



Tuberculosis

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Tuberculosis - General characteristic

1. Weakly Gram-positive bacilli
2. Nonmotile, obligate aerobes
3. Nonspore forming
4. The lipid mycolic acids, make up more than 60% of the total cell wall mass (for which the mycobacteria are named)
5. Facultative intracellular pathogens usually infecting phagocytes (e.g. macrophages).



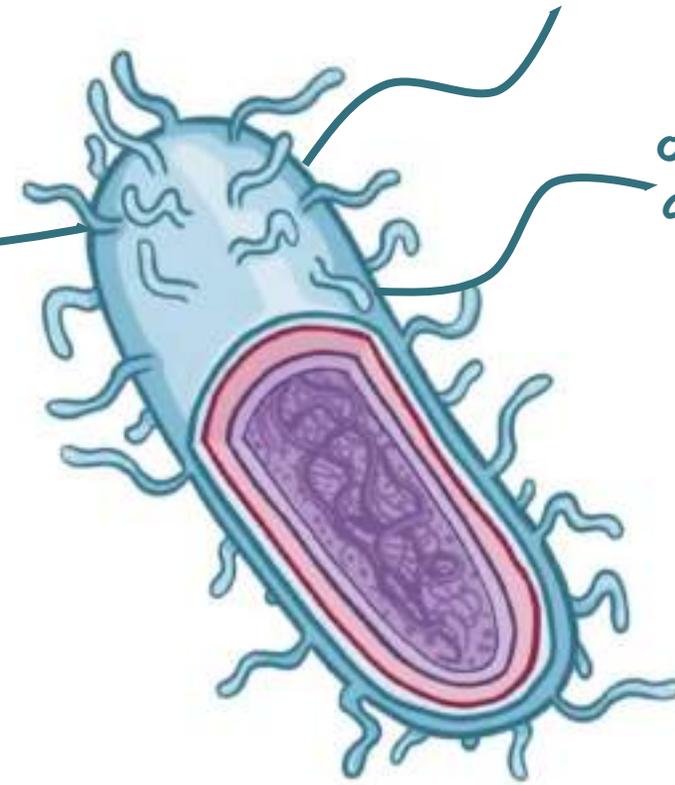
Tuberculosis - General characteristic

Waxy Cell Wall

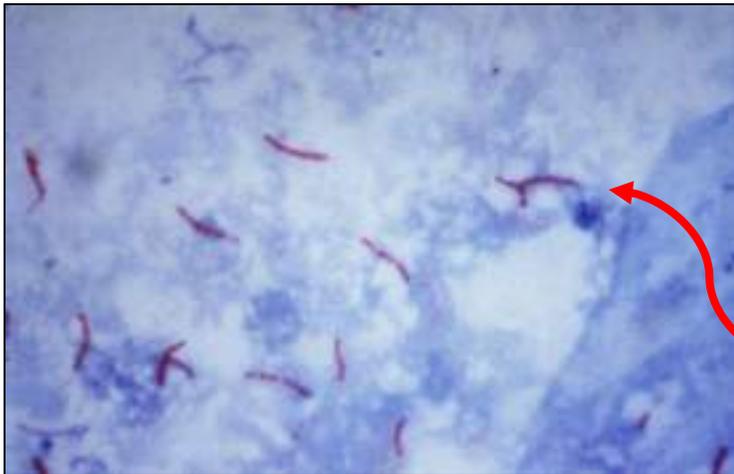
- Thick Mycolic acid layer
- Acid-Fast

Bacilli

obligate
aerobes



Ziehl-Neelsen stain



Bright Red

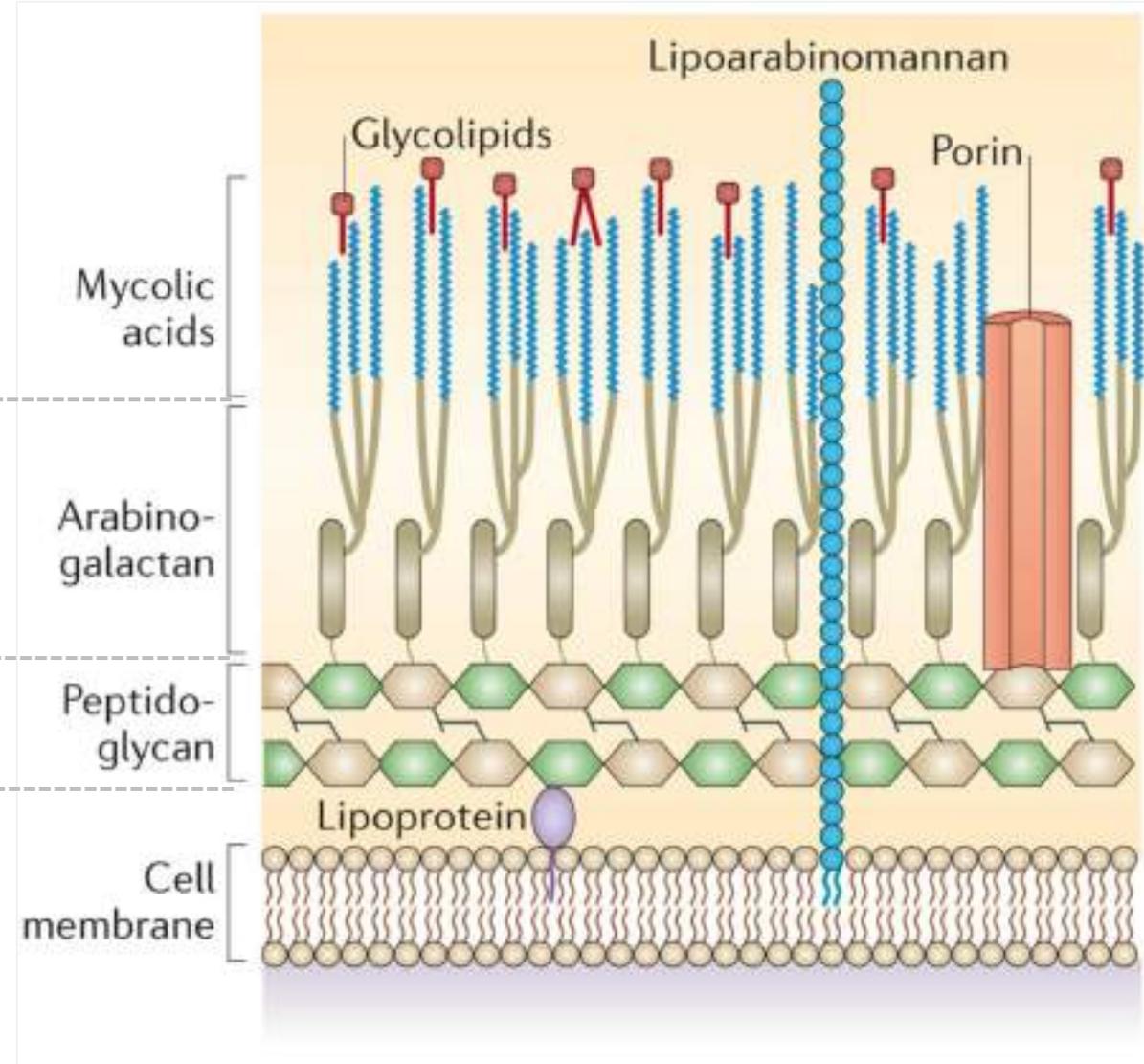


Tuberculosis - General characteristic

It confers very low permeability to antibiotics and responsible for acid fastness

A highly branched polysaccharide, serves to **connect peptidoglycan with the outer mycolic acid layer**

Maintains the rigidity of the cell wall



Tuberculosis – Transmission & Risk Factors

Source of Infection:

- Human (e.g. cases of pulmonary tuberculosis)
- Bovine (e.g. consumption of unpasteurized milk)

Mode of infection

1. **Inhalation mode:** tuberculosis is an airborne disease transmitted by inhalation of droplet nuclei while coughing and sneezing, or speaking of infected patients. The tiny dry droplets that contains bacteria (<5 μm in diameter) may remains suspended in the air for several hours.
2. **Inoculation mode:** the transmission through direct skin contact with infected patients is uncommon.

Risk factors

- Low immunity patients (AIDS)
- Posttransplantaion (renal, cardiac), diabetes, smoking, IV drug abuse, chronic renal failure

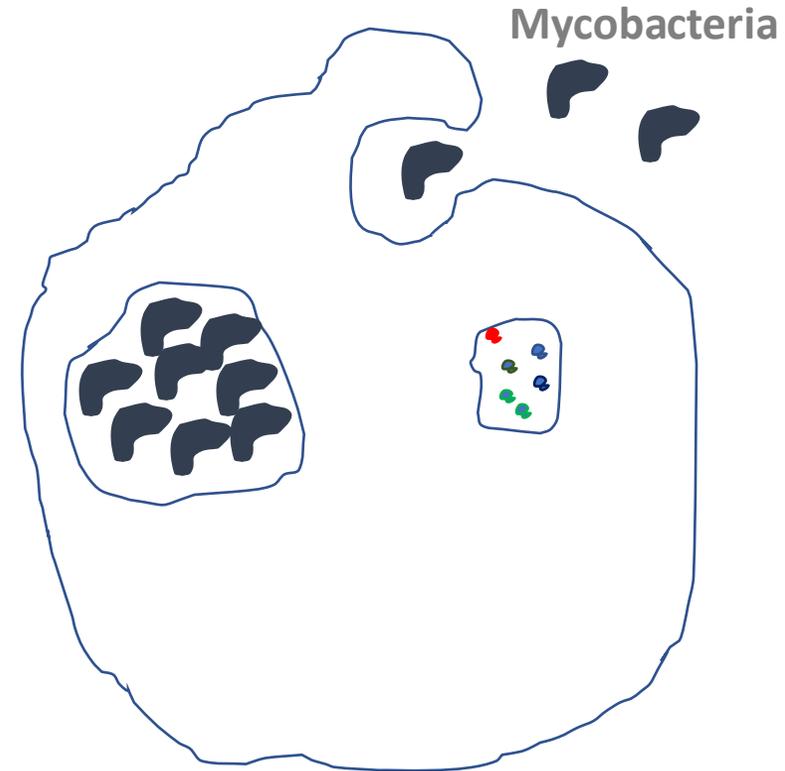
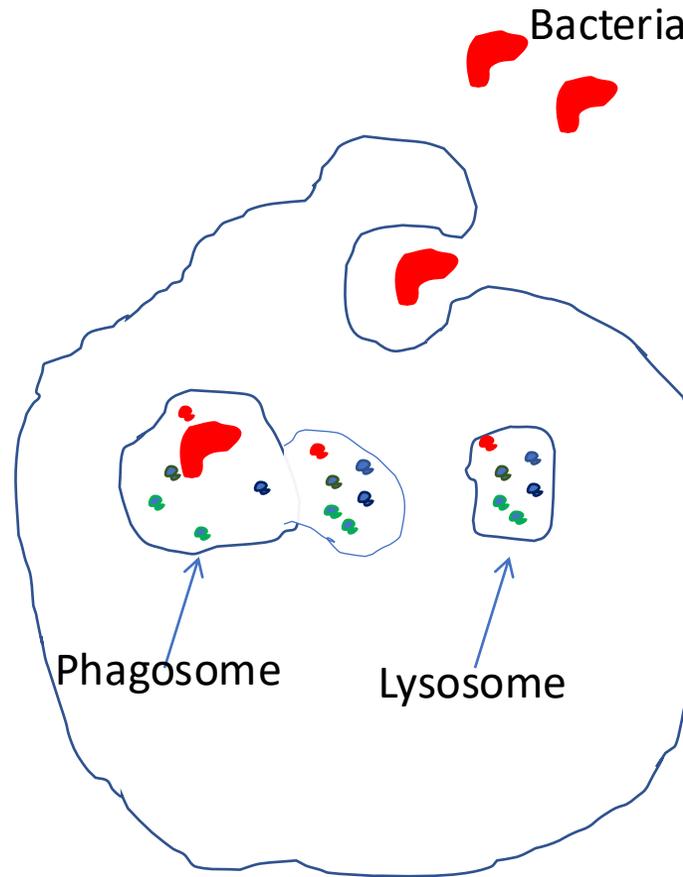


Tuberculosis – Epidemiology

- TB is the **second-most common** cause of death from infectious diseases **after AIDS**.
- **The infection dose (ID) 10 organisms.**
- 1/3 of the global world population is infected.
- 7-9 million new cases / year.
- Mortality without specific therapy: 70% of smear positive patients within 10 years.
- 2000-2020 one billion people were infected.
- 2000-2020: 35 million people died.
- Source of epidemics involve **school children and teachers** with unrecognized pulmonary tuberculosis, **homeless shelters, nursing homes, and health workers exposed to patients with unrecognized tuberculosis.**



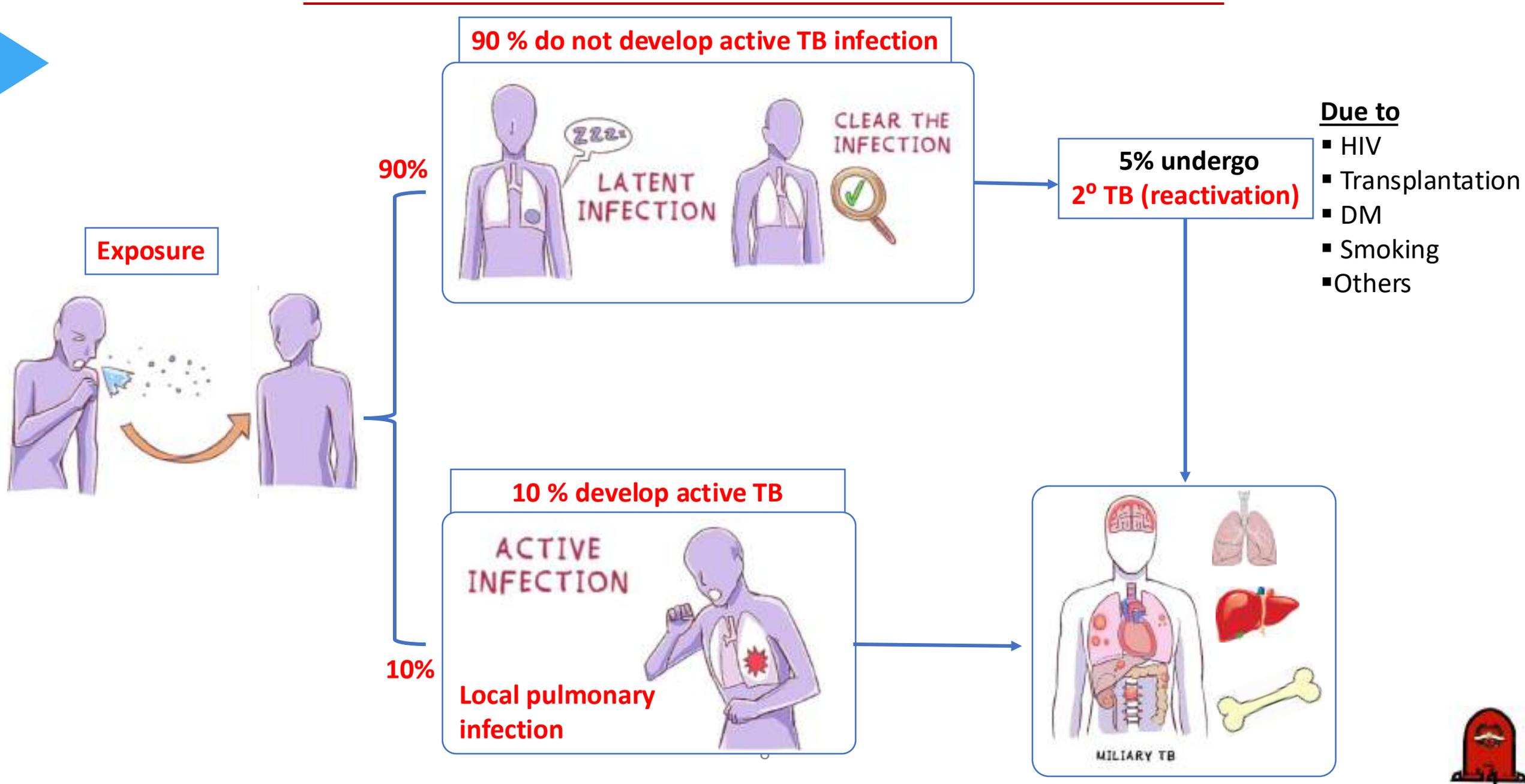
Q: Why Mycobacteria are can survive inside macrophages



- Mycobacteria inhibits phagosome lysosome fusion (**Sulfatides factor**)
- Bacteria will multiply
- Macrophage will burst
- Proteolytic enzymes will released outside causing tissue destruction



Classification of tuberculosis

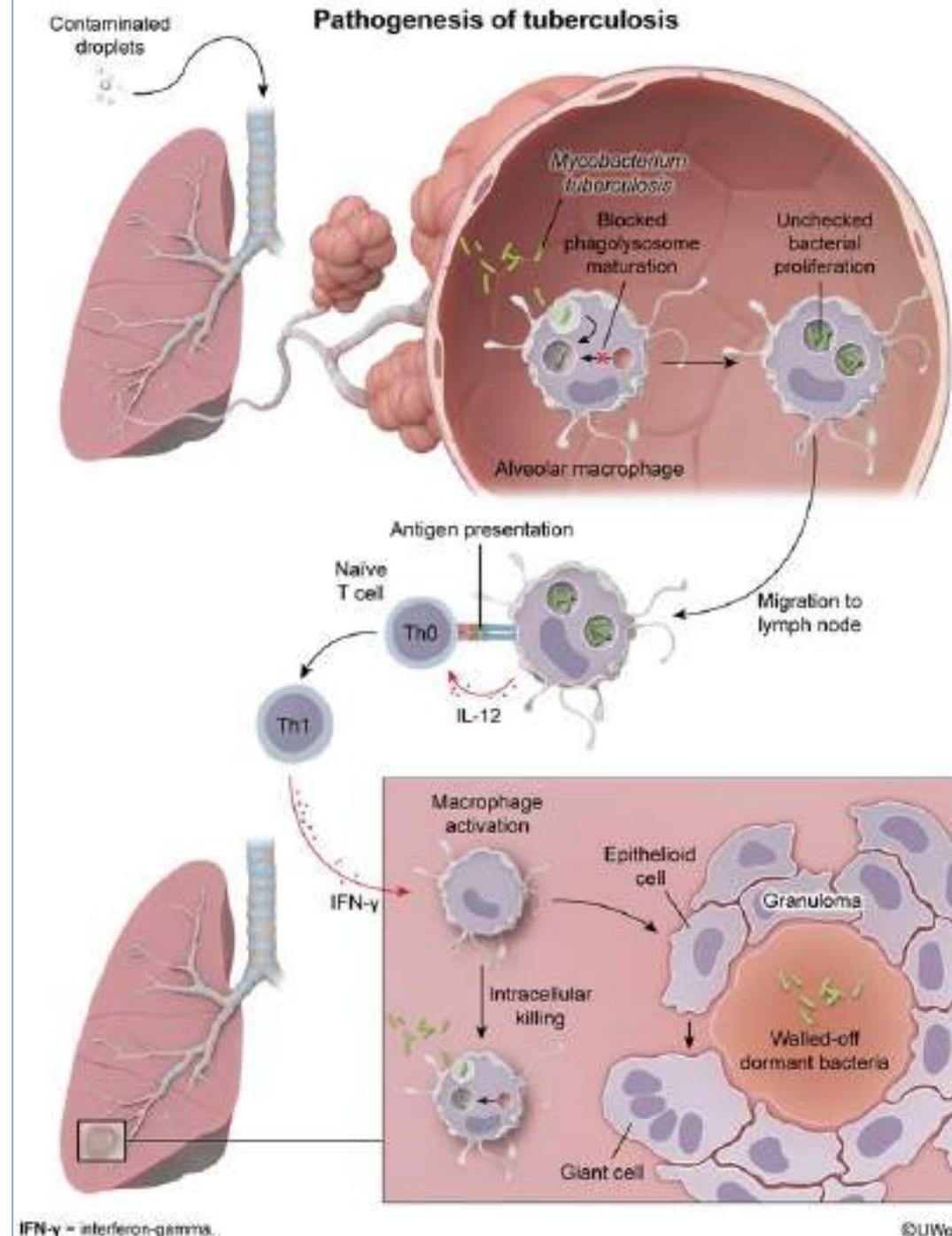


Primary TB

1. **Primary** tuberculosis is the response to the initial infection in an individual **not previously infected and sensitized** to *Mycobacterium*
2. **Droplet** containing tubercle bacilli are **deposited** in the **peripheral respiratory alveoli**
3. **Tubercle** bacilli are **engulfed** by alveolar **macrophages**.
4. The **majority** of **individuals** show **resistance** to infection and are able to contain the infection
5. **Macrophages** are **activated** by the **cytokines** at the site of infection. They be will **able to kill** and digest the tubercle bacilli.
6. These activated macrophages will aggregate around the center of the lesion and form a characteristic granuloma called tubercles



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Primary TB

* Signs of infection after exposure

- Mostly Asymptomatic
- Or Flu-like symptoms

* ~ 3 weeks → **cell-mediated immunity**
Immune cells surround the TB infection

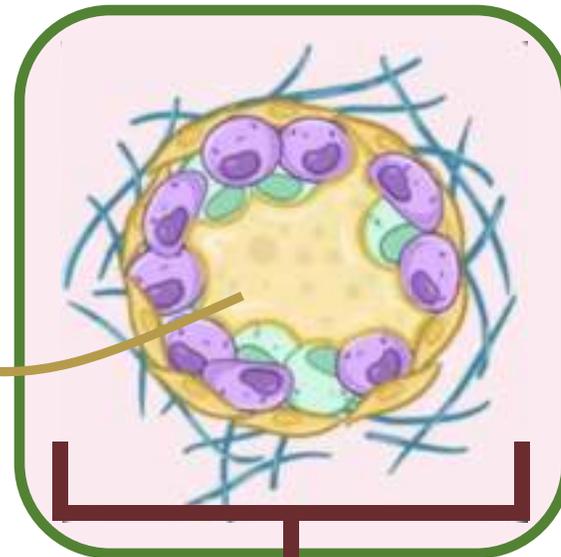
GHON Focus
+ Hilar lymph nodes

GHON Complex

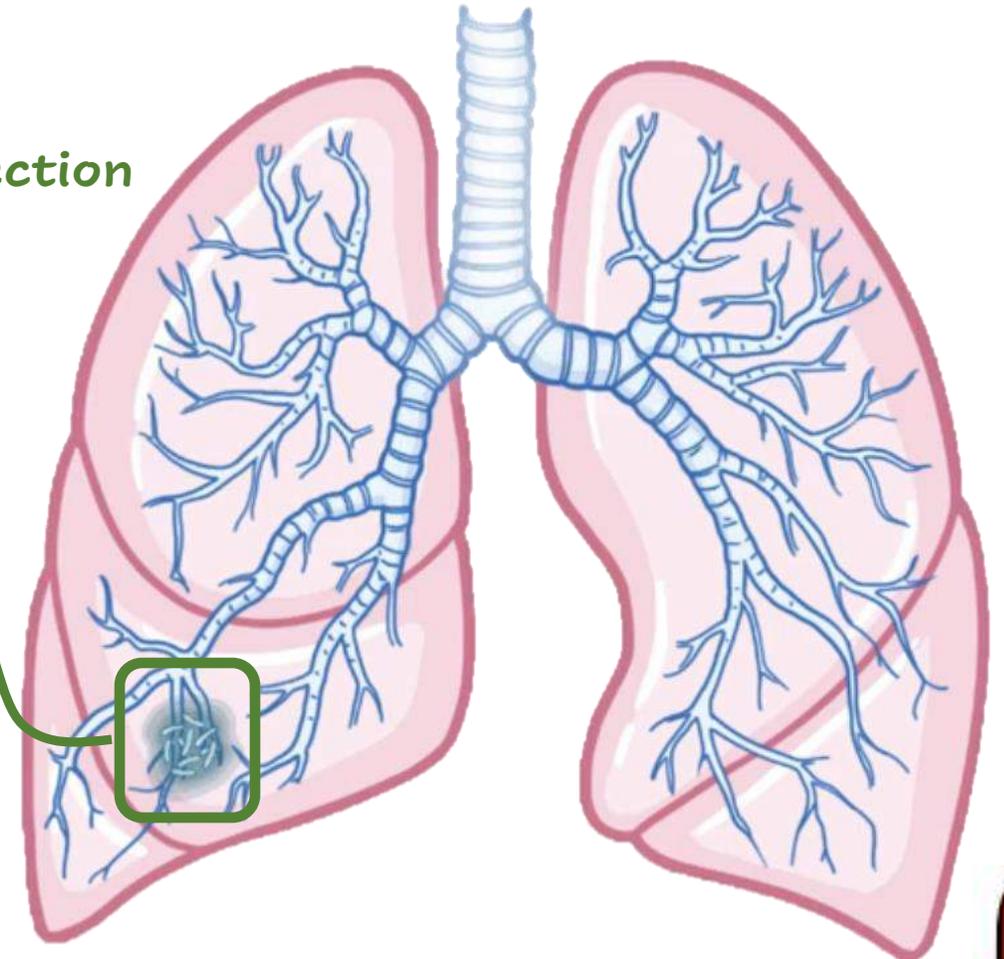
Granuloma

→ Wall off Bacteria and prevent spreading

Caseous Necrosis



GHON Focus



TB travels to the hilar lymph nodes

- Carried over by immune cells via lymph
- OR direct extension of Ghon focus

GhON Focus

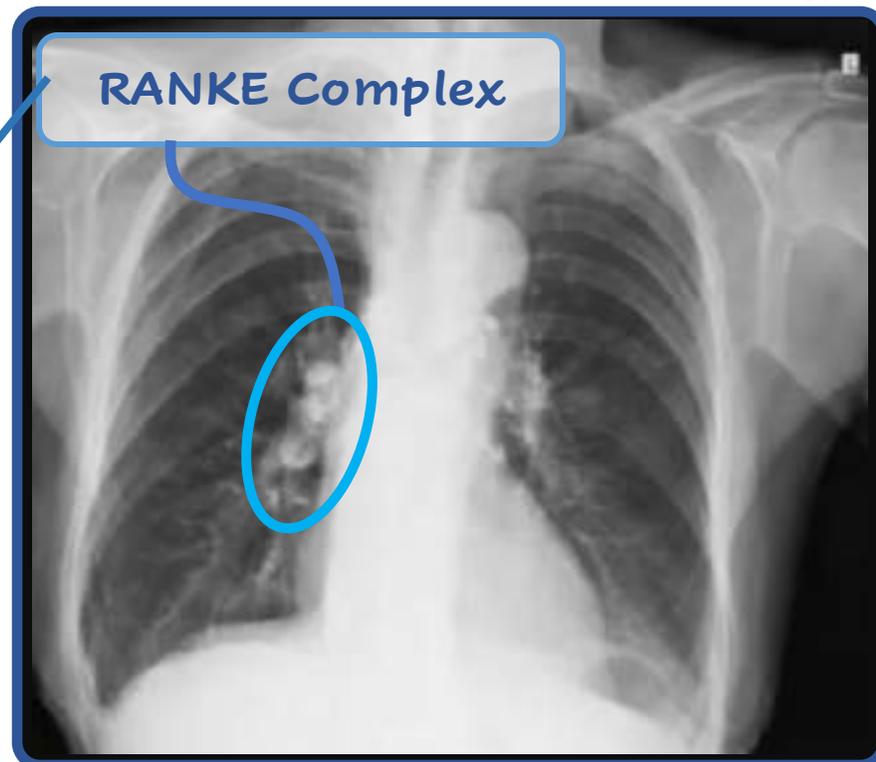
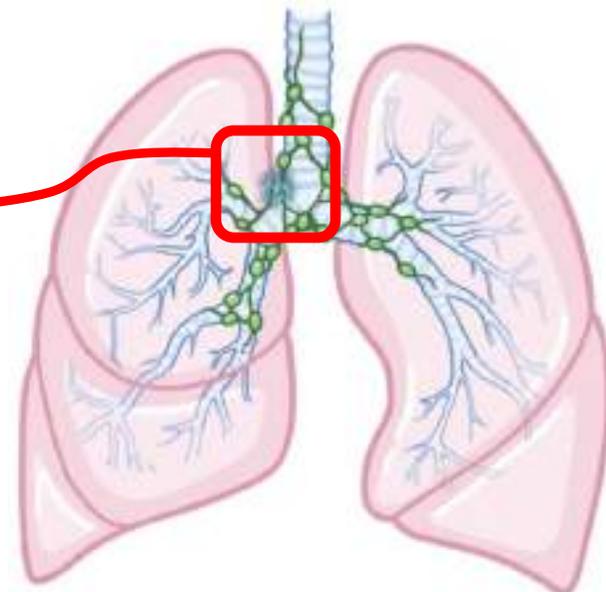
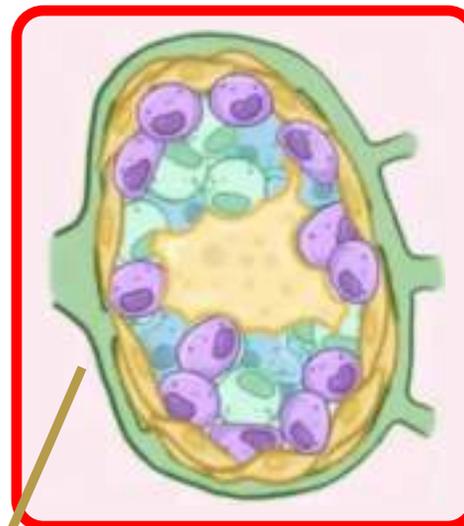
+ Hilar lymph nodes

GhON Complex

Tissue encapsulated within the granuloma

- Fibrosis
- & maybe Calcification

Produce Scar that can be seen on X-Ray



RANKE Complex

* Some Cases

TB is killed by the immune system

نهاية سعيدة 😊

* Other Cases

TB remains viable even TB is walled off

Alive BUT **dormant**

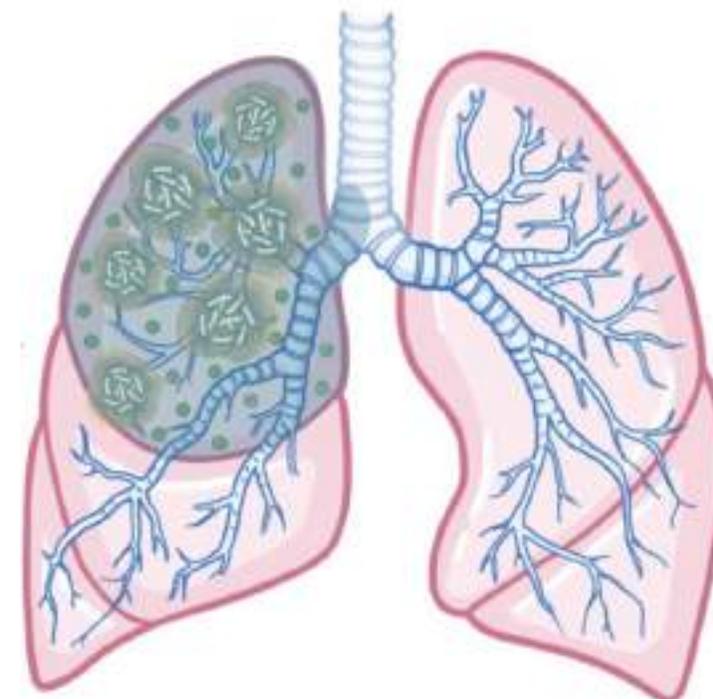
Secondary TB

Reinfection OR Immune system compromised (AIDS, chemotherapy, etc)

Reactivation

Patient is previously exposed → Strong immune response → memory T cells release **Cytokines (massive)** to control the infection

More Areas of Caseous necrosis → Cavities



Primary TB - Manifestations of Primary TB

- The primary stage of the disease may be symptom-free, or the individual may experience a flu-like illness.
- Patients develop flu-like illness (cough, fever, night sweats, weight loss etc). This can lead to delays in seeking care, and results in transmission of the bacteria to others.
- Healing in 3 weeks with fibrosis \pm calcification



Secondary (reactivation) tuberculosis

1. Occurs in 5-10% of patients had primary tuberculosis
2. The risk factors associated with **reactivation including**
 - A. Weakened immune system including:
 - HIV/AIDS
 - Diabetes
 - Certain cancers
 - Cancer treatment, such as chemotherapy
 - Drugs to prevent rejection of transplanted organs
 - Malnutrition
 - B. Poverty and drug abuse
 - C. Smoking
3. Reactivation usually occurs in body areas of relatively high oxygen tension and low lymphatic drainage, most often in the apex of the lung.



Secondary (reactivation) tuberculosis (Cont.)

4. The caseous necrosis become liquefied which containing a large number of bacilli which further spread by three ways:
 - Direct drainage into the airways and then get discharge into the environment while coughing and talking
 - Lymphatic spread
 - Hematogenous spread to various organs
5. The lesions show spreading and resulting in a large pulmonary cavity and bronchial spread



Manifestations of secondary TB

1. Cough is the common symptom
2. It is initially dry, but as the disease progresses sputum is produced and mixed with blood (hemoptysis).
3. Fever, malaise, fatigue, sweating, and weight loss
4. Radiographically, lung cavities with progressive destruction of lung tissue.



Cough



Blood stained sputum



Fever



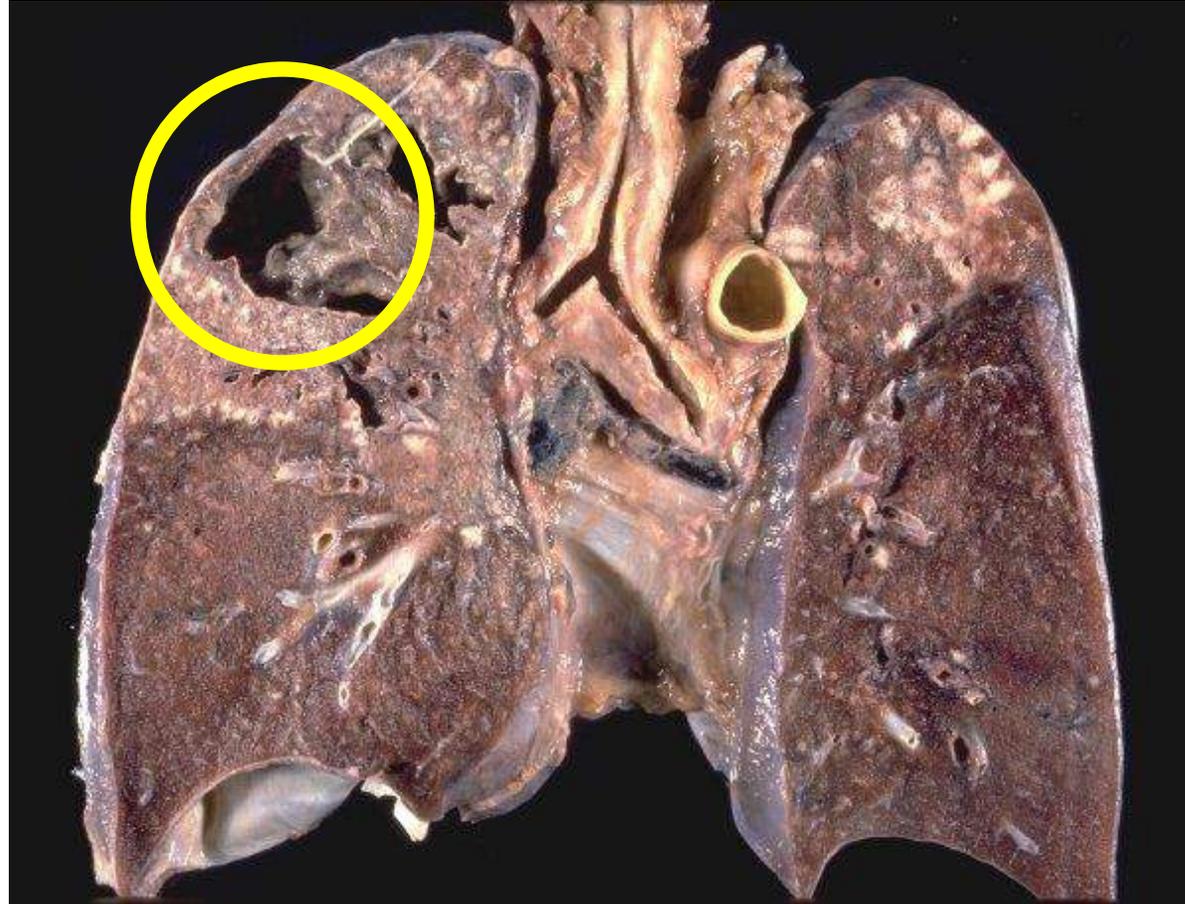
Weight loss



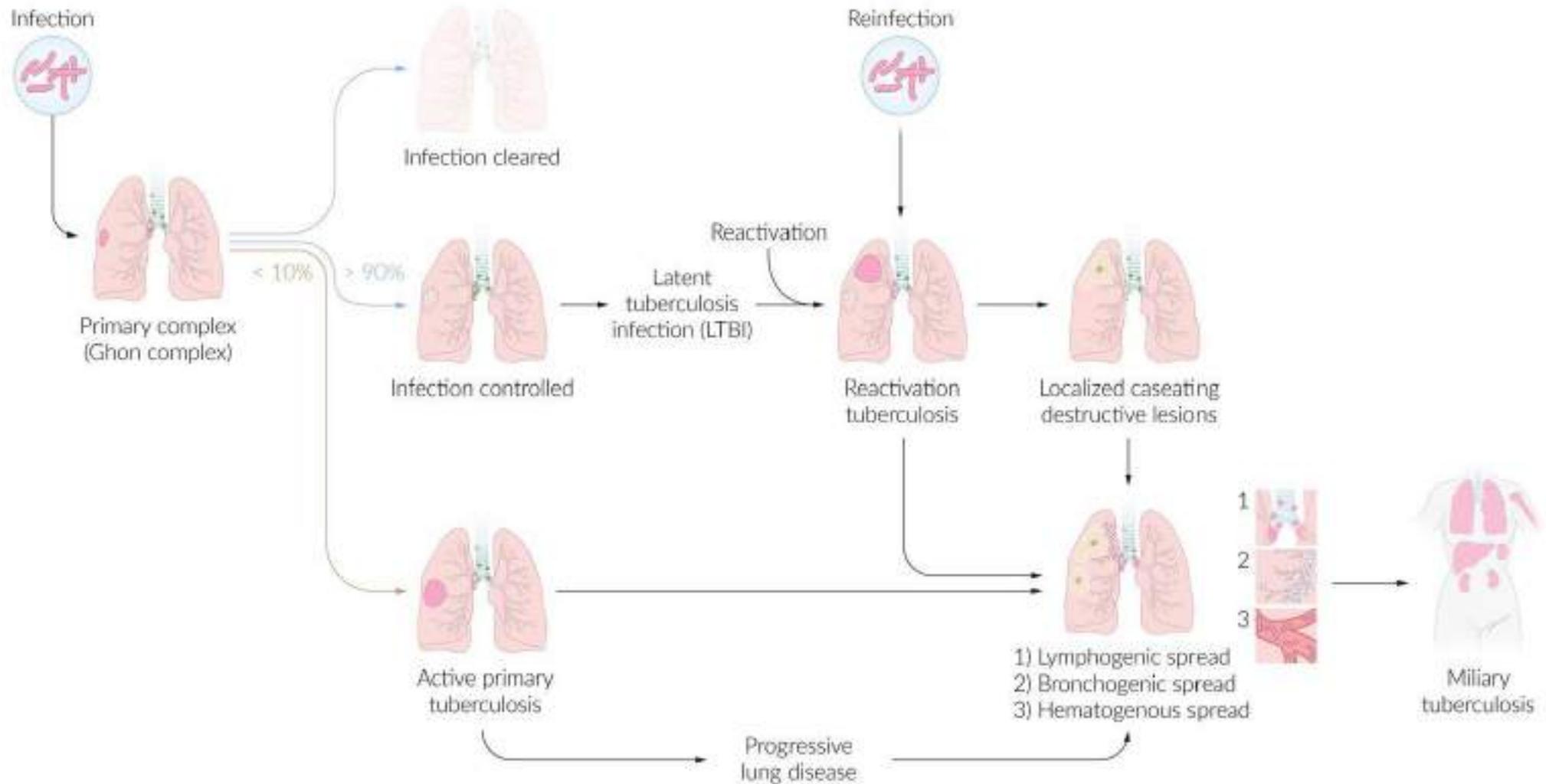
Night sweats



Lung cavitation



Outcomes



Outcomes

- **Local Progressive Pulmonary TB**

1. This can occur after primary or secondary TB
2. Occurs by the local extension to an entire lobe or segment

- **Disseminated (miliary) TB**

1. Miliary pulmonary disease
2. Spread through trachea to larynx leads to Laryngeal TB
3. Swallowing infected sputum leads to intestinal TB
4. Spread through pulmonary veins → Heart → arteries → systemic miliary TB.



Pathogenesis of TB

Miliary TB



X-ray of lung with miliary TB



CT scan of lung with miliary TB

Lung miliary TB



Pathogenesis of TB

Primary TB

Secondary (reactivation) TB

Progressive Pulmonary TB (entire lobe)

Miliary TB

Millet

Millet seeds

The diagram illustrates the progression of tuberculosis in the lungs. It shows three stages: 1. Primary TB, characterized by a single, well-defined nodule in the lung. 2. Secondary (reactivation) TB, showing multiple nodules of varying sizes, some with central cavitation. 3. Progressive Pulmonary TB (entire lobe), where the entire lung lobe is affected, showing extensive consolidation and multiple small nodules. A separate image shows Millet plants, and another shows Millet seeds, indicating their role as a source of infection for miliary TB.



When to suspect TB infection?

“Any person who presents with symptoms or signs suggestive of TB, in particular cough of long duration (more than 2 weeks) + hemoptysis + night sweats.”



Diagnosis – Active TB

Sample Type:

1. In pulmonary tuberculosis:
 - Sputum samples (most common) : Obtain ≥ 3 samples separated by 8 to 24-hour intervals (should include at least one early morning sample).
 - Gastric lavage → Usually indicated in children who are unable to expectorate
 - Bronchoalveolar lavage → Bronchoscopy is indicated if induced sputum or gastric lavage samples are insufficient.
2. In extrapulmonary tuberculosis (depending on the site of infection):
 - Lymph node aspirate, Pleural fluid, Urine, Synovial fluid, CSF
 - **Microbiological tests for active TB**
 - Acid-fast bacilli smear microscopy → Ziehl Neelsen stain or auramine rhodamine stain
 - PCR → for confirmation of AFB positive smears
 - Culture → Gold standard diagnostic test BUT Takes 2 to 6 weeks for positive cultures to develop
 - **Imaging studies:** CXR or CT scan



Diagnosis – Latent TB

- **Interferon- γ release assay (IGRA)** → preferred in those who have had the BCG vaccine
 - An ELISA test that measures the level of interferon- γ expressed by T cells after coming into contact with *Mycobacterium tuberculosis*.
 - In contrast to tuberculin skin testing, there are no false-positive results with IGRA in patients who received the Bacillus Calmette-Guérin (BCG) vaccine.
- **Tuberculin skin test** (purified protein derivative test, Mantoux test)
 - Latent tuberculosis is diagnosed by demonstration of type IV (delayed) hypersensitivity reaction against the tubercle bacillic antigens



Tuberculin skin test

- **Principle**

- Latent tuberculosis is diagnosed by demonstration of type IV (delayed) hypersensitivity reaction against the tubercle bacillic antigens

- **Antigens used in tuberculin test**

- PPD (purified protein derivative antigen): it is a purified preparation of the active M. tuberculosis proteins after growing on a semisynthetic medium

- **Reading**

- It is taken after 48-72 hours. At the site of inoculation, an induration surrounded by erythema is produced.



Tuberculin skin test

Mantoux test



Reading the Mantoux tuberculin skin test: (left, correct) only the induration is being measured; (right, incorrect) the erythema is being measured.



Tuberculin skin test (TST) thresholds

Induration size	Patient population
≥5 mm	<ul style="list-style-type: none"> • Individuals with HIV infection • Recent contacts of patient with known TB • Persons with nodular or fibrotic changes on chest x-ray consistent with previously healed TB • Organ transplant recipients & other immunosuppressed persons
≥10 mm	<ul style="list-style-type: none"> • Recent immigrants (<5 years) from TB-endemic areas • Injection drug users • Residents & employees in high-risk settings (eg, prisons, nursing homes, hospitals, homeless shelters) • Mycobacteriology laboratory personnel • Persons with conditions that result in higher risk for TB reactivation (eg, diabetes mellitus, leukemia, end-stage renal disease, chronic malabsorption syndromes, low body weight) • Children age <5 or those exposed to adults in high-risk categories
≥15 mm	<ul style="list-style-type: none"> • All of the above plus healthy persons

TB = tuberculosis.



Screening tests for LTBI (Self Study – not part of your exam except the red coloured text) Source: amboss.com

	Tuberculin skin test (purified protein derivative test, Mantoux test)	Interferon-γ release assay (IGRA)
Mechanism	<ul style="list-style-type: none"> Tests cell-mediated immunity against <i>M. tuberculosis</i> via delayed hypersensitivity reaction (type IV HSR) mounted by T cells 	<ul style="list-style-type: none"> Tests cell-mediated immunity against <i>M. tuberculosis</i>-specific antigens by measuring the amount of IFN-γ released by T cells using ELISA
Procedure	<ul style="list-style-type: none"> Step 1: 0.1 mL (or 5 units) of purified protein derivative (PPD) injected intradermally on the volar surface of the forearm resulting in wheal formation Step 2: transverse diameter of palpable induration checked 48–72 hours later 	<ul style="list-style-type: none"> One sample of whole blood is required.
Benefits	<ul style="list-style-type: none"> Inexpensive Preferred test in children < 5 years of age 	<ul style="list-style-type: none"> Only requires a single office visit Preferred test in individuals with prior BCG vaccination Results are available within 24 hours.
Limitations	<ul style="list-style-type: none"> Does not differentiate between active and latent TB Variability in test interpretation Requires two office visits False positives resulting from either of the following: <ul style="list-style-type: none"> Prior BCG vaccination Exposure to nontuberculous mycobacteria False negatives are possible in patients with any of the following: <ul style="list-style-type: none"> Sarcoidosis, Immunosuppressed state (anergy), Age < 6 months, Recent (within 8–10 weeks) or very old (many years) TB infection, Disseminated TB disease 	<ul style="list-style-type: none"> No differentiation between active and latent TB Expensive Errors in collecting and transporting blood can decrease accuracy.

Vaccinations - Bacillus Calmette-Guérin vaccine (BCG)

- **Composition:** live attenuated strain of *M. bovis*
- It is a live freeze-dried vaccine which must be reconstituted
- Administered intra-dermally at the deltoid region on the left side
- Should immunize infants and under 5 years with single dose of BCG
- **Contraindications**
 - Immunocompromised individuals
 - Pregnancy



Treatment

- Isoniazid
- Rifampin
- ethambutol
- pyrazinamide





Thank You

