

Tuberculosis

By

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Diseases

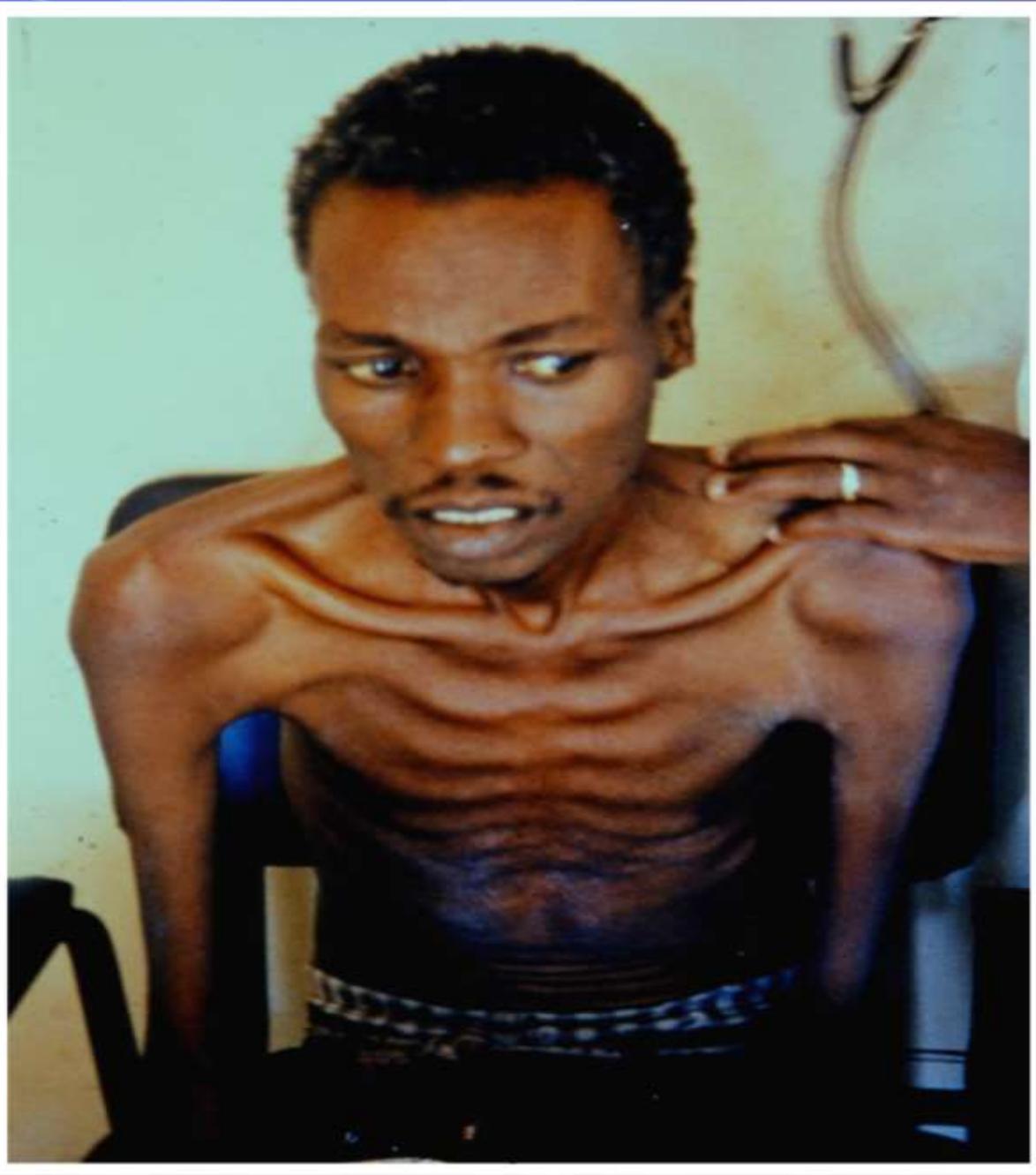
MARCH 24
WORLD
TUBERCULOSIS
DAY



History

- TB has been known as King's Evil, Pott's disease, consumption, and the White Plague.
- **Egyptian mummies** from 3500 BC have the presence of *Mycobacterium tuberculosis*
- It was isolated by **Robert Koch** in 1882





Epidemiology and Burden of Disease

THE TRUTH ABOUT TB

*Coughing up disturbing facts on
World Tuberculosis Day*

It is:
1 of top 10
causes of death
worldwide



7 countries account for **64% of TB deaths**

- India
- Indonesia
- China
- Philippines
- Pakistan
- Nigeria
- South Africa



It accounts for:

1.7 million
deaths worldwide

(95% of all TB deaths
occur in low and
middle-income countries)



2.5 lakh
child fatalities
worldwide



40%
of HIV-positive
deaths

All figs for 2016; Source: WHO

NEWS 18 creative

Burden of Tuberculosis

- **Annually** 8 million new cases
1.7 million deaths
- 95 % from **developing countries**
- The prevalence of **multidrug-resistant TB** (MDR -TB), is increasing

General Considerations

- ◆ Tuberculosis is a **chronic granulomatous** infection, potentially of lifelong duration, caused by *M. Tuberculosis*.
- ◆ The disease is **confined to the lungs** in most patients but may spread to any part of the body



Aetiology

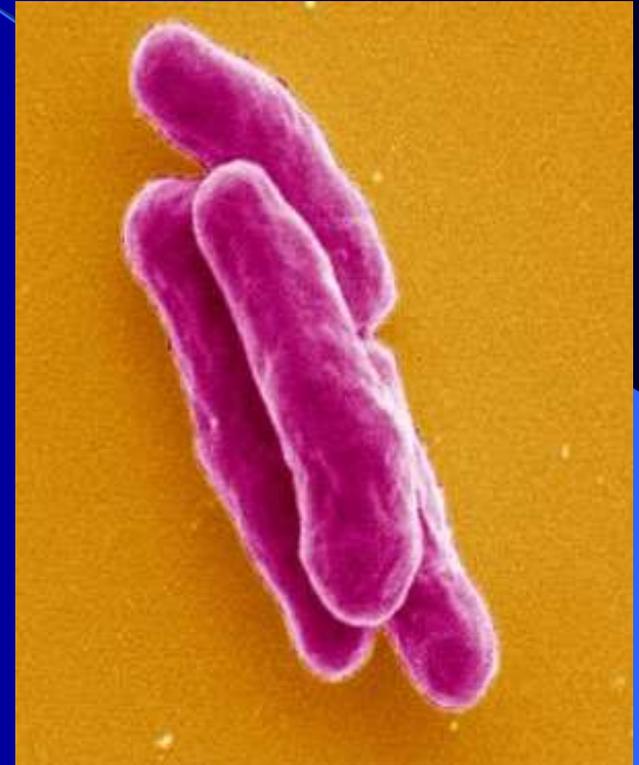
Caused by **rod shaped bacteria**

- *Mycobacterium tuberculosis*
- *Mycobacterium bovis*

Slow growing organism

Strictly aerobe.

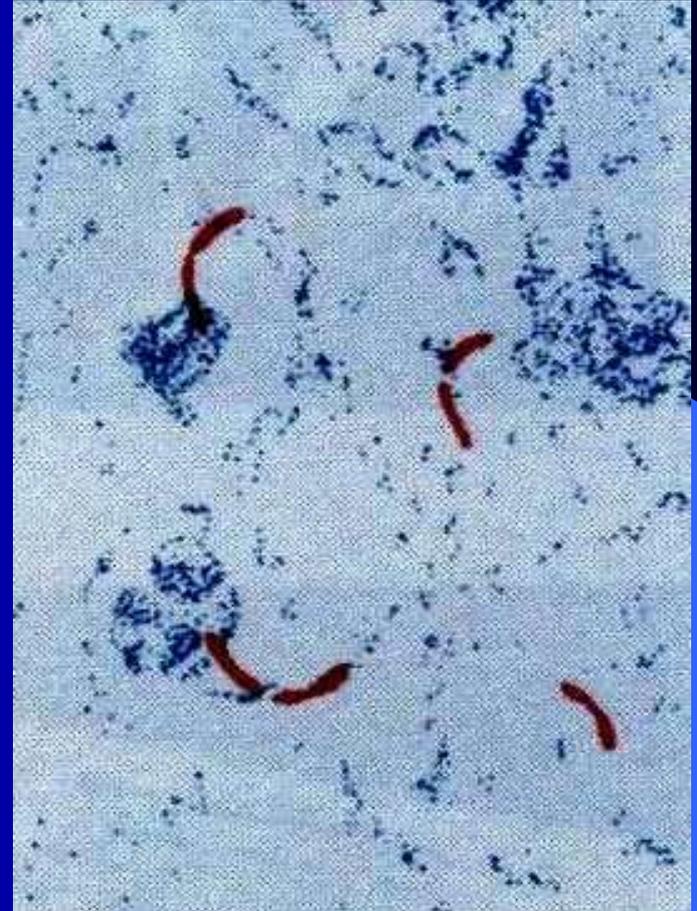
**Susceptible to sunlight, heat
and dryness.**



Aetiology

TB Bacillus is

- **Thin,**
- **Length 1-5 Microns,**
- **Somewhat Curved,**
- **Complex Cell Wall (Much Lipid Content) Responsible For Its Characteristic Coloration On Staining (**Acid - fast**).**



Mycobacteria unique cell wall structure

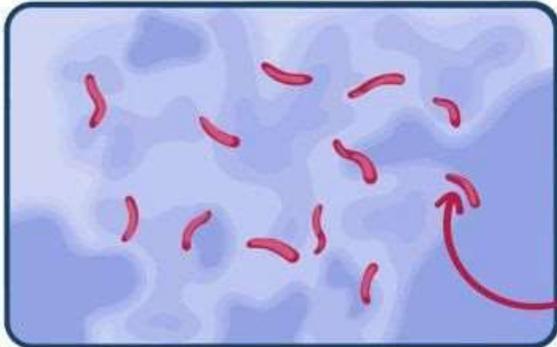


MYCOBACTERIUM TUBERCULOSIS (TB)

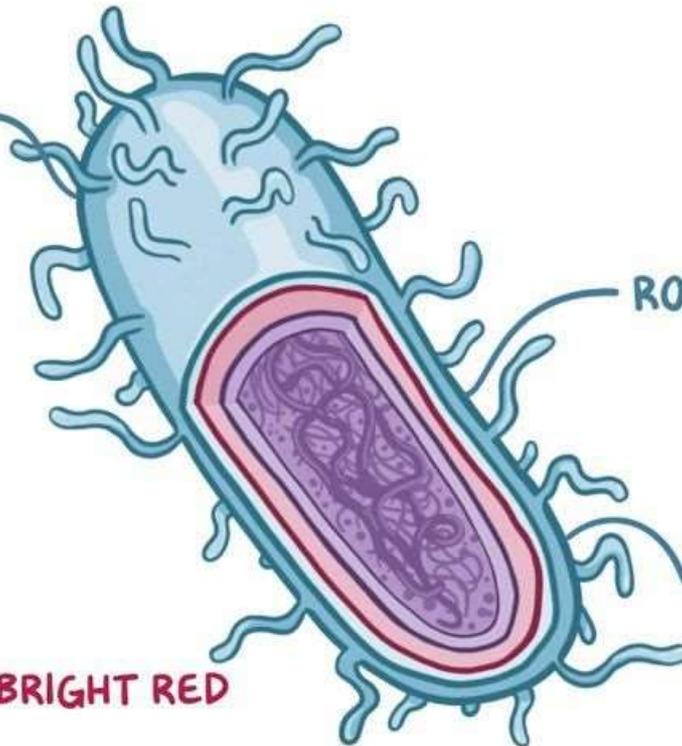
WAXY CELL WALL

- ↳ from MYCOLIC ACID
- ↳ "ACID-FAST"

ZIEHL-NEELEN STAIN



BRIGHT RED



ROD-SHAPED

NEEDS OXYGEN
STRICT AEROBES

Transmission Of Infection

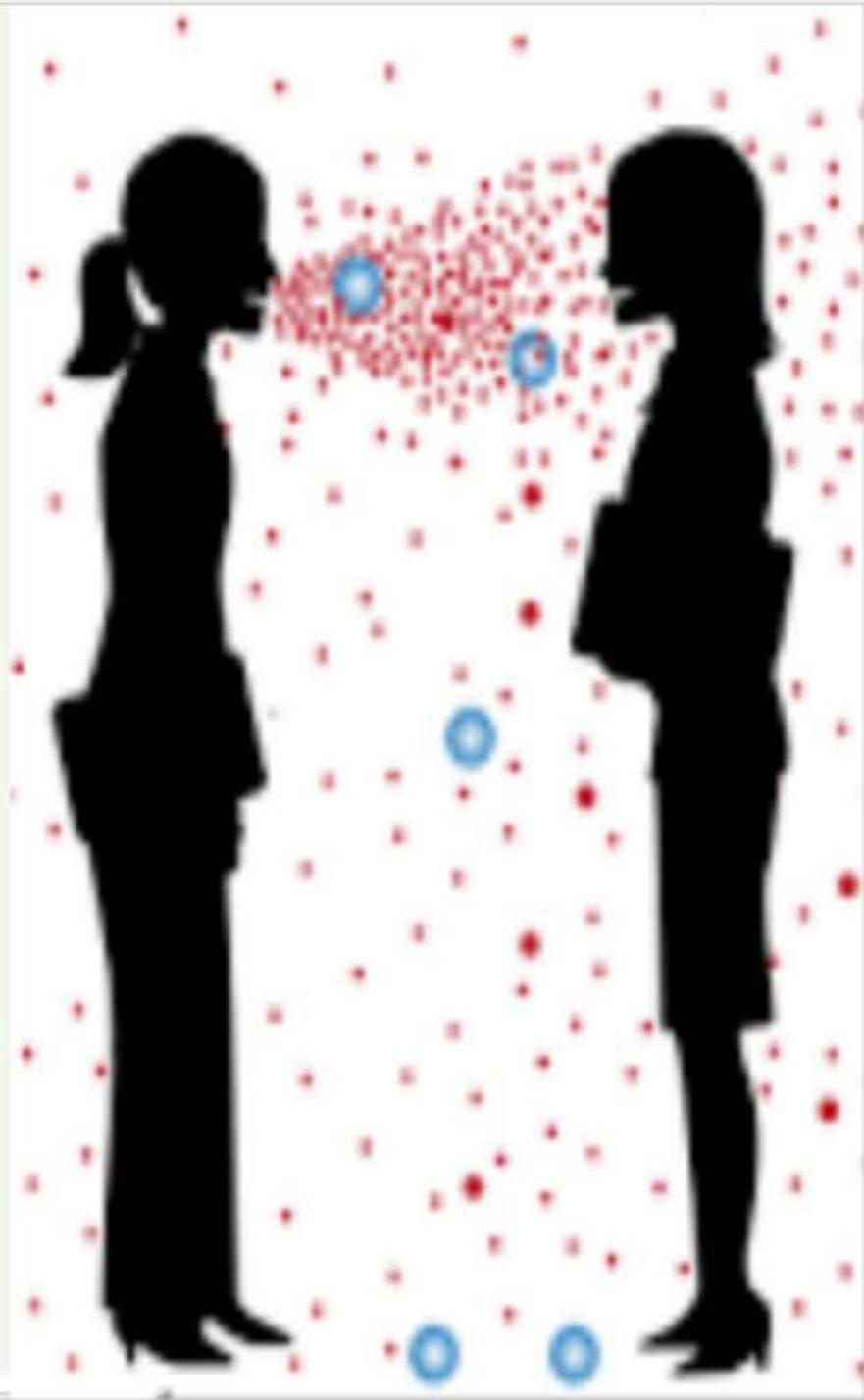
The background is a dark blue gradient. A thin, light blue curved line starts from the top left and arcs across the top. On the right side, there is a large, light blue triangular shape that points towards the center, partially overlapping the text.

Modes of transmission

- 1- **Air-borne** infection:
TB bacilli is 1-5 μm in length
remain in the air for long times.
- 2- Ingestion of **raw milk** & **diary**
products.
- 3- **Direct invasion** through wounds



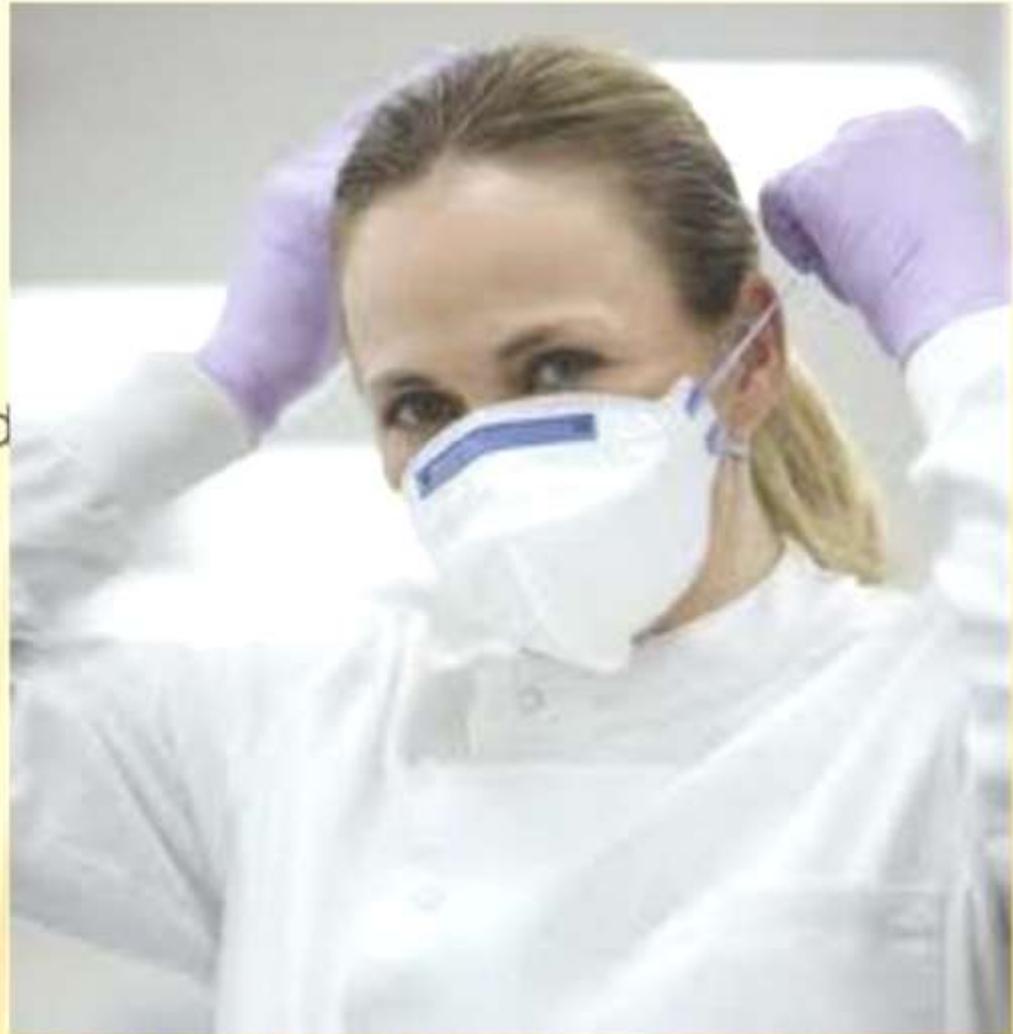
- **M. tuberculosis** may be expelled when an infectious person:
 - Coughs
 - Sneezes
 - Speaks
 - Sings
- **Transmission** occurs when another person inhales the organisms repeatedly they will become infected with tuberculosis.
- **TB** is spread easily in closed spaces over a long period of time.



REQUIRES

- ✘ Standard Precautions
- ✘ Private room
- ✘ Door must remain closed
- ✘ Air must be filtered
- ✘ Mask

- ✘ If transporting pt, Pt must wear mask.



AIRBORNE PRECAUTIONS

The transmission is determined by

- The degree of **infectiousness of case** .
 - **Untreated positive AFB smear** cases are the most infectious
 - Patient with **cavitary lesion** is more infective
- The **intimacy and duration** of that contact

High Risk Patients

1. Extremes of age.
2. Low immunity.
3. Contacts with open TB.
4. Over crowded populations.
5. Health workers.

Pathogenesis

**Tubercle
Bacilli**

The diagram illustrates the pathogenesis of tuberculosis. At the top, a red oval contains the text 'Tubercle Bacilli'. Below it, two cyan arrows point in opposite directions: one pointing up and one pointing down. At the bottom, another red oval contains the text 'Human Immunity'. This visualizes the reciprocal relationship between the pathogen and the host's immune system.

**Human
Immunity**

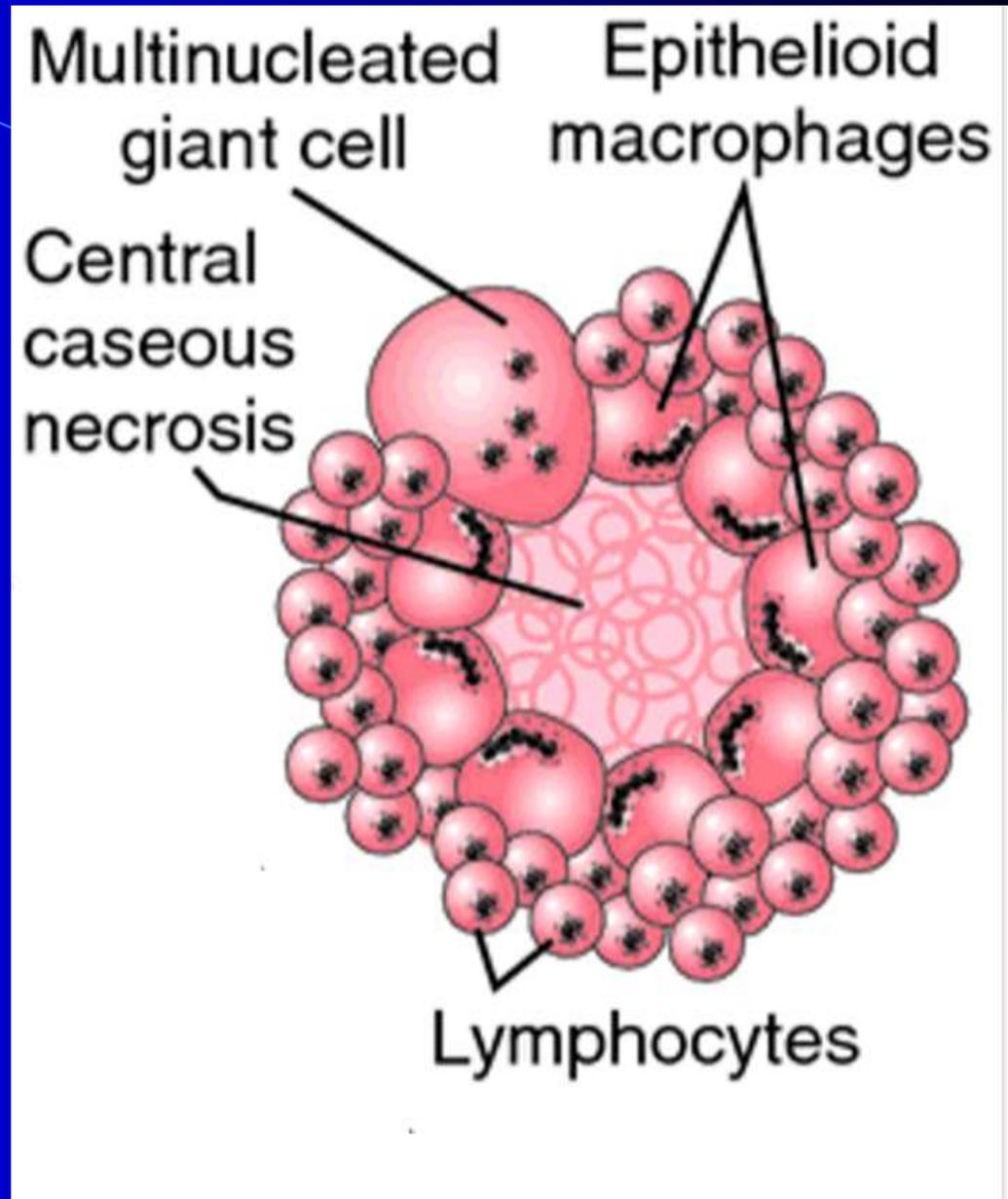
Human Immunity after TB

- After infection or given BCG vaccine, human will obtain **specific immunity** (*cell-mediated immunity*)
- The cellular immunity develops **within 4 - 8 weeks** after infection with TB bacilli.

- **Two types of cells are essential in the formation of TB granuloma**

Macrophages: directly phagocytes TB and presenting antigens to T lymphocyte → **Langhan's giant cells**

T lymphocytes(CD4+): induce protection through the production of lymphokines.

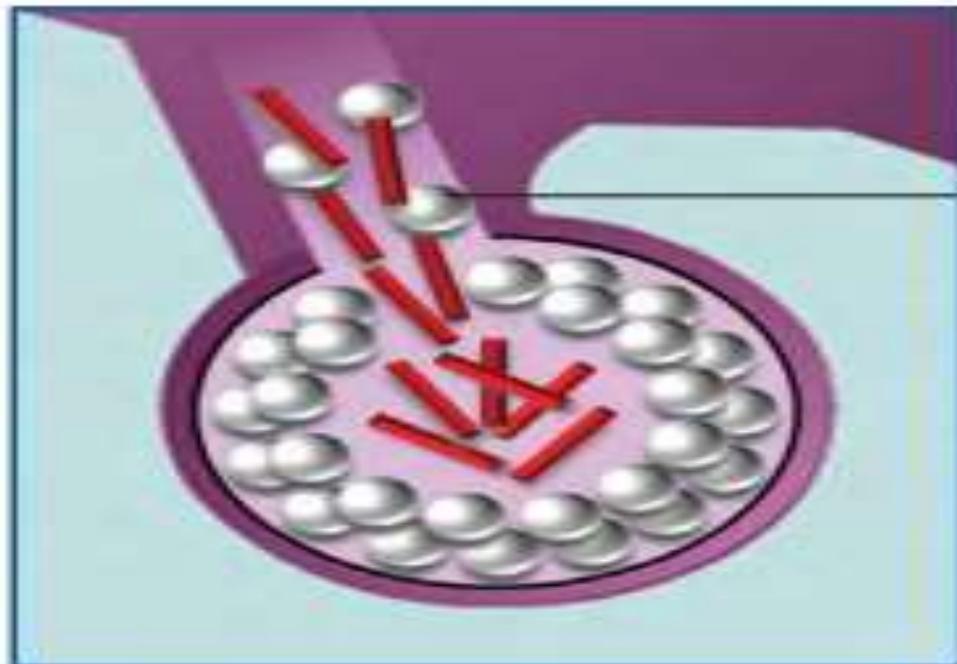


Caseating Granuloma

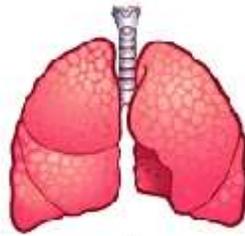




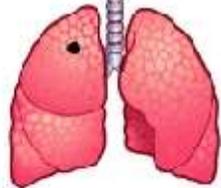
Special immune cells form a barrier shell (in this example, bacilli are in the lungs)



Shell breaks down and tubercle bacilli escape and multiply

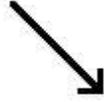
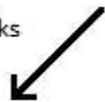


Normal lungs



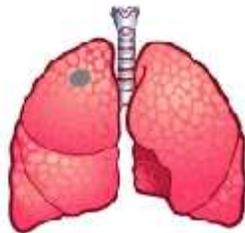
Primary infection with Ghon focus

2-8 weeks

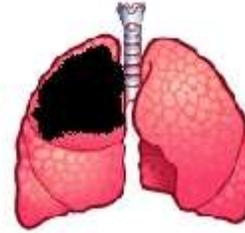


Post-primary immunity

Incomplete immunity



Healing and calcification
(Latent infection)



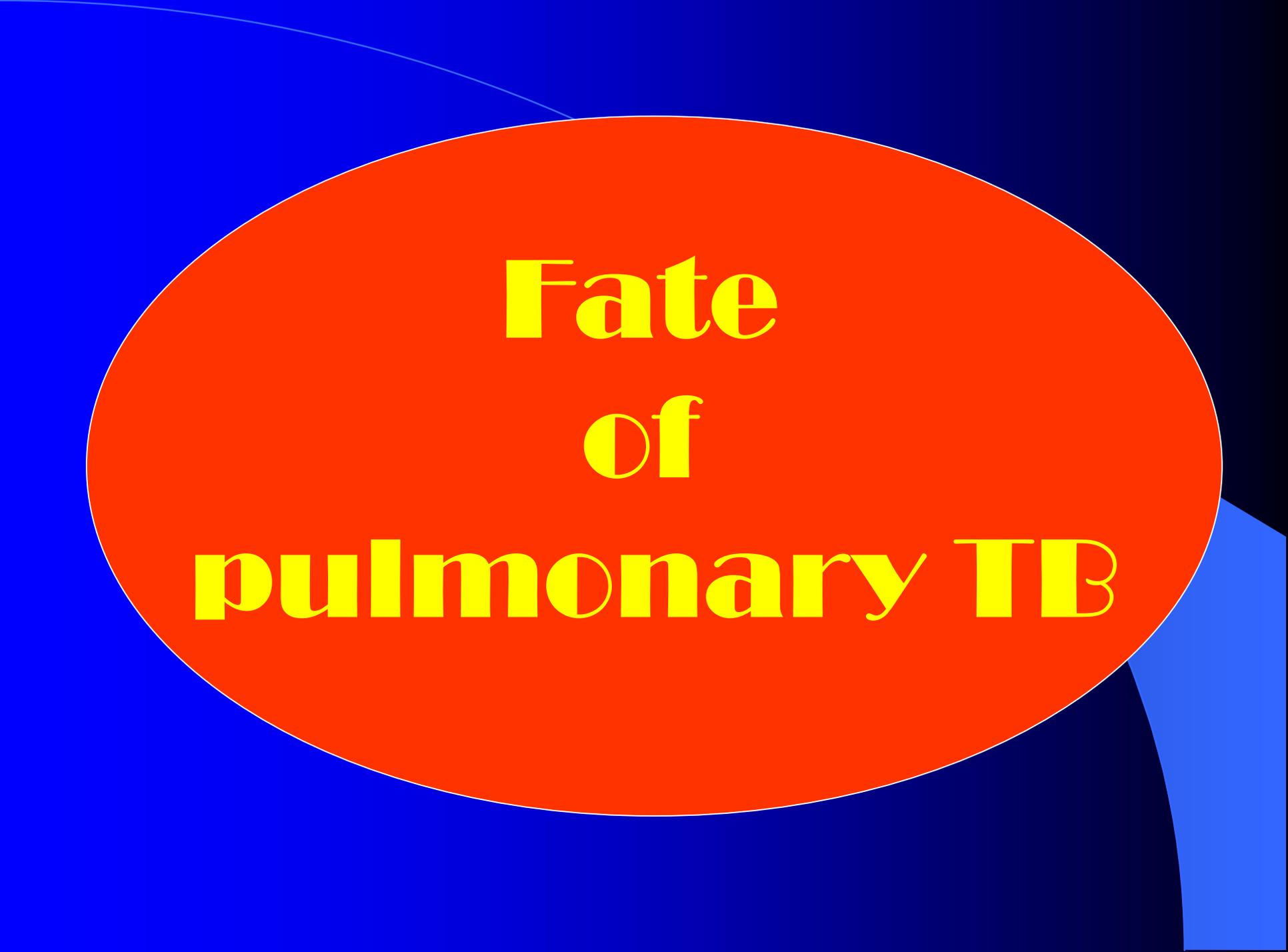
Active disease with lung
collapse/consolidation/effusion
and +/- miliary or extrapulmonary
involvement

Years



Reactivation due to
weakening of immune
system





**Fate
of
pulmonary TB**

I. *Primary pulmonary TB:*

1. Regression: 95%

- Healing by fibrosis and calcification
- **Ghons complex** after healing with fibrosis may undergo calcification which could be detected radiologically and called **Rank complex**

2. Progression

- **Pulmonary:** e.g. tuberculous pneumonia, lobar collapse (bronchial compression) or pleural effusion.
- **Extrapulmonary:**
- **Disseminated disease** e.g. lymphadenopathy (usually cervical), meningitis, pericarditis, or miliary disease

II. Post-primary TB/ Secondary TB

- Post-primary TB is the pattern of disease that occurs in a **previously sensitized host**. It occurs after a **latent period** of months or years after primary infection.
- It may occur either by:
 - ❑ **Reactivation** of latent bacilli in response to a trigger such as weakening of the immune system by HIV infection.
 - ❑ **Reinfection**.

Toolbox for Diagnosis of TB



Incubation period: 4-12 weeks.

Clinical Manifestations

- **Systemic symptoms:**

- Fever, Night sweats
- Anorexia, Weight loss,
- Fatigue.

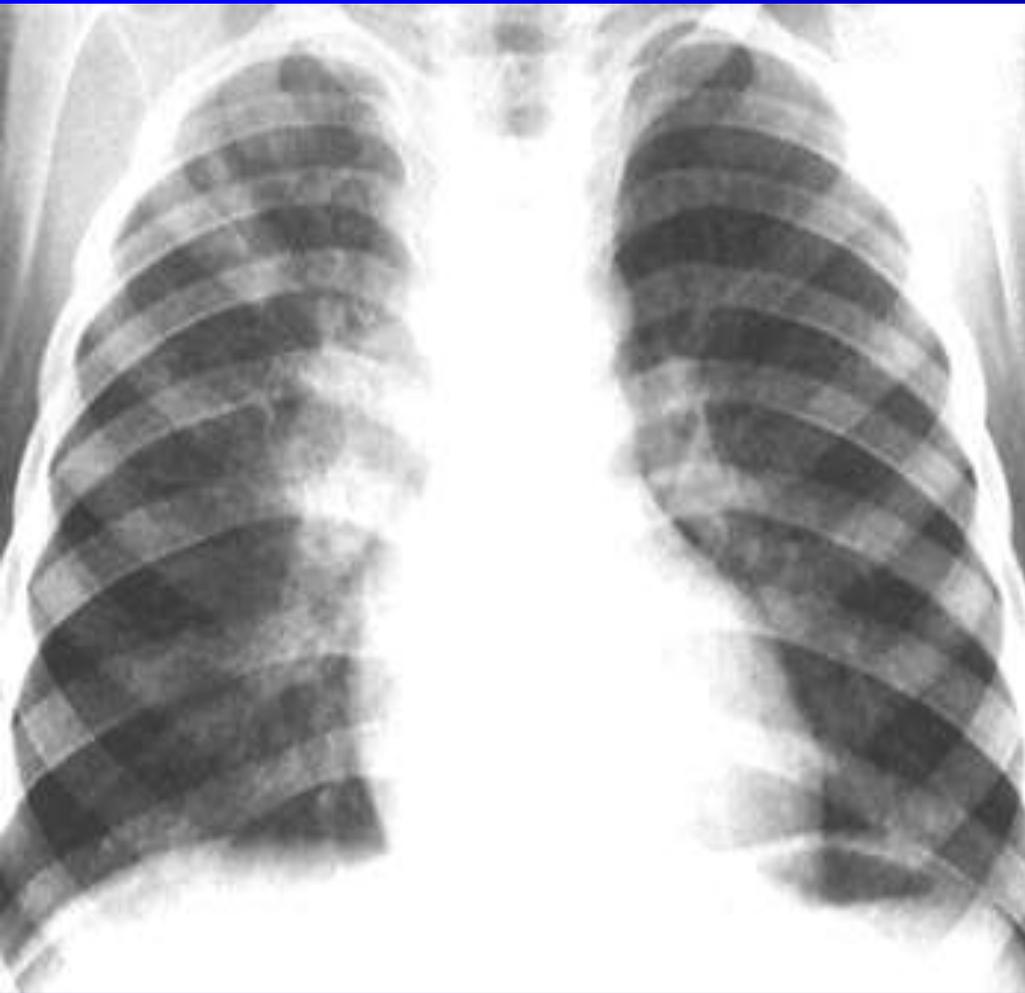
- **Respiratory symptoms:**

- **Persistent Cough:** A cough lasting three weeks or longer is a hallmark symptom.
- **Coughing up sputum or blood; hemoptysis,** may be due to cough of a caseous lesion or bronchial ulceration).
- **Chest Pain:** especially when breathing or coughing deeply.

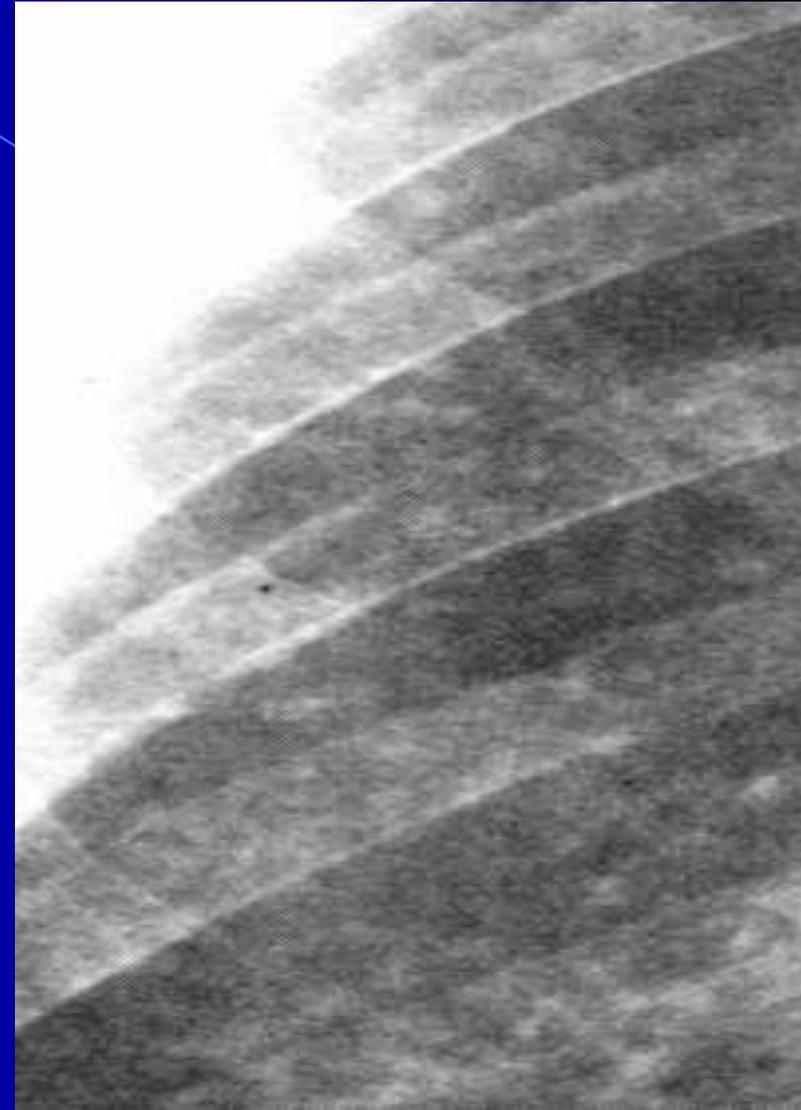
Radiology of TB

- Chest radiography is the **most important** method for diagnosis of TB.
- **TB characteristics** of a chest radiograph:
 - Pulmonary infiltration mainly in the **upper zone**
Patchy, Nodular, or Cavitations.
 - Presence of **calcification**.
 - **Persistence of the abnormal shadows** after nonspecific treatment with antibiotics.

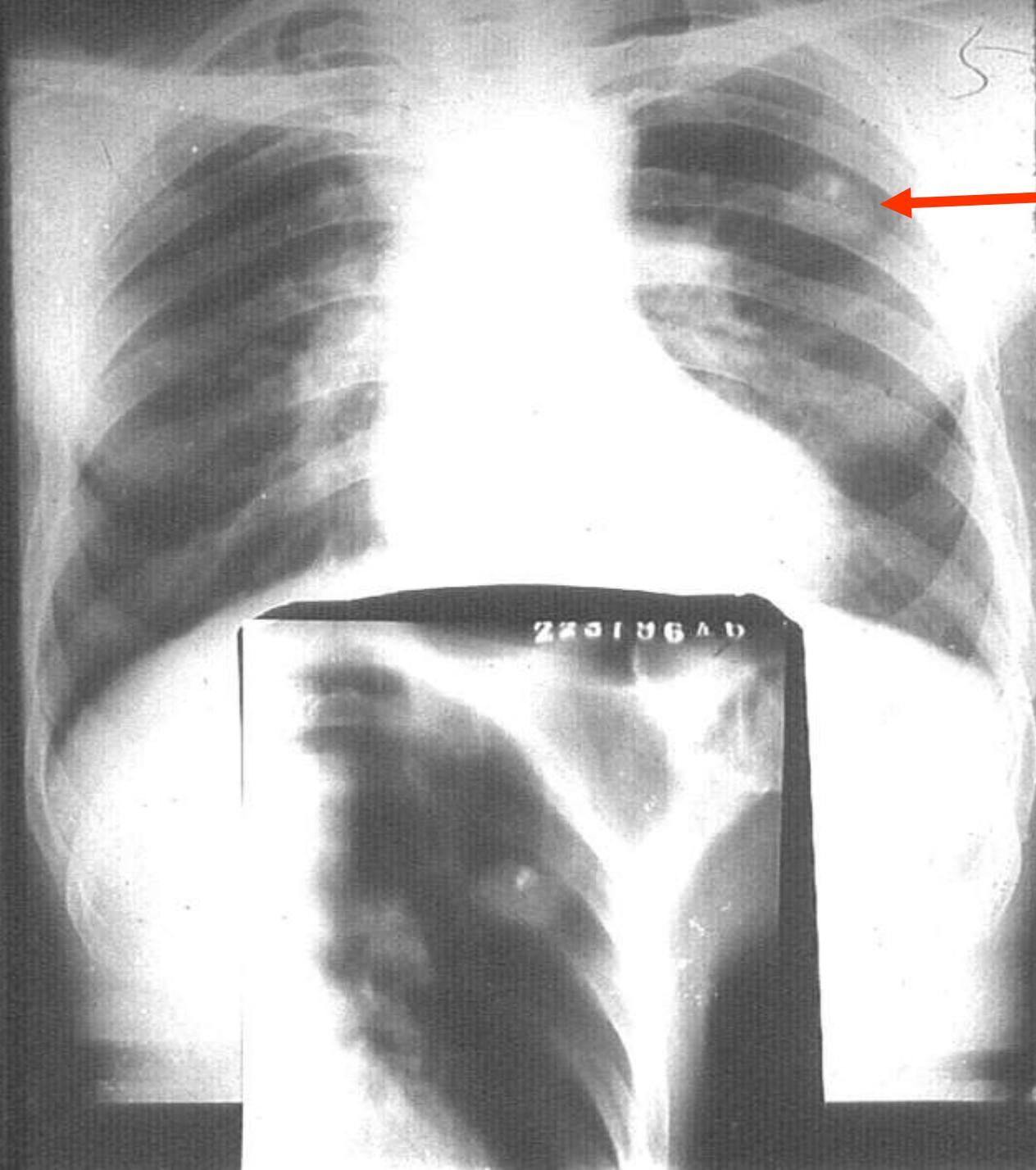
Primary complex



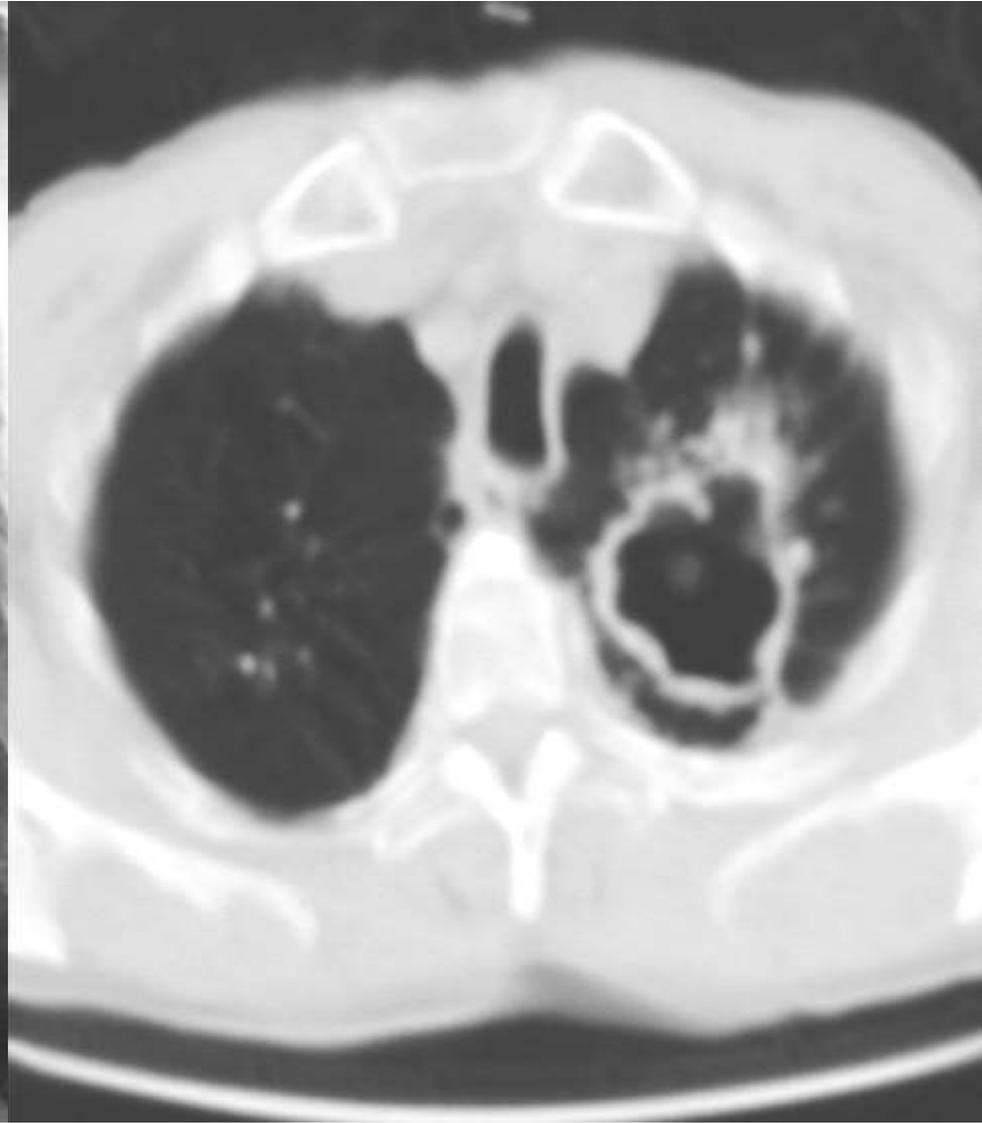
Milliary Tuberculosis







Tuberculoma



Chronic fibro-cavitary pulmonary tuberculosis







Laboratory Diagnosis

- Specimen examination
- Tuberculin testing

Types of specimens:

- Sputum.
- BAL.
- Pleural effusions
- Blood in case of haematogenous TB

1- Sputum smears stained by Z-N stain

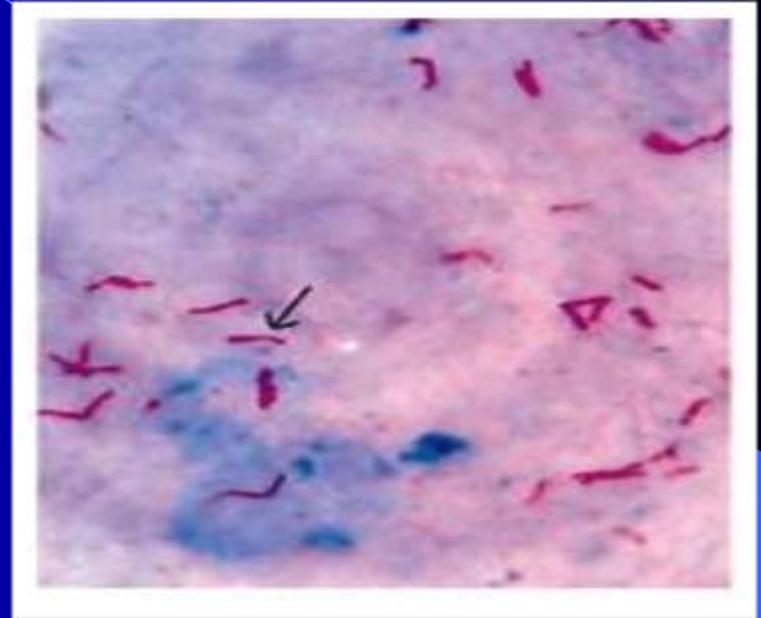
Three morning successive sputum samples are needed to diagnosis pulmonary TB.

Advantage:

- Cheap – Rapid
- Easy to perform
- Specificity of 98%

Disadvantages:

- Sputum has **low sensitivity** (need to contain 5000-10 000 AFB/ ml.).
- Young children & HIV infected persons** may not produce sputum containing AFB.



2- Cultures on LJ media

Lowenstein –Jensen medium is an egg based media

Advantages:

- **Specificity** about 99 %
- **More sensitive** (need lower no. of bacilli 10-100 / ml)
- **Susceptibility tests** for antituberculous drugs
(St, INH, Rif., E)

Disadvantages: Slowly growing (up to **8 weeks**)

CONTROL

NEGATIVE

POSITIVE



Mycobacterium tuberculosis growing on Lowenstein-Jensen (LJ) Medium

Recent Methods for Diagnosis

II-BACTEC 460 (Radiometric culture system)

- ❑ Specimens are cultured in a liquid medium (**Middle brook 7H9** broth base).
- ❑ Growing mycobacteria utilize the acid, releasing **radioactive CO₂** which is measured as **growth index (GI)** in the BACTEC instrument.

Advantages :

- **Rapid** (mycobacteria can be detected within 12 days.)
- Determining **drug susceptibility** .
- **Specificity** is very high

Disadvantages:

- **Expensive**
- Hazards of using **radioactive material**.

INVESTIGATIONS

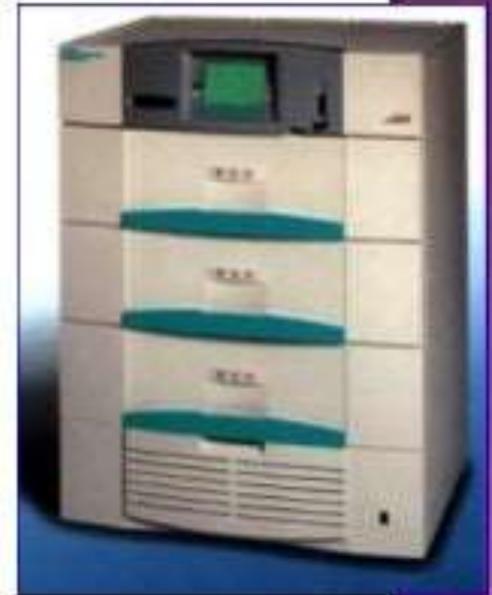
- **BACTEC media:** for faster culture (within 1-2wks)



Bactec 460



Bactec 9000MB



Bactec mgit 960b

II-Polymerase Chain Reaction (PCR)

Nucleic acid probe amplification tests in which **polymerase enzymes** are used to amplify (make many copies of specific DNA sequences extracted from mycobacterial cells.

Advantages:

- **Rapid procedure (3 – 4 hours)**
- **High sensitivity (1-10 bacilli / ml sputum)**

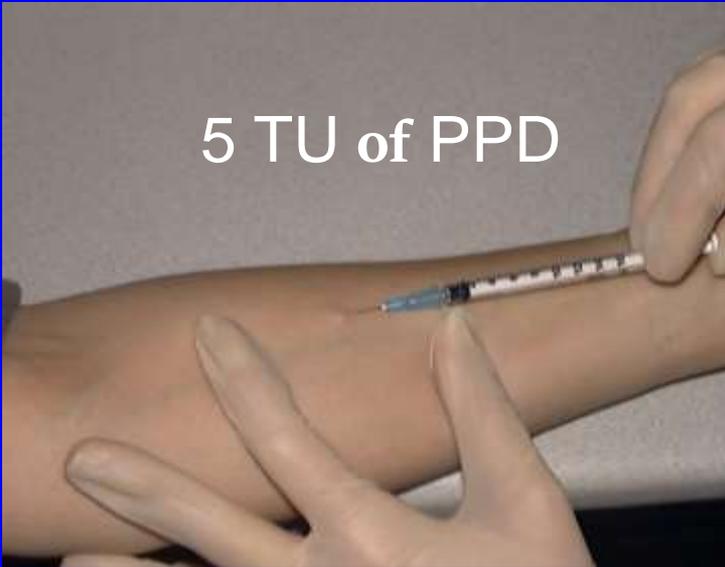
Disadvantages

- Very **expensive**.
- Can not differentiate between **living & dead bacilli**.

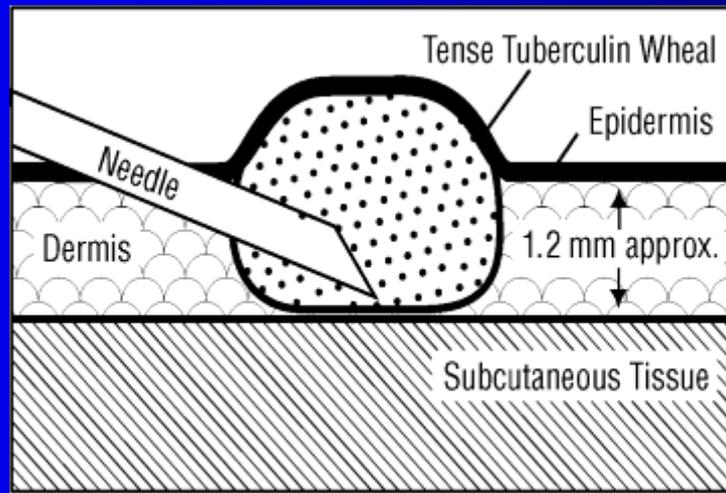
Tuberculin Skin Testing

Mantoux Test

5 TU of PPD



48 - 72
hours





Mantoux tuberculin skin test

Reading the TST

- Measure reaction in **48 to 72** hours
- Measure **induration**, not erythema
- **Record reaction in millimeters**, not “negative” or “positive”
- **Trained health care professional** measures and interprets the TST



- ❑ **Tuberculin skin testing** is the most common method used to screen for **latent M tuberculosis**.
- ❑ **Positive tuberculin skin** test indicates tuberculous infection , with or without disease

Positive \Rightarrow Infection and Immunity

Positive Tuberculin Test

Size of induration	Considered positive in :
≥ 5 mm for	<ol style="list-style-type: none">1. Close contacts of active pulmonary.2. HIV-immunocompromised persons3. Persons with fibrotic chest x-ray findings consistent with old TB.4. Organ transplant recipients or other immunosuppressed persons (including persons receiving long-term, high dose oral or parenteral corticosteroid therapy (>15 mg prednisone, or equivalent, daily for 1 month or longer).

Size of induration	Considered positive in :
<p>≥ 10 mm for</p>	<p>1. Persons with certain medical conditions e.g.</p> <ul style="list-style-type: none"> ○ Silicosis, ○ Chronic renal failure, ○ Diabetes mellitus, ○ Some cancers, leukaemia, and lymphoma ○ Gastrectomy/jejunioileal bypass <p>2. Health care and laboratory workers.</p> <p>3. Persons who have immigrated within the past 5 years from areas with high prevalence</p> <p>4. Persons with prolonged stay (>1month) in areas with high TB e.g. prisons</p> <p>5. Injection drug users.</p> <p>6. Persons over age 70 and children < 4 years of age.</p>
<p>≥ 15 mm for</p>	<p>Considered positive in all peoples even in vaccinated persons</p>

- *False negatives:*

- Anergy (immunocompromised)
- Recent TB infection
- Deeper injection of TST.

- *False positives:*

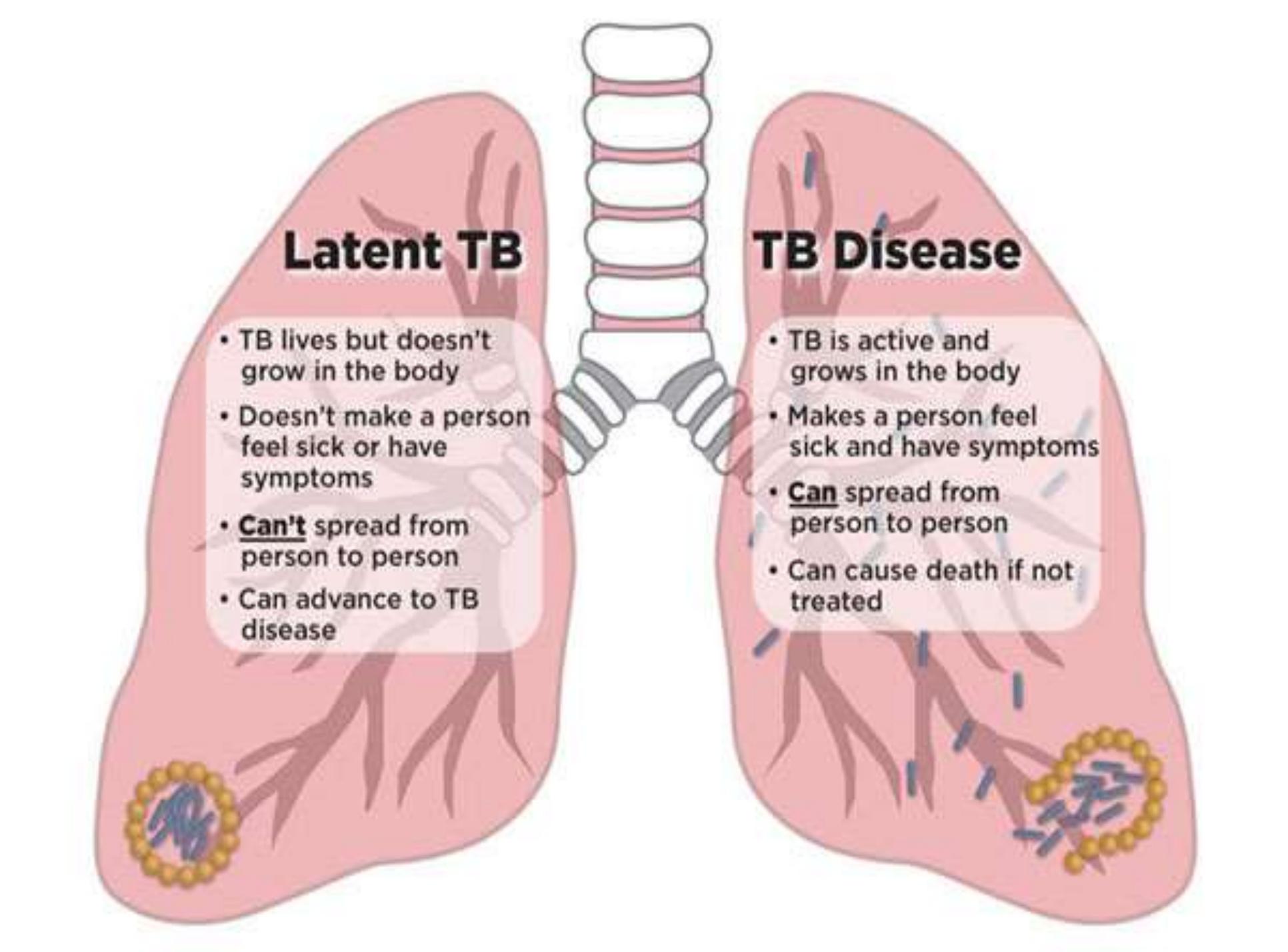
- BCG vaccination
- Nontuberculous mycobacterial infections
- Inaccurate reading of TST

- A reaction of **less than 5 mm** is considered **negative.**

• **Latent TB Infection (LTBI):** TB infection without evidence of clinically active disease:

- ❑ Positive tuberculin test,
- ❑ No symptoms of active disease,
- ❑ CXR usually normal, or abnormal, but no evidence of active disease,
- ❑ Sputa negative for acid-fast bacilli.

• **TB Disease:** active tuberculous infection of any organ

The diagram illustrates the human respiratory system, including the trachea and bronchi. It is split into two panels. The left panel, labeled 'Latent TB', shows a single cluster of blue rod-shaped bacteria within a yellow circular capsule in the lower part of the lung. The right panel, labeled 'TB Disease', shows a much larger and more active cluster of these bacteria in the lower part of the lung, with many individual bacteria also scattered throughout the lung tissue.

Latent TB

- TB lives but doesn't grow in the body
- Doesn't make a person feel sick or have symptoms
- **Can't** spread from person to person
- Can advance to TB disease

TB Disease

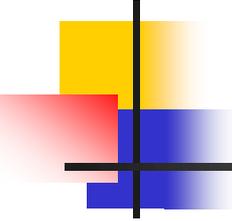
- TB is active and grows in the body
- Makes a person feel sick and have symptoms
- **Can** spread from person to person
- Can cause death if not treated

BCG and TST

- BCG is administered to more than **80% of children** in the world as part of the Extended Program of Immunization.
- **Reactivity from BCG** wanes after a few years and is unlikely to persist > 10 years,
-
- Reactions to the TST following BCG vaccination mostly range from **5-9 mm range**.
-
- TST reactions of **15 mm or greater** are likely to be positive



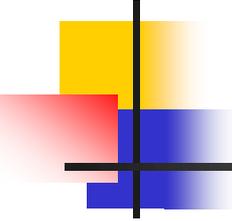




QuantiFERON[®] -TB Gold, "IGRA"

- **Whole blood assay**
 - **Stimulate lymphocytes with specific antigen ESAT-6 and CFP10**
 - **Measure IFN- γ level by**
 - **Enzyme-linked immunosorbent assay**

- **Approved by FDA, USA in May 2005**

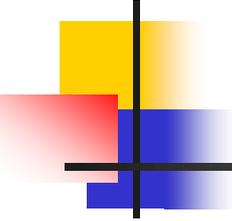


QuantiFERON[®] -TB Gold

Advantages Of QFT-G

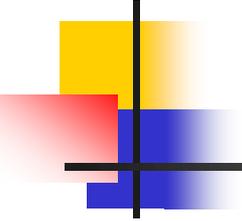
- **Greater specificity.**
 - No cross reactivity with previous **BCG** vaccination
 - No cross reactivity with **Non Tuberculous Mycobacteria (NTM)** .

- **Error elimination:**
 - Deeper injection in the TST produces a common error—the solution may be “washed out” by vascular flow, resulting in a possible **false-negative result**.



QuantiFERON[®] -TB Gold

- **Faster results.:**
 - QFT-G results are available as **quickly as 24 hours** after blood collection; the TST requires 2-3 day wait as well as a **return visit by the patient.**
- **QFT-G is an in vitro test**
 - Never exposes the person to its antigenic proteins, so not **generate “Booster Phenomenon”.**

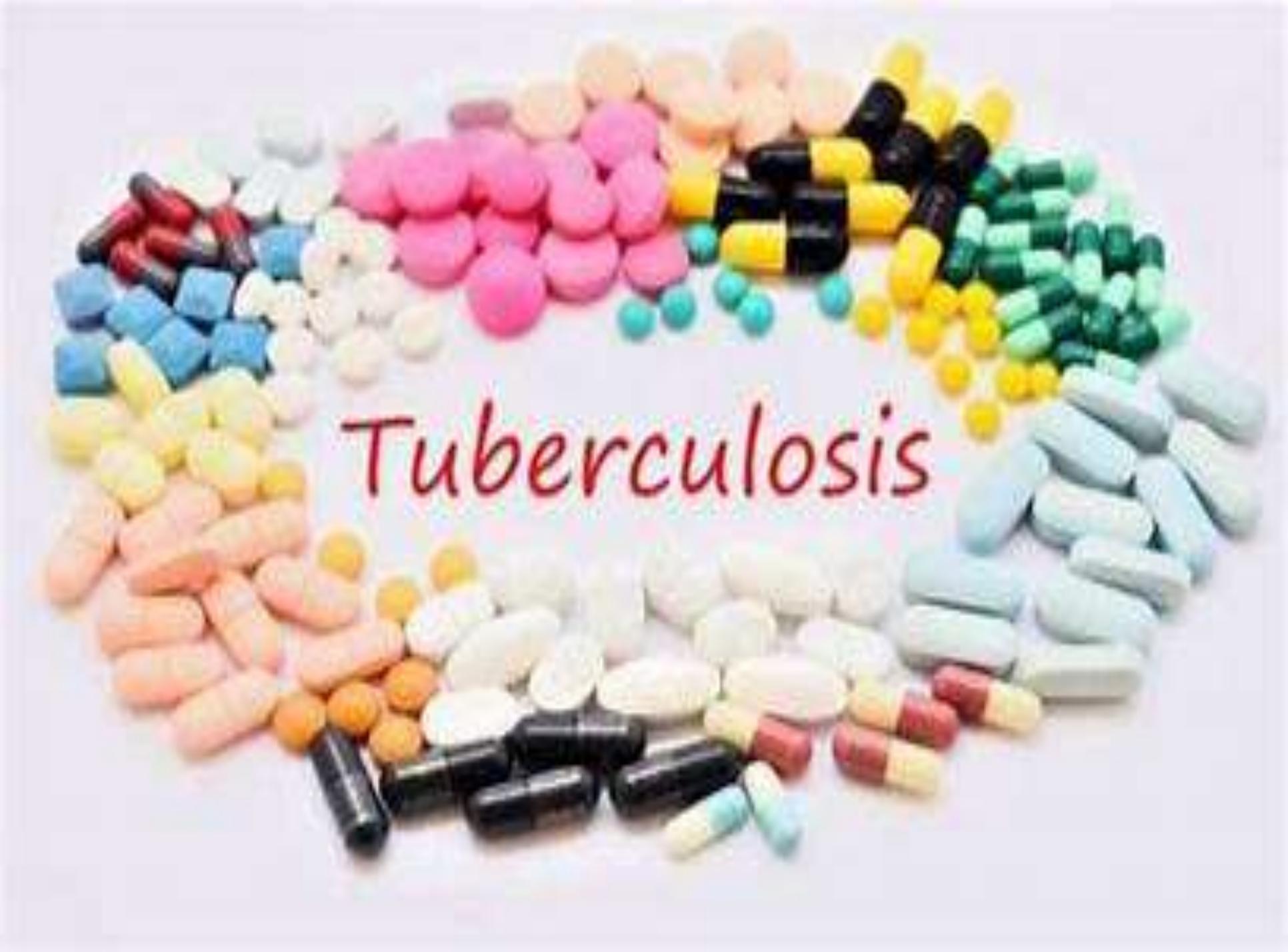


Differential Diagnosis

Pulmonary

Extra-Pulmonary

Anti TB Drugs

A circular arrangement of various colorful pills and capsules, including pink, blue, yellow, green, orange, white, black, and red, surrounding the word "Tuberculosis" written in red cursive script in the center.

Tuberculosis

Goals of antitubercular chemotherapy

Kill dividing bacilli: reduce bacillary load in the patient and achieve:

- Quick sputum negativity
- Interrupt transmission of TB
- Quick symptom relief and prevent comorbidities.

Kill persisting bacilli: To prevent relapse.

Prevent emergence of resistance:

Basic Principles of Treatment

- Determine the **patient's HIV status.**
- **Multiple drugs** to which the organisms are susceptible
- **Never add single drug** to failing regimen
- **Ensure adherence** to therapy (DOT)



	FIRST LINE	Second Line
C I D A L	Rifampin Isoniazid Streptomycin Pyrazinamide	Quinolone: Levo, O, cipro-floxacin Aminoglycosides: Amikacin, kana Capreomycin Rifamycins: Rifabutin Rifapentin Macrolides: Clarithro, azithro Linezolid
STATIC	Ethambutol	Cycloserine, PAS, Clofazimine, Ethionamide Thiacetazone

Treatment Recommendations

New Patients (not previously treated)

Initial Phase

(2 months)

INH, RIF, PZA, EMB daily

Continuation Phase

(4 months)

INH, RIF daily

INH, RIF 3x/wk

Table 3a: WHO recommended doses of the first-line anti-tuberculosis drugs

Drugs	Daily doses (mg/kg)	Route	Thrice weekly dosage (mg/kg/dose)
Isoniazid (H)	5 (4–6)	Oral	10 (8–12)
Rifampin (R)	10 (8–12)	Oral	10 (8–12)
Ethambutol (E)	15 (15–20)	Oral	30 (25–35)
Pyrazinamide (Z)	25 (25–30)	Oral	35 (30–40)
Streptomycin (S)	15 (12–18)	Oral	15 (12–18)

Table 3b: Recommended doses of second-line anti-TB drugs

Drugs	Daily doses (mg/kg)	Route	Maximum daily dose
Kanamycin (K)	15	IM	Up to 1 g
Amikacin (A)	15	IM	Up to 1 g
Ethionamide (Eto)	10–15	Oral	Up to 1 g
Cycloserine (Cs)	10	Oral	Up to 1 g
Para amino salicylic acid (PAS)	250	Oral	Up to 1 g
Ofloxacin (Ofx)	15–20	Oral	800–10000 mg
Levofloxacin	7.5–10	Oral	750-1000 mg
Moxifloxacin	7.5–10	Oral	400 mg

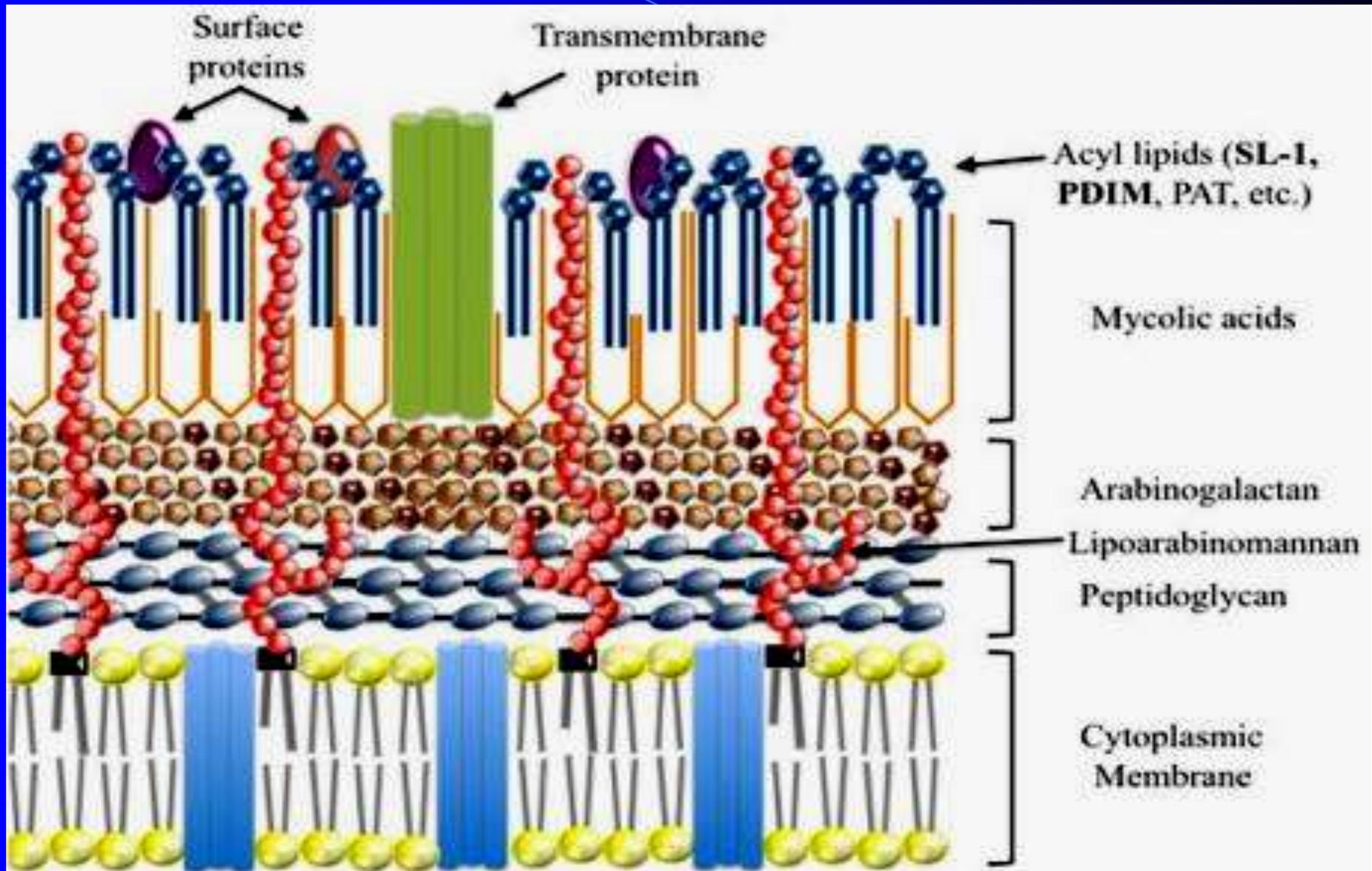
Drug Administration

- The first-line medications should be administered together as **single dose** rather than in divided doses.
- A single dose leads to:
 - **Higher peak serum concentrations**
 - **Potentially more effective,**
 - **Facilitates using DOT.**
- Thus, if patients have Epigastric distress or nausea with the first-line drugs, **dosing with food** is recommended.

1- Isoniazid (INH) First-line drug

- Isoniazid is a **principal agent** used to treat tuberculosis & **universally accepted** for initial treatment
- It should be included in **all TB treatment regimens** unless the organism is resistant
- Structural similarity to **pyridoxine**.
- **MOA:** Isoniazid **inhibits synthesis of mycolic acids**, which are essential components of mycobacterial cell walls.

Mycobacteria unique cell wall structure



Adverse effects

The two most important adverse effects of isoniazid therapy are :

- **Hepatotoxicity** and
- **Peripheral neuropathy**
 - It's a **dose-dependent** 2 - 20 % and probably relates to interference with **pyridoxine metabolism**
 - This rate can be reduced with the prophylactic administration of **25 mg of pyridoxine daily**

2-Rifampicin (RFP) First-line drug

- It can kill dormant organisms that are poorly accessible to many other drugs, such as **intracellular** organisms and those in Acidic environment of **caseous foci**.
- **MOA: It inhibits RNA synthesis** by binding to the β -subunit of DNA-dependent RNA polymerase and thereby inhibits RNA synthesis.

Adverse effects

The most important adverse effects of rifampicin therapy are :

- Hepatitis,
- Hepatic microsomal enzymes inducer,
- Gastrointestinal upset,
- Red discoloration of body fluids.

Rifampicin drug interactions

- Microsomal enzyme inducer → ↓ plasma concentration of certain drugs → ↓ drug efficacy.
- Examples:
 - Combined-oral contraceptives
 - Warfarin
 - Corticosteroids
 - Phenytoin
 - Sulphonylurea hypoglycaemics
 - Statins
 - Theophylline
 - Methadone
 - T4

3-Pyrazinamide (PZA) First-line drug

- Pyrazinamide is a **major oral agent** used against mycobacteria
- The drug exert greatest activity against **dormant** organisms contained within:
 - Macrophages
 - Acidic environment of caseous foci.

Adverse effects

The most important adverse effects of Pyrazinamide therapy are :

- **Hepatotoxicity** is a prominent side effect (1-3 %),
- **Hyperuricemia** may provoke acute gouty arthritis.
- **Gastrointestinal upset.**

4- Ethambutol

First-line drug

- It is used often to protect against the **emergency of drug resistance**
- **Bacteriostatic**
- The most common serious adverse effect is **dose-related optic neuritis**, causing loss of visual acuity and red-green color-blindness, but are reversible.

5-Streptomycin (SM) First-line drug

- It is administered only parenterally, **intramuscular**
- The dosage must be lowered and the frequency of administration reduced (to only two or three times per week) in most patients **over fifty years old** and in any patient with **renal impairment**

Adverse effects

- Ototoxicity
- Renal toxicity

Adverse Drug Reactions

Drug	Adverse Reaction	Signs and Symptoms
Isoniazid	- Peripheral neuropathy	- Tingling sensation in hands and feet
Rifampin	- Hepatitis, - Hepatic microsomal enzymes inducer, - Gastrointestinal upset, - Red discoloration of body fluids.	- Abnormal liver function test - ↓ effect of oral contraceptives, corticosteroids, theophylline, phenytoin, warfarin - Abdominal pain Anorexia, Nausea, Vomiting - Yellowish skin or eyes Dark urine

Adverse Drug Reactions

Caused by	Adverse Reaction	Signs and Symptoms
Pyrazinamide	<ul style="list-style-type: none">- GIT Upset- Arthralgia- Hyperuricemia	<p>Anorexia, nausea, vomiting</p> <p>Joint aches</p> <p>Gout (rare)</p>
Ethambutol	<ul style="list-style-type: none">- Optic neuritis	<p>Blurred vision</p> <p>Changed color vision</p>
Streptomycin	<ul style="list-style-type: none">- Ear damage- Kidney damage	<p>Loss of hearing, Ringing in the ears</p> <p>Abnormal kidney function test</p>

Extrapulmonary TB

- **In most cases, treat with same regimens used for pulmonary TB**

Bone and Joint TB, Miliary TB, or TB Meningitis in Children

- **Treatment extended > 6 months depending on site of disease**

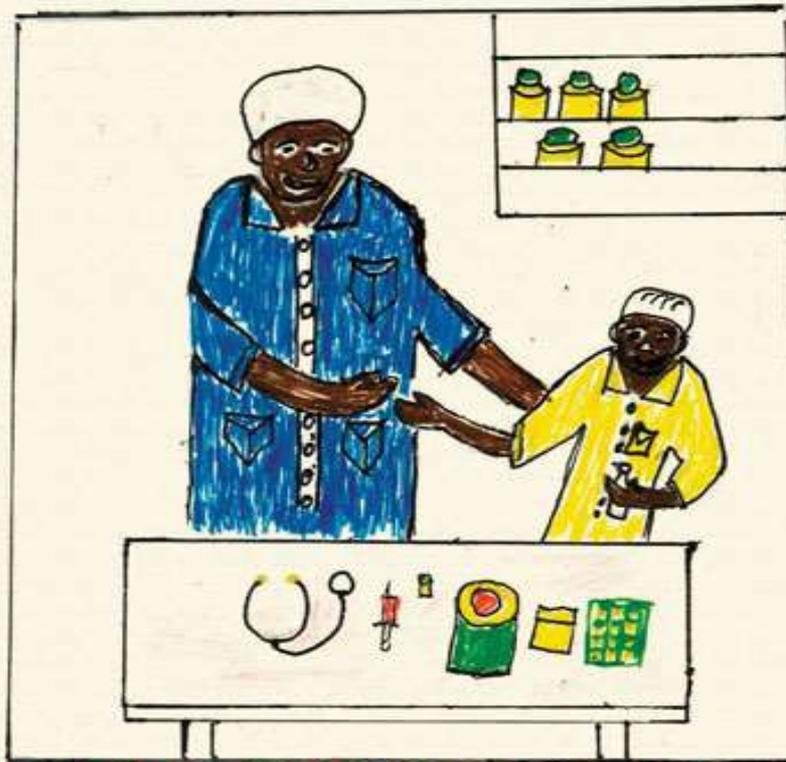


MDR-TB

- ❑ **IT is resistant to both INH and Rifampicin.**
- ❑ **We can select five anti-TB drugs , these drugs include:**
 - ❑ **Quinolones (Levofloxacin, ofloxacin),**
 - ❑ **Aminoglycosides (amikacin, kanamycin, capremycin)**
 - ❑ **EMB,**
 - ❑ **PZA,**
 - ❑ **Cycloserine,**
 - ❑ **Ethionamide.**
- ❑ **The whole therapy lasts at least 18 months.**

Did you know that ...

TB IS CURABLE!



TREATMENT IS FREE