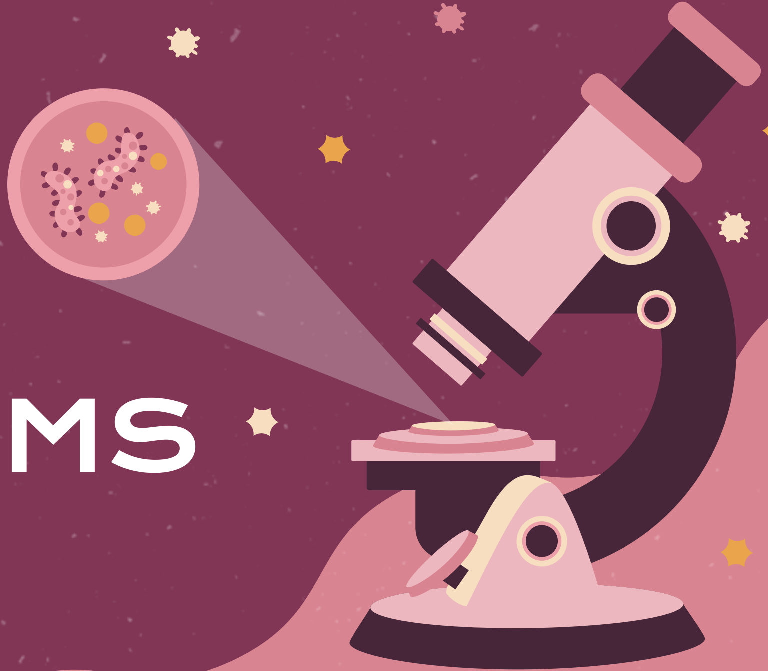
CASE 4
BODY SYSTEMS SUMMARY



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PATH417
2021W2

CASE SUMMARY

"53-year-old Robert immigrated from India about a year ago. Over the past month he has had fevers, chills, night sweats, and a chronic productive cough. He goes to see his family doctor who confirms a fever of 38.5°C. Upon auscultation she also finds crackles in the right lung and decreased breath sounds in the right lower lung field. She sends Robert for a chest X-ray and gives him three sterile containers with instructions to generate three deep sputum samples over three mornings. The samples are examined in the Microbiology Laboratory and Robert is informed that he has TB. The Public Health Unit is notified and Robert is sent to the local hospital for further assessment (and treatment)."

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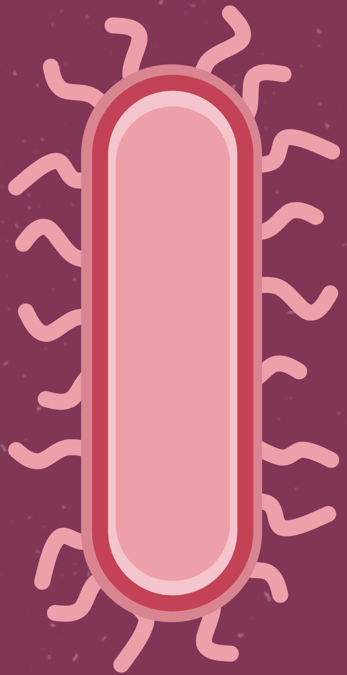
Mycobacterium tuberculosis overview

- **Aerobic**, nonmotile bacillus
- Complex, **waxy cell wall** composed of long-chain lipids[1]
- Acid-fast – hydrophobic outer layer
- **Slow-growing** (doubling time of 18-24 hrs)[1]
- Respiratory pathogen



01

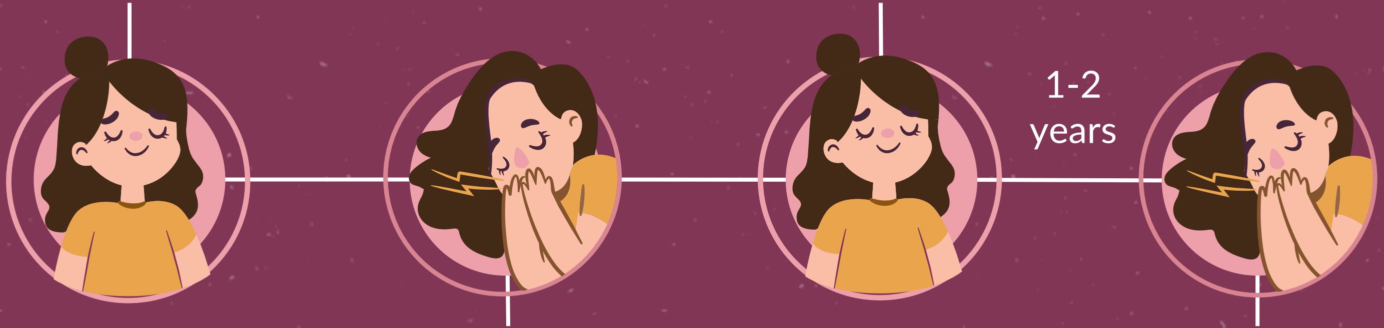
Signs and Symptoms

Describe the signs and symptoms presented in the case. What are the key History of Presenting illness elements presented? What laboratory samples are taken and why?

Stages of TB Disease[2]

Early
Asymptomatic infection

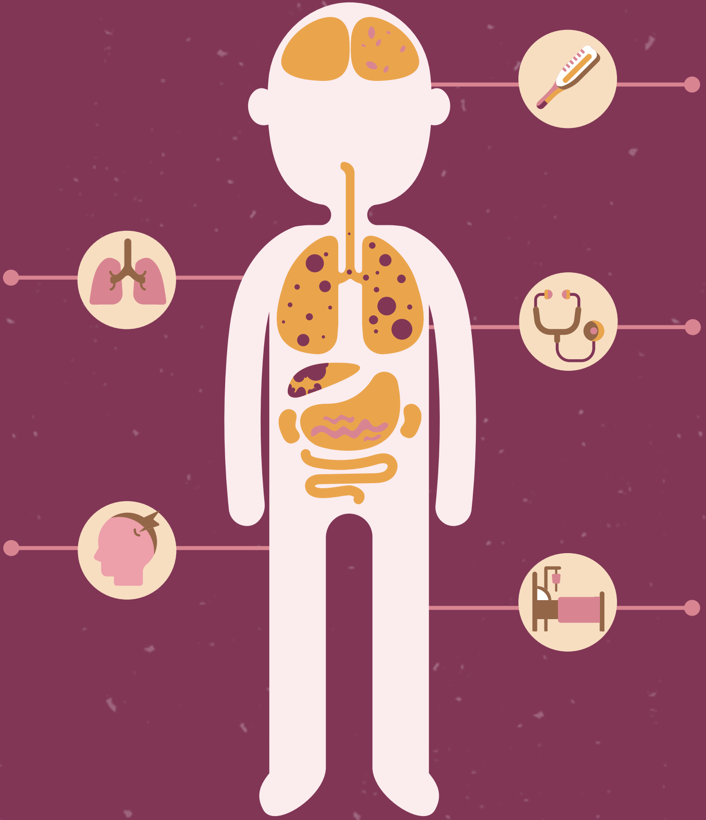
Latent
Asymptomatic infection



Primary
Fever, chills, chest pains, unproductive cough

Reactivation
Fever, night sweats, weight loss, productive cough

Robert's Signs



FEVER

The physician noticed that Robert has a fever of 38.5°C[5]

CRACKLES IN THE LUNG

Caused by excess fluid in the airways; exudate occurs as a result of lung infection[3]

DECREASED BREATH SOUNDS

Can be caused by air or fluid in or around the lung[6]

CHRONIC PRODUCTIVE COUGH

Exudate is dislodged by cough[4]

NIGHT SWEATS

Can be related to elevated temperatures during fever

Robert’s Symptoms

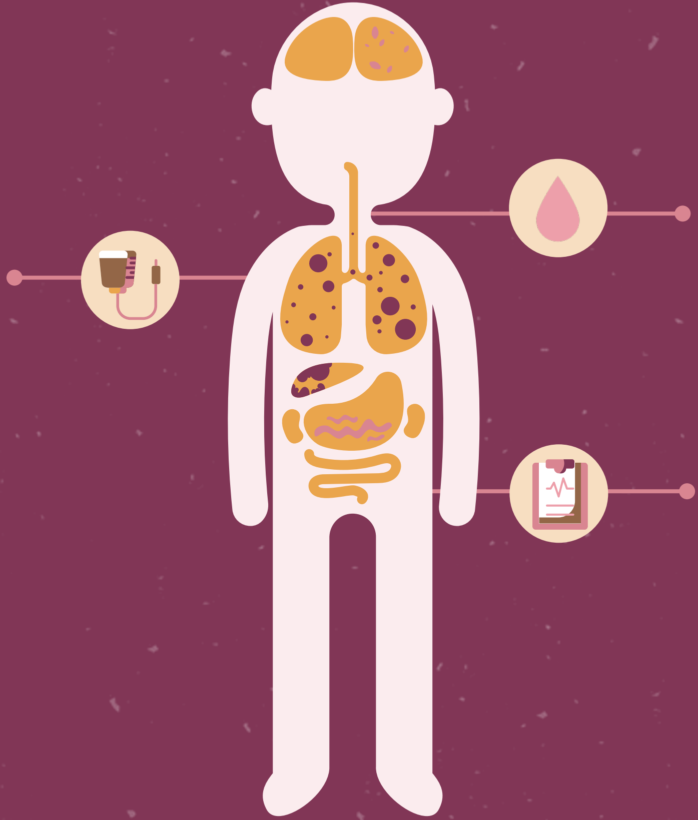
CHILLS

Robert has noticed himself feeling chills[7]

WHAT DO CHILLS SIGNIFY?

Chills can be an involuntary sign of your body trying **regulate its core temperature**. Shivering is a common stress response to raise your core body temperature.

Other Signs[7]



TENDER OR SWOLLEN LYMPH NODES

A sign of active immune response/inflammation

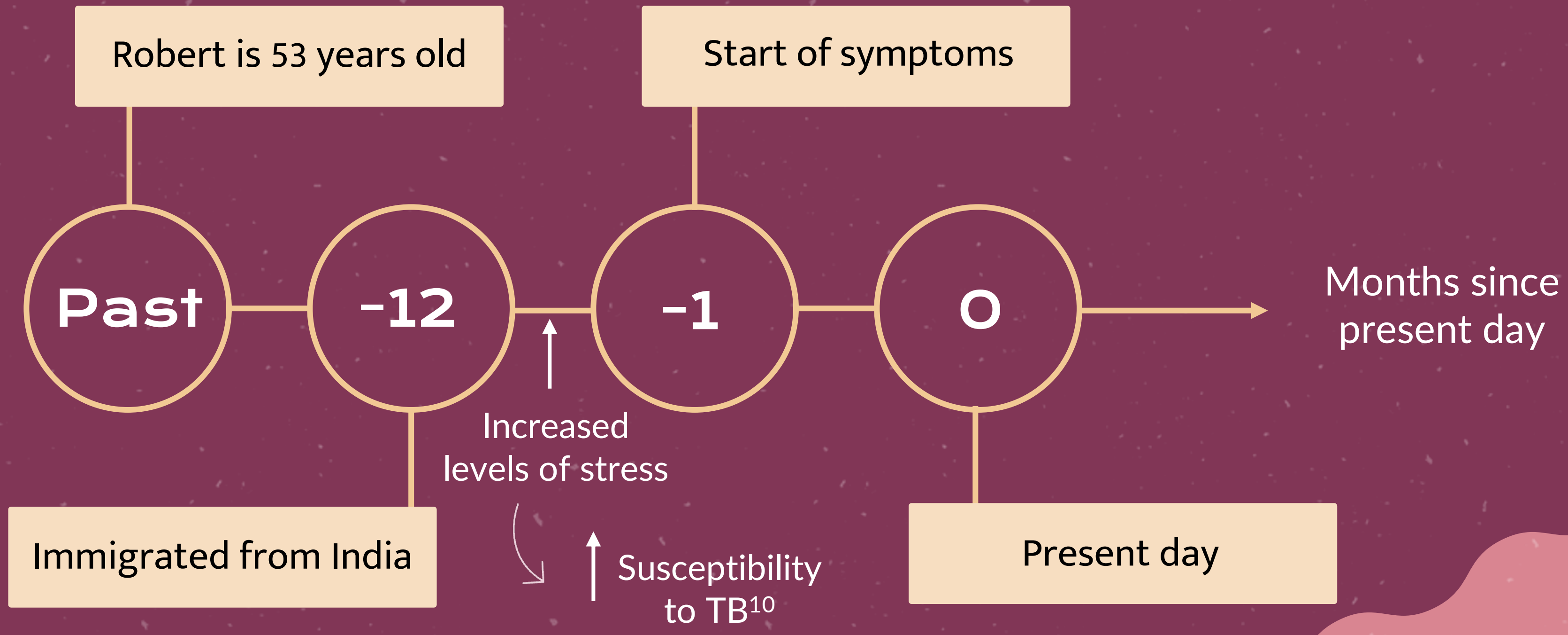
HEMOPTYSIS

Coughing up blood; due to erosion of blood vessels[8]

WEIGHT LOSS

History of Present Illness (HPI)

A description of the development of the patient's illness[9]



Tuberculosis in India

World's greatest TB pandemic, 192 cases per 100,000 people[11]

26%

of all incident TB cases worldwide[11]

38%

of global TB deaths[11]

Laboratory Samples

Chest X-ray

- To better understand the **extent of TB**[12]
- Further X-rays may be ordered to check spread to other organs

Deep sputum samples

- For positive **confirmation of TB** after examination under microscope[13]
- For evaluating **effectiveness of treatment**

Sputum

Aka phlegm, mucus that comes up from deep within the lungs when you cough[14]

Day 1 Day 2 Day 3

Samples collected **over 3 days** by coughing deeply and **spitting into a sterile container**[14]

Smear test

Culture

Acid-fast Bacilli Smear[15]

- Sputum smeared on glass slide
- Specialized dye applied which **stains mycobacteria pink**
- Rinsing in acid decolourizes other material
- Can provide **results in 1-2 days**
- **Most effective method** for confirming diagnosis of TB[16]
- Sensitivity of **34-80%**[17]

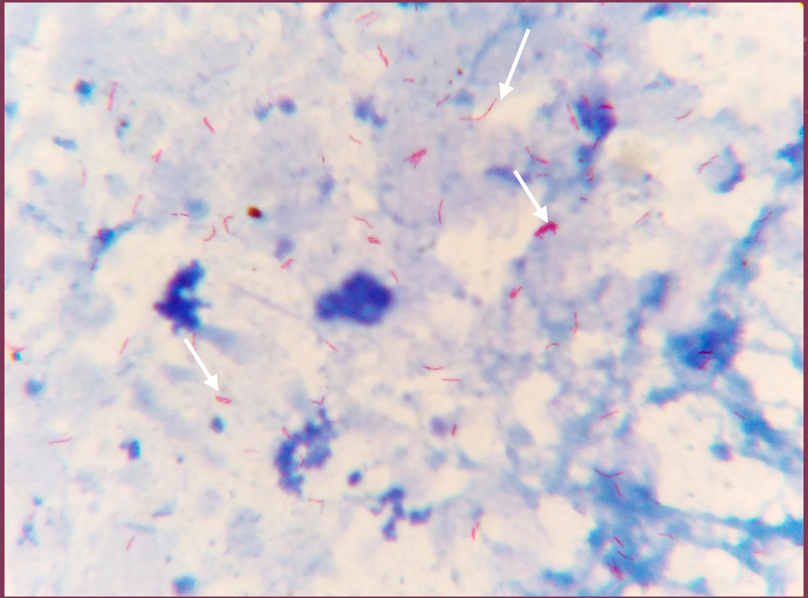


Figure 1. Sputum smear showing acid fast bacilli (Mtb). Reprinted from Wikimedia commons (1).

Acid-fast Bacilli Smear (cont)

- Bacilli are **counted**
- **Smears are rated** as 1-4 depending on quantity of acid-fast bacilli observed[17]
- Higher numbers = **more contagious**

Table 4.3
Smear Classification Results

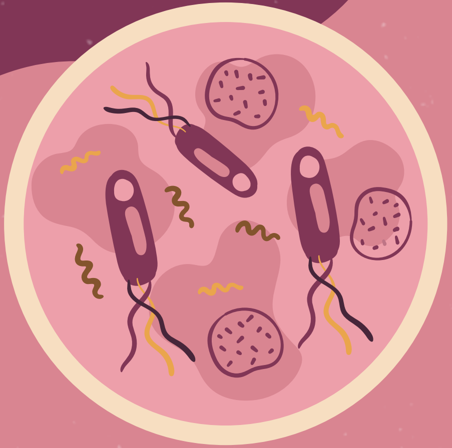
Smear Result (Number of AFB observed at 1000X magnification)	Smear Interpretation	Infectiousness of Patient
4+ (>9/field)	Strongly positive	Probably very infectious
3+ (1-9/field)	Strongly positive	Probably very infectious
2+ (1-9/10 fields)	Moderately positive	Probably infectious
1+ (1-9/100 fields)	Moderately positive	Probably infectious
+/- (1-2/300 fields)*	Weakly positive†	Probably infectious
No acid-fast bacilli seen	Negative	Probably not infectious**

* There are variations on labeling for this result, and include listing the number of AFB counted.

† Laboratories may report these smear results as "doubtful" or "inconclusive" based on CDC guidelines.

Figure 2. Acid-fast bacilli smear classification results. Reprinted from CDC gov (2)

Sputum Culture



- Gold standard
- Positive if bacterial growth observed
- Sensitivity of **80-93%**[16]
- Specificity of **98%**[16]
- Two types:
  - **Solid media** (4-8 weeks)[16]
  - **Liquid media** (1-2 weeks)[16]

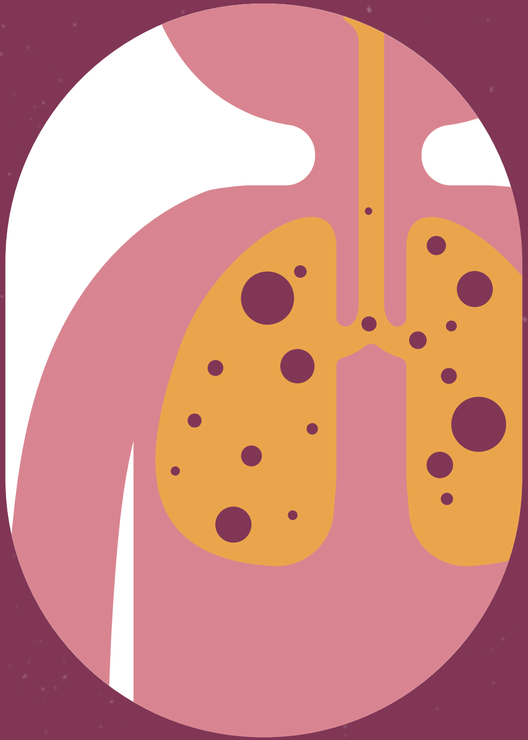
Nucleic Acid Amplification Test

- Definitive diagnosis from sputum smear requires either positive culture test or positive NAAT[17]
- **Amplifies pathogen-specific DNA** and RNA segments to quickly identify microorganism
- Consistent detection of Mtb within **hours**
- In absence of other tests, negative NAAT **cannot decisively rule out TB**[17]

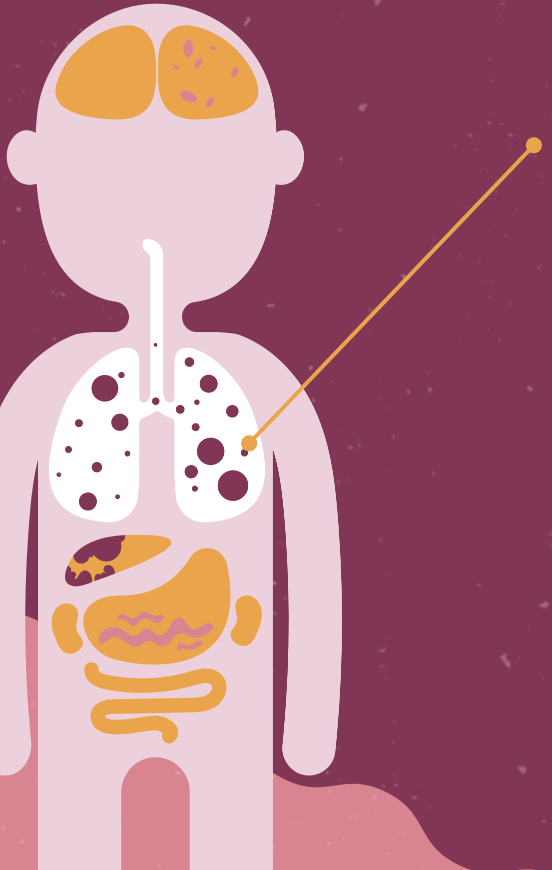
02

Affected Body System

Which body system is affected? In what way has the normal physiological functioning of this body system been disturbed by the infection?



Which body system is affected?



Lungs

- Lungs are exposed to air
- Mtb infects through **airborne dried mucous droplets**[18]
- Also affects **other respiratory system compartments**:
    - Nose
    - Pharynx
    - Trachea
    - Bronchi
    - Bronchioles

Mtb infection in the lungs

Encounter

Alveolar macrophages initiate inflammatory response[19]

Granuloma formation

Inflammation leads to formation of granuloma made of infected macrophages and immune cells[20,21]

Necrosis

Breakdown of granuloma leads to formation of cavity in lung tissue[22-24]

Pulmonary fibrosis

Accumulation of ECM proteins, thickening of walls of lung[25]

Bronchiectasis

Dilation of bronchi and thickening of bronchial wall[20]

Gas exchange impairment

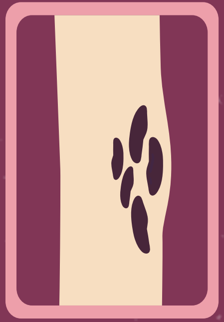
Narrowing of airways, inability to breath[18]

Respiratory system

<u>Difficulty breathing during Mtb infection can be attributed to:</u>

Formation of cavities

Narrowing of airways



Pulmonary fibrosis

Formation of cavities

- Lung cavitation caused by breakdown of granulomas
- Caseous necrosis:
    - Alveolar cells and nearby bronchial vessels are broken down[22]
    - **Necrotic tissue is coughed out**, leaving a cavity[23]

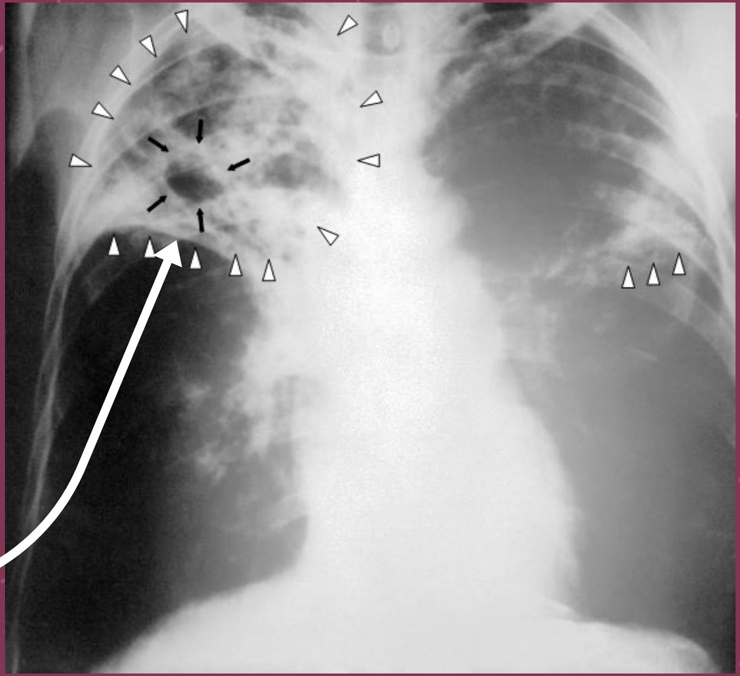


Figure 3. Chest X-ray of a patient with far-advanced tuberculosis showing cavitation. Reprinted from Wikimedia commons (3).

Narrowing of airways

Slows the movement of Mtb into healthy lung tissue[18]

- Inflammation causes swelling in **mucous membranes**[18]
- Bronchiectasis makes **bronchi less elastic**[26]

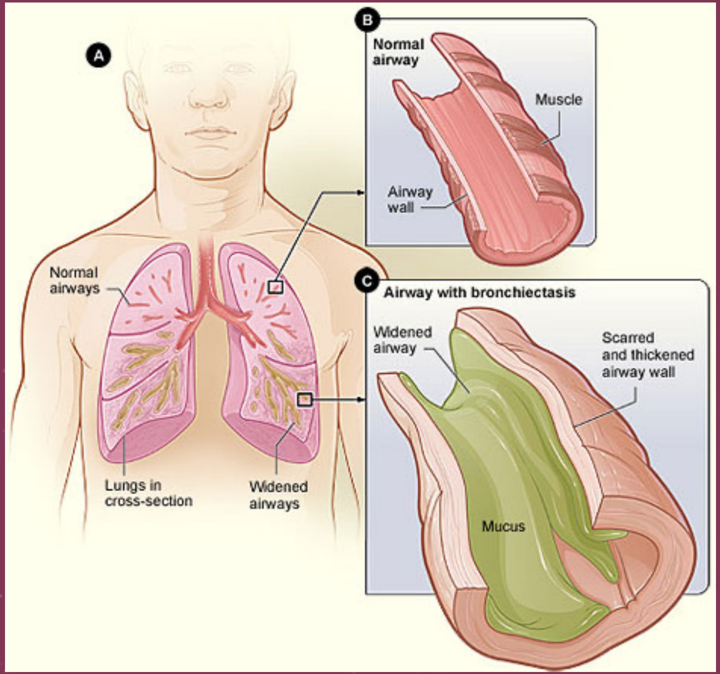


Figure 4. Cross section of normal airway and an airway with bronchiectasis. Reprinted from Wikimedia commons (4).

Pulmonary fibrosis

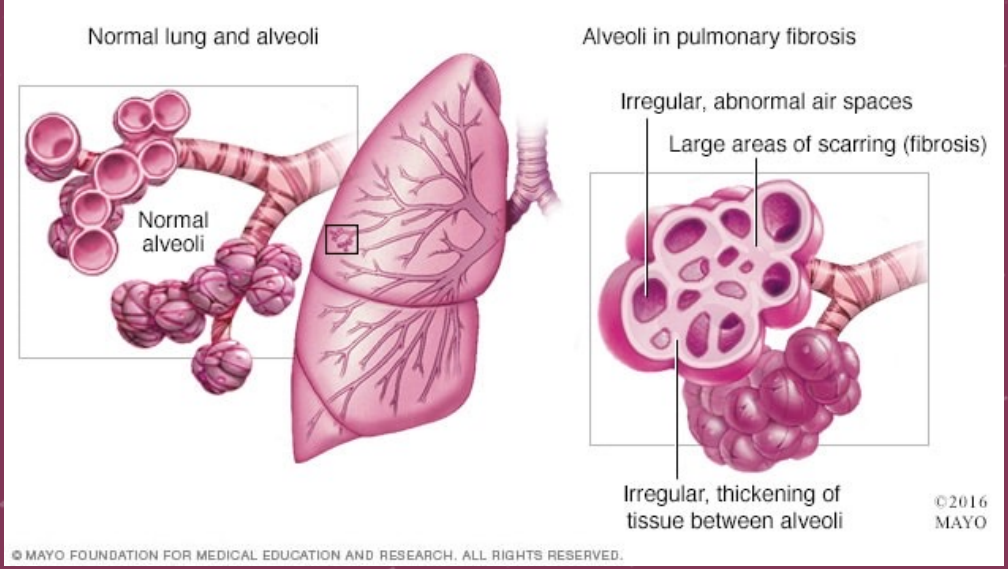


Figure 5. Diagram of pulmonary fibrosis. Reprinted from Mayo Clinic (5).

- **Extracellular matrix (ECM)** proteins deposit in lungs[25]
- Normal lung tissue replaced by **collagenous tissue**
- **Nodular infiltrates** can lead to chest pain and eventual respiratory failure[27]

Pleural effusion

- Rupture of caseous necrotic tissue can allow **TB antigens to enter pleural space**[28,29]
- Antigen stimulates **inflammation**
- Inflammation → increased permeability of nearby blood vessels
  - Increased **leukocyte migration**
  - Increased **pleural fluid production**[30]
  - Pleural fluid accumulation = effusion[31]

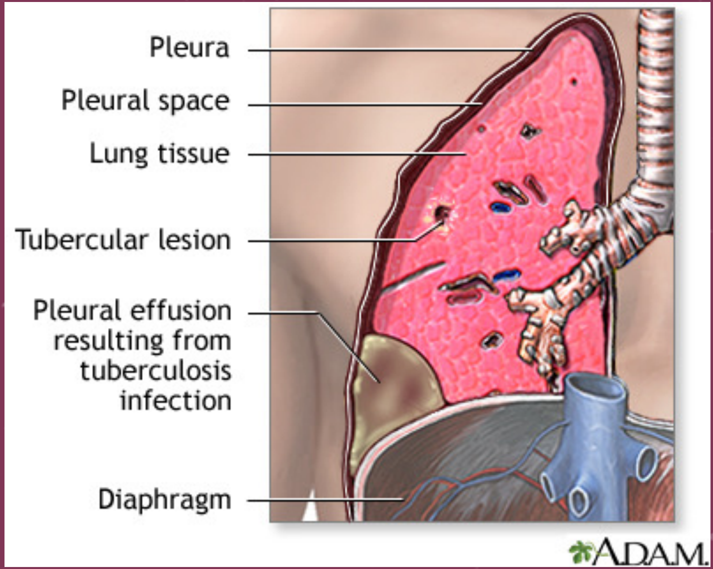
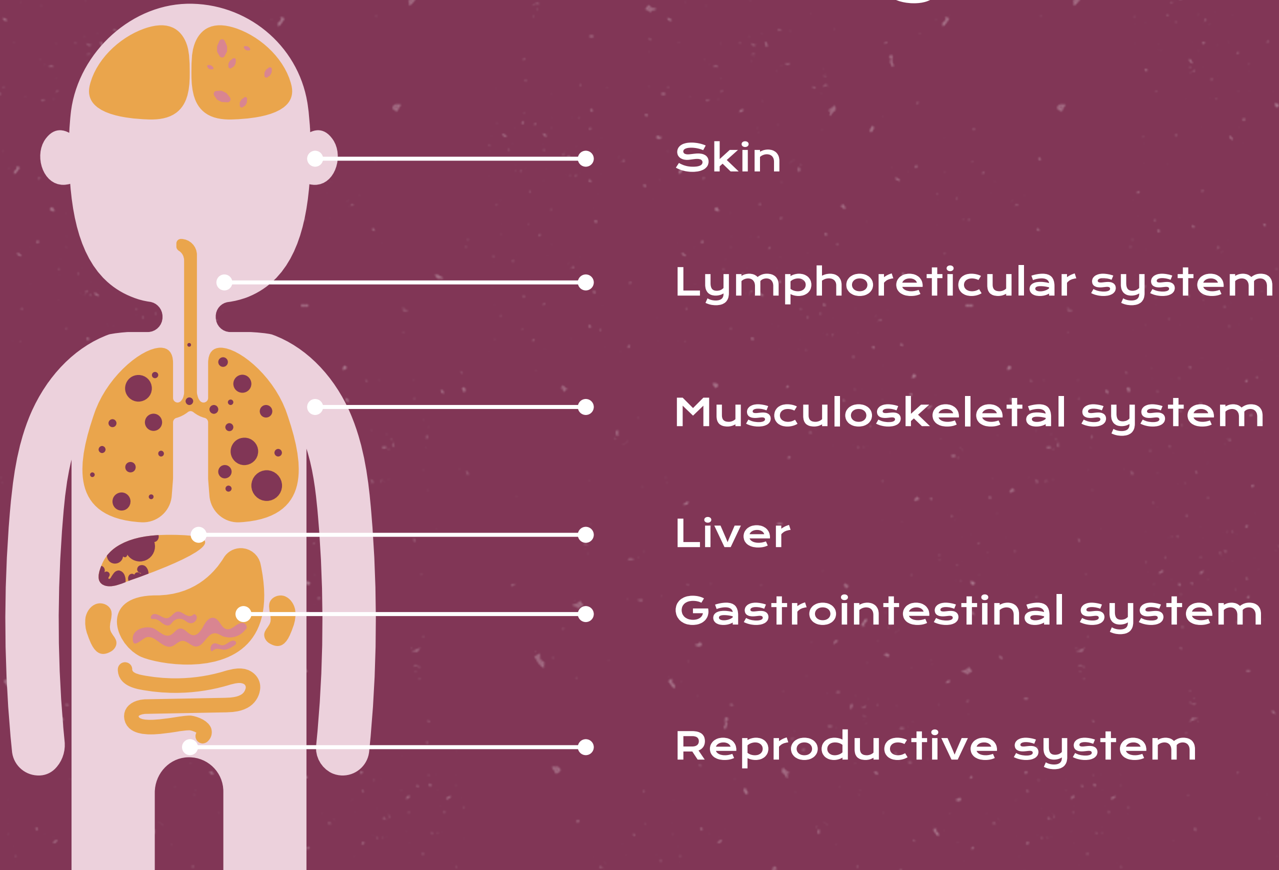


Figure 6. Diagram of pleural effusion. Reprinted from UFHealth (6).

Other affected systems[32]



Lymphatic system

TB Lymphadenitis: swelling in the lymph nodes (commonly in the neck); can result in ulceration of the surrounding skin[33]

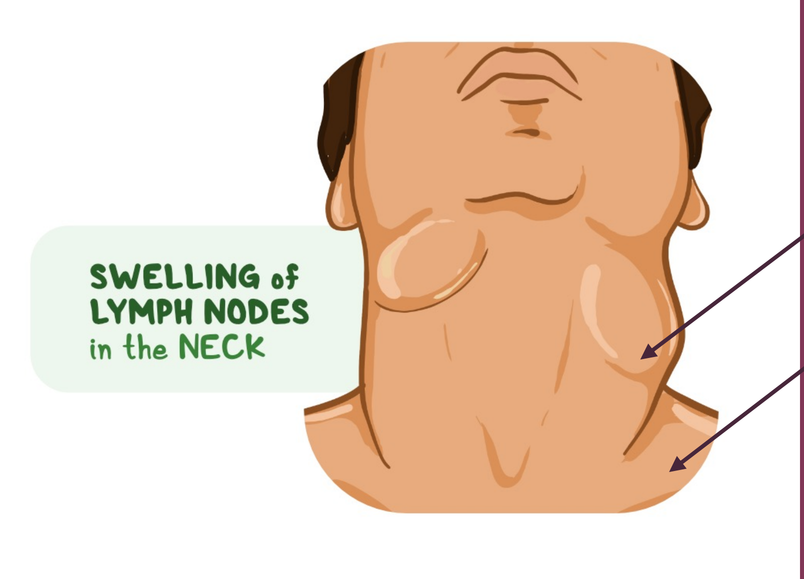


Figure 7. Diagram of cervical adenopathy. Adapted from Osmosis from Elsevier (7).

- Anterior and superior triangles of the neck
- Supraclavicular and axillary regions

Kidneys

- Mtb seeds **vascular renal cortex** during original infection or spreads there during reactivation[33]
- Healed **granulomatous lesions** in glomeruli can **burst into renal tubule**
- Granulomatous lesions in **ureter** can cause **narrowing**[33]

Figure 8. Tuberculosis infection in the kidney. Adapted from Eastwood et al. (8).

Nervous system

Mtb **crosses blood-brain barrier** and blood-cerobrospinal fluid barrier by:

- **Rearranging actin filaments** in endothelial cells lining capillaries, allowing transmigration[34]
- **Hijacking immune cells** and other cells able to cross these barriers[35]

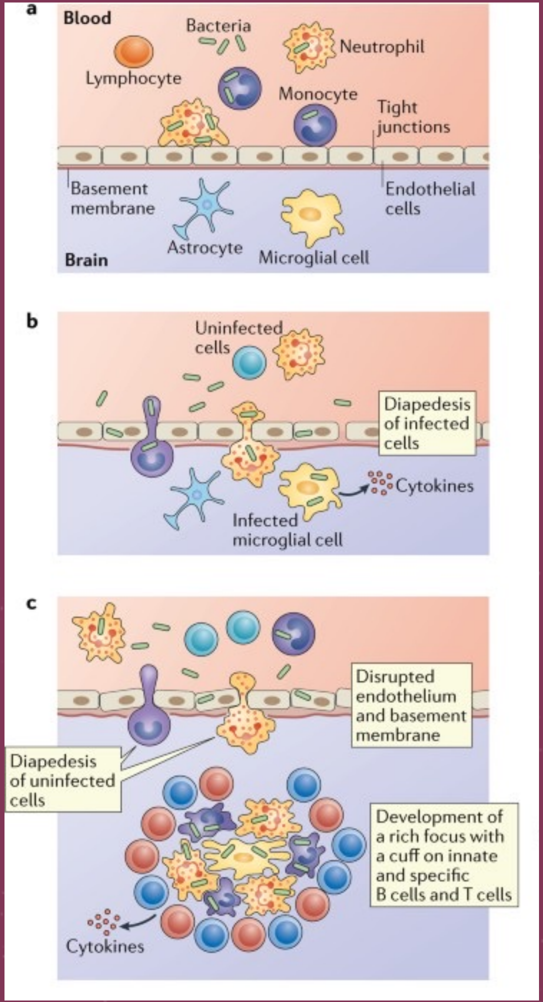


Figure 9. Tuberculosis infection in the lungs. Adapted from Wilkinson et al. (9).

Nervous system (cont)

In brain, Mtb stimulates **inflammation** → tissue damage

- **Disruption of basal structures** in proximity to neuroendocrine glands
- Changes in **neuroendocrine metabolism**[36]
- Formation of **exudate**
  - **Edema** → encephalitis
  - **Blocks circulation** of cerebrospinal fluid[37]
  - **Affects cranial nerves** → cranial nerve palsies[37]

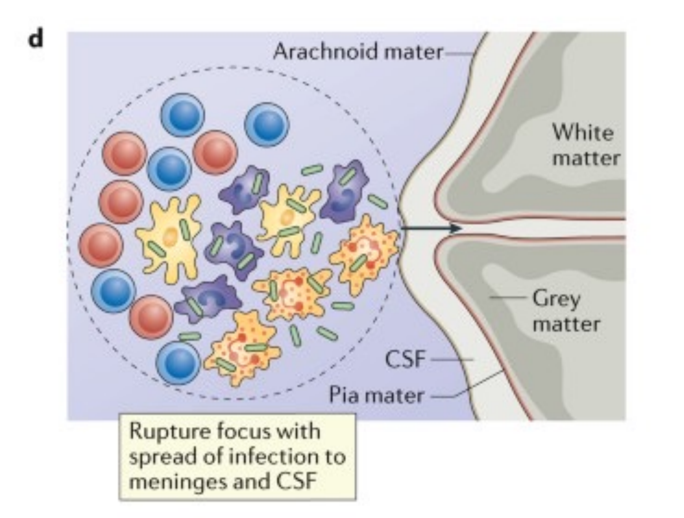


Figure 10. Tuberculosis infection in the lungs. Adapted from Wilkinson et al. (9).

Skeletal system

Spinal tuberculosis

- Mtb invades vertebral bodies
- Can cause gradually worsening back pain
- Collection of paraspinous fluid
- Advanced illness can cause compression of spinal cord or peripheral nerves[33]

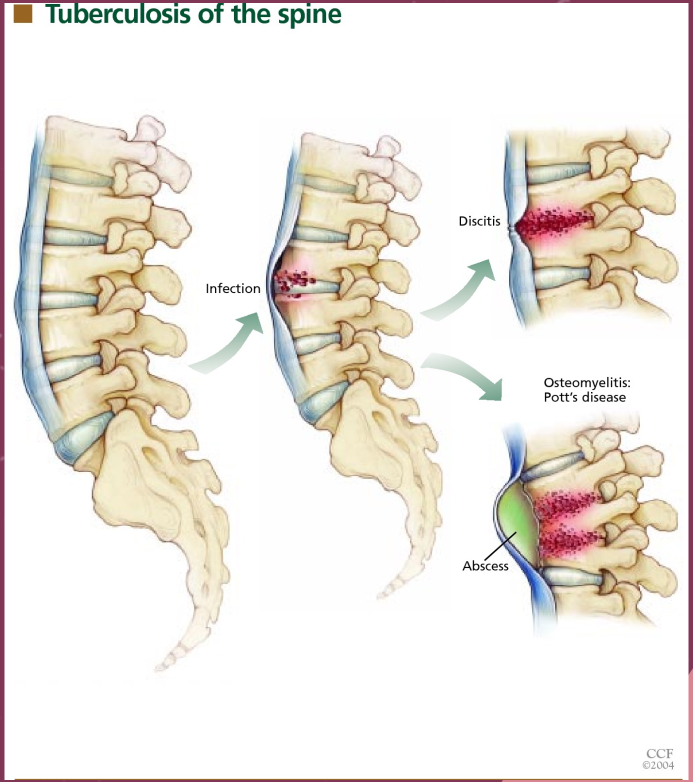


Figure 11. Tuberculosis of the spine. Reprinted from McLain & Isada. (10).

Skeletal system (cont)

Arthritic tuberculosis

- Affects **major, weight-bearing joints**
- Swelling, discomfort, loss of function
- Late presentation: cartilage deterioration, deformity, leaking sinuses[33]

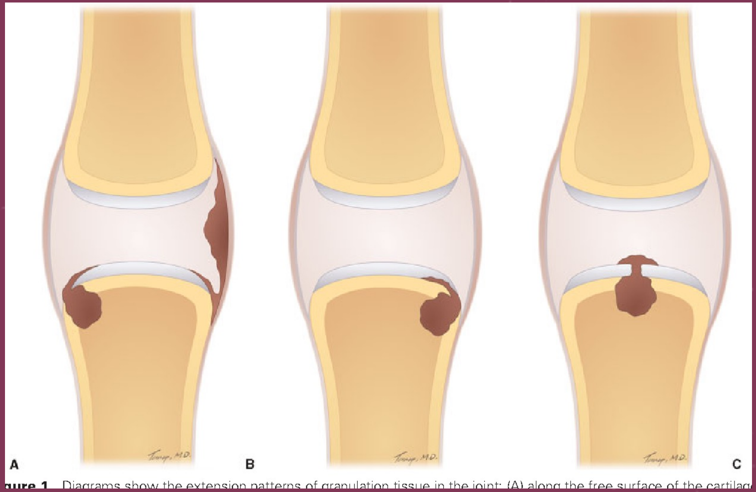


Figure 12. Tuberculosis arthritis. Reprinted from Pattamapaspong et al. (11).

Gastrointestinal system

Ileocecal TB (common site of gastrointestinal TB)

- Clinical and radiological similarities to patients with **Crohn's disease**
- Persistent **abdominal pain** (90%)[33]
- **Mass in the right lower quadrant** (25-50%)[33]

TB peritonitis

- Peritoneum becomes **studded with tubercles** which leak proteinaceous fluid ('**ascites**')[33]

03

Treatment

What treatments will be offered to Robert and how do these work?

85%

Success rate for treating TB infection[38]

60%

Mortality rate in developing countries with a lack of medical resources, emerging role of multidrug resistant strains of TB[39]

Treatment plan

Drug-susceptible TB	Extrapulmonary TB	TB meningitis and TB pericarditis
Minimum 6 months on rifampin-based regimens[40]	Up to 9 months (TB arthritis)[41]	Additional corticosteroid treatment for first 1-2 months[42]

Standard treatment regimen[43]

0 months — 6 months

Destruction of bacteria in all growth stages[44]

Drug
Isoniazid
Rifampin
Pyrazinamide
Ethambutamol

← May be discontinued if bacteria susceptible to other three drugs[43]

Drug
Isoniazid
Rifampin

Eliminate residual dormant bacilli[44]

Main goal of TB drug therapy:

Kill all **actively metabolizing bacilli** in lungs and eliminate **less actively replicating bacteria** which can cause relapse[44]

Mycolic acid

Virulence factor and potential target for therapeutics[44]

- Component of **Mtb cell wall**, along with peptidoglycan and other lipids
- Defends against chemical damage and dehydration of cell wall[45]
- **Prevents hydrophobic antibiotics** from penetrating cell wall
- Allows Mtb to **survive within macrophages**

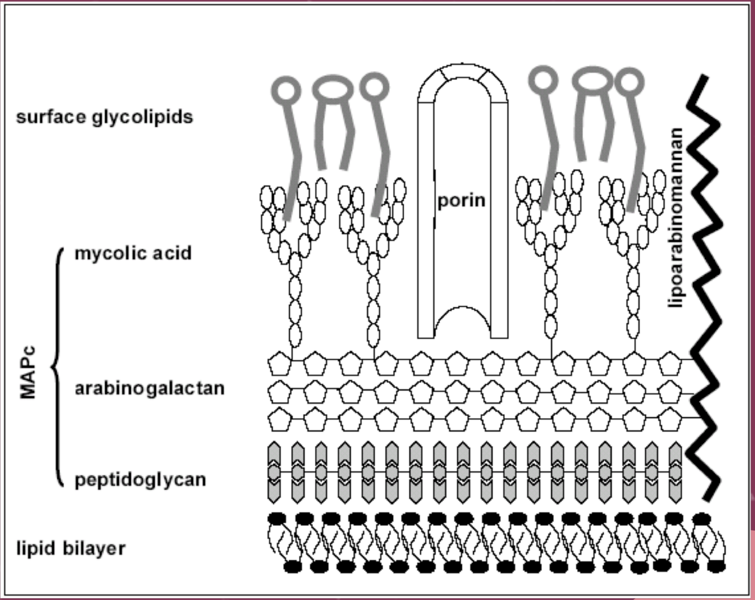


Figure 13. Mycolic acid in Mtb cell wall. Reprinted from SRI International (12).

Isoniazid: mechanism of action

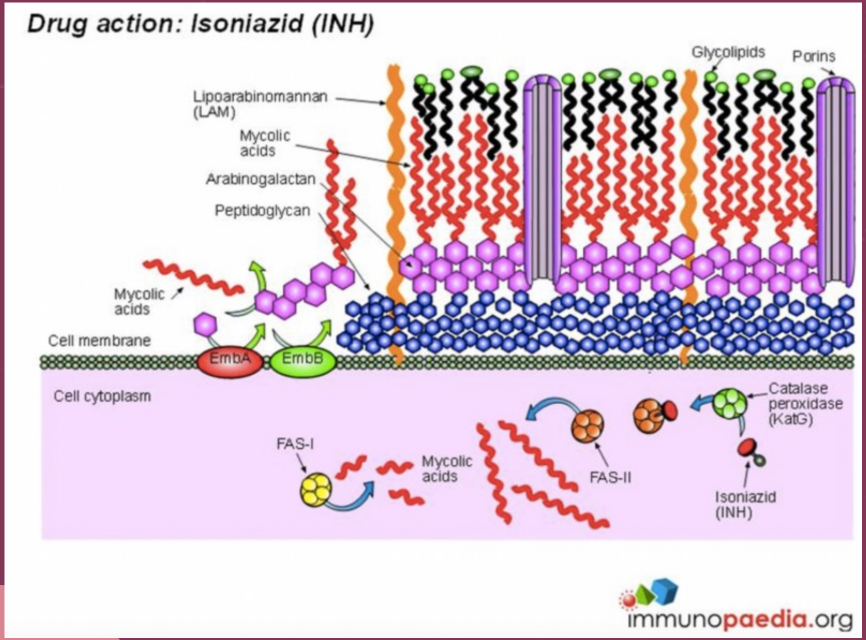


Figure 14. Mechanism of action of isoniazid. Reprinted from Immunopaedia (13).

1. Circulates through bloodstream, enters bacteria via **passive diffusion**[46]
2. **Prodrug activated** via **KatG**, a catalase-peroxidase enzyme
3. **Activated intermediate binds InhA**, a carrier protein which functions in the **type II fatty acid biosynthesis pathway** of Mtb[47]
4. InhA inhibition **disrupts mycolic acid biosynthesis** → disruption of cell wall

Rifampicin: mechanism of action

- Binds B subunit of DNA-dependent RNA polymerase[48]
- Blocks path of elongating RNA chain at 5’ end[49]
- Prevents RNA transcription/bacterial RNA synthesis

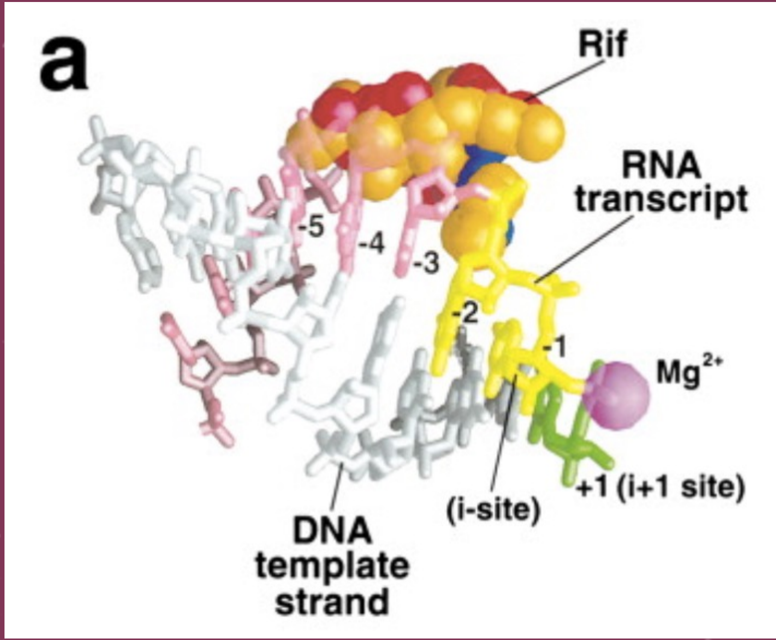


Figure 15. Rifampicin binding to RNA polymerase. Reprinted from Campbell et al. (14).

Rifampicin resistance

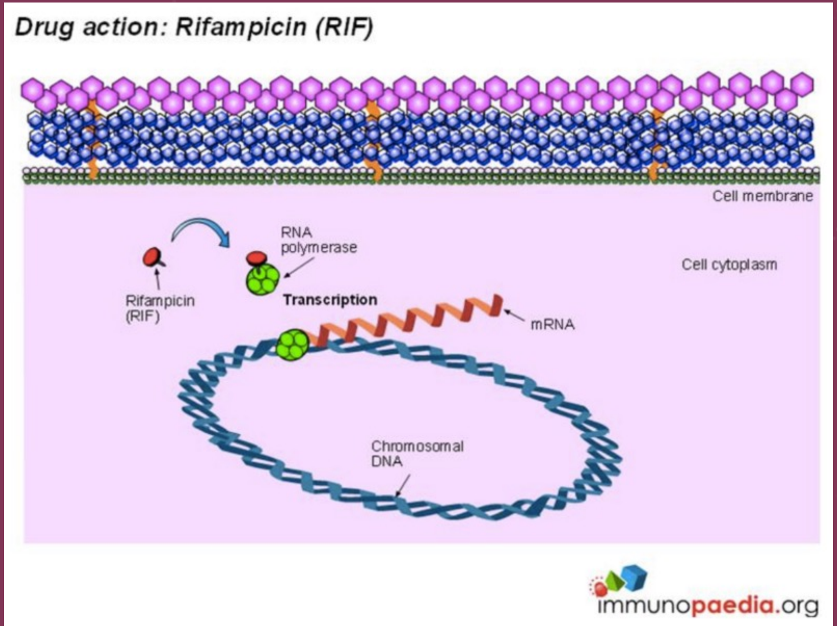


Figure 16. Mechanism of action of rifampicin. Reprinted from Immunopaedia (13).

- Rifampicin **does not interfere with substrate binding** or catalytic activity of DNA-dependent RNA polymerase
- If a **transcript has already been synthesized** and entered elongation phase, it is **resistant to the drug**[49]
- Monotherapy with rifampicin results in only **short-lived improvements** and development of **resistance** → use with isoniazid[50]

Pyrazinamide: mechanism of action

Sterilizing agent – kills nongrowing bacteria

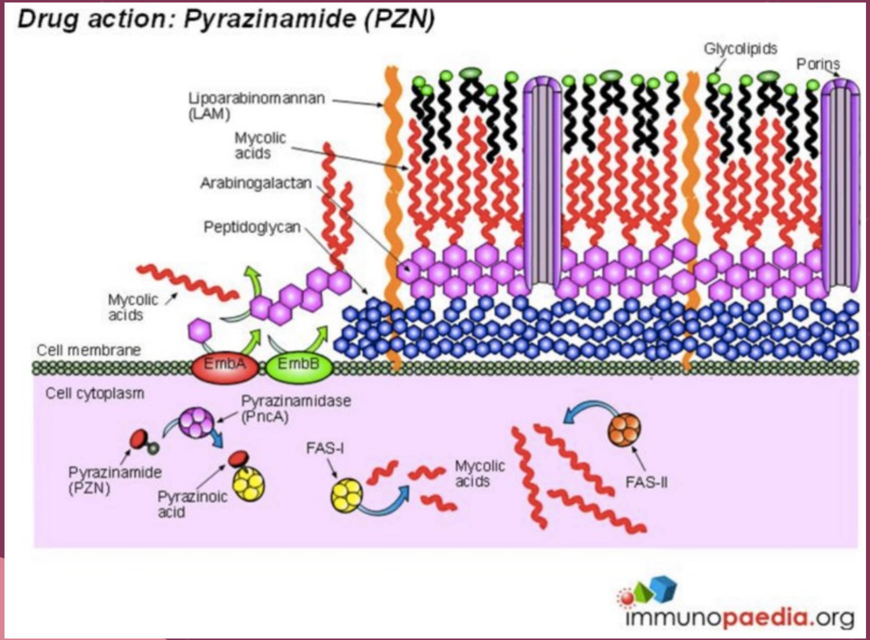


Figure 17. Mechanism of action of pyrazinamide. Reprinted from Immunopaedia (13).

1. Prodrug activated by Mtb's **PncA**, a nicotinamidase[51]
2. Active form (pyrazinoic acid) only functions at **acidic pH**
3. Accumulation of protonated drug causes **acidification of bacteria**, inhibiting enzyme function[51]

Effects of pyrazinamide[51]

Target	Effect	Inhibition of:
Fatty acid synthase	Inhibits fatty acid synthesis[52]	Growth and bacterial replication
Membrane	De-energizes membrane	Protein and RNA synthesis
Ribosomal protein S1	Inhibition of S1	Trans-translation

Ethambutol: mechanism of action

- Reduces production of cell wall components lipoarabinomannan and arabinogalactan[53]
- Inhibition of bacterial replication[54]

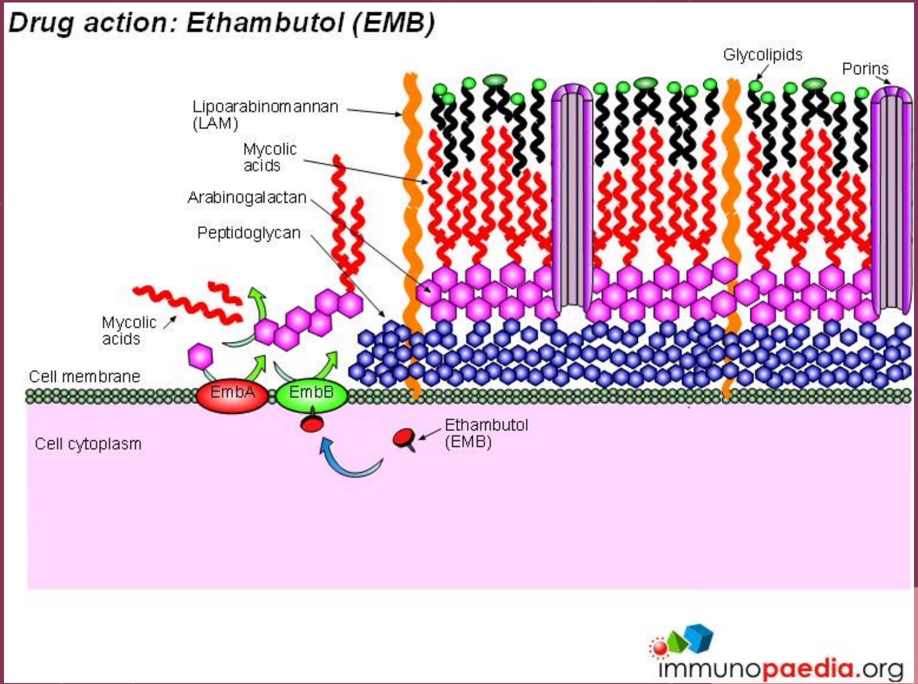


Figure 18. Mechanism of action of ethambutol. Reprinted from Immunopaedia (13).

Caveats of TB treatment

- Patients must continue taking TB medications for **months**
- **Improvement in symptoms** is seen only after a few **weeks of treatment**[55]
- Noncompliance can lead to:
    - Ineffective treatment
    - Higher chance of future complications[55]
    - Development of resistant strains of TB[55]

04

Public Health Unit

Why was the Public Health Unit notified in this instance?

33%

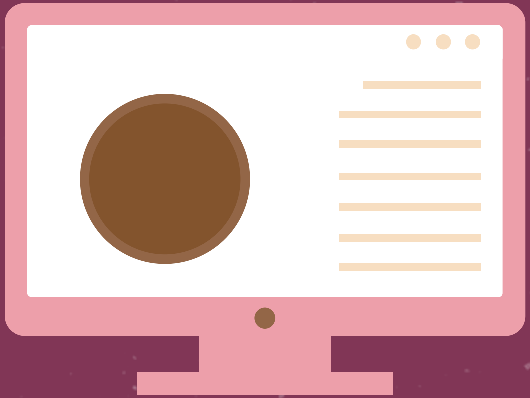
of the world's population is infected with latent TB[56]

>3,000,000

people die of tuberculosis every year[57]

Preventing transmission

- TB is a major concern for the Public Health Unit as it is **highly transmissible**
    - Spread in the air[56]
- Governments must identify individuals with **active** and **latent TB**[56]
- To prevent disease outbreaks, Public Health Unit must be **notified of a case within 24 hours**[58]



Epidemiology and Surveillance in BC[59]

- Contact tracing reports
- Identification of latent TB
- Identification of site of disease
- Case definitions of active TB
- Active and latent TB surveillance

Laboratory responsibilities

- Laboratories must **report suspected or confirmed TB cases** to the Public Health Unit:[60]
  - Date
  - Test results
  - Name and address of physician
- Failure to submit reports may result in **citations** and **fines**, especially if negative health outcomes result[60]

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