

*Self-Study Modules
on Tuberculosis, 1-5*

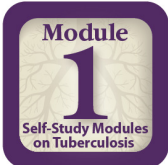
Centers for Disease Control and Prevention
Division of Tuberculosis Elimination
2016

CDC Self-Study Modules on Tuberculosis, 1-5

- **Module 1: Transmission and Pathogenesis of TB**
- **Module 2: Epidemiology of TB**
- **Module 3: Targeted Testing and the Diagnosis of Latent TB Infection and TB Disease**
- **Module 4: Treatment of Latent TB Infection and TB Disease**
- **Module 5: Infectiousness and Infection Control**

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*Self-Study Modules
on Tuberculosis*



Transmission and Pathogenesis of Tuberculosis

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Module 1: Objectives

At completion of this module, learners will be able to

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

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Module 1: Overview

- **History of TB**
- **TB Transmission**
- **Drug-Resistant TB**
- **TB Pathogenesis**
- **Progression from LTBI to TB disease**
- **Sites of TB disease**
- **TB Classification System**
- **Case Studies**

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History of TB

Module 1 – Transmission and Pathogenesis of Tuberculosis 6

History of TB (1)

- TB has affected humans for millennia
- Historically known by a variety of names, including:
 - Consumption
 - Wasting disease
 - White plague
- TB was a death sentence for many



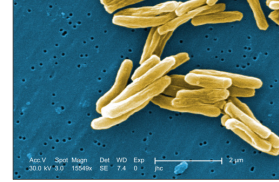
Vintage image circa 1919
Image credit: National Library of Medicine

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History of TB (2) Scientific Discoveries in 1800s

- Until mid-1800s, many believed TB was hereditary
- 1865 Jean Antoine-Villemin showed TB was contagious
- 1882 Robert Koch discovered *M. tuberculosis*, the bacterium that causes TB



Mycobacterium tuberculosis
Image credit: Janice Haney Carr

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History of TB (3) Sanatoriums

- Before TB antibiotics, many patients were sent to sanatoriums
- Patients followed a regimen of bed rest, open air, and sunshine
- TB patients who could not afford sanatoriums often died at home



Sanatorium patients resting outside

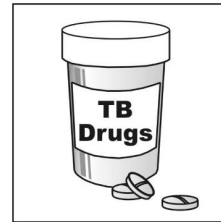
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Breakthrough in the Fight Against TB (1)

Drugs that could kill TB bacteria were discovered in 1940s and 1950s

- Streptomycin (SM) discovered in 1943
- Isoniazid (INH) and *p*-aminosalicylic acid (PAS) discovered between 1943 and 1952



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Breakthrough in the Fight Against TB (2)

- TB death rates in U.S. began to drop dramatically
- Each year, fewer people died from TB
- Most TB sanatoriums in U.S. had closed by mid 1970s

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TB Resurgence

- Increase in TB in mid 1980s
- Contributing factors:
 - Inadequate funding for TB control programs
 - HIV epidemic
 - Increased immigration from countries where TB is common
 - Spread of TB in homeless shelters and correctional facilities
 - Increase and spread of multidrug-resistant TB



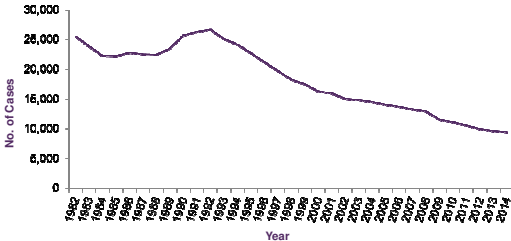
March 16, 1992 Newsweek Magazine Cover

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TB Prevention and Control Efforts

- Increased governmental funding for TB control programs began in 1992
- Number of TB cases declined from 1993 to 2014



Reported TB Cases, U.S., 1982-2014
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TB History Timeline

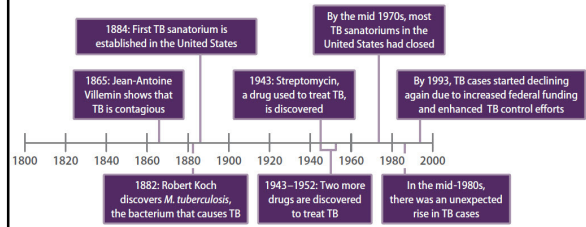


Figure 1.1 Timeline of major events in the history of TB.

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History of TB Study Question 1.1

In what year was each of the following discoveries made?

- TB was shown to be contagious
- The bacterium that causes TB was discovered
- The first drug that could kill TB bacteria was discovered

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TB Transmission

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TB Transmission (1)

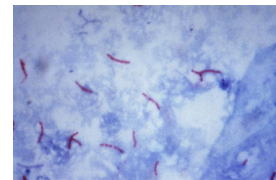
Transmission is defined as the spread of an organism, such as *M. tuberculosis*, from one person to another.

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TB Transmission (2) Types of Mycobacteria

- M. tuberculosis* causes most TB cases in U.S.
- Mycobacteria that cause TB:
 - M. tuberculosis*
 - M. bovis*
 - M. africanum*
 - M. microti*
 - M. canetti*
- Mycobacteria that do not cause TB
 - e.g., *M. avium*-complex



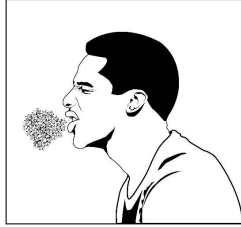
M. tuberculosis

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TB Transmission (3)

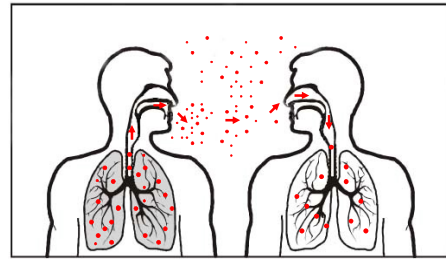
- TB is spread person to person through the air via droplet nuclei
- *M. tuberculosis* may be expelled when an infectious person:
 - Coughs
 - Speaks
 - Sings
- Transmission occurs when another person inhales droplet nuclei



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TB Transmission (4)



Dots in air represent droplet nuclei containing *M. tuberculosis*

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TB Transmission (5)

- Probability that TB will be transmitted depends on:
 - Infectiousness of the TB patient
 - Environment in which the exposure occurred
 - Frequency and duration of the exposure
 - Susceptibility (immune status) of the exposed individual
- The best way to stop transmission is to:
 - Isolate infectious persons
 - Provide treatment to infectious persons as soon as possible

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TB Transmission Study Question 1.2

What organism causes TB?

What are four other tuberculous mycobacteria?

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TB Transmission Study Question 1.3

How is TB spread?

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TB Transmission Study Question 1.4

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

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Drug-Resistant TB

Drug-Resistant TB (1)

- Caused by *M. tuberculosis* organisms resistant to at least one TB treatment drug
- Resistant means drugs can no longer kill the bacteria

Drug-Resistant TB (2)

Mono resistant	Resistant to any one TB treatment drug
Poly resistant	Resistant to at least any 2 TB drugs (but not both isoniazid and rifampin)
Multidrug resistant (MDR TB)	Resistant to at least isoniazid and rifampin, the 2 best first-line TB treatment drugs
Extensively drug resistant (XDR TB)	Resistant to isoniazid and rifampin, PLUS resistant to any fluoroquinolone AND at least 1 of the 3 injectable anti-TB drugs (e.g., amikacin, kanamycin, or capreomycin)

Drug-Resistant TB (3)

Primary Resistance	Caused by person-to-person transmission of drug-resistant organisms
Secondary Resistance (acquired)	Develops during TB treatment: <ul style="list-style-type: none"> • Patient was not treated with an appropriate regimen <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • Patient did not follow treatment regimen as prescribed

Drug-resistant TB Study Question 1.5

What is drug-resistant TB?

Drug-resistant TB Study Question 1.6

What is the difference between primary and secondary drug resistance?

TB Pathogenesis

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TB Pathogenesis (1)

Pathogenesis is defined as the way an infection or disease develops in the body.

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TB Pathogenesis (2) Latent TB Infection (LTBI)

- LTBI occurs when tubercle bacilli are in the body, but the immune system is keeping them under control
- LTBI is detected by the Mantoux tuberculin skin test (TST) or by an interferon-gamma release assay (IGRA), such as:
 - QuantiFERON®-TB Gold In-Tube (QFT-GIT)
 - T-Spot®. TB test (T-SPOT)
- People with LTBI are NOT infectious

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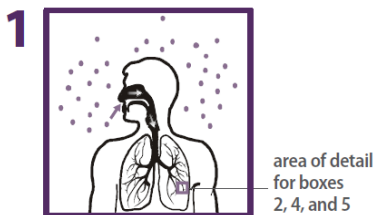
TB Pathogenesis (3) TB Disease

- TB disease develops when the immune system cannot keep tubercle bacilli under control
 - May develop very soon after infection or many years after infection
- About 10% of all people with normal immune systems who have LTBI will develop TB disease at some point in their lives
- People with TB disease are often infectious

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TB Pathogenesis (4)

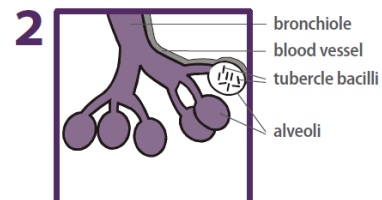


Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to small air sacs (alveoli)

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TB Pathogenesis (5)



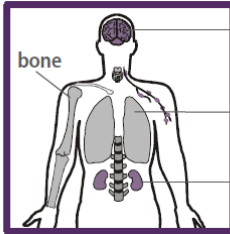
Tubercle bacilli multiply in alveoli, where infection begins

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TB Pathogenesis (6)

3



bone

brain

lung

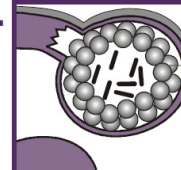
kidney

A small number of tubercle bacilli enter bloodstream and spread throughout body

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TB Pathogenesis (7) LTBI

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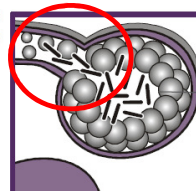
special immune cells form a barrier shell (in this example, bacilli are in the lungs)

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

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TB Pathogenesis (8) TB Disease

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

- If the immune system **CANNOT** keep tubercle bacilli under control, bacilli begin to multiply rapidly and cause TB disease
- This process can occur in different places in the body

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LTBI vs. TB Disease (1)

Person with 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 cough, fever, or weight loss
• TST or IGRA results usually positive	• TST or IGRA results usually positive
• Chest x-ray usually normal	• Chest x-ray usually abnormal

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LTBI vs. TB Disease (2)

Person with LTBI	Person with TB Disease (in the lungs)
• 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

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TB Pathogenesis Study Question 1.7

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

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TB Pathogenesis Study Question 1.8

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

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TB Pathogenesis Study Question 1.9

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

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TB Pathogenesis Study Question 1.10

How is LTBI detected?

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TB Pathogenesis Study Question 1.11

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

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TB Pathogenesis Study Question 1.12

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

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TB Pathogenesis

Progression from LTBI to TB Disease

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Progression to TB Disease (1)

- Risk of developing TB disease is highest the first 2 years after infection
- People with LTBI can be given treatment to prevent them from developing TB disease
- Detecting TB infection early and providing treatment helps prevent new cases of TB disease

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Progression to TB Disease (2)

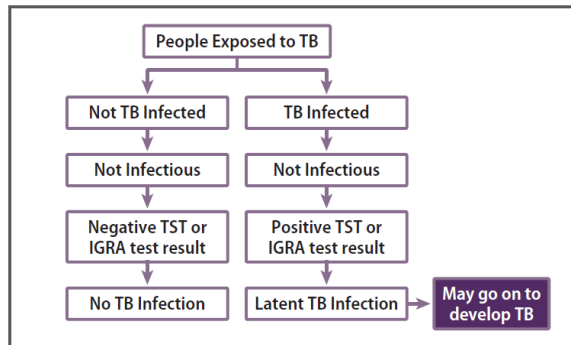
Some conditions increase probability of LTBI progressing to TB disease

- Infection with HIV
- History of untreated or inadequately treated TB disease
- Recent TB infection (within the past 2 years)
- Immunosuppressive therapy such as tumor necrosis factor-alpha (TNF) antagonists, systemic corticosteroids, or immunosuppressive drug therapy following organ transplantation
- Abusing drugs or alcohol or smoking cigarettes
- 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

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Progression to TB Disease (3)



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Progression to TB Disease (4) TB and HIV

In an HIV-infected person, TB can develop in one of two ways:

- Person with LTBI becomes infected with HIV and then develops TB disease as the immune system is weakened
- Person with HIV infection becomes infected with *M. tuberculosis* and then rapidly develops TB disease



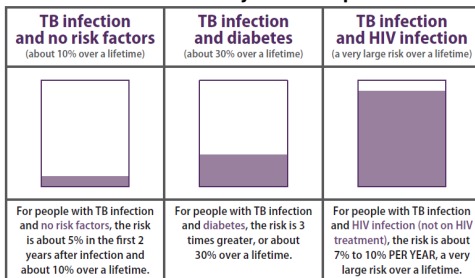
Image credit: Mississippi State Department of Health

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Progression to TB Disease (5) TB and HIV

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



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Progression to TB Disease Study Question 1.13

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

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Progression to TB Disease Study Question 1.14

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

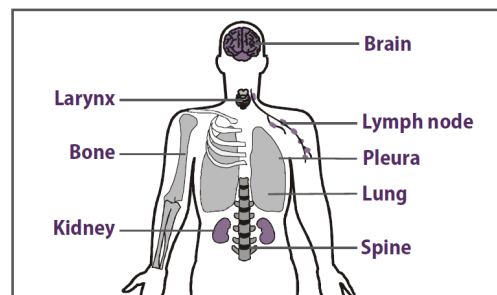
Progression to TB Disease Study Question 1.15

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

TB Pathogenesis Sites of TB Disease

Sites of TB Disease (1)

Bacilli may reach any part of the body, but common sites include:



Sites of TB Disease (2)

	Location	Frequency
Pulmonary TB	Lungs	Most TB cases are pulmonary
Extrapulmonary TB	Places other than lungs such as: <ul style="list-style-type: none"> • Larynx • Lymph nodes • Pleura • Brain • Kidneys • Bones and joints 	Found more often in: <ul style="list-style-type: none"> • HIV-infected or other immunosuppressed persons • Young children
Disseminated TB	Carried to all parts of body, through bloodstream	Rare

Sites for TB Study Question 1.16

What part of the body is the most common site for TB disease?

What are some other common sites?

TB Pathogenesis

TB Classification System

TB Classification System (1)

Based on pathogenesis of 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 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

TB Classification System (2)

Based on pathogenesis of TB

Class	Type	Description
3	TB, clinically active	Positive culture for <i>M. tuberculosis</i> 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 active TB disease
5	TB suspected	Signs and symptoms of TB disease, but diagnostic evaluation not complete

TB Classification System Study Question 1.17

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

Case Studies

Module 1: Case Study 1.1 (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.

Module 1: Case Study 1.1 (2)

Should this be considered a case of TB?

Should this man be considered infectious?

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Module 1: Case Study 1.2 (1)

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.

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Module 1: Case Study 1.2 (2)

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

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