services are often provided by state or local TB clinics and staffed by health department personnel or contracted service
providers. Patients may also seek medical care for LTBI or TB disease in the private medical sector. Regardless of where a person receives medical care, the primary responsibility for ensuring the quality and completeness of all TB-related services rests with state and local public health agencies.

Laboratory services should be readily accessible to perform and provide results of acid-fast bacilli (AFB) smear examinations within 24 hours of specimen collection. TB programs should work closely with laboratories to ensure the rapid delivery of specimens and prompt reporting of AFB smear results, culture results, and drug-susceptibility test results to the clinician and health department. Laboratory services should also be available to provide monitoring of bacteriologic response to therapy.

To ensure that standards of care are met, health departments should develop and maintain close working relationships with their community health care providers, laboratories, and pharmacies.

Coordinating care with other health care providers and facilities is crucial to the prevention and control of TB. Treatment plans must be specific to individual patient needs. As patients move among different settings, continuity of care may be compromised unless a system is in place to provide good coordination.

TB patients often receive care in a variety of settings, including the following:

- Private practices
- Hospitals
- HIV clinics
- Community clinics
- Correctional facilities
- Nursing homes

Expert TB medical consultation should be sought when necessary and can be accessed through the TB Centers of Excellence for Training, Education, and Medical Consultation (TB COEs). Other appropriate consultants may include health department employees or community clinicians with TB expertise who are under contract with the health department. Seeking expert TB medical consultation is especially critical for pediatric TB cases and for patients who have drug-resistant TB disease.
Training and Education

TB programs should provide clinical and public health education and training to all program staff. Staff members should receive TB education at regular intervals on their specific program responsibilities and be able to demonstrate proficiency in those areas. TB programs are encouraged to educate public and private health care providers, community members, public health officials, and policy makers on TB prevention and control based on local epidemiology and other individual program needs (Figure 7.1). TB programs should develop education and training programs with potential partners such as local health care providers, community clinics, and institutions of higher learning.

TB education and training resources are available from the CDC Division of TB Elimination (DTBE) and the TB COEs. The TB COEs support domestic TB control and prevention efforts through communication, education, and training activities, as well as providing expert TB medical consultation. DTBE funds the TB COEs, and each center is regionally assigned to cover all 50 states and the U.S. territories.

Find TB Resources is an online library that provides TB education and training materials.

Figure 7.1
Community Members Receiving TB Education
Surveillance and Information Management

Surveillance and information management systems should be a priority for all TB programs. Information technology can improve the care of patients with TB disease through standardized collection of data and tracking of test results. Other benefits include ready access to details regarding treatment regimens, administration of DOT, and drug-drug interactions. Advances in information technology allow for the analysis and rapid distribution of epidemiologic data, as well as management of individualized treatment plans.

Monitoring and Evaluation

The systematic monitoring and evaluation of TB program activities is a critical factor in improving program performance. TB programs should develop priorities for program evaluation based on the TB issues or challenges in their jurisdiction. Targets for program performance have been established by CDC to assist TB programs in treating TB patients, identifying and examining their contacts, and improving the quality of case reporting for national surveillance. In addition, national objectives have been set for completing LTBI treatment among contacts of infectious TB cases. These national program performance objectives provide a starting point for state and local TB programs to use for program evaluation, but each TB program should establish methods to evaluate its performance.

While program evaluation can provide TB programs with an evidence-based means of assessing and improving their TB control strategies, it can also be used for

- Program advocacy.
- Assessing staffing needs.
- Focusing training and capacity building.
- Directing limited resources to the most productive activities.
- Accounting for available resources.
- Generating additional resources.
- Recognizing achievement.
Roles and Responsibilities of the Private Health Sector

The private health sector plays an important role in TB prevention and control. This varied group of organizations and providers is critical in the effort to eliminate TB. As such, the public health sector should engage this group of stakeholders and educate them in the public health expertise necessary for TB elimination. Private health sector organizations and providers include the following:

- Clinicians
- Community health centers
- Federally qualified health centers
- Hospitals
- Academic institutions
- Professional medical organizations
- Community-based organizations
- Correctional facilities
- Civil surgeons
- Pharmaceutical and biotechnology industries
- Other non-government organizations

Clinicians

Clinicians in private medical practice play a vital role in TB control in communities throughout the United States (Figure 7.2). Hospital- and clinic-based medical practitioners, including those working in emergency departments, are often the first source of medical care for persons with TB disease. The role of private providers in TB control will increase as TB morbidity in the United States decreases and jurisdictions reduce or even eliminate public health clinical services for TB. Private medical providers should strive to

- Provide their medical staff with the skills and knowledge needed to screen, test, diagnose, and initiate treatment for TB disease and LTBI.
• Understand prevalent medical conditions of populations within their practice, especially medical conditions that have public health implications like TB.

• Be aware of applicable state laws and regulations for reporting TB disease.

• Screen all new patients for symptoms of TB disease and risk factors for LTBI and give those with risk factors a tuberculin skin test (TST) or a TB blood test.

• Place and read TSTs or administer blood tests for TB infection, ruling out presumptive TB disease.

• Diagnose TB promptly and seek hospitalization if necessary.

• Review risk factors for immunosuppressed patients receiving TB treatment.

• Work in partnership with the public health agency to develop a treatment plan that optimizes the likelihood that the patient will complete the recommended therapy.

Figure 7.2
Clinicians Play a Pivotal Role in TB Control
Community Health Centers

Community health centers typically provide primary health care services to populations that encounter barriers to those services at other sites in the health care system, including persons who are

- Low-income.
- Homeless.
- Substance users.
- Uninsured.
- Immigrants, refugees, or others born outside the United States.

Patients at high risk for TB disease often receive primary and emergency health care in community health centers. Community health centers in some inner-city areas might primarily serve homeless persons, whereas centers in neighborhoods with concentrations of certain racial and ethnic populations might become primary health care providers for immigrants and refugees. Newly arriving refugee families are frequently directed to community health centers to receive health screening services which often include targeted testing and treatment for LTBI. For these reasons, community health centers are a critical part of efforts to control and prevent TB disease and should

- Provide their medical staff with the skills and knowledge needed to screen, test, diagnose, and initiate treatment for TB disease and LTBI.
- Ensure availability of diagnostic services (e.g., sputum smears for AFB, cultures for *M. tuberculosis*, and chest radiographs).
- Provide consultation and referral of patients for hospitalization, if necessary.
- Report patients with presumptive TB disease to the health department.
- Develop close working relationships with other physicians, hospitals, and clinical laboratories.
- Develop close working relationships with the public health agency that serves their jurisdiction.
- Establish recommended TB infection control practices to protect patients and staff.
- Educate patients about the personal and public health implications of TB disease and LTBI.
• Increase interventions for HIV care (e.g., testing and counseling, treatment of other opportunistic infections, antiretroviral therapy [ART]) for TB patients co-infected with HIV.

• Increase capacity of staff in all settings to provide comprehensive care (e.g., increase ability to provide care for HIV-related illness in TB clinics and increase ability of staff providing care for HIV/AIDS to include follow-up of TB patients).

**Federally Qualified Health Centers**

A Federally Qualified Health Center (FQHC) is a community-based organization that provides comprehensive, preventive care services to persons of all ages, regardless of their ability to pay or their health insurance status. Thus, FQHCs are a critical component of the health care safety net. FQHCs play an important role in TB prevention and control in the underserved community, including providing testing and treatment for migrant and seasonal workers and homeless individuals.

**Hospitals**

Hospitals with active outpatient and emergency room services often serve as sites of acute and primary medical care for homeless persons, inner-city residents, immigrants and refugees, and others at high risk for TB disease. Hospital staff frequently provide medical consultation services for the diagnosis and management of TB disease. To ensure that hospitals are effective in providing care and treatment for patients with TB, hospital leadership should

• Develop a TB infection control policy to ensure that patients presumed to have infectious TB disease are isolated in airborne infection isolation (AII) rooms.

• Implement effective TB infection control measures for all patients and staff.

• Provide key diagnostic tests for TB disease and LTBI.

• Promptly report all patients with a presumptive or confirmed diagnosis of TB disease to their state and local public health agency.

• Develop a written policy and plan for prevention of the nosocomial transmission of TB disease in their facility.

• Provide TB training and ongoing education for their staff.

• Ensure patients with TB are discharged on the appropriate anti-TB drug regimen.

• Plan discharge arrangements in advance and coordinate patient follow-up between the hospital and the jurisdictional public health agency.
**Academic Institutions**

Academic institutions, including schools of medicine, pharmacy, public health, and nursing, can have a major impact on TB control in the United States and worldwide. Students from diverse disciplines, such as the clinical and laboratory sciences, nursing, epidemiology, and health services, should be introduced to applicable concepts of TB. TB is a major cause of preventable illness and death in developing countries, and it warrants serious consideration when academic institutions plan courses of study.

Conferences, grand rounds, and other presentations hosted by academic institutions are excellent opportunities to provide ongoing TB education to students and to the community at large. Trained specialists and researchers at academic institutions can provide clinical, radiographic, and epidemiologic consultation to medical practitioners. Many academic institutions manage university-based hospitals which often serve populations at high risk for TB infection and disease. University hospitals can become models for TB risk assessment, inpatient care, and infection control practice, and they can serve as tertiary care sites for an entire community or region. To aid communities in the fight against TB, academic institutions should

- Ensure that TB is included in appropriate curricula.
- Serve as repositories of expertise in the treatment and management of TB disease and LTBI.
- Conduct research in diagnostics, drugs, and vaccines for TB infection and disease.
- Partner with public health agencies to provide additional sites for TB education, training, and clinical research opportunities.

**Professional Medical Organizations**

Professional medical organizations are important partners in TB control efforts because of their influence in medical practice, research, education, advocacy, and public health. Greater participation of professional medical organizations in TB control can help maintain the clinical expertise necessary to diagnose and manage TB. Organizations whose memberships include primary care practitioners can make significant contributions to the control, prevention, and elimination of TB by

- Training and educating their members and other health professionals in the clinical and public health aspects of TB risk assessment, diagnosis, treatment, control, and prevention.
• Participating in the development or endorsement of guidelines, influencing school curricula, and establishing and supporting fellowship training programs.

• Providing support for adequate funding for TB control and research.

• Endorsing the importance of greater U.S. involvement in global control of TB by linking U.S.-based health professionals with other health professionals around the world.

Community-Based Organizations

Community-based organizations (CBOs) can be particularly effective in providing information and education on TB disease and LTBI to their constituencies. As part of the communities they serve, CBOs are often highly regarded, and their messages might be more positively accepted than messages delivered by state or local health departments. Organizations providing services to populations at risk for TB disease should

• Partner with state and local public health TB programs and medical care providers from the community to facilitate access to diagnostic, treatment, and prevention services.

• Become involved in support initiatives, including state and local TB advisory committees and coalitions.

• Coordinate with public health agencies and educational institutions to develop education programs that are culturally and linguistically tailored to the target populations.

• Provide information and education on TB and HIV to increase community awareness of both infections and their inter-relationship.

Correctional Facilities

Correctional facilities are common sites for the transmission of TB. Prevalence of TB disease and LTBI are substantially higher in prisons and jails than in the general population.

Targeted testing and treatment of LTBI and TB disease in correctional facilities can have a substantial public health impact, but successful treatment completion varies depending on the length of time inmates stay incarcerated. Testing and treatment activities are carried out more effectively in prisons because the length of stay is generally sufficient to permit completion of treatment. Jails are convenient
sites for targeted testing, but subsequent treatment of LTBI and TB disease has proved challenging because inmates do not ordinarily stay in jail for extended periods of time. Detainees in jail are also more likely than prison inmates to be abruptly transferred among institutions. In either case, there is often not sufficient consideration for health issues.

To mitigate the risk of TB transmission to the incarcerated population, the facility staff, and the larger community, correctional facilities have a responsibility to

- Coordinate with the public health agency in their jurisdiction to develop and maintain an accurate epidemiologic profile of the risk for LTBI and TB disease in their inmate population.
- Establish effective programs to screen for TB disease and provide targeted testing and treatment programs for detainees and staff.
- Respond promptly when TB cases occur within the facility.
- Provide ongoing, competency-based TB education for all detainees and staff.
- Establish ongoing working relations with public health agencies, hospitals, and other community partners.
- Develop firm linkages for referral of persons undergoing treatment for TB disease and LTBI upon discharge.
- Develop TB infection control programs to protect inmates, detainees, staff, and visitors from exposure to TB disease following the requirements of the Occupational Safety and Health Administration (OSHA) and other regulatory agencies.
- Evaluate the effectiveness of their TB control plan on a regular basis.

**Civil Surgeons**

Persons living in the United States who apply to adjust their immigration status are required to be tested for TB infection and evaluated for TB disease by U.S.-based physicians known as civil surgeons. Civil surgeons are licensed physicians who are certified by the U.S. Citizenship and Immigration Services to conduct a mandatory health screening examination of non-U.S.-born persons living in the United States. The CDC Division of Global Migration and Quarantine (DGMQ) develops the requirements that civil surgeons must follow when evaluating persons as part of their application process. These requirements are called Technical Instructions. Although CDC has a responsibility for providing guidance on screening and treatment, it has no regulatory role in monitoring the quality or outcomes of these examinations.
Civil surgeons are a critical component of TB control because of their access to a high-risk population. If conducted correctly, health screening of immigrants can identify non-U.S.-born persons with LTBI or TB disease for whom treatment is necessary. Although civil surgeons receive immigration-focused training, little information is available on their knowledge, attitudes, and practices. To ensure that the health screening examinations are effective in TB testing and treatment, civil surgeons should

- Understand current guidelines for the diagnosis and treatment of TB disease and LTBI.
- Establish a working relationship with state and local public health agencies.
- Use interferon-gamma release assays (IGRAs) instead of the tuberculin skin test (TST) to test all applicants 2 years of age or older (TST cannot be used as a substitute for an IGRA).
- Report applicants with LTBI to the health department.
- Report presumptive and confirmed cases of TB disease to the health department.
- Develop a referral mechanism for further evaluation and treatment of persons with TB disease and LTBI.

**Other Key Organizations**

Other key partners in TB control include non-government organizations that also work with public and private partners to develop new TB diagnostics, drugs, and vaccines. Their goals include identifying and addressing obstacles to the development of new anti-TB tools among private industry, public and academic researchers, and philanthropic organizations. Some non-government organizations working in the field of TB include

- **National Tuberculosis Controllers Association** whose mission is “to protect the public’s health by advancing the elimination of tuberculosis in the U.S. through the concerted action of state, local, and territorial programs.”
- **We Are TB**, a non-profit “survivor network that is fighting to achieve change in TB diagnostics, treatment regimens, and funding to support US-based public health programs.”
• **TB Community Engagement Network** that supports communities at risk for TB and builds capacity among health care providers and others who serve and support these populations.

• **Stop TB USA** whose mission is “to eliminate TB as a public health threat in the U.S.”

• **Stop TB Partnership** (hosted by the United Nations) whose mission is “to serve every person who is vulnerable to TB and ensure that high-quality diagnosis, treatment, and care is available to all who need it.”

• **TB Alliance**, a nonprofit organization “dedicated to the discovery, development and delivery of better, faster-acting and affordable tuberculosis drugs that are available to those who need them.”

Pharmaceutical and biotechnology industries are also partners in TB control because of their essential role in developing new diagnostics, drugs, and vaccines. To further contribute to TB control and prevention efforts, the pharmaceutical and biotechnology industries should

• Understand the dimensions of the global TB epidemic and realize their key role in developing the necessary tools for diagnosis, treatment, and prevention of TB disease.

• Examine the costs of new product development and consider the markets for such products in developing countries.

• Coordinate with other stakeholders to ensure access to essential products for people with LTBI and TB disease.
Knowledge Check

Select the best answer for each question.

1. The federal government has the primary responsibility for preventing and controlling TB.
   A. True
   B. False

2. Why are community-based organizations particularly effective in providing information and education on TB disease to their constituencies?
   A. They are often highly regarded by the populations they serve.
   B. Their messages might be accepted more positively than those delivered by the state and/or local health department.
   C. They have unlimited funds to purchase quality educational materials.
   D. A, B, and C are all correct
   E. Only A and B are correct

See page 195 for answer key.
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</table>
acid-fast bacilli (AFB) mycobacteria that, when stained, retain color even after they have been washed in an acid solution; may be detected under a microscope in a stained smear.

airborne infection isolation (AII) room formerly called a “negative pressure isolation room,” a room with special characteristics, including negative-pressure ventilation, to prevent the spread of droplet nuclei expelled by a TB patient.

alveoli the small air sacs of the lung at the end of each airway; when droplet nuclei reach these air sacs, TB infection begins.

anergy the inability to react to a skin test because of a weakened immune system, often caused by HIV infection or severe illness.

antigen protein substance that can produce an immune response.

BCG bacilli Calmette-Guérin, a vaccine for TB disease that is used in many countries but rarely used in the United States; may cause a false-positive reaction to the Mantoux tuberculin skin test (TST) but does not affect interferon-gamma release assay (IGRA) results.

boosted reaction a positive reaction to a TST, due to a boosted immune response from a TST given in the past year; two-step testing is used in TB testing programs to tell the difference between boosted reactions and reactions caused by a recent infection.
booster phenomenon

A phenomenon in which people (especially older adults) who are skin tested many years after becoming infected with *M. tuberculosis* may have a negative reaction to an initial TST, followed by a positive reaction to a TST given up to a year later; this happens because the first TST boosts the immune response. Two-step testing is used in TB testing programs to tell the difference between boosted reactions and reactions caused by recent infection.

case

A person with presumed or confirmed TB disease.

case management

A strategy health departments can use to manage patient care and help ensure patients successfully complete treatment.

cavity

A hollow space within the lung, visible on a chest x-ray, that may contain many tubercle bacilli; often occurs in people with severe pulmonary TB disease.

civil surgeons

Domestic health care providers who screen immigrants living in the United States and applying for a permanent residence visa or citizenship.

contacts

Persons exposed to someone with infectious TB disease; can include family members, roommates or housemates, close friends, coworkers, classmates, and others.

corticosteroid

A type of steroid, either natural or man-made, often used to treat arthritis, certain allergies, or other immune disorders.

culture

To grow organisms in media (substances containing nutrients) so that they or the product of this process can be identified; a positive culture for *M. tuberculosis* contains tubercle bacilli, whereas a negative culture contains no detectable tubercle bacilli.

directly observed therapy (DOT)

A strategy devised to help patients adhere to treatment wherein a designated person watches the TB patient swallow each dose of the prescribed drugs to ensure adherence to and tolerability of the regimen.
disseminated TB  TB disease that occurs when tubercle bacilli enter the bloodstream or lymph system and are carried to all parts of the body where they grow and cause disease in multiple sites, e.g., miliary TB

droplet nuclei  very small droplets (1 to 5 microns in diameter) containing *M. tuberculosis* that may be expelled when a person who has infectious TB coughs, speaks, or sings; the droplets can remain suspended in the air for several hours, depending on the environment

drug-resistant TB  TB caused by *M. tuberculosis* organisms that are able to grow in the presence of a particular drug; TB that is resistant to at least one anti-TB drug

erythema  redness around the site of the injection when a TST is done; erythema is not measured as part of the reaction size because redness does not indicate that a person has TB infection

ethambutol (EMB)  a drug used to treat TB disease; may cause vision problems and should be used cautiously in children who are too young to be monitored for changes in their vision

extensively drug-resistant TB (XDR TB)  a type of MDR TB that is resistant to isoniazid and rifampin, plus resistant to any fluoroquinolone and at least one of three injectable anti-TB drugs (amikacin, kanamycin, or capreomycin)

extrapulmonary TB  TB disease that occurs in places other than the lungs, such as the lymph nodes, the pleura, the brain, the kidneys, or the bones; most types of extrapulmonary TB are not infectious

false-negative reaction  a negative reaction to the TST or IGRA in a person who has TB infection

false-positive reaction  a positive reaction to the TST or IGRA in a person who does not have TB infection
**first-line TB treatment drugs**  
of the approved drugs to treat TB, isoniazid, rifampin, ethambutol, and pyrazinamide are considered first-line anti-TB drugs; they form the core of a standard treatment regimen. They are considered “first-line” because together they constitute the most powerful, least expensive, and most tolerable treatment regimen.

**fluoroquinolones**  
a class of synthetic broad-spectrum antibacterial drugs; examples of fluoroquinolones used to treat TB are levofloxacin and moxifloxacin.

**genotype**  
distinct genetic pattern of an organism.

**genotyping**  
laboratory-based approach used to analyze the genetic material (i.e., DNA) of *M. tuberculosis* that caused TB disease in a person.

**high efficiency particulate air (HEPA) filters**  
special filters that can be used in ventilation systems to help remove droplet nuclei from the air.

**immunosuppressive therapy**  
therapy that suppresses, or weakens, the immune system.

**induced sputum**  
sputum that is obtained by having the patient inhale a saline (saltwater) mist, causing the patient to cough deeply; this procedure is used to help patients cough up sputum if they cannot do so on their own.

**induration**  
swelling that can be felt around the site of injection after a TST is done; the reaction size is the diameter of the swollen area, measured across the forearm.

**infectious**  
capable of spreading infection; a person who has infectious TB disease expels droplets containing *M. tuberculosis* into the air when he or she coughs, speaks, or sings.
<table>
<thead>
<tr>
<th>Term</th>
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<tr>
<td>interferon-gamma (IFN-γ)</td>
<td>protein that is normally produced by the body in response to infection; IGRA interpretations are based on the amount of IFN-γ that is released or on the number of cells that release IFN-γ</td>
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<tr>
<td>interferon-gamma release assay (IGRA)</td>
<td>a type of blood test that measures a person’s immune reactivity to <em>M. tuberculosis</em>; in the United States, the QuantiFERON®-TB Gold Plus (QFT-Plus) and the T-SPOT®.TB test (T-Spot) are currently available IGRAss</td>
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<td>isolate</td>
<td>a group of organisms isolated or separated from a specimen; in an <em>M. tuberculosis</em> isolate, the organisms have been grown in culture and identified as <em>M. tuberculosis</em></td>
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<td>isoniazid (INH)</td>
<td>a drug that is used for treating LTBI and TB disease; although inexpensive and relatively safe, it may cause hepatitis and other adverse reactions in some patients</td>
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<td>latent TB infection (LTBI)</td>
<td>refers to a condition when a person is infected with <em>M. tuberculosis</em> but does not have TB disease; persons with LTBI carry the <em>M. tuberculosis</em> organism that causes TB, but they do not have TB disease symptoms, do not feel sick, and cannot spread TB germs to others; most persons with LTBI have a positive result to the TST or to an IGRA</td>
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<td>Mantoux tuberculin skin test (TST)</td>
<td>a method of testing for TB infection; a needle and syringe are used to inject 0.1 ml (5 tuberculin units) of purified protein derivative (PPD) tuberculin solution between the layers of the skin (intradermally), usually on the forearm; the reaction to this test, usually a small swollen area (induration), is measured 48 to 72 hours after the injection and is interpreted as positive or negative depending on the size of the reaction and the patient’s risk factors for TB</td>
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<td>miliary TB</td>
<td>a type of disseminated TB disease that occurs when tubercle bacilli enter the bloodstream and are carried to all parts of the body where they grow and cause disease in multiple sites; the chest x-ray of a patient with miliary TB often looks like millet seeds scattered throughout the lung</td>
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**multi-drug resistant TB (MDR TB)**

TB that is resistant to at least the drugs isoniazid and rifampin; MDR TB is more difficult to treat than drug-susceptible TB.

**mycobacteria**

A group of bacteria that can cause a variety of diseases.

**Mycobacterium avium complex**

A nontuberculous mycobacteria (NTM) that can cause pulmonary infections often confused with MTB as well as opportunistic infections.

**Mycobacterium bovis**

A type of tuberculous mycobacteria that can cause disease similar to TB; usually infects cows, but it can infect other mammals including humans; these mycobacteria were often spread to humans through contaminated milk before pasteurization became common practice; *M. bovis* rarely affects humans in the United States today.

**Mycobacterium tuberculosis complex**

The *M. tuberculosis* complex includes seven other TB-causing mycobacteria: *M. bovis, M. africanum, M. microti, M. canetti, M. caprae, M. pinnipedii,* and *M. mungi;* these mycobacteria are sometimes called tuberculous mycobacteria because they can cause TB disease or other similar diseases; *Mycobacterium tuberculosis* is the most common cause of TB in humans and is sometimes called the tubercle bacillus.

**negative pressure**

The difference in air pressure between two areas; a room that is under negative pressure has a lower pressure than adjacent areas, preventing air from flowing out of the room and into adjacent rooms or areas.

**nucleic acid amplification (NAA)**

A technique that amplifies (copies) DNA and RNA segments; often used in assays for direct detection of *M. tuberculosis* in clinical specimens

**panel physicians**

Overseas health care providers who screen U.S. immigration applicants for TB disease.

**pathogenesis**

How an infection or disease develops in the body.
| **peripheral neuropathy** | damage to the sensory nerves of the hands and feet that causes tingling, numbness, or pain |
| **polymerase chain reaction (PCR)** | a type of NAA technique used to make many copies of a segment of DNA or RNA |
| **primary drug resistance** | drug resistance caused by person-to-person transmission of drug-resistant organisms |
| **pulmonary TB** | TB disease that occurs in the lungs, typically causing a cough and an abnormal chest x-ray; pulmonary TB is usually infectious if untreated; most TB cases reported in the United States are pulmonary TB |
| **pyrazinamide (PZA)** | first-line drug for the treatment of TB disease; may cause hepatitis and other adverse reactions in some patients |
| **pyridoxine** | another name for vitamin B6; it is given to TB patients to prevent peripheral neuropathy; should always be given to pregnant and breastfeeding women on isoniazid and to patients with diabetes or HIV |
| **QuantiFERON®-TB Gold Plus (QFT-Plus)** | an IGRA (blood test) used to determine TB infection; the QFT-Plus measures the response of immune cells to simulated TB proteins when they are mixed with a small amount of whole blood |
| **resistant** | an organism's ability to grow despite the presence of a particular drug |
| **rifabutin (RBT)** | a drug used to treat TB disease; used as a substitute for rifampin (RIF) in the treatment of all forms of TB |
| **rifampin (RIF)** | a key drug used to treat TB disease; also used for LTBI treatment; rifampin has several possible side effects (e.g., hepatitis, turning body fluids orange, drug-drug interactions, and flu-like symptoms) |
**rifapentine (RPT)** a drug used to treat TB disease; also used in the 12-dose LTBI treatment regimen

**smear** a small amount of specimen that has been placed onto a glass slide, stained, washed in an acid solution, and then placed under the microscope for examination; used to detect acid-fast bacilli in a specimen

**sputum** phlegm from deep in the lungs; collected in a sterile container for processing and examination of TB disease

**secondary drug resistance** also referred to as acquired drug resistance; develops during TB treatment, either because the patient was not treated with the appropriate treatment regimen or because the patient did not follow the treatment regimen as prescribed

**silicosis** a lung disease caused by inhaling silica dust (released by breaking rocks or used in the production of glass and ceramics); occurs most often in mining, construction, and foundry workers

**transmission** the spread of an organism, such as *M. tuberculosis*, from one person to the other; the probability of transmission depends on the contagiousness of the patient, the type of environment, the length of exposure, and the susceptibility of the exposed individual

**T-SPOT®.TB Test (T-Spot)** an IGRA (blood test) used to determine TB infection; the T-Spot measures the number of T cells that secrete IFN-γ upon activation by *M. tuberculosis* antigens

**tubercle bacilli** another name for the *Mycobacterium tuberculosis* organisms that cause TB disease

**tuberculin skin test (TST)** a test used to detect TB infection (see Mantoux tuberculin skin test)
| **tumor necrosis factor-alpha (TNF-alpha) antagonists, inhibitors, or blockers** | medications used to treat inflammatory or autoimmune diseases such as rheumatoid arthritis, Crohn’s disease, psoriatic arthritis, and juvenile rheumatoid arthritis |
| **window period** | the time between a person’s last exposure to infectious TB and when a TST or IGRA can reliably detect infection with *M. tuberculosis* |
| **Xpert MTB/RIF assay** | a nucleic acid amplification (NAA) test that simultaneously identifies *Mycobacterium tuberculosis* complex and rifampin resistance in a sputum sample |


