Professor Lester's BIOL 210
Self-Study Module on Tuberculosis
(Adapted from the CDC)

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.

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.

You will study this packet on TB. Highlight important information, take notes, and come prepared to answer specific questions using this information. You will be required to work individually. You will not have time to answer all of the questions in class unless you have studied this packet first.

NEW TERMS

Look for the following new terms in this module and in the glossary.

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 or certain allergies

diabetes mellitus – a disease in which the body's ability to use sugar is weakened

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 injection – using a needle and syringe to inject drugs into the body

drug-resistant TB –TB caused by organisms that are able to grow in the presence of a particular drug; TB that is resistant to at least one first-line antituberculosis drug

extensively drug resistant TB (XDR TB) – a rare type of MDR TB that is resistant to isoniazid and rifampin, plus resistant to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., 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

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 U.S., QuantiFERON®-TB Gold and QuantiFERON®-TB Gold In-Tube are currently available IGRAs

latent TB infection (LTBI) – refers to the condition when a person is infected with tubercle bacilli but has not developed TB disease. Persons with LTBI carry the organism that causes TB but do not have TB disease symptoms and they cannot spread TB germs to others. Persons with LTBI usually have a positive result to the Mantoux tuberculin skin test or the QuantiFERON®-TB Gold test

Mantoux tuberculin skin test (TST) – a method of testing for TB infection; a needle and syringe are used to inject 0.1 ml of 5 tuberculin units of liquid tuberculin 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

miliary TB – 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

mycobacterium – a kind of bacterium; mycobacteria can cause a variety of diseases

Mycobacterium africanum – a type of tuberculous mycobacterium, closely related to *M. tuberculosis*, that can cause a disease similar to TB; it is very rare in the United States

Mycobacterium avium **complex** – a common type of nontuberculous mycobacterium that can cause disease in humans

Mycobacterium bovis – a type of tuberculous mycobacterium that can cause a disease similar to TB; usually occurs in cows. 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 canetti – a type of tuberculous mycobacterium that can cause disease in humans

Mycobacterium microti – a type of tuberculous mycobacteria that can cause generalized tuberculosis

Mycobacterium tuberculosis – the organism that causes TB in humans and is sometimes called the tubercle bacillus; belongs to a group of bacteria called mycobacteria

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); but is not MDR TB

primary drug-resistant TB – drug-resistant TB 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 test (QFT-G) – a blood test used to determine TB infection. The QFT-G measures the response to TB proteins when they are mixed with a small amount of blood

secondary drug-resistant TB – also referred to as acquired drug-resistant TB; 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 used in the production of glass and ceramics; occurs most often in mining and foundry workers

transmission – the spread of an organism, such as *M. tuberculosis*, from one person to another; probability of transmission depends on the contagiousness of the patient, the type of environment, the length of exposure, and the virulence or strength of the organism

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** in glossary)

tuberculous mycobacteria – mycobacteria that can cause TB disease or other diseases very similar to TB; the tuberculous mycobacteria include *M. tuberculosis*, *M. bovis*, *M. africanum*, *M. canetti*, and *M. microti*

virulence – refers to the ability of an organism to produce a disease. The virulence (strength) of a bacteria is associated with the severity of the disease

READING MATERIAL

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. 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 often 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, proved 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 got 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 got TB.

By the mid-1970s, most TB sanatoriums in the United States had closed. As cases started to decline, 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.

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

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 be maintained since TB continues to be reported in almost every state throughout the country and not all states have seen a decrease in the number of their TB cases. Moreover, even today, TB can be fatal if not treated. A timeline of major events in the history of TB is shown in Figure 1.1.

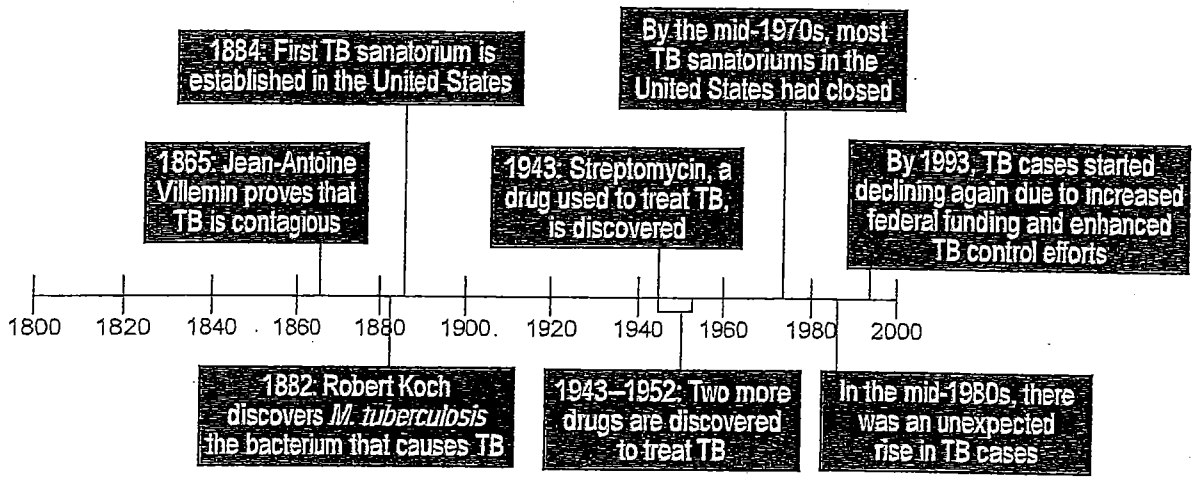


Figure 1.1 Timeline of major events in the history of TB.

Transmission

TB is caused by an organism called *Mycobacterium tuberculosis.*

Mycobacteria are members of the bacteria family. These organisms can cause a variety of diseases. Some mycobacteria are called **tuberculous** 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 tuberculous disease include ***M. bovis, M. africanum, M. microti***, and ***M. canetti.***

Mycobacteria that do not cause TB are often called **nontuberculous mycobacteria**. 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, **transmission** may occur. Transmission is the spread of an organism such as *M. tuberculosis* from one person to another.

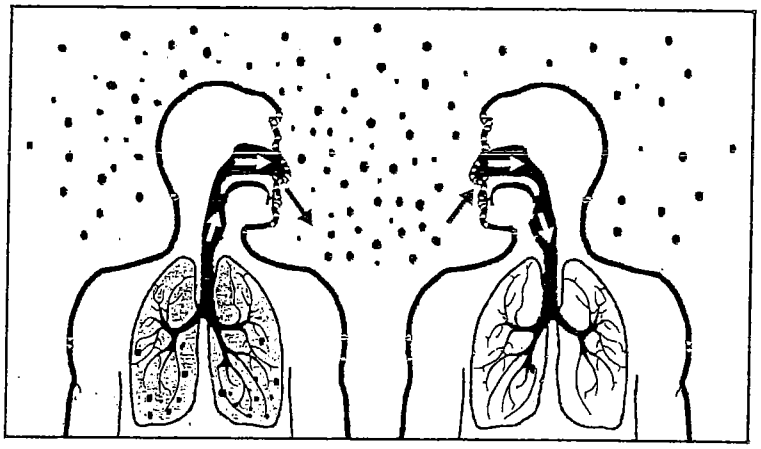


Figure 1.2 Transmission of TB. TB is spread from person to person through the air. The dots in the air represent droplet nuclei containing tubercle bacilli.

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:

- How infectious or contagious is the TB patient?
- In what kind of environment did the exposure occur?
- How long did the exposure last?
- How virulent (strong) are the tubercle bacilli?

Close contacts of TB patients are at highest risk of becoming infected.

Close contacts of TB patients are at highest risk of becoming infected with *M. tuberculosis*. They may be family members, roommates, friends, coworkers, or others. Close contacts are more likely to become infected with *M. tuberculosis* than contacts who spent less time with a person while the person was infectious.

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. 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.

Drug-resistant TB

Drug-resistant TB is caused by *M. tuberculosis* organisms that are resistant to at least one of the first-line TB treatment drugs.

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 can be **mono-resistant** if the tubercule 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 second-line 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 it can survive in a patient's body even after treatment with the first-line drugs is started*. Also, because it takes 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 the appropriate treatment 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 drug-resistant TB should be closely monitored to see if they are responding to treatment; they should remain in isolation until it is shown that they are no longer infectious.

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

Pathogenesis

Infection begins when droplet nuclei reach the alveoli.

When a person inhales air that contains water droplets 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).

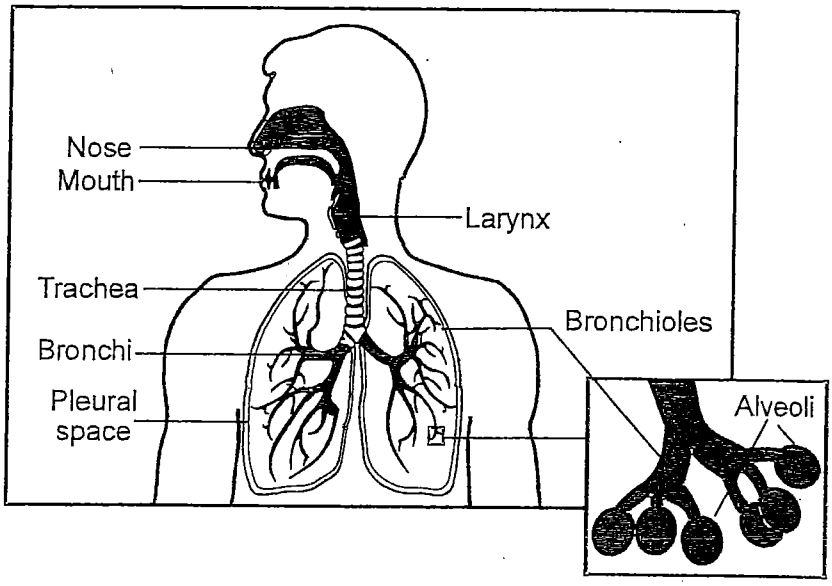


Figure 1.3 The lungs and the alveoli.

In the alveoli, some of the tubercle bacilli are killed, but a few multiply in the alveoli and enter the 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 immune system is keeping them 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 and inactive. The immune system does this by producing special immune cells that surround the tubercle bacilli. The cells form a shell that acts as a fence and keeps the bacilli contained and inactive.

LTBI is detected by the tuberculin skin test or the QuantiFERON®-TB Gold test.

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

People with LTBI are NOT infectious.

People who have LTBI but not TB disease are **NOT infectious** — in other words, they cannot spread the infection to other people. These people usually 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

Latent TB Infection (LTBI)	TB Disease (in the lungs)
Inactive tubercle bacilli in the body	**Active** tubercle bacilli in the body
Tuberculin skin test or QuantiFERON®-TB Gold test results usually positive	Tuberculin skin test or QuantiFERON®-TB Gold test 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**
No symptoms	**Symptoms** such as cough, fever, weight loss
Not infectious	**Often infectious** before treatment
Not a case of TB	**A case** of TB

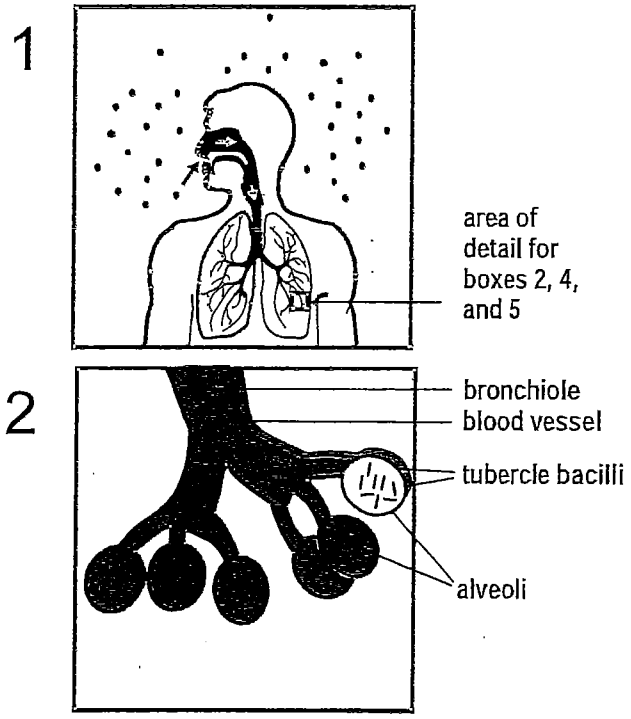
TB Disease

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

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

Some people with LTBI develop TB disease. 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. 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 stay infected, but free of disease, for the rest of their lives (Figure 1.5). However, some conditions can greatly increase the risk of developing TB disease.



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

Tubercle bacilli multiply in the alveoli.

Figure 1.4 Pathogenesis of LTBI and TB disease.

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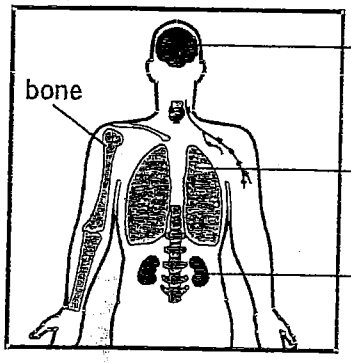

A small number of tubercle bacilli enter the bloodstream and spread throughout the body. The tubercle bacilli may reach any part of the body, including areas where TB disease is more likely to develop (such as the lungs, kidneys, brain, or bone).

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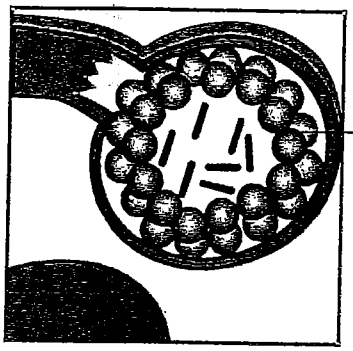

Within 2 to 8 weeks, the immune system produces special immune cells called macrophages that surround the tubercle bacilli. The cells form a barrier shell that keeps the bacilli contained and under control (**LTBI**).

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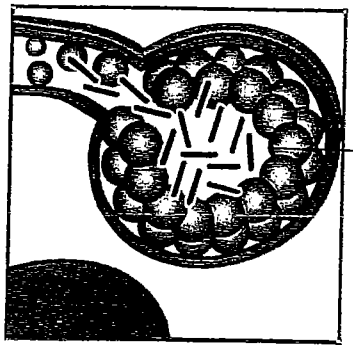


If the immune system cannot keep the tubercle bacilli under control, the bacilli begin to multiply rapidly (**TB disease**). This process can occur in different places in the body, such as the lungs, kidneys, brain, or bone (see diagram in box 3).

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

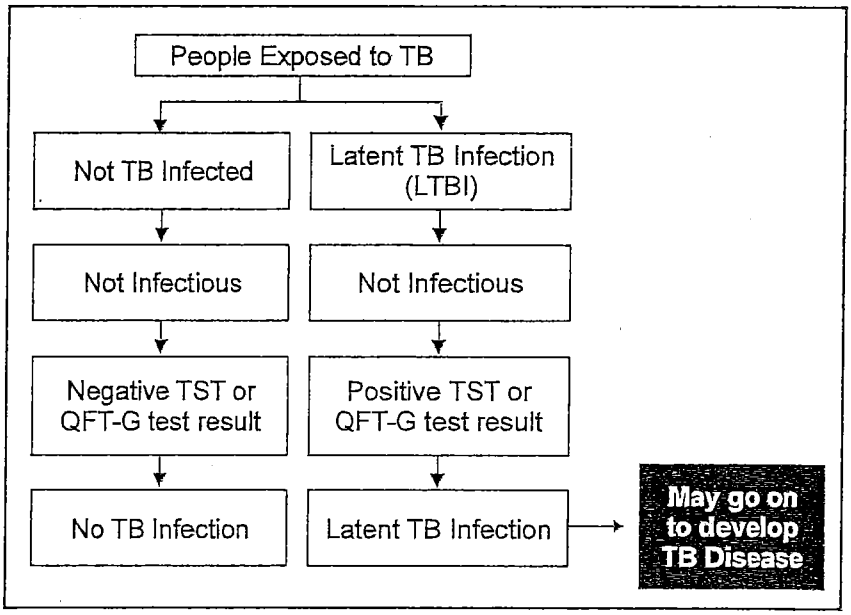


Figure 1.5 Progression of TB. People who are exposed to TB may or may not develop TB infection. People with LTBI may or may not develop TB disease.

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 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
- Chest x-ray findings suggestive of previous TB
- Substance abuse (especially illegal injection drug use)
- Recent TB infection (within the past 2 years)
- Prolonged therapy with corticosteroids and other immunosuppressive therapy, such as prednisone and tumor necrosis factor-alpha [TNF-α] antagonists
- Organ transplant
- Silicosis
- Diabetes mellitus
- Severe kidney disease
- Certain types of cancer (e.g., leukemia, Hodgkin's disease, or cancer of the head and neck)
- Certain intestinal conditions
- Low body weight (10% or more below ideal)

For definitions of some of these terms, please see the 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, 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 as high, or about 30% over a lifetime (Figure 1.6).

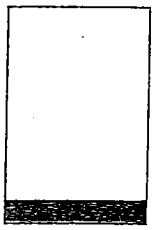
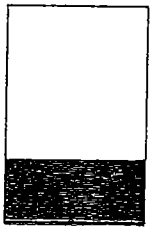
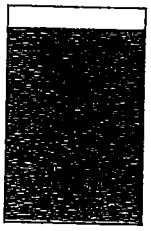
TB infection and no risk factors (about 10% over a lifetime)	TB infection and diabetes (about 30% over a lifetime)	TB infection and HIV infection (a very high risk over a lifetime)
		
For people with TB infection and **no risk factors**, the risk is about 5% in the first 2 years after infection and about 10% over a lifetime.	For people with TB infection and **diabetes**, the risk is 3 times as high, or about 30% over a lifetime.	For people with TB infection and **HIV infection**, the risk is about 7% to 10% PER YEAR, a very high risk over a lifetime.

Figure 1.6 Risk of developing TB disease over a lifetime.

In an HIV-infected person, TB disease can develop in either of 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.