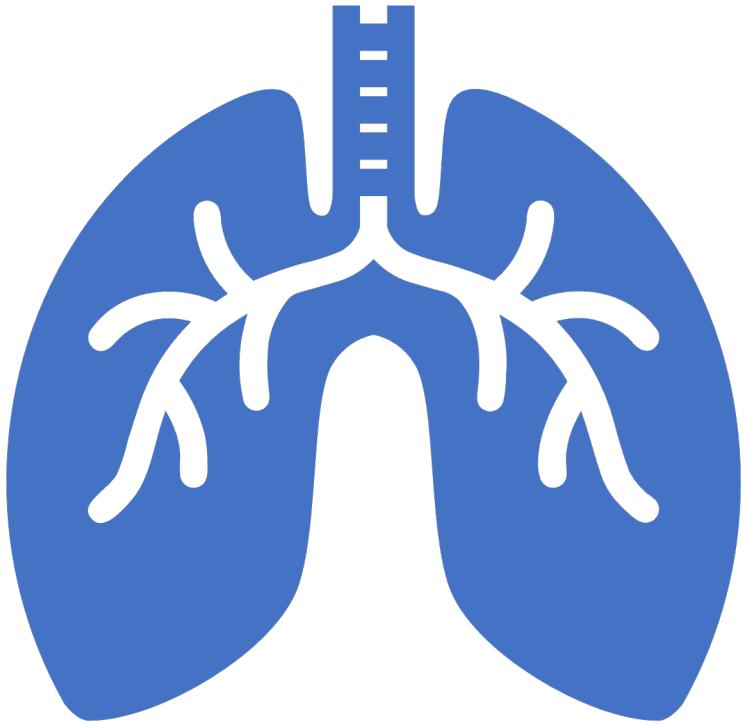


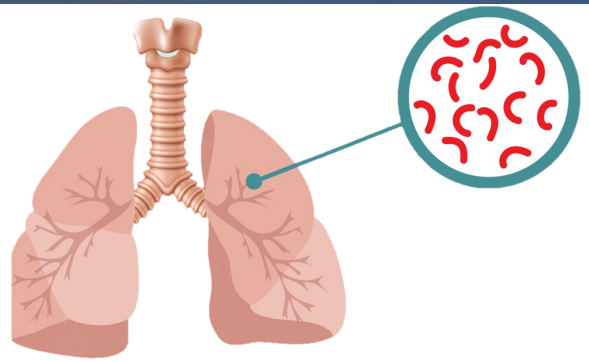
Tuberculosis -The Body System

Catherine Gai

Presentation Overview

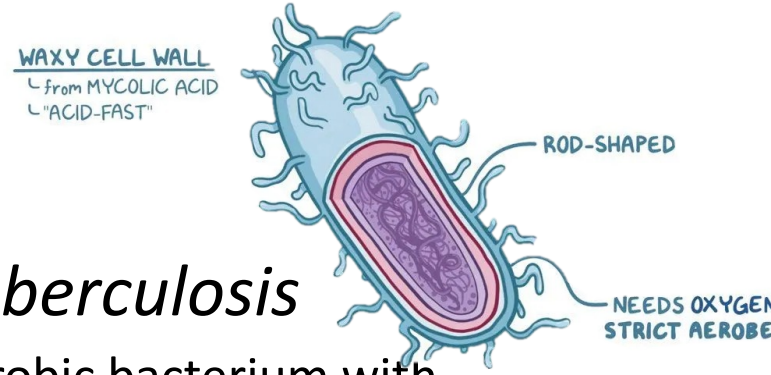
0. **Introduction: Background Information**
1. **Signs & symptoms; Key History of Presenting Illness; Laboratory samples and results**
2. **Body systems affected & physiological changes**
3. **Treatments & mechanism of action for each medication**
4. **Reasons to notify public health agencies**

Introduction



Tuberculosis

- An infectious disease that primarily affects the lungs and respiratory system
- Caused by *Mycobacterium tuberculosis*, which is transmitted through aerosol droplets
- Typical symptoms include coughing, chest pain, difficulty breathing, fever, and night sweats
- After initial infection, the bacteria remain latent and can be reactivated



Mycobacterium tuberculosis

- A slow-growing aerobic bacterium with cell wall made of peptidoglycans and complex lipids (mycolic acid) which function as virulence factors
- The free lipids on the outer layer make it a 'Acid-fast bacillus'
- It enters host through aerosol droplets and are deposited in the alveoli
- Its multiplication and dissemination induce host immune responses that cause extensive damages

[2,4]

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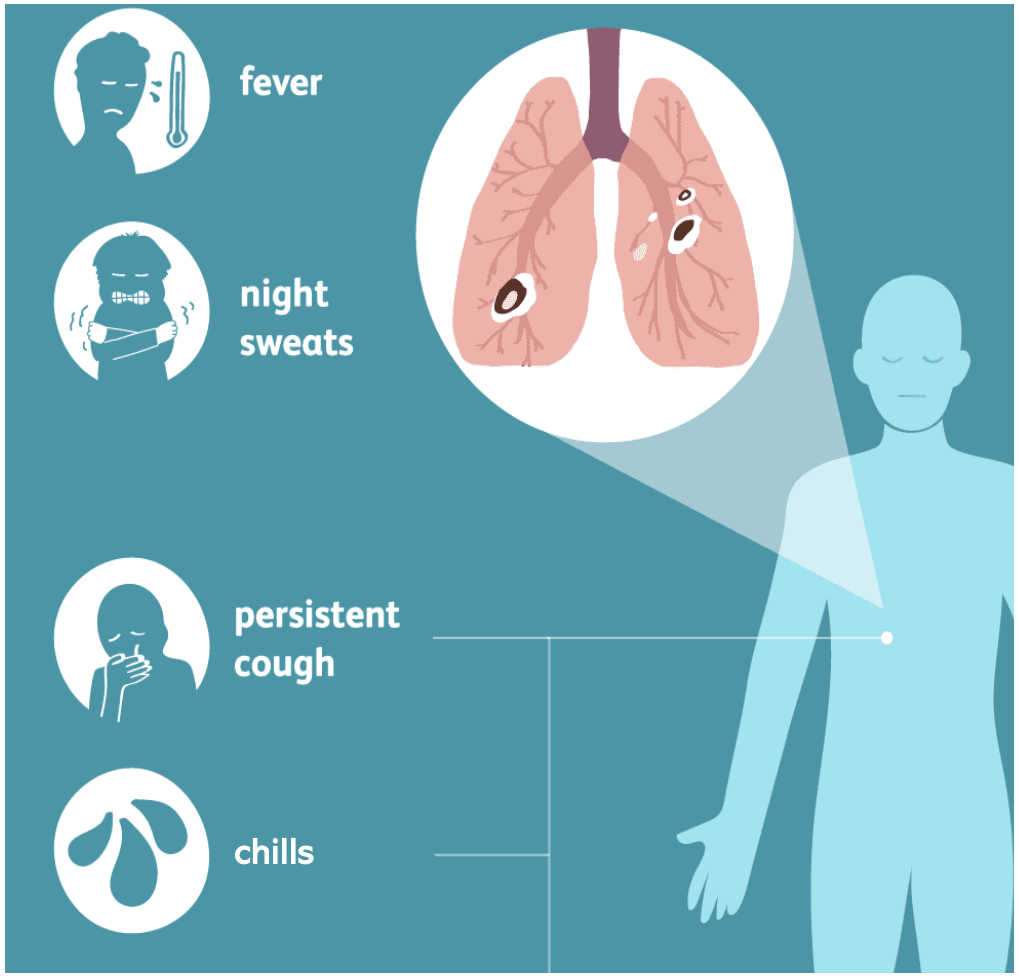


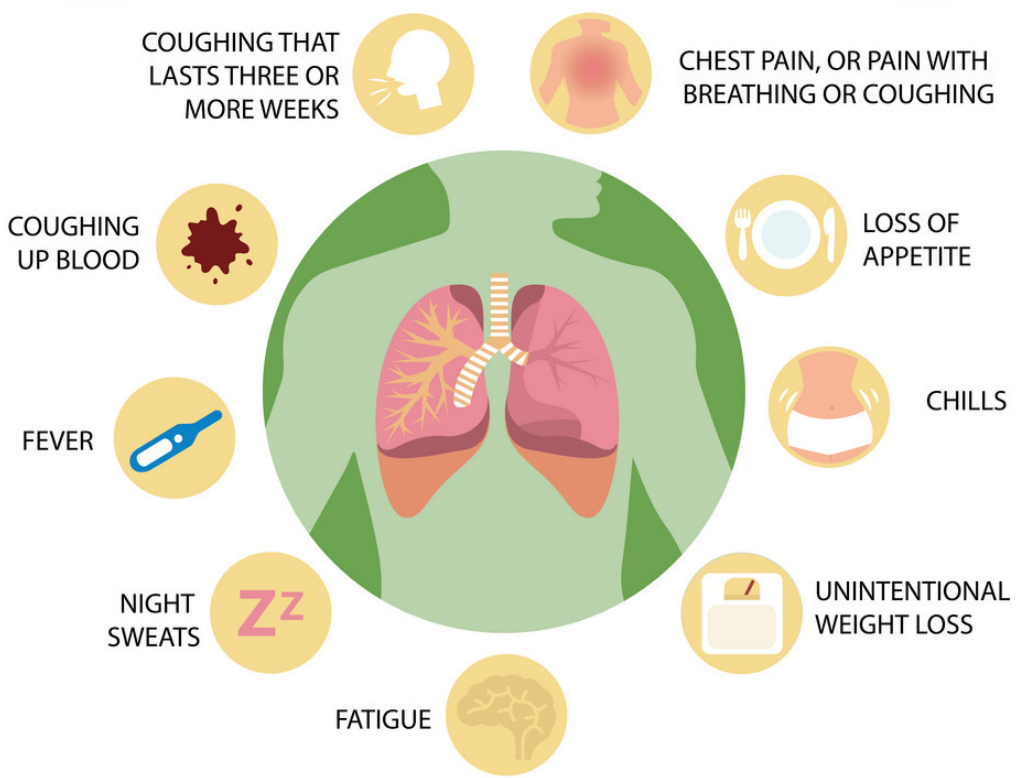
Signs & Symptoms in Robert's Case

- Fever of 38.5°C
- Findings from auscultation of lungs
  - Crackles in the right lung
    - Abnormal clicking / rattling noises during inhalation
      - Due to excess secretion in the airway
  - Decreased breath sounds in the right lower lung field
    - May be due to:
      - Air / fluid in the lungs
      - Increased thickness of chest wall
      - Reduced airflow to the lungs
- Chronic productive cough
- Night sweats
- Chills

[2,5,6]

Tuberculosis (TB) Disease Progression & Other Possible Signs & Symptoms

- Early primary infection
  - Likely asymptomatic
- As infection progresses, patient may present with
  - Pleuritic chest pain
  - Difficulty sleeping
  - Chronic coughing
- Reactivated (secondary) TB symptoms
  - Weight loss
  - Persistent coughing with bloody sputum
- Other symptoms include
  - Swollen lymph nodes in the neck
  - Fatigue
  - Loss of appetite

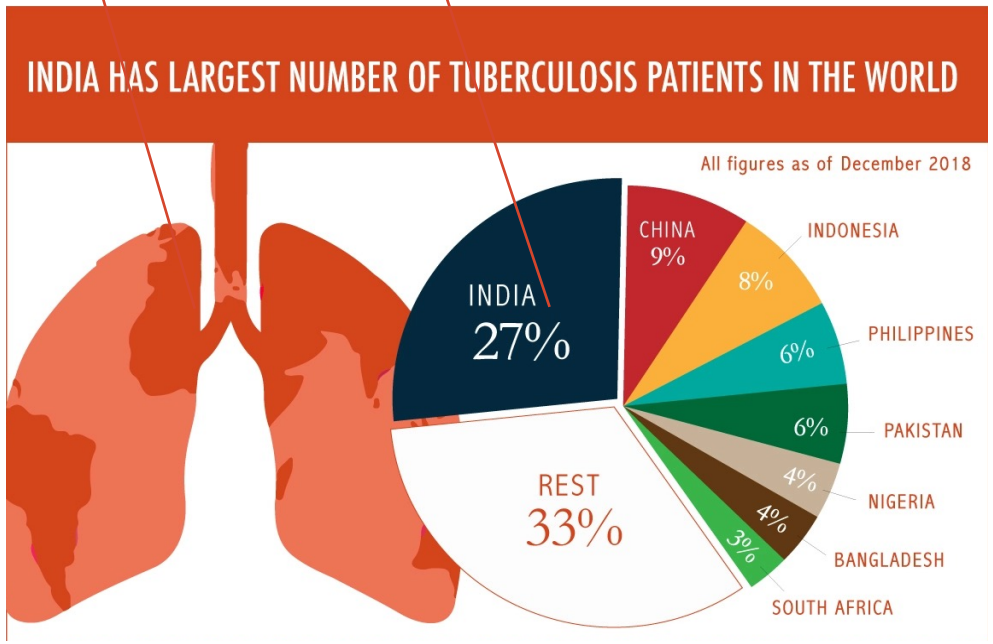


History of Present Illness

- HPI describes the development of disease and serves as the basis for guiding clinical decision-making:
  - Robert is 53 years old
    - Older people are relatively more vulnerable to TB infection
  - He immigrated from India a year ago
    - Suggests high likelihood of TB infection
    - India has the world's greatest TB pandemic (27% of all TB cases)
  - Prolonged symptoms for the past month
    - Suggests active TB disease

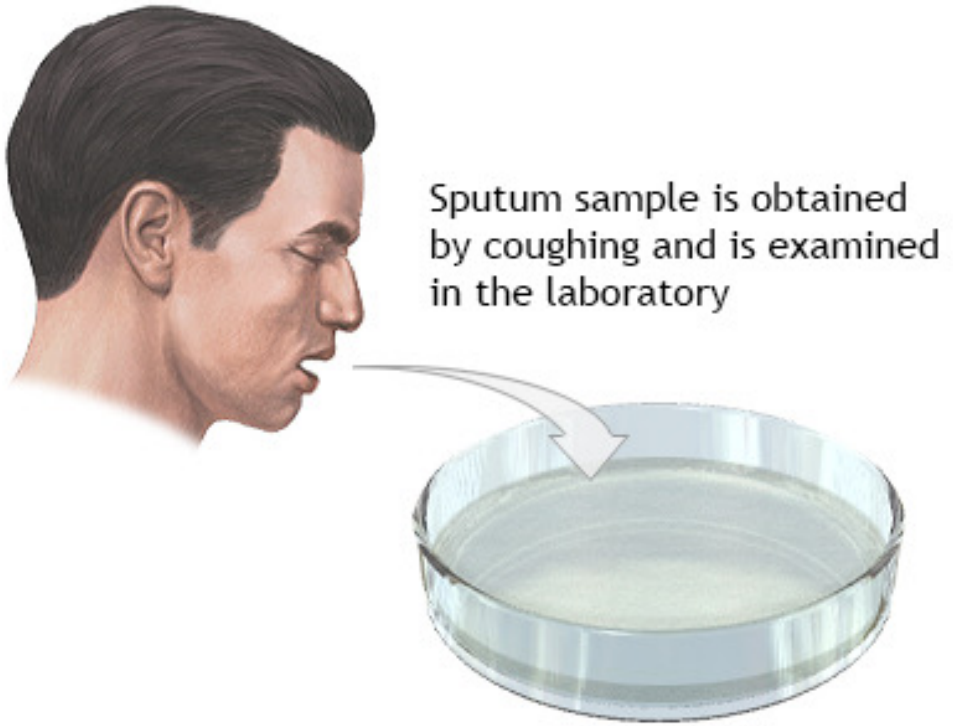
38% of overall # of TB death

24% of global gap between projected incidence rate and # of newly diagnosed cases

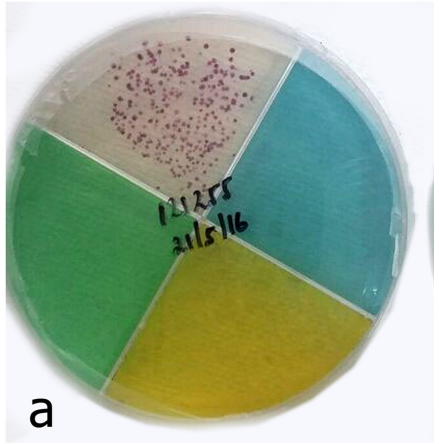


Tests & Laboratory Samples

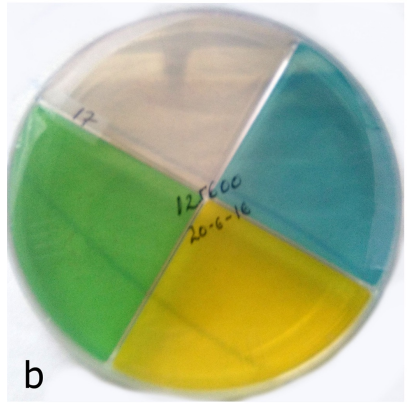
- Chest X-ray
  - Used to understand the extent of infection
    - For Robert, there would be abnormalities / spots on his right lung
- 3 deep sputum samples over 3 mornings
  - Sputum is a thick mucus made in the lungs; it is often coughed up due to respiratory infection
  - Samples are taken on different days for accuracy
  - Samples are examined under the microscope to confirm TB infection
    - For Robert, the sputum test would have been positive for *Mycobacterium tuberculosis* (Mtb)
  - 2 tests can be done on the sputum sample



Laboratory Samples Continued



Positive for Mtb growth (red microcolonies) on the clear quadrant



Negative for Mtb growth on clear quadrant

- 2 tests for the sputum samples
  - Smear test
    - Sample is smeared onto a glass slide for examination
    - Mtb is counted in the smear
      - The higher the #, the more contagious the patient is
  - TB Culture test
    - The gold standard
      - Negative culture test – no Mtb found
      - Positive culture test (active TB disease) – Mtb proliferates
    - Takes 1-8 weeks to develop
    - 2 types of media can be used
      - Solid media
        - The gold standard for growing Mtb
        - Slower to develop
      - Liquid media

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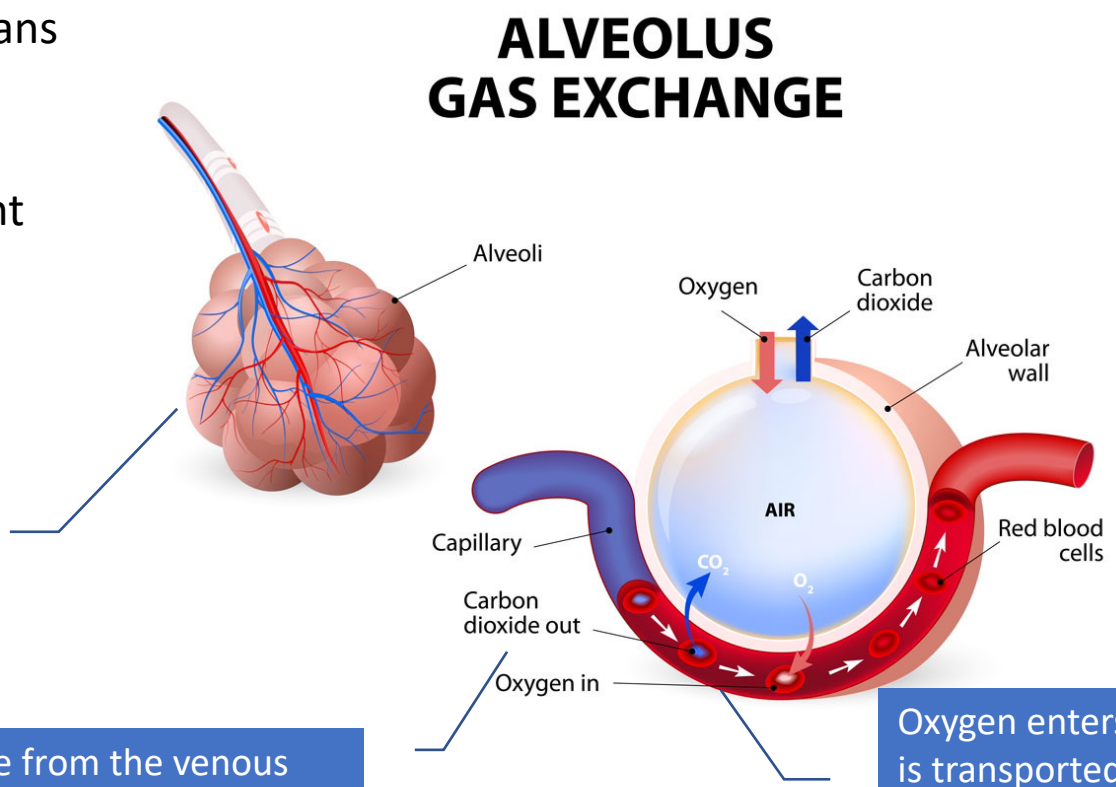
Normal Physiological Functioning of the Lung

- The lungs are the foundational organs of the respiratory system
- Basic function is to facilitate gas exchange between the environment and the bloodstream / tissue



Lung -> lobes -> alveoli (Primary location for gas exchange)

Carbon dioxide from the venous system leaves the capillary network

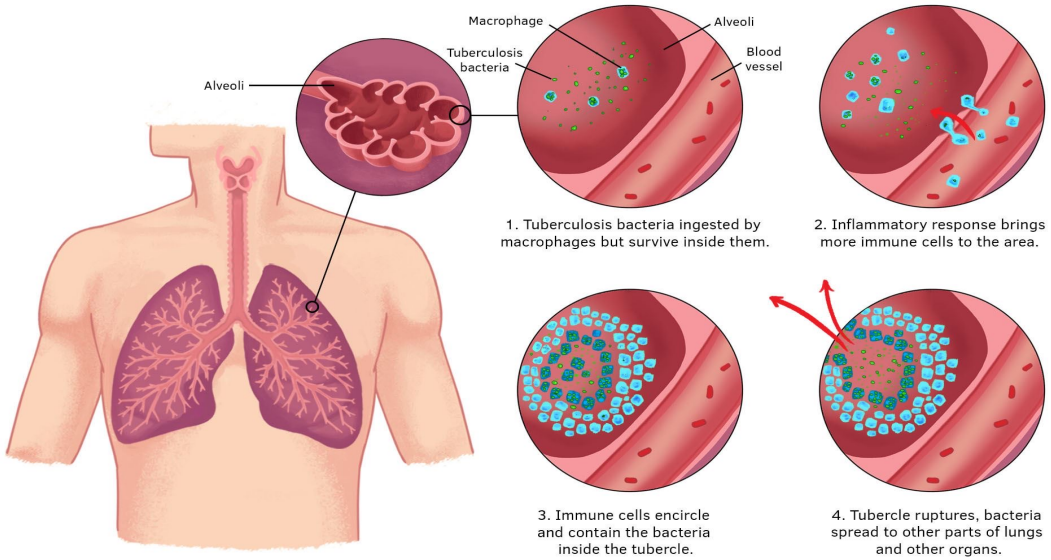
Oxygen enters the alveoli, then is transported into the capillary network / arterial system

[2,6,11]

Respiratory System is Affected by TB

1. Mtb is phagocytosed by alveolar macrophages, but it is not killed

2. Inflammatory response recruits more immune cells to the site



3. Granuloma sequesters Mtb / infected macrophages

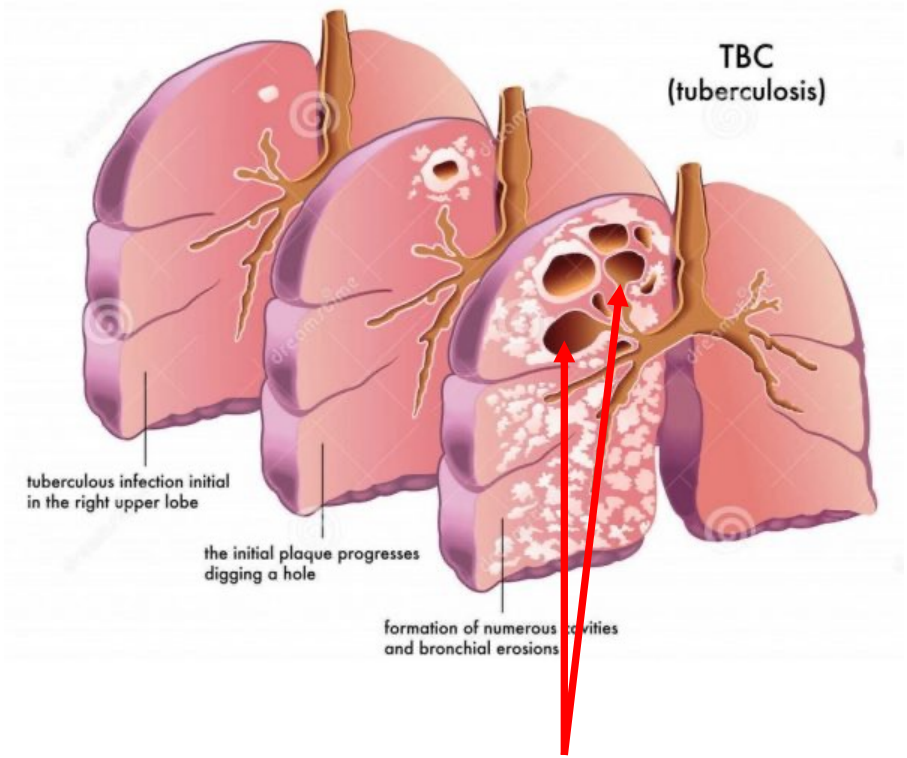
4. Tubercle rupture leads to Mtb dissemination

- The direct damage is found in the lungs, where Mtb is deposited in the alveoli and induces an inflammatory response

[1-4,6-16]

Respiratory System Damage

- Inflammatory response
  - Leads to increased permeability of surrounding capillary & leukocyte migration
  - Leads to increased pleural fluid accumulation
    - Manifested as chest pain during respiration
- Bronchi breakdown leads to caseous necrosis formation
  - Coughed out by patient, and leads to cavity formation
  - Cavity may distort airway, or cause bronchiectasis
- Bronchiectasis
  - Bronchial wall thickening and losing elasticity
  - Manifested as inability to breath
- Pulmonary fibrosis
  - Lung tissue is scarred and damaged / being replaced by collagenous tissue



Cavities & erosion

[6-11,19,21-26]

Mtb Dissemination to Other Organs

- Hematogenous dissemination (Miliary TB) may lead to damages in the
  - Musculoskeletal system
    - Spinal damage / swelling or loss of function in joints
      - E.g. Pott's disease; Tuberculous arthritis
  - GI system (ileocecal, jejunoileal, anorectal)
    - Abdominal pain / diarrhea
  - Central nervous system
    - Tuberculous meningitis / brain damage due to exudate formation
- Via the lymphatics; can lead to
  - Tuberculous lymphadenitis
- Sexual transmission
  - May result in infertility

[17-21,25]

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Treatments

Overview

- 85% success rate, if there is
  - Swift diagnosis and treatment
  - A complete follow through with the treatment plan
- In developing countries, mortality rate is 60% without the appropriate treatment

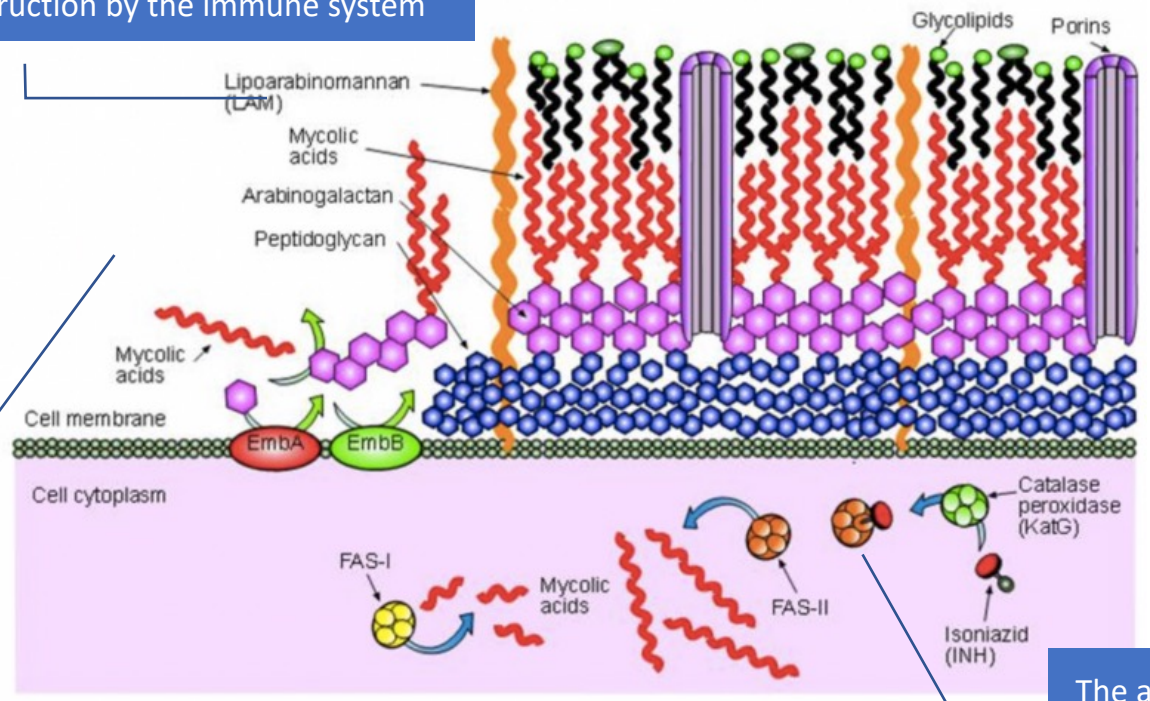
Treatment For Robert

- Robert will be offered antituberculosis medication
  - For drug-susceptible TB, this means..
    - An initial phase with
      - Rifampin + Isoniazid + Pyrazinamide + Ethambutol
    - Minimal treatment period is 6 months
      - First 2 months
        - Goal is to destruct bacteria in all growth stages
      - Remaining 4 months
        - Treatment with only Rifampin (eliminates residual dormant bacilli) + Isoniazid (kills Rifampin-resistant mutants)

[1,2,5-12,30]

Mechanism of Action: Isoniazid

This interference with bacterial cell wall synthesis makes it vulnerable to destruction by the immune system



- Has several bacterial targets
- Must be taken together with other drugs
- Isoniazid is a prodrug; it is activated by the bacterial enzyme catalase
- It enters the bacteria through passive diffusion

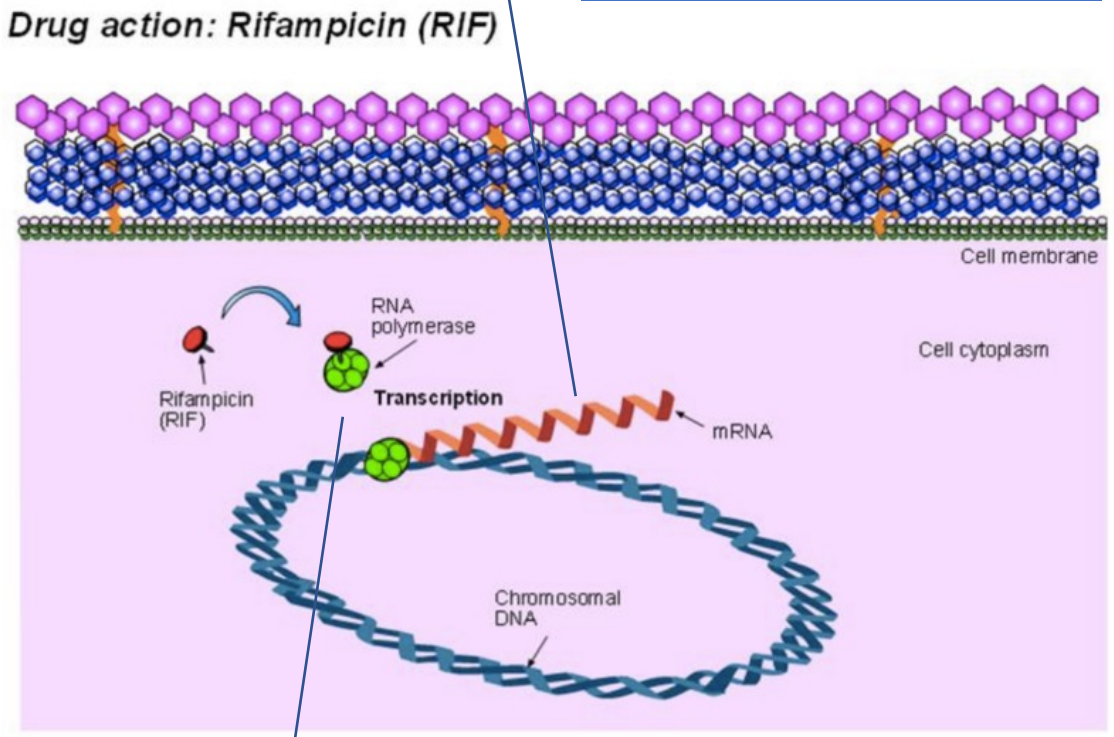
Mycolic acid is an important part of bacterial cell wall / virulence factor

The active drug binds bacterial enzymes and interfere with mycolic acid synthesis

Mechanism of Action: Rifampin

- Rifampin is a lipophilic drug
- It is always used in combination with Isoniazid, because
  - Monotherapy leads to short-lived improvements only
  - As well as increased prevalence of drug-resistant bacteria
- It has high affinity for the DNA-dependent RNA polymerase
  - However, it does not interfere with substrate binding/catalytic activity

Blocks RNA synthesis and subsequently Mtb replication



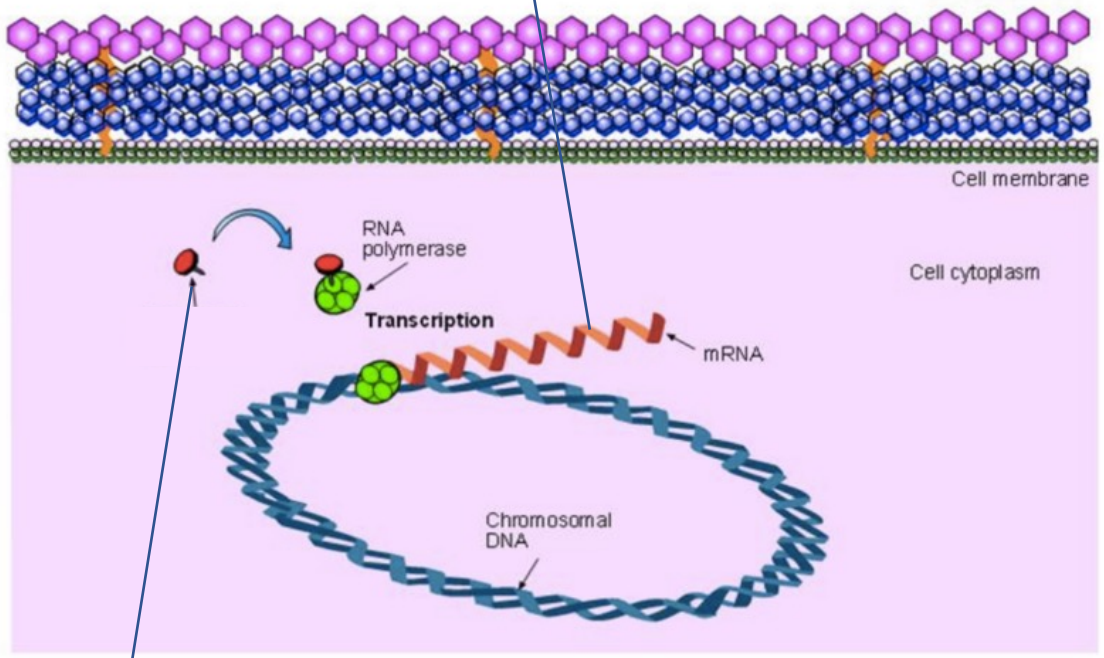
Inhibition of bacterial DNA-dependent RNA polymerase

[12,20,21,22]

Mechanism of Action: Rifapentine

- Rifapentine has the same mechanism of action as Rifampin; the difference being that:
  - Rifampin has a shorter half-life and a higher minimum inhibitory concentration
  - Rifampin is given once daily whereas Rifapentine is given once weekly

Blocks RNA synthesis and subsequently Mtb replication



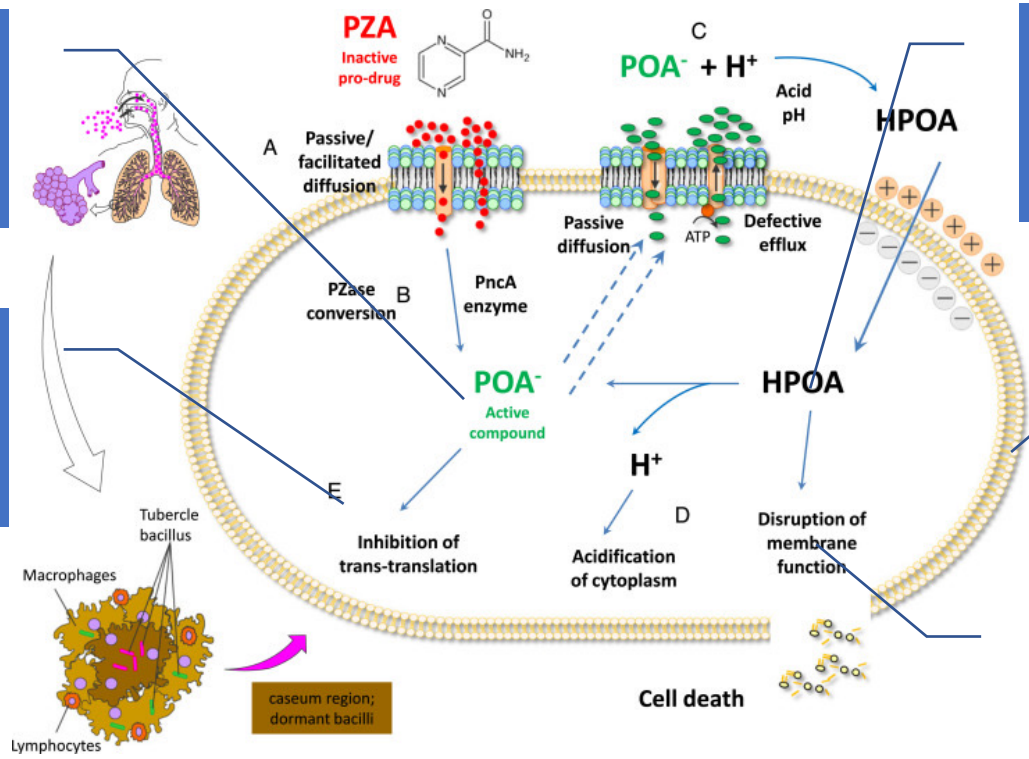
Inhibition of bacterial DNA-dependent RNA polymerase

Mechanism of Action: Pyrazinamide

- Pyrazinamide inhibits Mtb growth and has multiple targets

PZA (prodrug) is converted to its active form (pyrazinoic acid) through the enzyme pyrazinamidase, which is encoded by the pncA gene in Mtb

Target: Inhibition of ribosomal protein S1 – prevents trans-translation, a process essential for bacterial growth



Under acidic conditions, protonated POA diffuse into and accumulate in the bacillus and inhibit various bacterial mechanisms

Target: Inhibition of fatty acid synthase – prevents fatty acid synthesis / bacterial growth

Target: de-energizing the bacterial cell membrane by affecting membrane transport

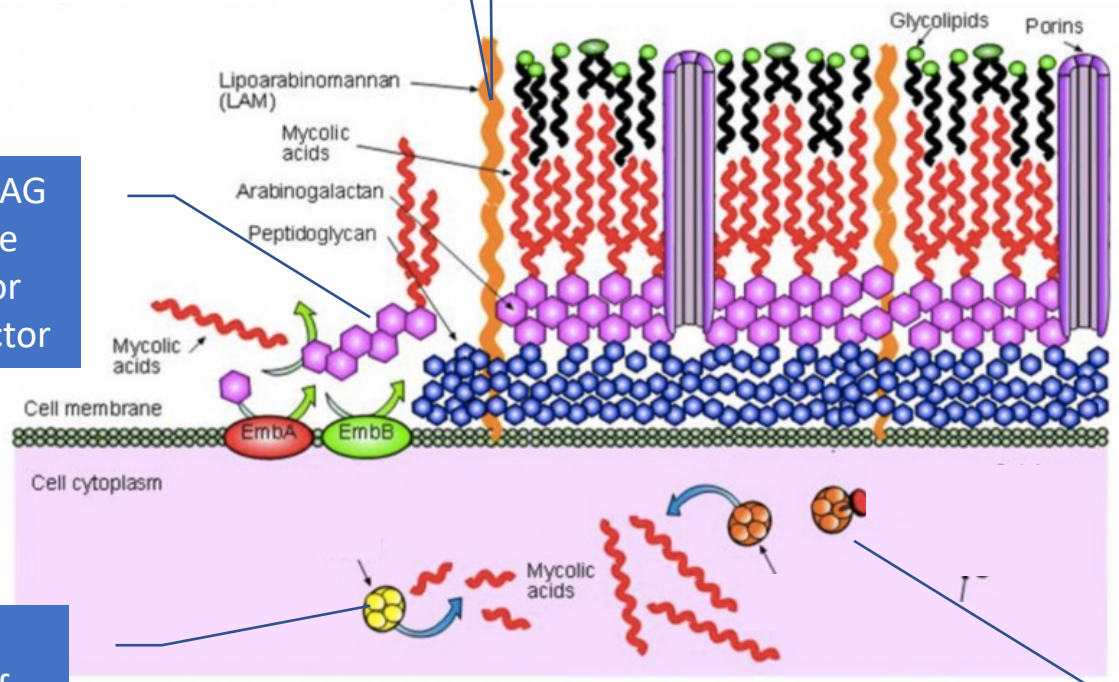
[10, 25-27]

Mechanism of Action: Ethambutol

- Ethambutol is a biostatic agent
- In the treatment plan, Ethambutol is used during the induction period
  - Functions as protection for unrecognized resistance to the other drugs

LAM and AG are important bacterial cell wall components

LAM is another surface molecule involved in interaction with host cells



Reduced concentrations of AG in the cell wall reduces the number of binding sites for mycolic acid, a virulence factor

This prevents Mtb multiplication; it also interferes with Mtb interaction with host

Arabinosyltransferase is involved in the synthesis of Lipoarabinomannan (LAM) and Arabinogalactan (AG)

Ethambutol diffuses into Mtb and inhibits activity of Arabinosyltransferase

[28,29]

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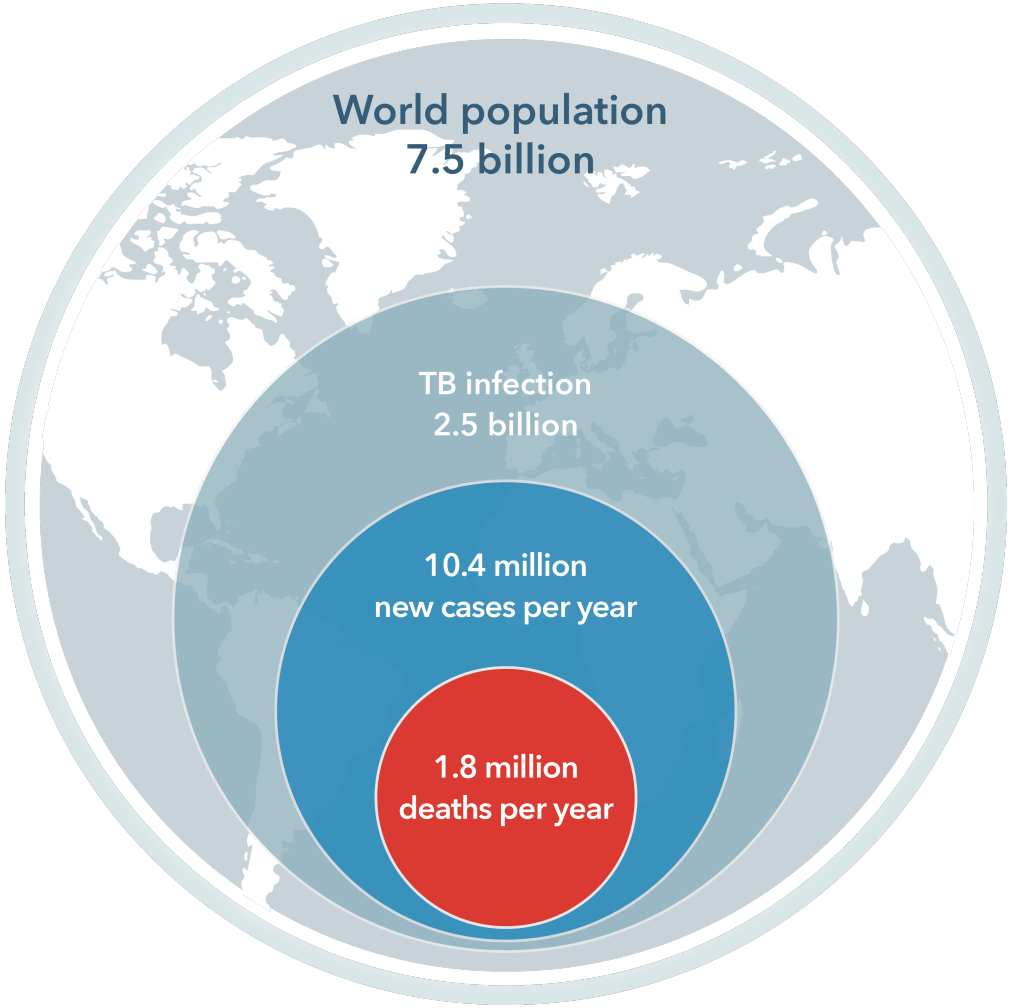
A Global Public Health Concern

TB is a highly contagious disease

- 33% of the global population is infected with latent TB
- Public health agencies need to identify individuals with active or latent TB disease, to control and prevent an outbreak
  - They should be notified as soon as possible
  - Suspected or confirmed cases of TB (date, test results, physician's name, location, and contact tracing reports) should be reported
  - In our case
    - It is important to notify public health authorities, given that Robert is an immigrant from India, a country with the highest # of TB cases
    - We need to determine if the infection occurred in Canada or India



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