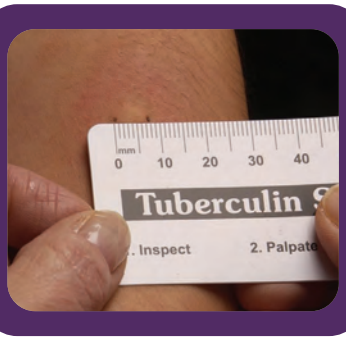
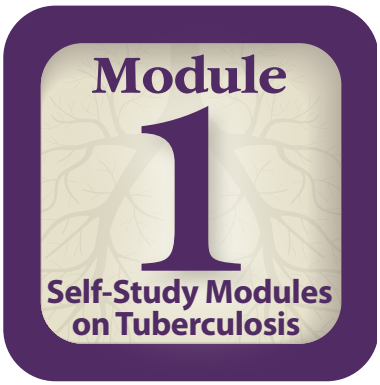
Self-Study Modules on Tuberculosis



Module 1

Transmission and Pathogenesis of Tuberculosis

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Division of Tuberculosis Elimination



Transmission and Pathogenesis of Tuberculosis

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Division of Tuberculosis Elimination

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Module 1 Self-Study Modules on Tuberculosis

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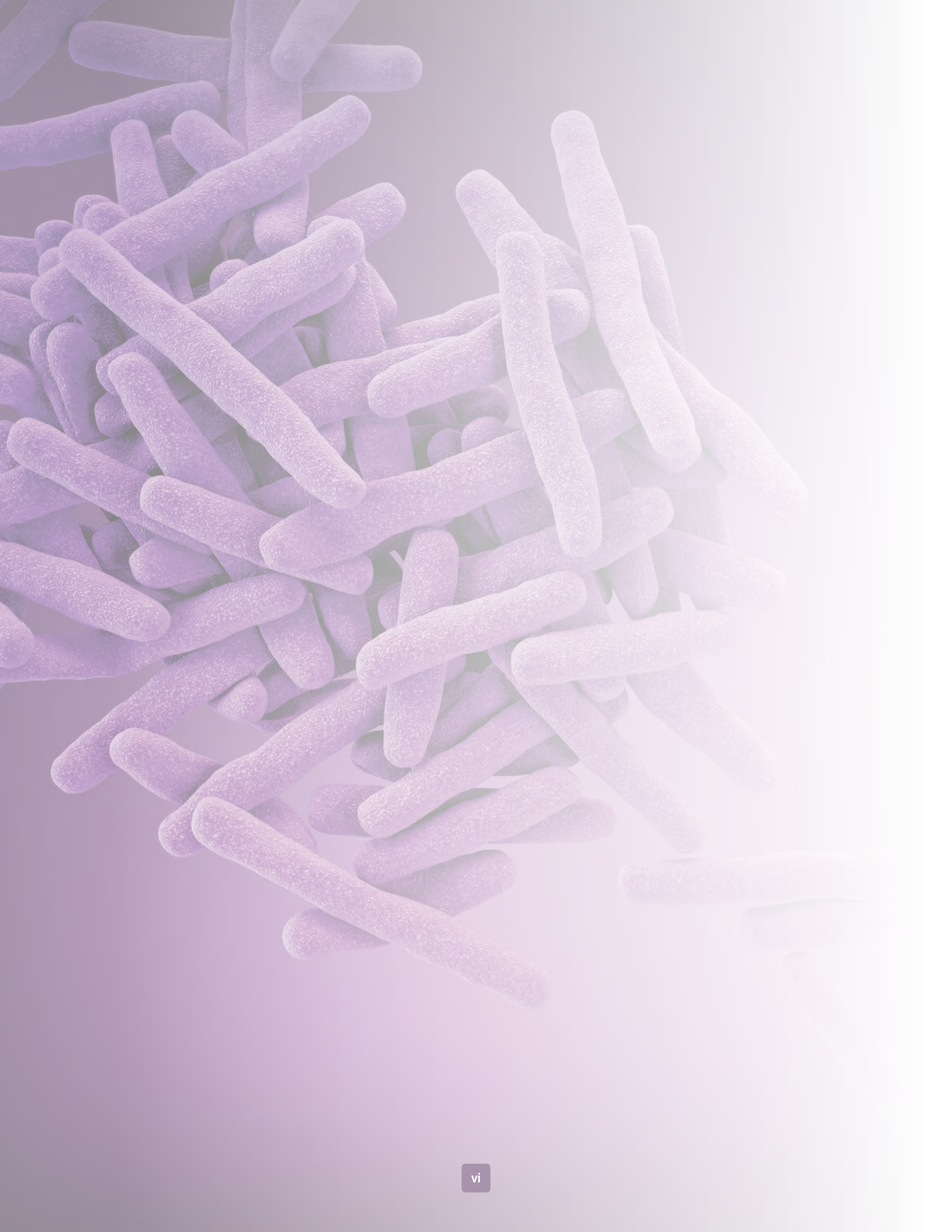
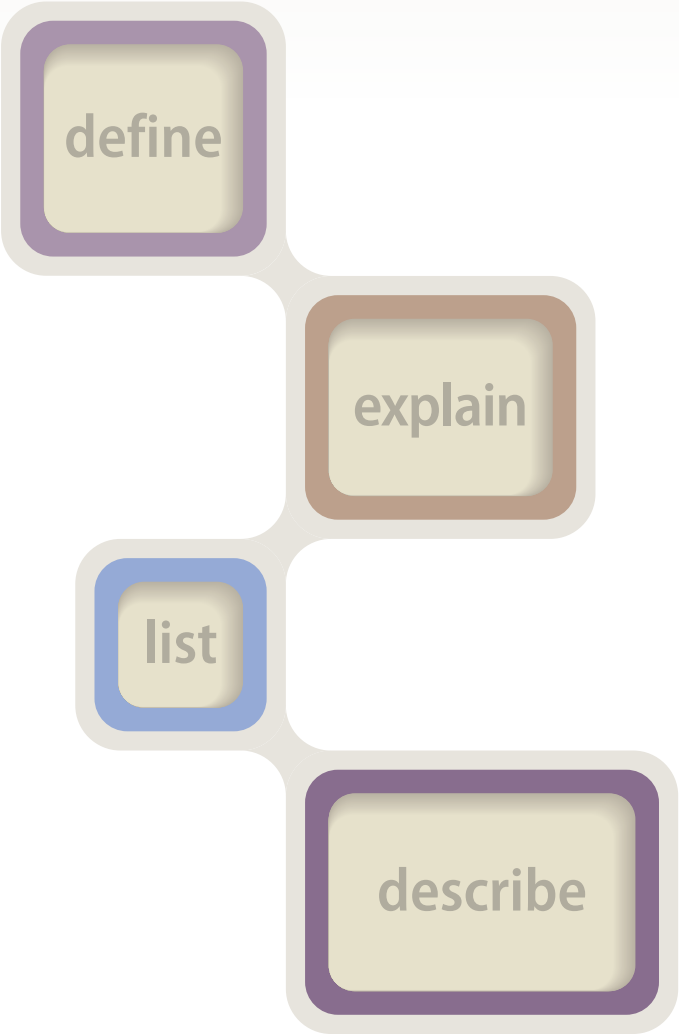


Background

In this module, you will learn about the history of tuberculosis (TB). You will also learn how TB is spread from person to person (transmission) and how TB disease develops in the body (pathogenesis). Our understanding of the transmission and pathogenesis of TB has guided us in developing strategies for controlling the spread of TB and for treating latent TB infection (LTBI) and TB disease. As a public health worker, you should understand these concepts so that you can educate the patients you serve.

Note: The *Self-Study Modules on Tuberculosis* are a series of educational modules designed to provide information about TB in a self-study format. The target audiences include outreach workers, nurses, physicians, administrators, health educators, and students from a variety of settings. The Modules should not be used as a substitute for guidelines and should not be used for patient care decisions.



Objectives

After working through this module, you will be able to

1. Briefly describe the history of TB.
2. Explain how TB is spread (transmission).
3. Define drug-resistant TB.
4. Explain the difference between LTBI and TB disease.
5. Explain how LTBI and TB disease develop (pathogenesis).
6. Describe the classification system for TB.

New Terms

New terms introduced in this module are included below. These terms appear in **bold** in the module text.

AIDS—acquired immunodeficiency syndrome, a condition in which the immune system is weakened and therefore less able to fight certain infections and diseases; AIDS is caused by infection with the human immunodeficiency virus (HIV)

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

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

diabetes mellitus—a disease in which blood glucose levels are above normal; diabetes can increase susceptibility to some infectious diseases, including TB

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, sneezes, 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

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 (such as 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

first-line TB treatment drugs—of the approved drugs to treat TB, isoniazid, rifampin, ethambutol, and pyrazinamide are considered the 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.

HIV—human immunodeficiency virus, the virus that causes AIDS

immune system—cells and tissues in the body that protect the body from foreign substances

immunosuppressive therapy—therapy that suppresses, or weakens, the immune system

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, sneezes, speaks, or sings

interferon-gamma release assay (IGRA)—a type of blood test that measures a person's immune reactivity to *M. tuberculosis*. In the United States, QuantiFERON®-TB Gold In-Tube test and the T-SPOT®.*TB* test (T-Spot) are currently available IGRAs.

latent TB infection (LTBI)—refers to the condition when a person is infected with *M. tuberculosis* but does not have TB disease. Persons with LTBI carry the organism that causes TB, but they do not have TB disease symptoms, and they cannot spread TB germs to others. Most persons with LTBI have a positive result to the tuberculin skin test or to an interferon-gamma release assay.

Mantoux tuberculin skin test (TST)—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; the routine methodology for tuberculin skin testing worldwide; supersedes all older methods

miliary TB—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 patients with miliary TB often looks like millet seeds scattered throughout the lung

mono-resistant TB—TB that is resistant to one TB treatment drug

multidrug-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 opportunistic infections in immunocompromised persons; often disseminated infections

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

***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 since they can cause TB disease or other diseases very similar to TB. *Mycobacterium tuberculosis* is the most common cause of TB in humans; it is sometimes called the tubercle bacillus.

nontuberculous mycobacteria— mycobacteria that do not cause TB disease and are not usually spread from person to person; one example is *M. avium*-complex

pathogenesis—how an infection or disease develops in the body

poly-resistant TB—TB that is resistant to at least two TB treatment drugs (but not both isoniazid and rifampin, i.e., it is not the same as MDR TB)

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 cases.

QuantiFERON®-TB Gold In-Tube test (QFT-GIT)—a blood test used to determine TB infection. The QFT-GIT measures the response to simulated TB proteins when they are mixed with a small amount of blood.

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, which is released by breaking rocks or is used in the production of glass and ceramics; occurs most often in mining, construction, and foundry workers

T-SPOT®.*TB* Test (T-Spot)—a blood test used to determine TB infection; the T-Spot measures the number of T cells that have been activated by simulated *M. tuberculosis* antigens

transmission—the spread of an organism, such as *M. tuberculosis*, from one person to another. 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.

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

x-ray—a test that produces images of the inside the body. X-ray beams pass through the body and are absorbed in different amounts depending on the density of the material they pass through. Dense materials, such as bone, show up as white on x-rays. Air in the lungs shows up as black. Fat and muscle appear as varying shades of gray.

History of TB

TB has affected humans for centuries. Until the 1940s and 1950s, there was no antibiotic treatment for TB.

Tuberculosis—a disease also historically known as consumption, wasting disease, and the white plague—has affected humans for centuries. Until the mid-1800s, people thought that tuberculosis, or TB, was hereditary or attributable to an unhealthy life. They did not realize that it could be spread from person to person through the air. Also, until the 1940s and 1950s, there was no antibiotic treatment for TB. For many people, a diagnosis of TB was a slow death sentence.

Until the 1950s, many people with TB were sent to sanatoriums, special rest homes where they followed a prescribed routine every day.

In 1865 a French surgeon, Jean-Antoine Villemin, showed that TB was contagious, and in 1882 a German scientist named Robert Koch discovered the bacterium that causes TB. Yet, half a century passed before drugs were discovered that could treat TB. Until then, many people with TB were sent to sanatoriums, special rest homes where they followed a prescribed routine every day. No one knows whether sanatoriums really helped people with TB; even if they did, many people with TB could not afford to go to a sanatorium, and they died at home.

In the 1940s and 1950s, drugs were discovered to treat TB. After this, the death rate for TB in the United States dropped dramatically, and fewer and fewer people died from TB.

A breakthrough came in 1943. An American scientist, Selman Waksman and one of his assistants, Albert Schatz, discovered a drug that could kill TB bacteria. Between 1943 and 1952, two more drugs were found. After these discoveries, many people with TB were treated, and the death rate for TB in the United States dropped dramatically. Each year, fewer and fewer people died from TB.

By the mid-1970s, most TB sanatoriums in the United States had closed. As cases and deaths declined, people began to hope that TB could be eliminated from the United States, like polio and smallpox.

In the mid-1980s, the number of TB cases started increasing again.

In the mid-1980s, however, TB cases started increasing again. This rise in cases has been attributed to several factors, which are discussed further in *Module 2, Epidemiology of Tuberculosis*. Because of the rise in TB, federal and state funding for TB control was increased. The increase in funding was used to help health departments and other organizations boost their efforts to prevent and control the disease. These efforts were successful and since 1993, TB cases in the United States overall have been steadily declining. However, prevention and control efforts must

Since 1993, due to enhanced prevention and control efforts, the number of TB cases has been declining.

be maintained, since TB continues to be reported in every state throughout the country. Moreover, even today, TB can be fatal if not treated in time. A timeline of major events in the history of TB is shown in Figure 1.1.

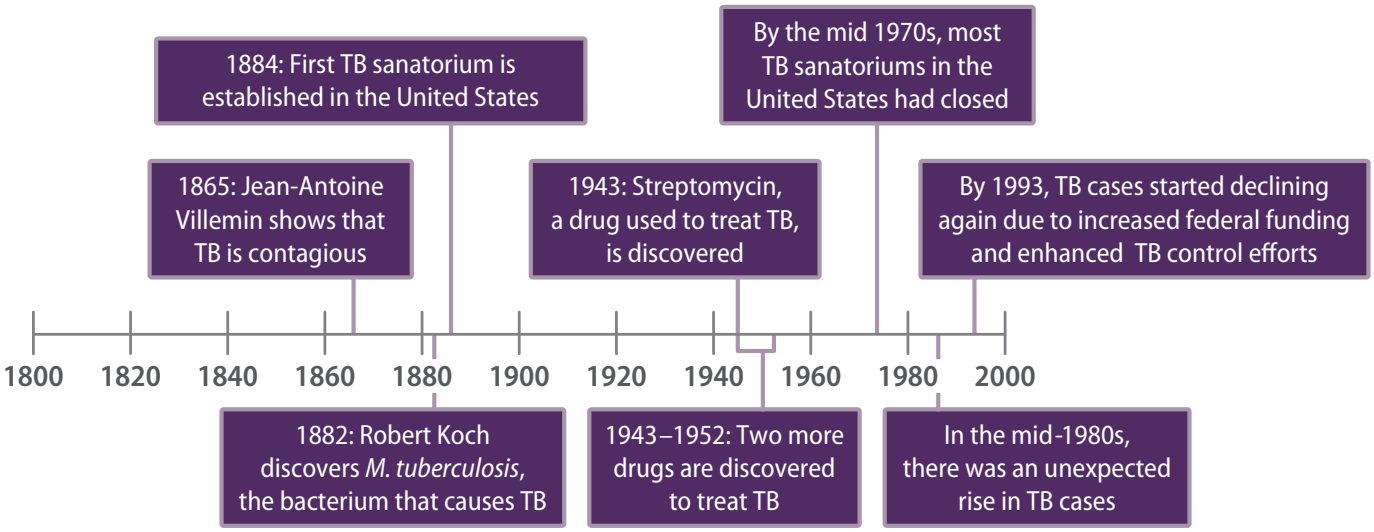


Figure 1.1 Timeline of major events in the history of TB.

Study Question 1.1

1.1 In what year was each of the following discoveries made?

a. TB was shown to be contagious _____

b. The bacterium that causes TB was discovered _____

c. The first drug that could kill TB bacteria was discovered _____

Answers to study questions are on pages 26–29

Transmission

TB is caused by an organism called Mycobacterium tuberculosis.

Mycobacteria are a group of bacteria that can cause a variety of diseases. Some mycobacteria are grouped as ***Mycobacterium tuberculosis* complex** because they cause TB or diseases similar to TB. In the United States the vast majority of TB cases are caused by an organism called ***Mycobacterium tuberculosis***. *M. tuberculosis* organisms are also called tubercle bacilli. Other mycobacteria that can cause human tuberculosis disease include ***M. bovis, M. africanum***, ***M. microti***, and ***M. canetti***.

Mycobacteria that cause diseases that can be confused with TB are often called **nontuberculous mycobacteria**. Nontuberculous mycobacteria can also confuse laboratory tests for TB (for more information on tests used to diagnose TB, refer to *Module 3, Targeted Testing and the Diagnosis of Latent Tuberculosis Infection and Tuberculosis Disease*). One common type of nontuberculous mycobacteria is the ***M. avium*-complex**. Nontuberculous mycobacteria are not usually spread from person to person.

TB is spread from person to person through the air.

TB is spread from **person to person** through the air. When a person with **infectious** TB disease (TB that can be spread) coughs, sneezes, speaks, or sings, tiny particles containing *M. tuberculosis* may be expelled into the air. These particles, called **droplet nuclei**, are about 1 to 5 microns in diameter—less than 1/5000 of an inch. Droplet nuclei can remain suspended in the air for several hours, depending on the environment.

Transmission is the spread of an organism such as M. tuberculosis *from one person to another.*

If another person inhales air that contains these droplet nuclei, infection may result from this **transmission**. Transmission is the spread of an organism such as *M. tuberculosis* from one person to another.

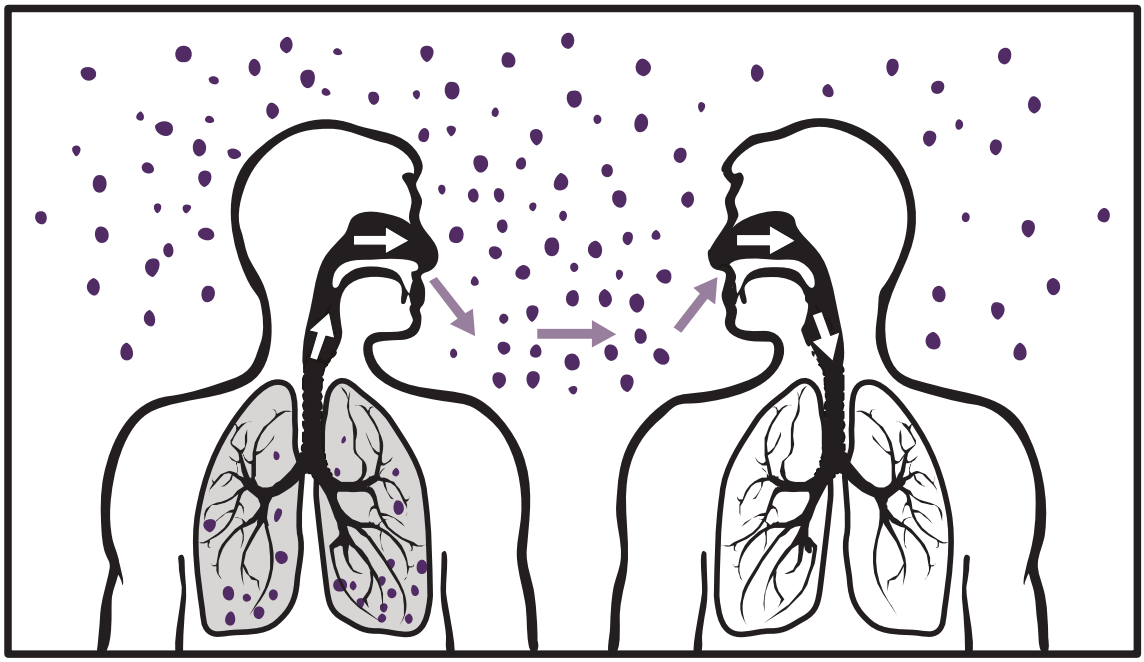


Figure 1.2 Transmission of TB. TB is spread from person to person through the air. The dots in the air represent droplet nuclei containing tubercle bacilli.

Not everyone who is exposed to an infectious TB patient becomes infected.

Not everyone who is exposed to an infectious TB patient becomes infected with *M. tuberculosis*. The probability that TB will be transmitted depends on four factors:

- Infectiousness of the TB patient
- Environment in which the exposure occurred
- Frequency and duration of the exposure
- Susceptibility (immune status) of the exposed individual

Persons who spend a lot of time in enclosed spaces with people who have infectious TB disease are the most likely to be infected with *M. tuberculosis*. These persons, or contacts, may include family members, friends, roommates, or coworkers. Refer to *Module 8, Contact Investigations for Tuberculosis*, for more information on contact investigations.

The best way to stop transmission is to isolate infectious persons and to start giving them the standard TB treatment as soon as possible.

The best way to stop transmission is to isolate infectious persons and to start giving them the standard TB treatment as soon as possible. The length of time required for a TB patient to become noninfectious after starting TB therapy varies and cannot be determined with certainty. However, once the standard TB therapy is started, and as long as the patient follows the prescribed treatment regimen, the infectiousness of the TB patient can rapidly decline. For more information on infectiousness, refer to *Module 5, Infectiousness and Infection Control*.

Drug-resistant TB

Drug-resistant TB is caused by *M. tuberculosis* organisms that are resistant to the drugs normally used to treat the disease. This means those drugs can no longer kill the bacteria.

Drug-resistant TB is caused by M. tuberculosis *organisms that are resistant to the drugs normally used to treat the disease.*

Drug-resistant TB can be **mono-resistant** if the tubercle bacilli are resistant to any one TB treatment drug, or **poly-resistant** if resistant to at least two TB drugs (but not both isoniazid and rifampin). A patient is diagnosed with **multidrug-resistant TB (MDR TB)** if the tubercle bacilli are resistant to at least isoniazid and rifampin, the two best **first-line TB treatment drugs**. A patient is diagnosed with **extensively drug-resistant TB (XDR TB)** if the tubercle bacilli are resistant to isoniazid and rifampin, plus resistant to any fluoroquinolone and at least one of three injectable anti-TB drugs (such as amikacin, kanamycin, or capreomycin).

Drug-resistant TB can be transmitted in the same way as drug-susceptible TB. However, drug-resistant TB is more difficult to treat because the bacilli can survive in a patient's body even after treatment with the first-line drugs is started*. Also, it may take longer to diagnose drug-resistant TB. These patients may be infectious for a longer period of time. This may result in more people being infected.

Drug-resistant TB can be caused in two different ways: **primary** and **secondary** (acquired). Primary resistance is caused by person-to-person transmission of drug-resistant organisms. Secondary resistance develops during TB treatment, either because the patient was not treated with an appropriate regimen or because the patient did not follow the treatment regimen as prescribed. In other words, if patients do not take all of their pills, or if they do not take their pills as often as prescribed, they could develop secondary drug-resistant TB. Patients with TB should be closely monitored to see if they are responding to treatment and they should remain in isolation until it is shown that they are no longer infectious.

Diagnosis and treatment of drug-resistant TB is discussed in more detail in *Module 3, Targeted Testing and the Diagnosis of Latent Tuberculosis Infection and Tuberculosis Disease* and *Module 4, Treatment of Latent Tuberculosis Infection and Tuberculosis Disease*.

Infectiousness and the transmission of TB is discussed in more detail in *Module 5, Infectiousness and Infection Control*.

* Drug-susceptible TB can be treated with the first-line TB treatment drugs.

Study Questions 1.2–1.6

1.2 What organism causes TB? What are four other tuberculous mycobacteria?

1.3 How is TB spread?

1.4 The probability that TB will be transmitted depends on what four factors?

1.5 What is drug-resistant TB?

1.6 What is the difference between primary and secondary drug resistance?

Answers to study questions are on pages 26–29

Pathogenesis

Infection may begin when droplet nuclei reach the alveoli.

When a person inhales air that contains droplet nuclei containing *M. tuberculosis*, most of the larger droplets become lodged in the upper respiratory tract (the nose and throat), where infection is unlikely to develop. However, smaller droplet nuclei may reach the small air sacs of the lung (the **alveoli**), where infection may begin (Figure 1.3). The following section describes the **pathogenesis** of TB (the way TB infection and disease develop in the body).

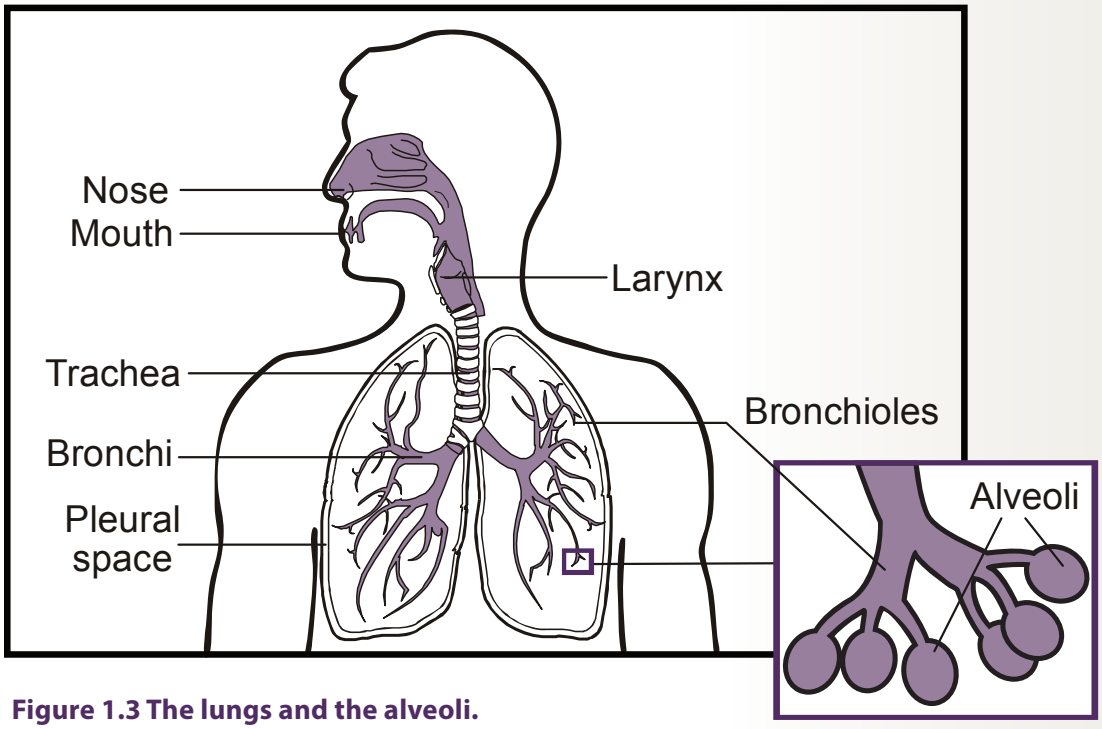


Figure 1.3 The lungs and the alveoli.

In the alveoli, some of the tubercle bacilli are killed, but a few multiply in the alveoli and enter the lymph nodes and bloodstream and spread throughout the body. Bacilli may reach any part of the body, including areas where TB disease is more likely to develop. These areas include the upper portions of the lungs, as well as the kidneys, the brain, and bone. Within 2 to 8 weeks, however, the body's immune system usually intervenes, halting multiplication and preventing further spread. The **immune system** is the system of cells and tissues in the body that protect the body from foreign substances. At this point, the person has **latent TB infection (LTBI)**.

Latent TB Infection (LTBI)

LTBI means that tubercle bacilli are in the body, but the body's immune system is keeping the bacilli under control.

Latent TB infection (LTBI) means that tubercle bacilli are in the body, but the body's immune system is keeping the bacilli under control. The immune system does this by producing special immune cells that surround the tubercle bacilli. The cells form a shell that acts as a barrier and keeps the bacilli contained.

LTBI is detected by the tuberculin skin test (TST) or an interferon-gamma release assay (IGRA).

LTBI is detected by the **Mantoux tuberculin skin test (TST)** or an **interferon-gamma release assay (IGRA)** such as the **QuantiFERON®-TB Gold In-Tube (QFT-GIT) test** or the **T-SPOT®.*TB* test (T-Spot)**. Most people with LTBI have a positive TST or IGRA result. *Module 3, Targeted Testing and the Diagnosis of Latent Tuberculosis Infection and Tuberculosis Disease*, discusses the TST and IGRAs in more detail.

People with LTBI are NOT contagious.

People who have LTBI, but not TB disease, are **NOT** contagious—in other words, they cannot spread the infection to other people. Most of these people have a normal chest **x-ray**. It is important to remember that LTBI is not considered a case of TB. Major similarities and differences between LTBI and TB disease are shown in Table 1.1.

Table 1.1— LTBI vs. TB Disease.

Person with Latent TB Infection (LTBI)	Person with TB Disease (in the lungs)
▪ Has a small number of TB bacteria in his or her body that are alive, but under control	▪ Has a large number of **active** TB bacteria in his or her body
▪ **Cannot** spread TB bacteria to others	▪ May spread TB bacteria to others
▪ Does **not** feel sick, but may become sick if the bacteria become active in his or her body	▪ May feel sick and may have symptoms such as a cough, fever, or weight loss
▪ Tuberculin skin test or interferon-gamma release assay results usually positive	▪ Tuberculin skin test or interferon-gamma release assay results usually positive
▪ Chest x-ray usually **normal**	▪ Chest x-ray usually **abnormal**
▪ Sputum smears and cultures **negative**	▪ Sputum smears and cultures may be **positive**
▪ Should consider treatment for LTBI to prevent TB disease	▪ Needs treatment for TB disease
▪ **Does not** require respiratory isolation	▪ May require respiratory isolation
▪ **Not a case** of TB	▪ **A case** of TB

Study Questions 1.7–1.9

1.7 When a person inhales droplet nuclei containing *M. tuberculosis*, where do the droplet nuclei go?

1.8 After the tubercle bacilli reach the small air sacs of the lung (the alveoli), what happens to the tubercle bacilli?

1.9 In people with LTBI (but not TB disease), how does the immune system keep the tubercle bacilli under control?

Answers to study questions are on pages 26–29

Study Questions 1.10–1.11

1.10 How is LTBI detected?

1.11 What are the major similarities and differences between LTBI and TB disease? List characteristics of each.

Answers to study questions are on pages 26–29

Case Study 1.1

A 30-year-old man visits the health department for a TST because he is required to have one before starting his new job as a health care worker. He has an 18 mm positive reaction to the TST. He has no symptoms of TB, and his chest x-ray findings are normal.

Should this be considered a case of TB?

Should this man be considered infectious?

Answers to case studies are on page 30

TB Disease

TB disease develops when the immune system cannot keep the tubercle bacilli under control and the bacilli begin to multiply rapidly.

Some people with LTBI develop TB disease later. TB disease develops when the immune system cannot keep the tubercle bacilli under control and the bacilli begin to multiply rapidly. The risk that TB disease will develop is higher for some people than for others. The pathogenesis of LTBI and TB disease is shown in Figure 1.4.

TB disease can develop very soon after infection or many years after infection.

TB disease can develop very soon after infection or many years after infection. In the United States, unless treated, about 5% of the people who have recently been infected with *M. tuberculosis* will develop TB disease in the first year or two after infection. Another 5% will develop TB disease later in their lives. In other words, **about 10% of all people with normal immune systems who have LTBI will develop TB disease at some point in their lives.** The remaining 90% will remain free of disease for the rest of their lives (Figure 1.5). However, some conditions can greatly increase the risk of developing TB disease.

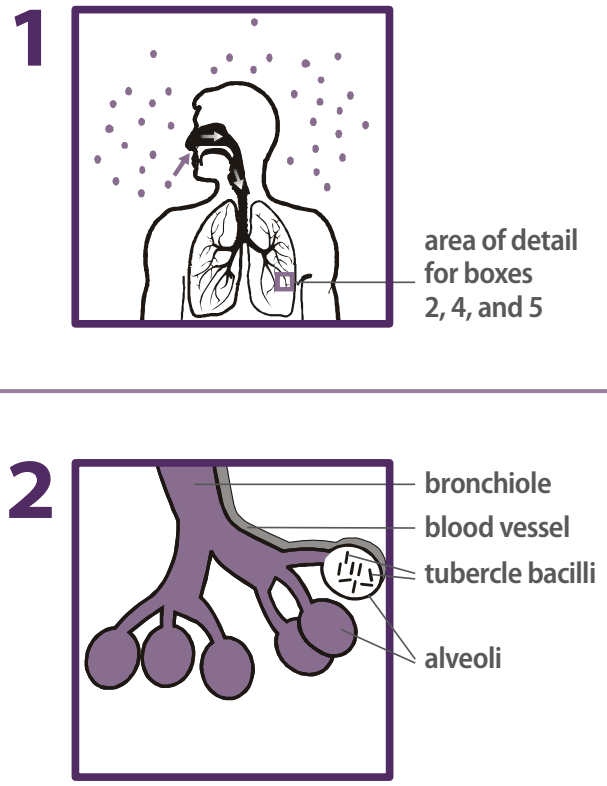


Figure 1.4 Pathogenesis of LTBI and TB disease.

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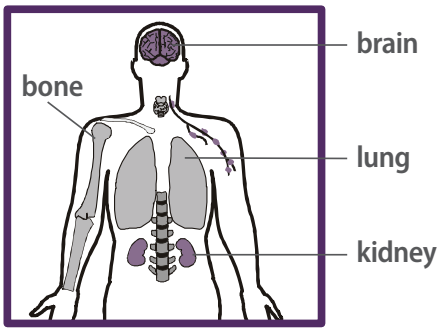

A small number of tubercle bacilli enter the lymph nodes and bloodstream and spread throughout the body. The tubercle bacilli may reach any part of the body, including areas where TB disease is more likely to develop (such as the lungs, kidneys, brain, or bone).

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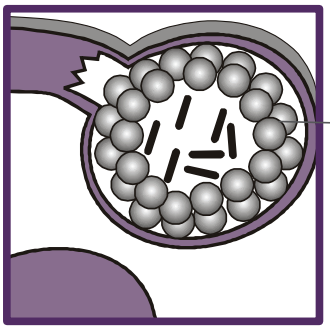
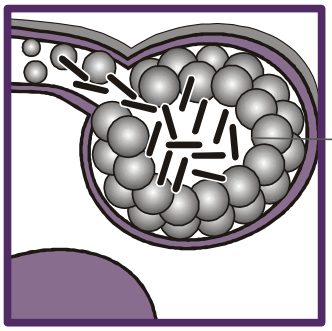


special immune cells form a barrier shell (in this example, bacilli are in the lungs)

Within 2 to 8 weeks, the immune system produces special immune cells called macrophages that surround the tubercle bacilli. The cells form a barrier shell that keeps the bacilli contained and under control (LTBI).

5



shell breaks down and tubercle bacilli escape and multiply (in this example, TB disease develops in the lungs)

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 places in the body, such as the lungs, kidneys, brain, or bones (see diagram in box 3).

Figure 1.4 Pathogenesis of LTBI and TB disease (continued).

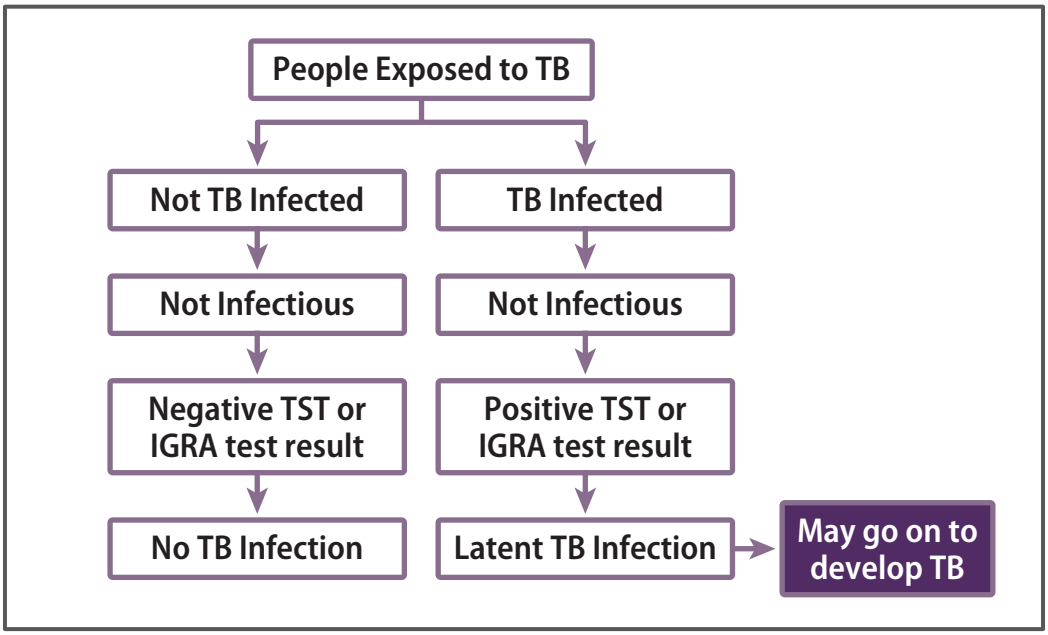


Figure 1.5 Progression of TB. People who are exposed to TB may or may not become infected. People with LTBI may or may not develop TB disease later.

The risk of developing TB disease is highest in the first 2 years after infection.

Because about half the risk of developing TB disease is concentrated in the first 2 years after infection, it is important to detect new infection early. People with LTBI can be given treatment to prevent them from getting sick with TB disease. This is discussed in *Module 4, Treatment of Latent Tuberculosis Infection and Tuberculosis Disease*. Thus, detecting new infection early helps prevent new cases of TB. Table 1.1 shows the major similarities and differences between LTBI and TB disease.

Some conditions increase the risk that LTBI will progress to disease.

Some conditions increase the risk that LTBI will progress to disease. The risk may be about 3 times higher (as with diabetes) to more than 100 times higher (as with **human immunodeficiency virus** [HIV] infection) for people who have these conditions than for those who do not. Some of these conditions that increase the risk are

- Infection with HIV
- History of untreated or inadequately treated TB disease
- Recent TB infection (within the past 2 years)
- Abusing drugs or alcohol or smoking cigarettes
- 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

- **Silicosis**
- **Diabetes mellitus**
- Chronic renal failure
- Certain types of cancer (e.g., leukemia, cancer of the head, neck, or lung)
- Certain intestinal conditions
- Low body weight

For definitions of some of these terms, please see the *Modules 1–5 Glossary* or the New Terms section at the beginning of this module.

Transmission and Pathogenesis of TB

People who are infected with both M. tuberculosis *and HIV are much more likely to develop TB disease than people who are infected only with* M. tuberculosis.

When the immune system is weakened, the body may not be able to control the multiplication and spread of tubercle bacilli. For this reason, people who are infected with both *M. tuberculosis* and HIV are much more likely to develop TB disease than people who are infected only with *M. tuberculosis*. The risk of developing TB disease is 7% to 10% **each year** for people who are infected with both *M. tuberculosis* and HIV (if the HIV is not being treated), whereas it is 10% **over a lifetime** for people infected only with *M. tuberculosis*. For people with LTBI and diabetes, the risk is 3 times greater, or about 30% over a lifetime (Figure 1.6).

In an HIV-infected person, TB disease can develop in two ways. First, a person with LTBI can become infected with HIV and then develop TB disease as the immune system is weakened. Second, a person who has HIV infection can become infected with *M. tuberculosis* and then rapidly develop TB disease.

TB infection and no risk factors (about 10% over a lifetime)	**TB infection and diabetes** (about 30% over a lifetime)	**TB infection and HIV infection** (a very large risk over a lifetime)
For people with TB infection and **no risk factors**, the risk is about 5% in the first 2 years after infection and about 10% over a lifetime.	For people with TB infection and **diabetes**, the risk is 3 times greater, or about 30% over a lifetime.	For people with TB infection and **HIV infection (not on HIV treatment)**, the risk is about 7% to 10% PER YEAR, a very large risk over a lifetime.

Figure 1.6 Risk of developing TB disease over a lifetime.

Study Questions 1.12–1.15

1.12 What happens if the immune system cannot keep the tubercle bacilli under control and the bacilli begin to multiply rapidly?

1.13 What percentage of people with LTBI (but not HIV infection) usually develop TB disease?

1.14 What conditions increase the risk that LTBI will progress to disease?

1.15 How does being infected with both *M. tuberculosis* and HIV affect the risk for TB disease?

Answers to study questions are on pages 26–29

Case Study 1.2

A 45-year-old woman is referred to the health department by her private physician because she was found to have LTBI as part of an employee testing program. She is overweight, with high blood pressure. Upon further questioning, she reports that she has injected illegal drugs in the past, but has never been tested for HIV infection.

What conditions does this woman have that increase the risk that she will develop TB disease?

Answers to case studies are on page 30

Sites of TB Disease

Pulmonary TB occurs in the lungs.

TB disease can occur in different places in the body and in more than one place at the same time (Figure 1.7). **Pulmonary TB** is TB that occurs in the lungs. Most TB cases are pulmonary. Most patients with pulmonary TB have a cough and an abnormal chest x-ray, and they should be considered contagious until they meet certain criteria (see *Module 5, Infectiousness and Infection Control*).

Extrapulmonary TB occurs in places other than the lungs.

Extrapulmonary TB occurs in places other than the lungs, such as the larynx, the lymph nodes, the pleura (the membrane surrounding each lung), the brain, the kidneys, or the bones and joints. Extrapulmonary TB occurs more often in HIV-infected or other immunosuppressed persons, or young children. Some patients who have extrapulmonary TB also have pulmonary TB.

Most types of extrapulmonary TB are not considered contagious (this will be discussed in *Module 5, Infectiousness and Infection Control*). However, extrapulmonary TB is often accompanied by pulmonary TB, which could be contagious. Of note, extrapulmonary TB that occurs in the larynx should be considered contagious.

Disseminated TB 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.

Disseminated TB 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. **Miliary TB** is a type of disseminated TB. This condition is rare, but life threatening. It is called miliary TB because the chest x-ray has the appearance of millet seeds scattered throughout the lung.

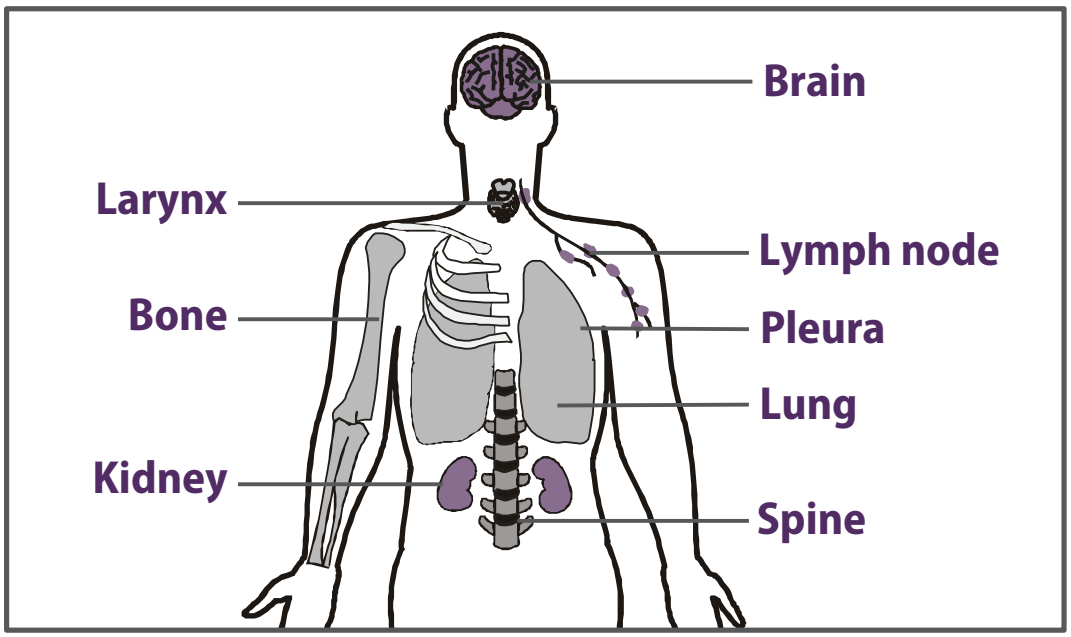


Figure 1.7 Common sites of TB disease.

Classification System

The current classification system is based on the pathogenesis of TB.

Many systems have been used by health departments and private health care providers to classify various TB conditions. The current classification system, sometimes referred to as the American Thoracic Society (ATS) classification system (Table 1.2), is based on the pathogenesis of TB. Thus, it is important for public health workers to be familiar with this system. In particular, public health workers should be aware that any patient with a classification of 3 or 5 should be receiving treatment for TB and should be reported promptly to the local or state health department.

Table 1.2 - Classification System for TB.

Class	Type	Description
0	No TB exposure Not infected	No history of TB exposure Negative result to a TST or to an IGRA
1	TB exposure No evidence of infection	History of TB exposure Negative result to a TST or to an IGRA (done at least 8 to 10 weeks after exposure)
2	TB infection No TB disease	Positive result to a TST or to an IGRA Negative smears, molecular tests, and cultures No clinical or x-ray evidence of active TB disease
3	TB, clinically active	Positive culture for *M. tuberculosis* OR Positive result to a TST or to an IGRA, and clinical, bacteriological, or x-ray evidence of current active TB disease
4	Previous TB disease (not clinically active)	Medical history of TB disease Abnormal but stable x-ray findings Positive result to a TST or to an IGRA Negative smears, molecular tests, and cultures (if done) No clinical or x-ray evidence of current TB disease
5	TB suspected	Signs and symptoms of TB disease, but diagnostic evaluation not complete

Study Questions 1.16–1.17

1.16 What part of the body is the most common site for TB disease? What are some other common sites?

1.17 What is the classification system for TB based on? What is it used for?

Answers to study questions are on pages 26–29

Additional Resources

1. Bates B. Bargaining for Life: A Social History for Tuberculosis, 1876–1938. Philadelphia: University of Pennsylvania Press; 1992.
2. CDC. Core Curriculum on Tuberculosis: What the Clinician Should Know, Sixth Edition. Atlanta, GA: Department of Health and Human Services, CDC; 2013. www.cdc.gov/tb/education/corecurr/index.htm.
3. CDC. Extensively Drug-Resistant Tuberculosis—United States, 1993–2006. MMWR 2007; 56 (11): 250–253. www.cdc.gov/mmwr/preview/mmwrhtml/mm5611a3.htm.
4. CDC. Plan to Combat Extensively Drug-Resistant Tuberculosis. MMWR 2009; 58 (RR-03): 1–43. www.cdc.gov/mmwr/preview/mmwrhtml/rr5803a1.htm?s_cid=rr5803a1_e.
5. CDC. Tuberculosis Associated with Blocking Agents Against Tumor Necrosis Factor-Alpha—California, 2002–2003. The Americas, 2004. MMWR 2004; 53 (30): 683-686. www.cdc.gov/mmwr/preview/mmwrhtml/mm5330a4.htm.
6. DuBos R, DuBos J. The White Plague: Tuberculosis, Man, and Society. New Brunswick, NJ: Rutgers University Press; 1987.
7. Ryan F. The Forgotten Plague: How the Battle Against Tuberculosis Was Won—And Lost. Boston: Little, Brown and Co; 1992.

Answers to Study Questions

1.1 In what year was each of the following discoveries made?

a. TB was shown to be contagious 1865

b. The bacterium that causes TB was discovered 1882

c. The first drug that could kill TB bacteria was discovered 1943

1.2 What organism causes TB? What are four other tuberculous mycobacteria?

TB is caused by an organism called *Mycobacterium tuberculosis*. *M. bovis, M. africanum, M. microti,* and *M. canetti* are four other tuberculous mycobacteria.

1.3 How is TB spread?

TB is spread from person to person through the air. When a person with infectious TB disease coughs, sneezes, speaks, or sings, tiny particles containing *M. tuberculosis* may be expelled into the air. These particles, called droplet nuclei, are about 1 to 5 microns in diameter—less than 1/5000 of an inch. Droplet nuclei can remain suspended in the air for several hours, depending on the environment.

1.4 The probability that TB will be transmitted depends on what four factors?

- Infectiousness of the TB patient
- Environment in which the exposure occurred
- Frequency and duration of the exposure
- Susceptibility (immune status) of the exposed individual

1.5 What is drug-resistant TB?

Drug-resistant TB is caused by *M. tuberculosis* organisms that are resistant to at least one anti-TB drug. Drug-resistant TB can be difficult to treat.

1.6 What is the difference between primary and secondary drug resistance?

Primary resistance is caused by person-to-person transmission of drug-resistant organisms. Secondary resistance develops during TB treatment. Either the patient was not treated with the right TB drugs or the patient did not properly follow the prescribed treatment regimen.

1.7 When a person inhales droplet nuclei containing *M. tuberculosis*, where do the droplet nuclei go?

Most of the larger droplets become lodged in the upper respiratory tract, where infection is unlikely to develop. However, the droplet nuclei may reach the small air sacs of the lung (the alveoli), where infection may begin.

Answers to Study Questions, Continued

1.8 After the tubercle bacilli reach the small air sacs of the lung (the alveoli), what happens to the tubercle bacilli?

At first, the tubercle bacilli multiply in the alveoli and a small number enter the lymph nodes and bloodstream and spread throughout the body. Bacilli may reach any part of the body, including areas where TB disease is more likely to develop. These areas include the upper portions of the lungs, as well as the kidneys, the brain, and bone. Within 2 to 8 weeks, however, the body's immune system intervenes, halting multiplication and preventing further spread in most persons.

1.9 In people with LTBI (but not TB disease), how does the immune system keep the tubercle bacilli under control?

The immune system produces special immune cells that surround the tubercle bacilli. The cells form a barrier shell that keeps the bacilli contained and under control.

1.10 How is LTBI detected?

LTBI is detected by the Mantoux tuberculin skin test (TST) or an interferon-gamma release assay (IGRA) such as the QuantiFERON®-TB Gold In-Tube (QFT-GIT) test or the T-SPOT®. *TB* test (T-Spot).

1.11 What are the major similarities and differences between LTBI and TB disease? List characteristics of each.

LTBI

- Tubercle bacilli are in the body, but under control.
- The TST and IGRA results are usually positive.
- Usually the chest x-ray is normal.
- Sputum smears (or smears from other specimens), molecular tests, and cultures are negative.
- People with LTBI
  - Do not have symptoms (are not sick)
  - Are not infectious
  - Are not counted as having a case of TB

Answers to Study Questions, Continued

TB disease

- Tubercle bacilli are active in the body.
- The TST and IGRA results are usually positive.
- Usually the chest x-ray is abnormal (if the disease is in the lungs).
- Sputum smears (or smears from other specimens), molecular tests, cultures, or a combination of these tests may be positive for *M. tuberculosis*.
- People with TB disease
  - May have symptoms (are sick)
  - May spread TB bacteria to others
  - Are counted as having a case of TB

1.12 What happens if the immune system cannot keep the tubercle bacilli under control and the bacilli begin to multiply rapidly?

When this happens, TB disease develops. The risk that TB disease will develop is higher for some people than for others.

1.13 What percentage of people who have LTBI (but not HIV infection) usually develop TB disease?

In the United States, about 5% of the people who have recently been infected with *M. tuberculosis* will develop TB disease in the first year or two after infection. Another 5% will develop disease later in their lives. In other words, about 10% of all people who have LTBI will develop disease at some point. The remaining 90% will remain free of disease for the rest of their lives.

1.14 What conditions increase the risk that LTBI will progress to disease?

- Infection with HIV
- History of untreated or inadequately treated TB disease
- Recent TB infection (within the past 2 years)
- Abusing drugs or alcohol or smoking cigarettes
- 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
- Silicosis
- Diabetes mellitus

Answers to Study Questions, Continued

- Chronic renal failure
- Certain types of cancer (e.g., leukemia, cancer of the head, neck, or lung)
- Certain intestinal conditions
- Low body weight

1.15 How does being infected with both *M. tuberculosis* and HIV affect the risk for TB disease?

Because their immune systems are weakened, people who are infected with both *M. tuberculosis* and HIV are much more likely to develop TB disease than people who are infected only with *M. tuberculosis*. Studies suggest that the risk of developing TB disease is 7% to 10% each year for people who are infected with both *M. tuberculosis* and HIV (if the HIV is not treated), whereas it is 10% over a lifetime for people infected only with *M. tuberculosis*.

In an HIV-infected person, TB disease can develop in two ways. First, a person with LTBI can become infected with HIV and then develop TB disease as the immune system is weakened. Second, a person who has HIV infection can become infected with *M. tuberculosis* and then rapidly develop TB disease.

1.16 What part of the body is the most common site for TB disease? What are some other common sites?

The lungs are the most common site for TB disease. Other common sites include:

- Larynx
- Lymph nodes
- Pleura (the membrane surrounding the lungs)
- Brain
- Kidneys
- Bones and joints

1.17 What is the classification system for TB based on? What is it used for?

The current classification system is based on the pathogenesis of TB. Many health departments and private health care providers use this system when describing patients.

Case Study Answers

1.1 A 30-year-old man visits the health department for a TST because he is required to have one before starting his new job as a health care worker. He has an 18 mm positive reaction to the TST. He has no symptoms of TB, and his chest x-ray findings are normal.

Should this be considered a case of TB?

No. The man described above has latent TB infection. He has an 18 mm positive reaction to TST, but no evidence of TB disease. Therefore, this is not a case of TB.

Should this man be considered infectious?

No, he should not be considered infectious. This man has LTBI, not TB disease. People with TB infection and no evidence of TB disease are not infectious.

1.2 A 45-year-old woman is referred to the health department by her private physician because she was found to have LTBI as part of an employee testing program. She is overweight, with high blood pressure. Upon further questioning, she reports that she has injected illegal drugs in the past, but has never been tested for HIV infection.

What conditions does this woman have that increase the risk that she will develop TB disease?

Drug abuse increases the risk that LTBI will progress to TB disease. This woman may also be at risk for HIV infection because of her injection drug use. HIV is the strongest known risk factor for developing TB disease. This woman should be offered HIV counseling, testing, and referral. Overweight and high blood pressure are NOT risk factors for TB disease.

Notes

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