

## Tuberculosis

TB (disease) was called “consumption” because patients appeared to be consumed from within

Tuberculosis is called *Mycobacterium tuberculosis* (Mtb)

→ MTB are bacilli-shaped bacteria

Discovered in 1882 by Robert Koch

→ Previously assumed to be an inherited disease before bacterium was discovered

1.6 million deaths to TB per year (more than any other infectious disease until COVID-19)

→ Has been causing a COVID-scale pandemic every year for over 200 years

→ 90% of deaths occur in the developing world

## Challenges of Mtb Research

Must be handled at Biosafety level 3 out of 4 BSL levels

→ Control over airflow / sanitation (expensive and difficult)

Mtb grows very slowly

1. Divides every 20 hours
2. Takes 2-3 weeks to form a colony
3. Hard to perform rapid antibiotic susceptibility testing
4. Hard to treat (antibiotics preferentially kill dividing bacteria)

## Symptoms

1. Bloody cough
2. Weight loss (wasting)
3. Fever
4. Nausea

Slow progression but often leads to death

Has been causing disease in humans for at least 50,000 years but accelerated by industrial revolution

## Characteristics of Mtb

1. Humans are the only natural reservoir of Mtb
  - Mice can be infected, but not naturally
2. Mtb is an **intracellular bacterial pathogen**: can ONLY replicate inside human cells

3. Has a thick waxy coat which provides resistance to immune response and antibiotics

Extra layers of mycolic acids (long chains of hydrocarbons) serving as a lipid barrier

Resistant to phagocytosis / poor antibody binding

## Transmission

After inhalation, Mtb initially replicates in alveolar macrophages

→ Infectious dose can be as low as 1 bacterium

→ Waxy coat / Disruption of phagosome maturation

Early “5 minute” phagosome doesn’t fully acidify into a lysosome, so the bacteria are not killed

## TB Life Cycle

1. Aerosol transmitted; low infection dose ( $\sim 1-10$  CFU)
2. Initially infects alveolar macrophages
3. Very heterogeneous and complex outcomes
4. Active disease associated with uncontrolled lung inflammation in about 10% of individuals

80% of infections result in latent TB (No symptoms or transmission)

Few can eradicate the bacteria

Bacteria trapped in granuloma but cannot be eradicated

Can be “converted” to active TB in  $\sim 10\%$  of population

Keeps TB in population

## Granulomas

Formerly called tubercles, granulomas are organized aggregates of immune cells and bacteria

→ Helps contain but not (necessarily) eliminate Mtb

A “hallmark” of Mtb infection

## Vaccination

Bacille Calmette-Guerin (BCG) is a live-attenuated vaccine from cows

Given to many kids in developing countries and protects against TB meningitis (infection of nervous system)

Does not protect against pulmonary TB in adults (major form in adults)

## Latent to Active TB

Normally:

1. 5% chance of conversion within a year
2. 5-15% change in remaining lifetime

Someone with AIDS:

1. 8% chance per year
2. 80% chance within 10 years

Patients on anti-TNF (Humira, Remicade, etc.) also at increase risk

## Methods of Diagnosis

Chest X-Rays: Characterized by cavitary lesions

→ Imprecise, and latent TB may not show up at all

Smear Test: Patients cough up sputum and Mtb bacteria in sputum can be visualized with acid-fast (Ziehl-Neelsen) stain

- Inexpensive, fast, and specific
- Few false positives, but many false negatives (Needs  $> 10,000$  bacilli/mL)
- cannot detect latent TB

Culture Test: Grown from sputum sample

- More sensitive than smear test but slower and more difficult
- Solid (3-4 weeks); Liquid (2 weeks)

Latent TB cannot be detected directly

- Diagnosed indirectly by looking for immune response to Mtb
  1. Tuberculin skin test (TST): Immune reaction to TB antigens in skin
  2. Interferon gamma release assay (IGRA): Measures an immune reaction to TB antigens in a test tube

## TST

Purified protein derivative (PPD) consists of “purified” Mtb antigens

Injected intradermally and then observed 48-72 hours later for a bump forming at site

Anyone given BCG vaccine will give a positive test even if uninfected

**IGRA**

Detects a cytokine called interferon gamma (produced by T cells in response to Mtb antigens)

Detects antigens unique to Mtb and not found in BCG

**Antibiotics**

## First Line Antibiotics

1. Isoniazid (INH) **Memorize**
2. Rifampin (RIF) **Memorize**
3. Pyrazinamide (PZA)
4. Ethambutol (EMB)

## Second Line Antibiotics

1. Fluoroquinolones (e.g. ciprofloxacin)
2. Injectables

6 month first-line treatment for drug-sensitive TB

Multi drug resistant TB (MDR TB) resistant to INH and RIF (Requires 1-2 years of second line antibiotics)

1. 4% of new cases and 19% of previously treated cases in 2016 were MDR TB
2. 240,000 people died from MDR TB
3. 6% of people with MDR TB have XDR TB

Extensively drug resistant TB (XDR TB) resistant to INH, RIF, and some second line drugs (often incurable, surgery sometimes required)

**HIV-AIDS and TB**

- 1.