Module 1: Transmission and Pathogenesis of Tuberculosis

Slide 1: (Title Slide.) Self-Study Modules on Tuberculosis, 1-5. Centers for Disease Control and Prevention, Division of Tuberculosis Elimination, 2016.

Slide 2: 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

Slide 3: (Title Slide.) Self-Study Modules on Tuberculosis: Transmission and Pathogenesis of Tuberculosis

Slide 4: 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.

Slide 5: 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

Slide 6: (Title Slide.) History of TB

Slide 7: 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
- **[IMAGE: Red Cross Christmas Seal Campaign vintage image circa 1919. Image says "The Next to Go. Fight Tuberculosis." Image credit: National Library of Medicine.]**

Slide 8: 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
- **[IMAGE: *Mycobacterium tuberculosis.* Image credit: Janice Haney Carr.]**

Slide 9: 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
- **[IMAGE: Sanatorium patients resting outside]**

Slide 10: 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
- **[IMAGE: TB drugs pill bottle]**

Slide 11: 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

Slide 12: 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
- **[IMAGE: March 16, 1992 Newsweek Magazine cover titled, "TB: Why It's back. How We Can Protect Ourselves"]**

Slide 13: TB Prevention and Control Efforts

- Increased governmental funding for TB control programs began in 1992
- Number of TB cases declined from 1993 to 2014
- **[Image: The resurgence of TB in the mid-1980s was marked by several years of increasing case counts until its peak in 1992. Case counts began decreasing again in 1993, and 2014 marked the twenty-second year of decline in the total number of TB cases reported in the United States since the peak of the resurgence. From 1992 until 2002, the total number of TB cases decreased 5%–7% annually. From 2002 to 2003, however, the total number of TB cases decreased by only 1.4%. An unprecedented decrease occurred in 2009, when the total number of TB cases decreased by more than 10% from 2008 to 2009. In 2014, a total of 9,421 cases were reported from the**

50 states and the District of Columbia (DC). This represents a decline of 1.5% from 2013 and 64.7% from 1992.]

Slide 14: TB History Timeline

- **[IMAGE: 1865: Jean-Antoine Villemin shows that TB is contagious. 1882: Robert Koch discovers *M. tuberculosis*. 1884: First TB sanatorium established in U.S. 1943: Streptomycin (SM) a drug used to treat TB is discovered. 1943-1952: Two more drugs are discovered to treat TB. Mid-1970s: Most TB sanatoriums in U.S. closed. Mid-1980s: Unexpected rise in TB cases. 1993: TB cases decline due to increased funding and enhanced TB control efforts.]**

Slide 15: History of TB: Study Question 1.1

- In what year was each of the following discoveries made?
  - TB was shown to be contagious - 1865
  - The bacterium that causes TB was discovered - 1882
  - The first drug that could kill TB bacteria was discovered - 1943

Slide 16: (Title Slide.) TB Transmission

Slide 17: TB Transmission (1)

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

Slide 18: 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*
- **[IMAGE: *M. tuberculosis*]**

Slide 19: 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
- **[IMAGE: Man coughing.]**

Slide 20: TB Transmission (4)

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

- **[IMAGE: TB is spread person to person through the air. In this image, the dots in the air represent droplet nuclei containing tubercle bacilli. Droplet nuclei containing *M. tuberculosis* expel into the air from one person's lungs and are inhaled into another person's lungs.]**

Slide 21: 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

Slide 22: TB Transmission: Study Question 1.2

- What organism causes TB?
  - *M. tuberculosis*
- What are four other tuberculous mycobacteria?
  - *M. bovis, M. africanum, M. microti, and M. canetti*

Slide 23: TB Transmission Study Question 1.3

- How is TB spread?
  - TB is spread from person to person through the air via droplet nuclei containing *M. tuberculosis*.

Slide 24: TB Transmission Study Question 1.4

- The probability that TB will be transmitted depends on what four factors?
  - Infectiousness of the TB patient
  - Environment in which exposure occurred
  - Frequency and duration of the exposure
  - Susceptibility (immune status) of the exposed individual

Slide 25: (Title Slide.) Drug-Resistant TB

Slide 26: Drug-Resistant TB (1)

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

Slide 27: 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)

Slide 28: Drug-Resistant TB (3)

Primary Resistance	Caused by person-to-person transmission of drug-resistant organisms
Secondary Resistance (acquired)	Develops during TB treatment: - Patient was not treated with an appropriate regimen OR - Patient did not follow treatment regimen as prescribed

Slide 29: Drug-resistant TB: Study Question 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.

Slide 30: Drug-resistant TB: Study Question 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 follow the prescribed treatment regimen.

Slide 31: (Title slide.) TB Pathogenesis

Slide 32: TB Pathogenesis (1)

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

Slide 33: 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

Slide 34: 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

Slide 35: TB Pathogenesis (4)

- Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to small air sacs (alveoli)
- **[Image: Tubercle bacilli are inhaled and enter the lungs.]**

Slide 36: TB Pathogenesis (5)

- Tubercle bacilli multiply in alveoli, where infection begins
- **[IMAGE: Section of the bronchiole, alveoli, and tubercle bacilli within the alveoli.]**

Slide 37: TB Pathogenesis (6)

- A small number of tubercle bacilli enter bloodstream and spread throughout body
- **[IMAGE: Anatomical view showing the brain, lung, kidney, and bones.]**

Slide 38: TB Pathogenesis (7): LTBI

- 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)
- **[IMAGE: Close view of the alveoli, where special immune cells form a barrier shell around the tubercle bacilli. In this example, the bacilli are in the lungs.]**

Slide 39: TB Pathogenesis (8): TB Disease

- 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
- **[IMAGE: Close view of the alveoli, where the special immune cells break down and the tubercle bacilli escapes. In this example, TB disease develops in the lungs.]**

Slide 40: 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**

Slide 41: 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**

Slide 42: TB Pathogenesis Study Question 1.7

- When a person inhales droplet nuclei containing *M. tuberculosis*, where do the droplet nuclei go?
    - Most of the larger droplet nuclei become lodged in the upper respiratory tract, where infection is unlikely to develop
    - However, droplet nuclei may reach the small air sacs of the lung (the alveoli), where infection may begin

Slide 43: 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?
    - Tubercle bacilli multiply in alveoli and some enter the lymph nodes and bloodstream and spread throughout the body
    - Bacilli may reach any part of the body
    - Within 2 to 8 weeks, the immune system usually intervenes, halting multiplication and preventing further spread

Slide 44: 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?

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

Slide 45: TB Pathogenesis Study Question 1.10

- How is LTBI detected?
  - LTBI is detected by the Mantoux tuberculin skin test (TST) or blood tests such as interferon-gamma release assays (IGRAs), which include the QuantiFERON®-TB Gold In-tube (QFT-GIT) or the T-SPOT®.*TB* test (T-SPOT).

Slide 46: TB Pathogenesis Study Question 1.11

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

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**
• **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**

Slide 47: 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?
  - When this happens, TB disease develops. The risk that TB disease will develop is higher for some people than for others.

Slide 48: (Title Slide.) TB Pathogenesis: Progression from LTBI to TB Disease

Slide 49: 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

Slide 50: 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

Slide 51: Progression to TB Disease (3)

- **[IMAGE: Flowchart. People who are exposed to TB may or may not develop TB infection. People with LTBI may or may not develop TB disease.]**

Slide 52: 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: Poster that reads, "TB/ HIV. Double Trouble. People with HIV infection face greater risk of also developing TB. Don't take chances. Get tested." Image credit: Mississippi State Department of Health.]**

Slide 53: 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
- **[IMAGE: For persons 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.)**

Slide 54: Progression to TB Disease: Study Question 1.13

- What percentage of people who have LTBI (but not HIV infection) usually develop TB disease?
    - About 10% of all people with LTBI will develop TB disease at some point
        - In U.S., about 5% of recently infected will develop TB disease in first year or two after infection
        - Additional 5% will develop disease later in life
    - Remaining 90% will remain free of disease for the rest of their lives

Slide 55: Progression to TB Disease: Study Question 1.14

- What conditions appear to increase the risk that LTBI will progress 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

Slide 56: Progression to TB Disease: Study Question 1.15

- How does being infected with both *M. tuberculosis* and HIV affect the risk for TB disease?
    - Much more likely to develop TB disease
    - Risk of developing TB disease is 7% to 10% EACH YEAR (if HIV is not being treated)
    - In an HIV-infected person, TB disease can develop in two ways:
        1. Person with LTBI becomes infected with HIV and then develops TB disease as the immune system is weakened
        2. Person with HIV infection becomes infected with *M. tuberculosis* and then rapidly develops TB disease

Slide 57: (Title Slide.) TB Pathogenesis: Sites of TB Disease

Slide 58: Sites of TB Disease (1)

- Bacilli may reach any part of the body, but common sites include: brain, larynx, lungs, kidneys, lymph nodes, spine, and bones.
- **[IMAGE: Anatomical view showing the brain, larynx, lung, kidney, lymph nodes, pleura, spine, and bones.]**

Slide 59: Sites of TB Disease (2)

	Location	Frequency
Pulmonary TB	**Lungs**	**Most TB cases are pulmonary**
Extrapulmonary TB	**Places other than lungs such as:** ▪ **Larynx** ▪ **Lymph nodes** ▪ **Pleura** ▪ **Brain** ▪ **Kidneys** ▪ **Bones and joints**	**Found more often in:** **- HIV-infected or other immunosuppressed persons** **- Young children**
Disseminated TB	**Carried to all parts of body, through bloodstream**	**Rare**

Slide 60: Sites for TB Study Question 1.16

- What part of the body is the most common site for TB disease?
  - Lungs are the most common site
- What are some other common sites?
  - Larynx
  - Lymph nodes
  - Pleura (membrane around the lungs)
  - Brain
  - Kidneys
  - Bones and joints

Slide 61: (Title Slide.) TB Pathogenesis: TB Classification System

Slide 62: 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**

Slide 63: TB Classification System (2)

- **Based on pathogenesis of TB**

Class	Type	Description
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 active TB disease**
5	**TB suspected**	**Signs and symptoms of TB disease, but diagnostic evaluation not complete**

Slide 64: TB Classification System Study Question 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.

Slide 65: (Title Slide.) Case Studies

Slide 66: 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.

Slide 67: Module 1: Case Study 1.1 (2)

- Should this be considered a case of TB?

    - No. The man described above has LTBI. He has an 18 mm positive reaction to the 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.

Slide 68: 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.

Slide 69: Module 1: Case Study 1.2 (2)

- 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.