Disclosures

• None

• Opinions expressed are not necessarily those of the Centers for Disease Control or the Indian Health Service
Objectives

• Describe current epidemiology of TB
• Explain how *M. tuberculosis* is transmitted
• Describe the pathogenesis of *M. tuberculosis*
Tuberculosis Epidemiology and History
Question 1: How Old is *M. tuberculosis*?

A) 150 years  
B) 325 years  
C) 1000 years  
D) 4000 years
TB Natural History

- One of the oldest recorded human afflictions
- Bone TB from individuals who died 4,000 years ago
- Assyrian clay tablets from the 7th century BC-hemoptysis
- Historically known by a variety of names, including:
  - Consumption
  - Wasting disease
  - White plague

TB Natural History

- Until mid-1800s, many believed TB was hereditary or a working man’s disease
- 1865 Jean Antoine-Villemin proved TB was contagious
- 1882 Robert Koch discovered *M. tuberculosis*, the bacterium that causes TB

*Image credit: Janice Haney Carr*  
CDC.gov - Transmission and Pathogenesis of Tuberculosis
Famous TB patients

• Ringo Starr
• Desmond Tutu
• Nelson Mandela
• Cat Stevens
• George Orwell
• Florence Nightingale
• Eleanor Roosevelt

• Vivien Leigh
• Tina Turner
• Carlos Santana
• Alexander Graham Bell
• Frederic Chopin
• John Henry “Doc” Holliday

Source: Jane Foster, Canadian Lung Association, York Region
Historical TB Care

• 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

Photo: CDC TB 101
Tuberculosis in the Dakotas

Photo source: North Dakota Newspaper Association
Breakthrough in the Fight Against TB

- 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
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 in homeless shelters and correctional facilities
  • Increase and spread of multidrug-resistant TB
Reported TB Cases United States, 1982–2015*

*Updated as of March 2016 -Source: CDC

9,563 cases
First increase in US TB cases in 23 years

*Updated as of March 2016 -Source: CDC

Mayo Clinic Center for Tuberculosis
Global TB

Estimated TB incidence rates, 2013

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.


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TB Case Rates,* United States, 2014

Source: CDC – Trends in Tuberculosis 2014
Cases of Active TB Nationally in American Indians / Alaska Natives - 2000 - 2014

Source: CDC NCHHSTP Atlas – 2016
Question 2: If you wanted to vacation in a state with the lowest chance of encountering TB, where would you go?

A) California  
B) Texas  
C) Wyoming  
D) New York  
E) Florida
TB Case Number Increases in States with Large American Indian / Alaska Native Populations (2014 to 2015)

- Arizona: +2.6%
- Alaska: +8.1%
- Oklahoma: +13.6%
- Nevada: +14.9%
- Utah: +19.4%
- Wyoming: +100%
- South Dakota: +112%

Source: CDC MMWR 2016
Tuberculosis Transmission
Mycobacterium tuberculosis

- Small, aerobic, non-motile, rod shaped bacillus
- Cell wall: lipid bilayer
  - Doesn’t stain well
  - Can live in dry environment for weeks
  - Can withstand some disinfectants
- Divides at slow rate of 16-20 hours
Mycobacterium tuberculosis

- Can be identified under a regular light microscope
- Cell wall has mycolic acid, so lab uses either:
  - Ziehl-Neelsen stain - bright red
  - Auramine-rhodamine stain - fluorescence microscopy
Mycobacterium tuberculosis: Transmission

- TB is spread person to person through the air via droplet nuclei

- *M. tuberculosis* may be expelled when an infectious person:
  - Coughs
  - Sneezes
  - Speaks
  - Sings

- Transmission occurs when another person inhales droplet nuclei
TB Transmission

Occurs when another person inhales droplet nuclei containing tubercle bacilli
TB Transmission

- The infectious particles are deposited on the mucous of the nasopharynx or tracheo-bronchial tree and are expelled by mucociliary clearance.

- Bacteria in droplets may enter the lungs and travel to the small alveoli.

- *In a small number of cases, the bacillus is transmitted to humans from infected cows through drinking non-pasteurized milk or cheese.*
Patient Factors Influencing TB Transmission

- Intensity of coughing
- Pulmonary cavities
- Smear positive sputum
- Cough inducing procedures
- TB in the lungs, larynx, airway
- People not receiving TB therapy

Photo source: CDC
Other TB Transmission Factors

• Probability that TB will be transmitted depends on:
  • Infectiousness of person with TB disease
  • Environment in which exposure occurred
  • Length of exposure
  • Virulence (strength) of the tubercle bacilli

• The best way to stop transmission is to:
  • Isolate infectious persons
  • Provide effective treatment to infectious persons as soon as possible
The GOOD News

• Only 20-50% of patients with TB are contagious

• Infectiousness declines rapidly when treatment is initiated

The BAD News

• We don’t always know who the infectious patients are at the start

• Patients aren’t always compliant with steps to limit transmission
Question 3: Which factor does not impact TB transmission?

A) Infectiousness of the person with TB disease
B) Environment in which exposure occurred
C) Length of exposure
D) Ethnicity of the person with TB disease
E) Virulence (strength) of the bacteria
Pathogenesis of Tuberculosis
TB Pathogenesis

Tuberculosis bacilli multiply in the alveoli, where infection begins.
TB Pathogenesis

A small number of tuberculosis bacilli enter the bloodstream and spread throughout the body. The bacilli may reach any part of the body, including areas where TB disease is more likely to develop (such as the brain, larynx, lymph node, lung, spine, bone, kidney).
TB Pathogenesis

- Within 2 to 8 weeks, MTB can be phagocytosed by alveolar immune cells
- The phagocytosed immune cells transport the MTB to local lymph nodes for T cell priming and cloning
- The immune cells form a barrier shell that keeps the bacilli contained and under control (LTBI)
TB pathogenesis

- If the immune system cannot keep the tubercle bacilli under control, the bacilli begin to multiply rapidly (TB disease).
- This process can occur in different areas in the body, such as the lungs, kidneys, brain, or bone.
Events following entry of bacilli- Stage 1

- Phagocytosis of MTB by alveolar macrophage
- Destruction of MTB, but some evade destruction and continue to multiply and then infect bystander macrophages

A VERY SIMPLISTIC diagram of the bacterium (purple) being ingested by the white blood cell (blue) and then breaking out of the vacuole.
Events following entry of bacilli- Stage 2

- Influx of Polymononuclear cells (PMN) and Monocytes-differentiate into Macrophage
- In some cases, it fails to eliminate the bacilli completely
- Logarithmic growth of bacilli-little tissue destruction
Events following entry of bacilli - Stage 3

• Stage of Latency (Granuloma) disrupts under conditions of failing immune surveillance & leads to endogenous reactivation of dormant bacilli

• Characterized by caseation necrosis
The Great Tuberculosis Paradox

Exposure of close contacts to *M. tuberculosis*

We assume that a significant proportion (~50–70% of exposed individuals) may clear infection through:

(i) Innate immunity i.e. no detectable T-cell priming (IGRA-ve; TST-ve), or

(ii) Adaptive immunity i.e. evidence of T-cell priming (IGRA+ve; TST+ve)

Presumed infection indicated by conversion of TST or IGRA

- ~95% Containment
- ~5% Clinically detectable active or subclinical disease

Reversion of TST or IGRA

Reinfection

Mayo Clinic Center for Tuberculosis
Natural History of TB

- TB patient
- Exposed contact
- TST-
- TST+
- TB

- 75% chance of TST+ after contact
- 25% chance of developing TB after TST+
- 10% of TST+ patients develop TB
TB Pathogenesis - Latent TB Infection (LTBI)

- Occurs when tubercle bacilli are in the body, but the immune system is keeping them under control.
- Detected by the Mantoux tuberculin skin test (TST) or by blood tests such as interferon-gamma release assays (IGRAs) which include:
  - QuantiFERON®-TB Gold test (QFT-G)
  - QuantiFERON®-TB Gold In-Tube (QFT-GIT)
  - T-Spot®.TB test (T-SPOT)

- People with LTBI are NOT infectious.
## LTBI vs. TB Disease

<table>
<thead>
<tr>
<th>Latent TB Infection (LTBI)</th>
<th>TB Disease (in the lungs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inactive</strong>, contained tubercle bacilli in the body</td>
<td><strong>Active</strong>, multiplying tubercle bacilli in the body</td>
</tr>
<tr>
<td>TST or blood test results usually positive</td>
<td>TST or blood test results usually positive</td>
</tr>
<tr>
<td>Chest x-ray usually <strong>normal</strong></td>
<td>Chest x-ray usually <strong>abnormal</strong></td>
</tr>
<tr>
<td>Sputum smears and cultures <strong>negative</strong></td>
<td>Sputum smears and cultures may be <strong>positive</strong></td>
</tr>
<tr>
<td><strong>No symptoms</strong></td>
<td><strong>Symptoms</strong> such as cough, fever, weight loss</td>
</tr>
<tr>
<td><strong>Not infectious</strong></td>
<td><strong>Often infectious</strong> before treatment</td>
</tr>
<tr>
<td><strong>Not a case</strong> of TB</td>
<td><strong>A case</strong> of TB</td>
</tr>
</tbody>
</table>

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**CDC TB 101**

Mayo Clinic Center for Tuberculosis
TB Pathogenesis: Progression from LTBI to TB Disease
Progression to TB Disease

People Exposed to TB

Not TB Infected

Not Infectious

Negative TST or QFT-G test result

No TB Infection

Latent TB Infection (LTBI)

Not Infectious

Positive TST or QFT-G test result

Latent TB Infection

May go on to develop TB disease
Progression to TB Disease

- 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
Progression to TB Disease: Risk Factors

- HIV Infection
- Diabetes
- Substance abuse
- Immunosuppressive therapy (TNF alpha, steroids, chemotherapy)
- Organ transplants
- Chronic kidney disease
- Recent TB infection
An HIV infected person can develop TB in 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
Progression to TB Disease: TB and HIV

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

<table>
<thead>
<tr>
<th>TB infection and NO risk factors</th>
<th>TB infection and HIV infection (pre-Highly Active Antiretroviral Treatment [HAART])</th>
</tr>
</thead>
<tbody>
<tr>
<td>![TB infection no risk factors]</td>
<td>![TB infection with HIV risk factors]</td>
</tr>
<tr>
<td>Risk is about 5% in the first 2 years after infection and about 10% over a lifetime</td>
<td>Risk is about 7% to 10% PER YEAR, a very high risk over a lifetime</td>
</tr>
</tbody>
</table>
Sites of TB Disease

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

- Brain
- Lymph node
- Pleura
- Lung
- Spine
- Kidney
- Bone
- Larynx
## Sites of TB Disease

<table>
<thead>
<tr>
<th></th>
<th>Location</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulmonary TB</strong></td>
<td>Lungs</td>
<td>Most TB cases are pulmonary</td>
</tr>
<tr>
<td><strong>Extrapulmonary TB</strong></td>
<td>Places other than lungs such as:</td>
<td>Found more often in:</td>
</tr>
<tr>
<td></td>
<td>- Larynx</td>
<td>- HIV-infected or other immunosuppressed persons</td>
</tr>
<tr>
<td></td>
<td>- Lymph nodes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Pleura</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Brain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Kidneys</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Bones and joints</td>
<td></td>
</tr>
<tr>
<td><strong>Miliary TB</strong></td>
<td>Carried to all parts of body, through bloodstream</td>
<td>Rare</td>
</tr>
</tbody>
</table>
Working Together, perhaps we can eliminate TB!