Tuberculosis

By

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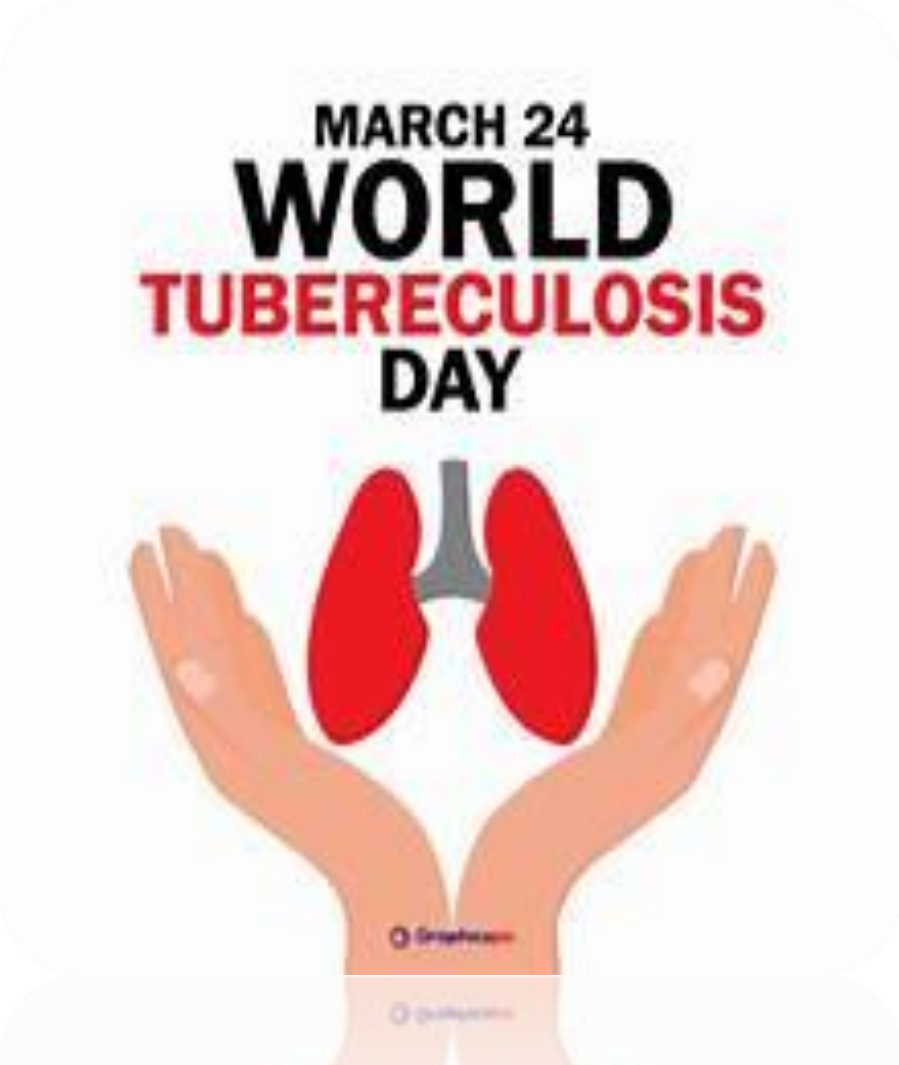


History

- 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

It accounts for:

1.7 million

deaths worldwide

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

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

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

2.5 lakh

child fatalities worldwide

40%

of HIV-positive deaths

All figs for 2016; Source: WHO

NEWS18 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

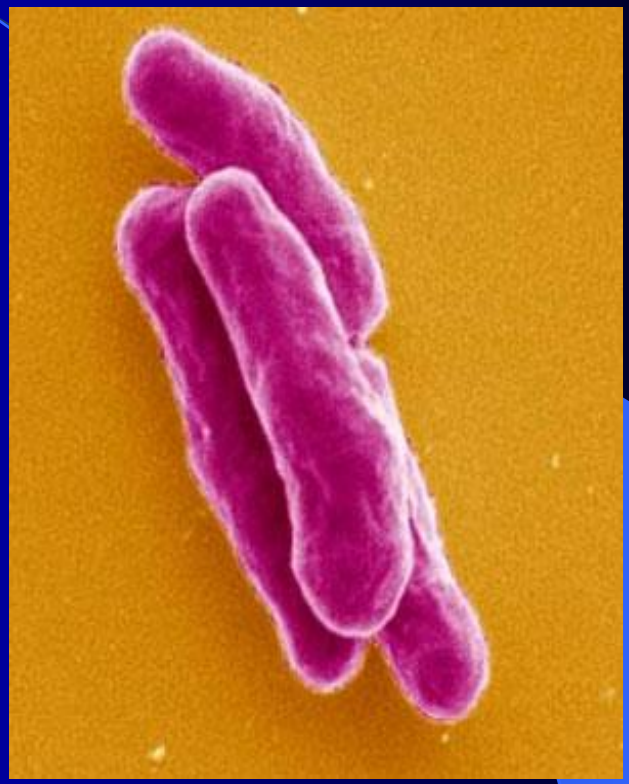
Caused by rod shaped bacteria

- *Mycobacterium tuberculosis*
- *Mycobacterium bovis*

Slow growing organism

Strictly aerobe.

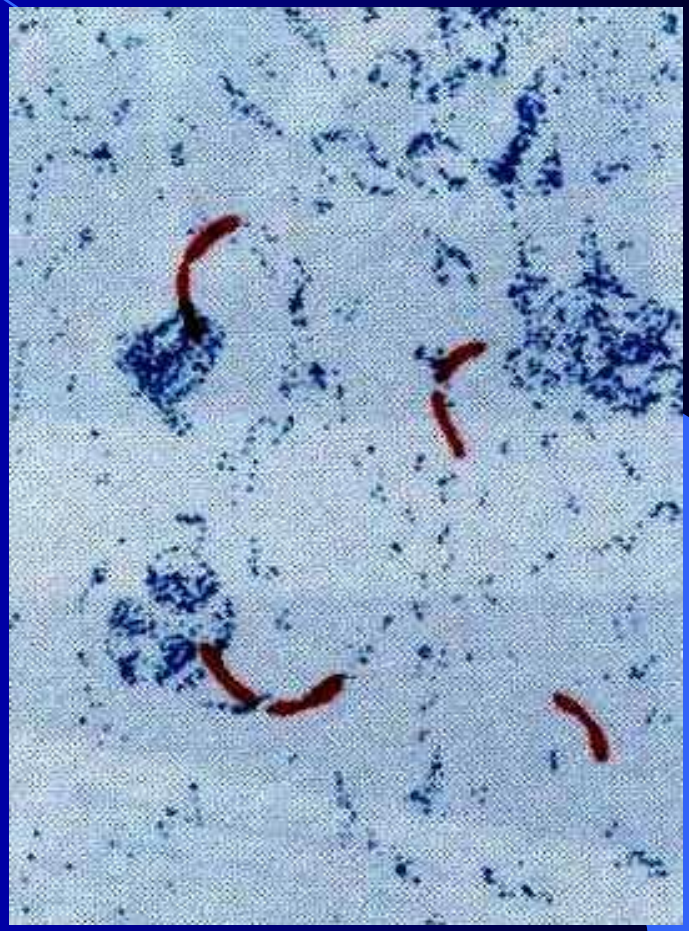
Susceptible to sunlight, heat and dryness.



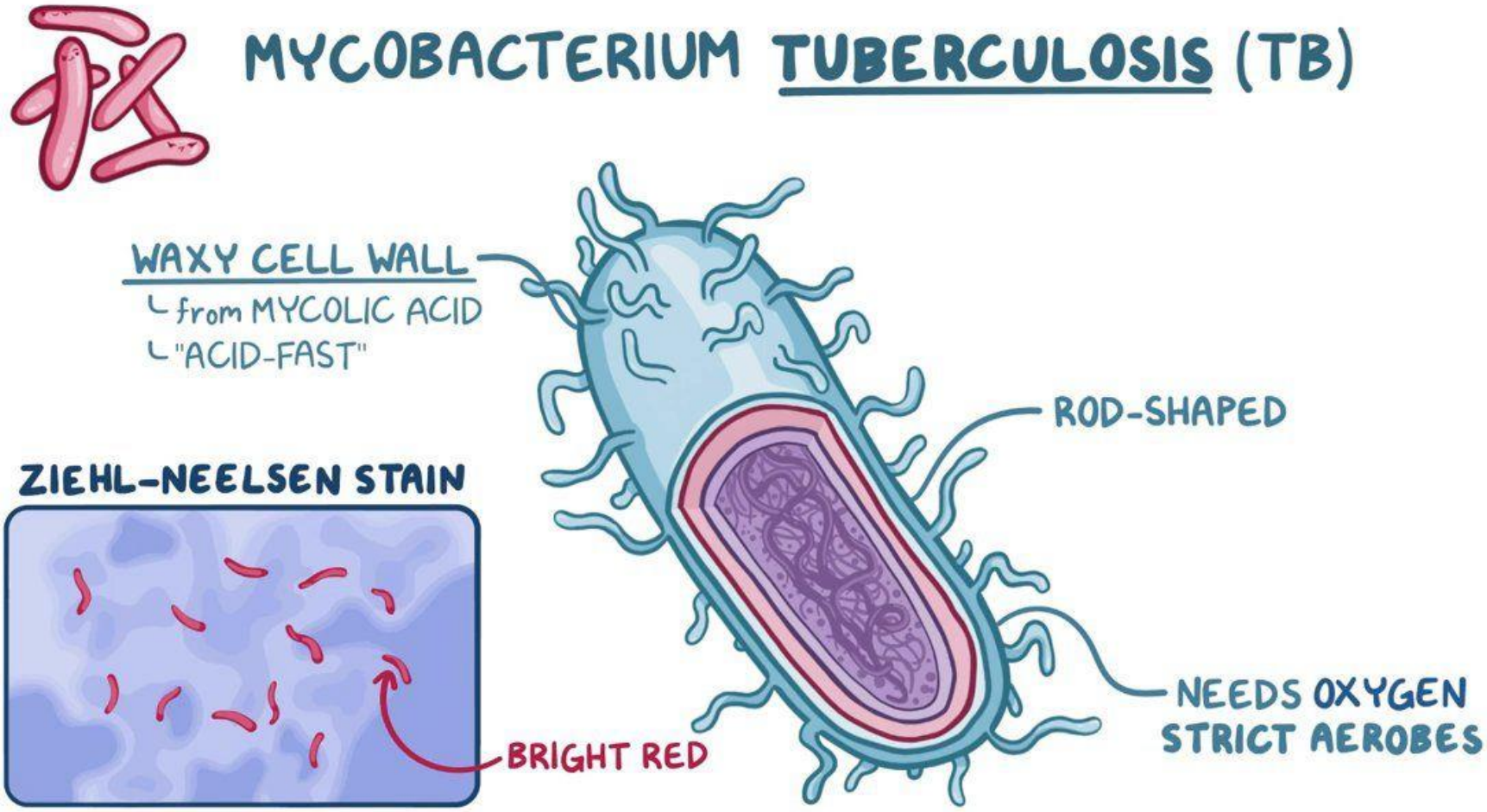
Aetiology

TB Bacillus is

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



Mycobacteria unique cell wall structure



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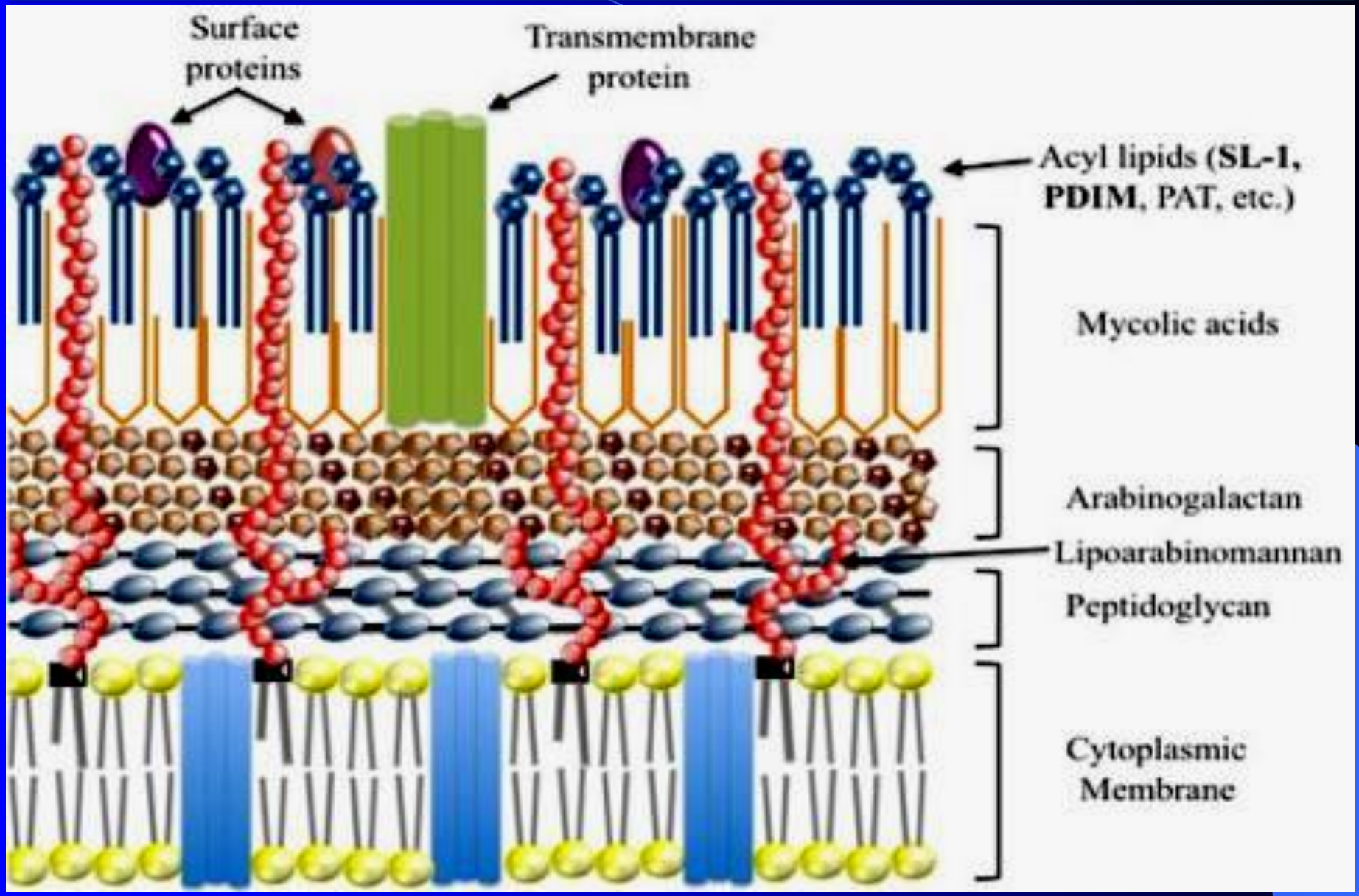


Transmission Of Infection

Modes of transmission

1- Air-borne infection:

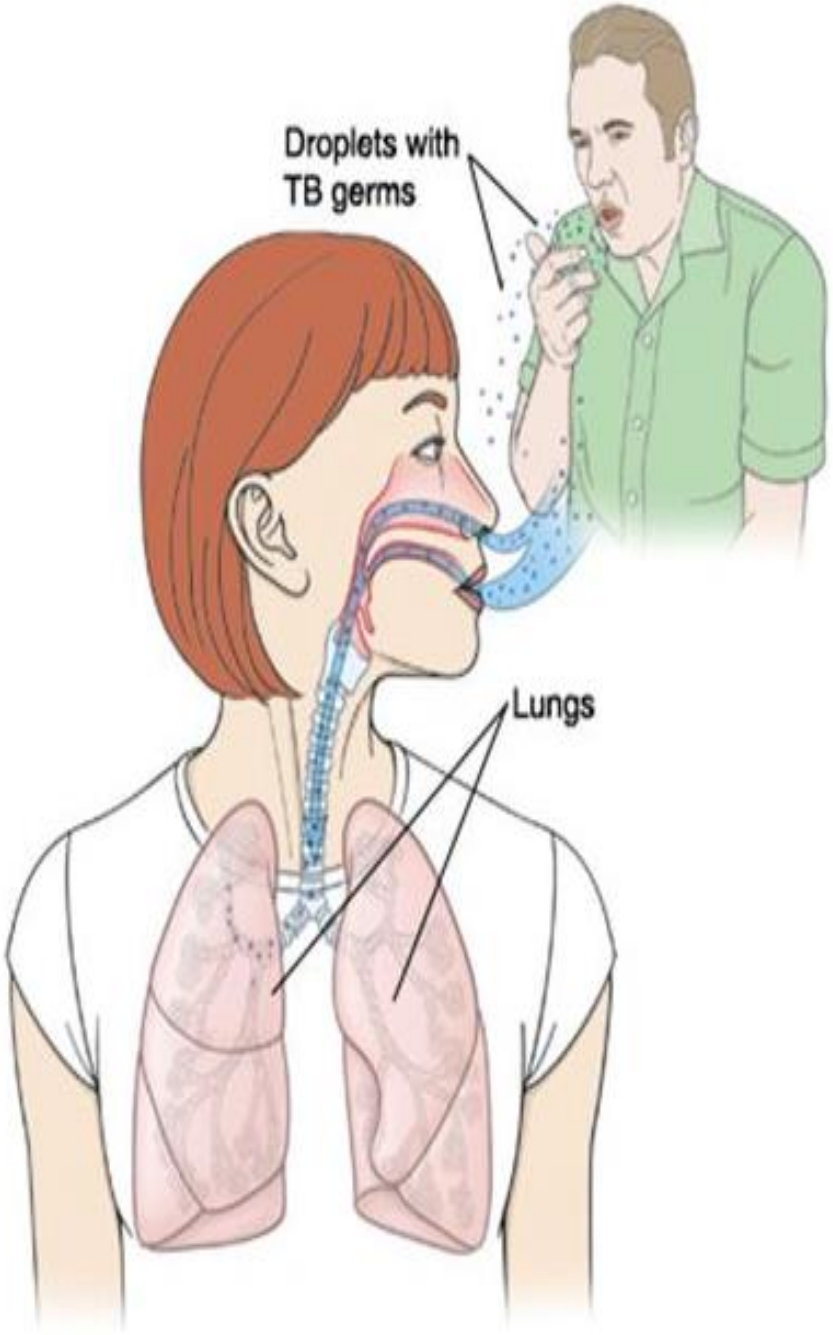
TB bacilli is 1-5 µm in length

remain in the air for long times.

2- Ingestion of raw milk & diary products.

3- Direct invasion through wounds

- TB is spread from person to person through the air via droplet nuclei
- 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.

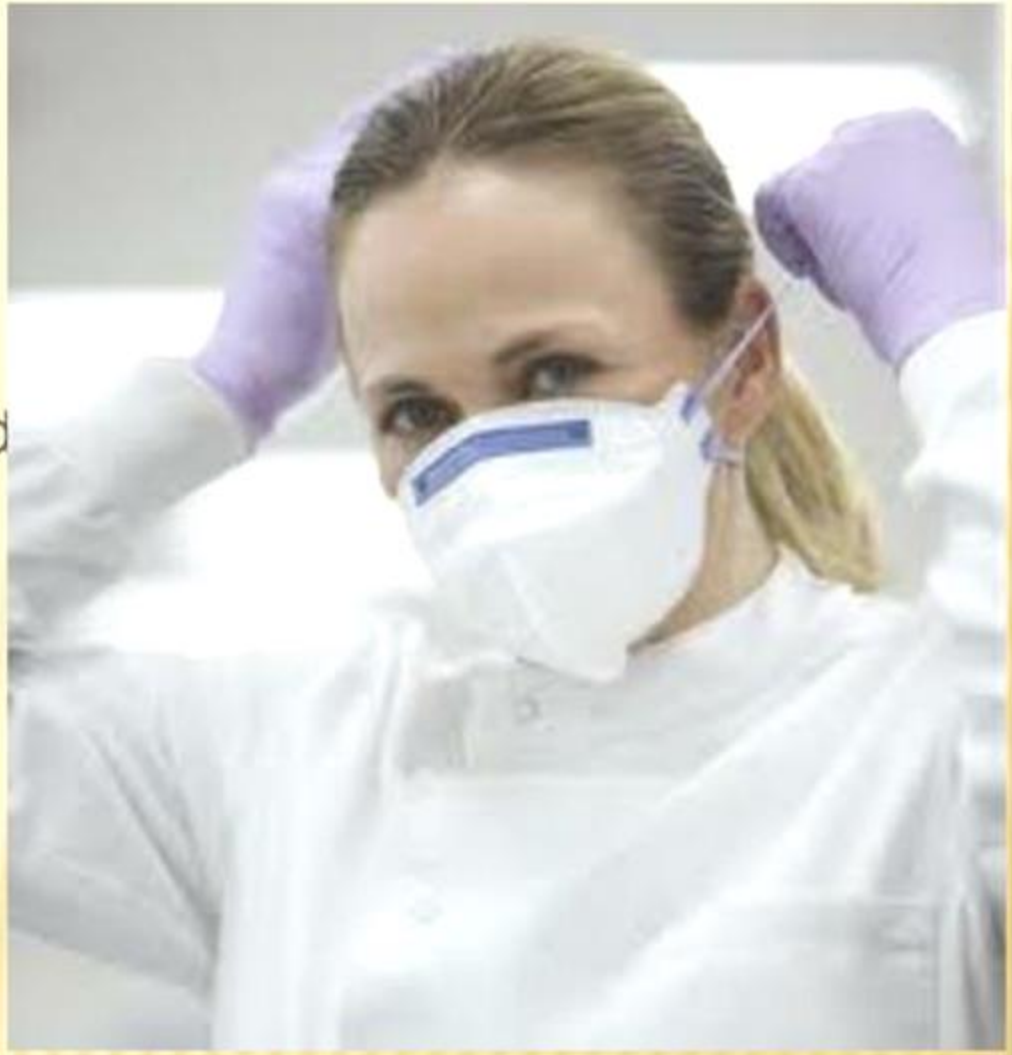


AIRBORNE PRECAUTIONS

REQUIRES

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

- If transporting pt, Pt must wear mask.



The transmission is determined by

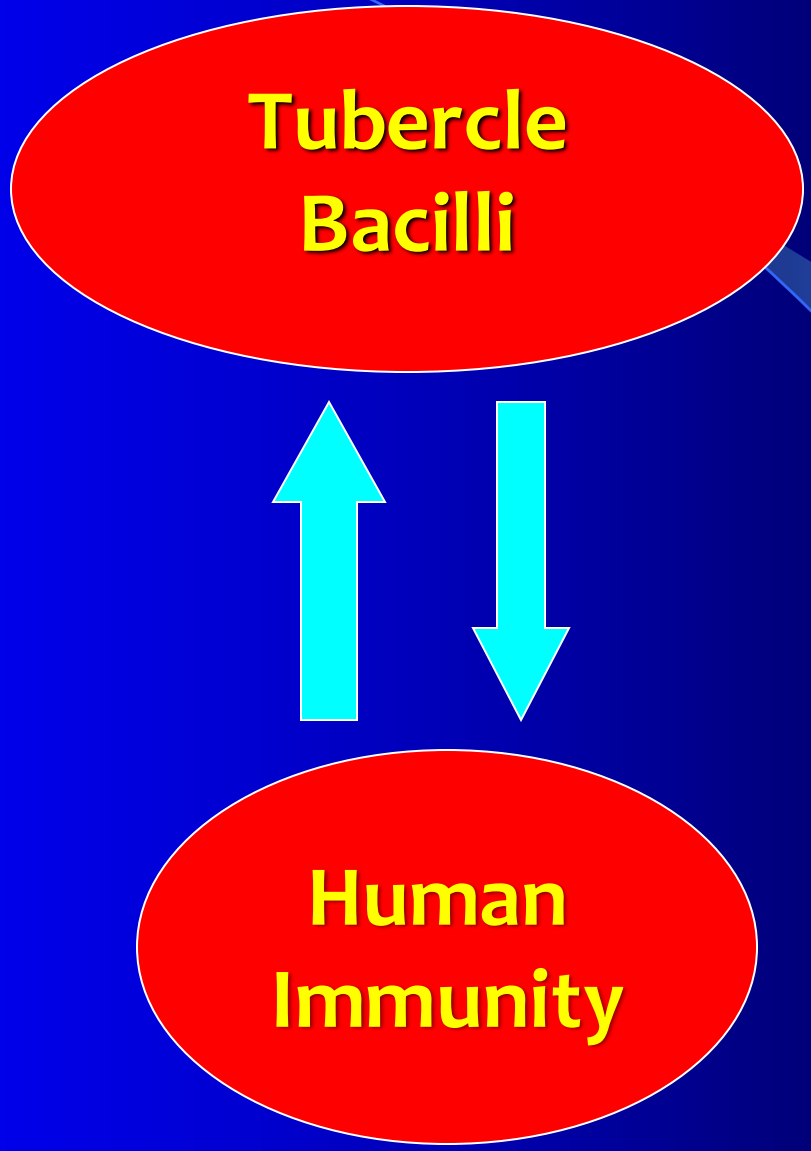
- The degree of infectiousness of case .
  - Untreated positive AFB smear cases are the most infectious
  - Patient with cavitary lesion is more infective
- The intimacy and duration of that contact

High Risk Patients

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

Incubation period: 4-12 weeks.

Pathogenesis



Human Immunity after TB

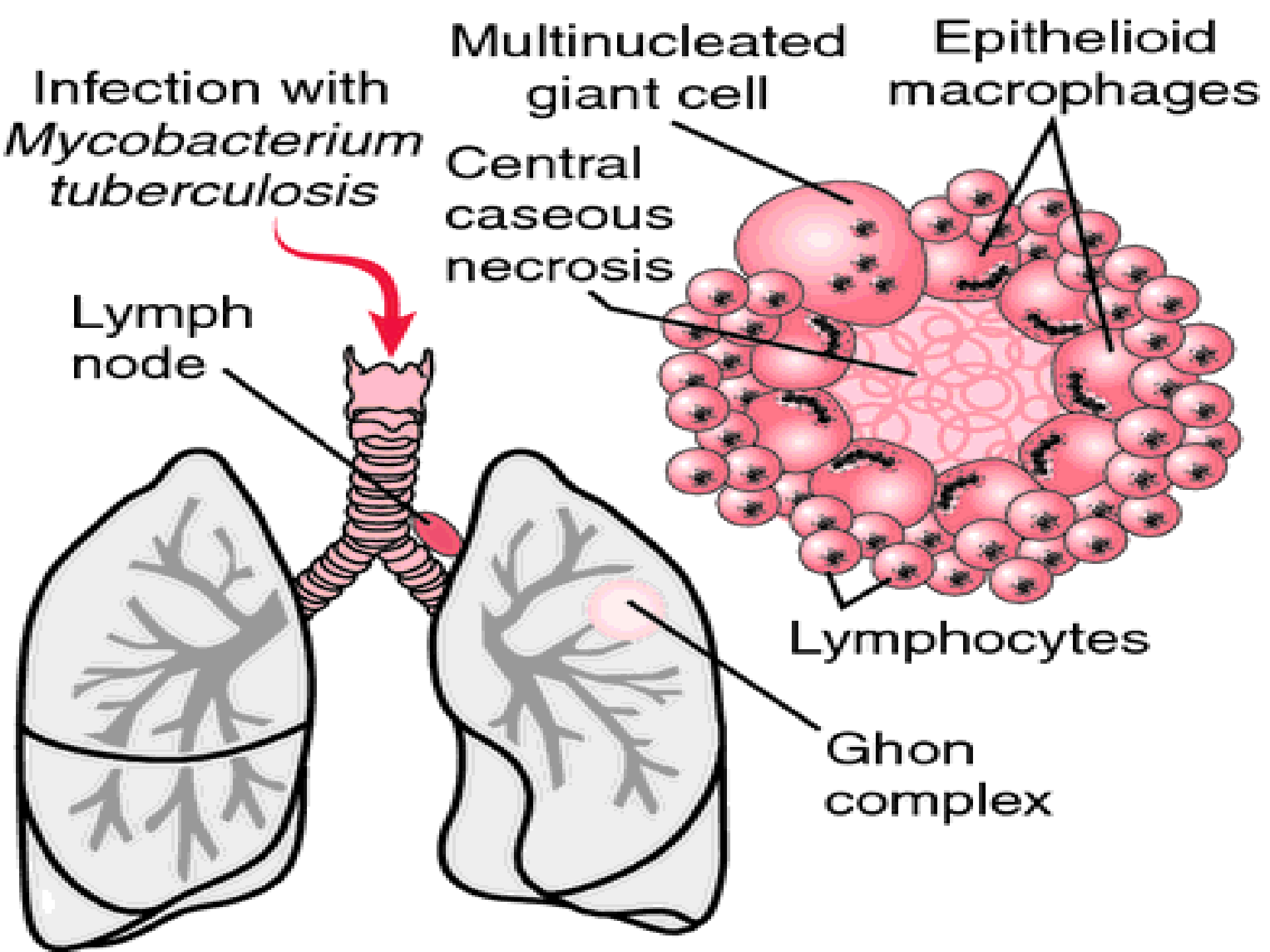
- After infection or given BCG vaccine, human will obtain specific immunity (*cell- mediated immunity*)

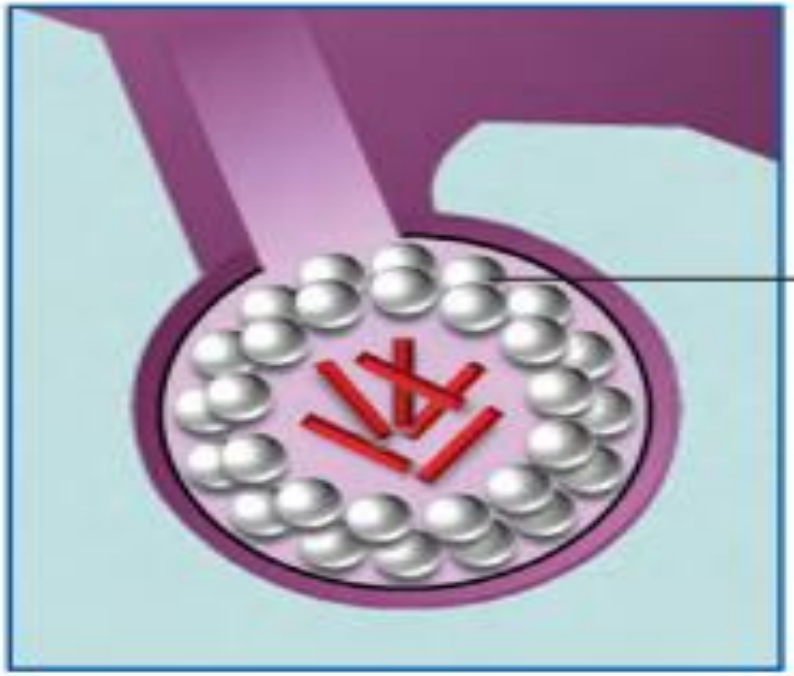
- The cellular immunity develops within 4 - 8 weeks after infection with TB bacilli .

Human Immunity after TB

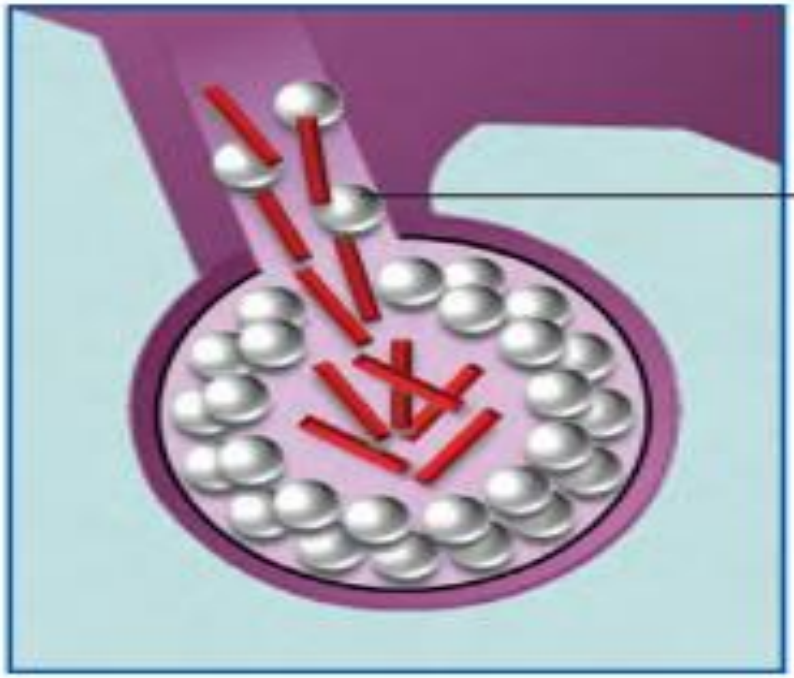
- Many immunologic cells involve in the formation of pulmonary tuberculosis.

- Two types of cells are essential in the formation of TB
  - Macrophages: directly phagocytes TB and presenting antigens to T lymphocyte
  - T lymphocytes(CD4+): induce protection through the production of lymphokines
  - Langhan's giant cells

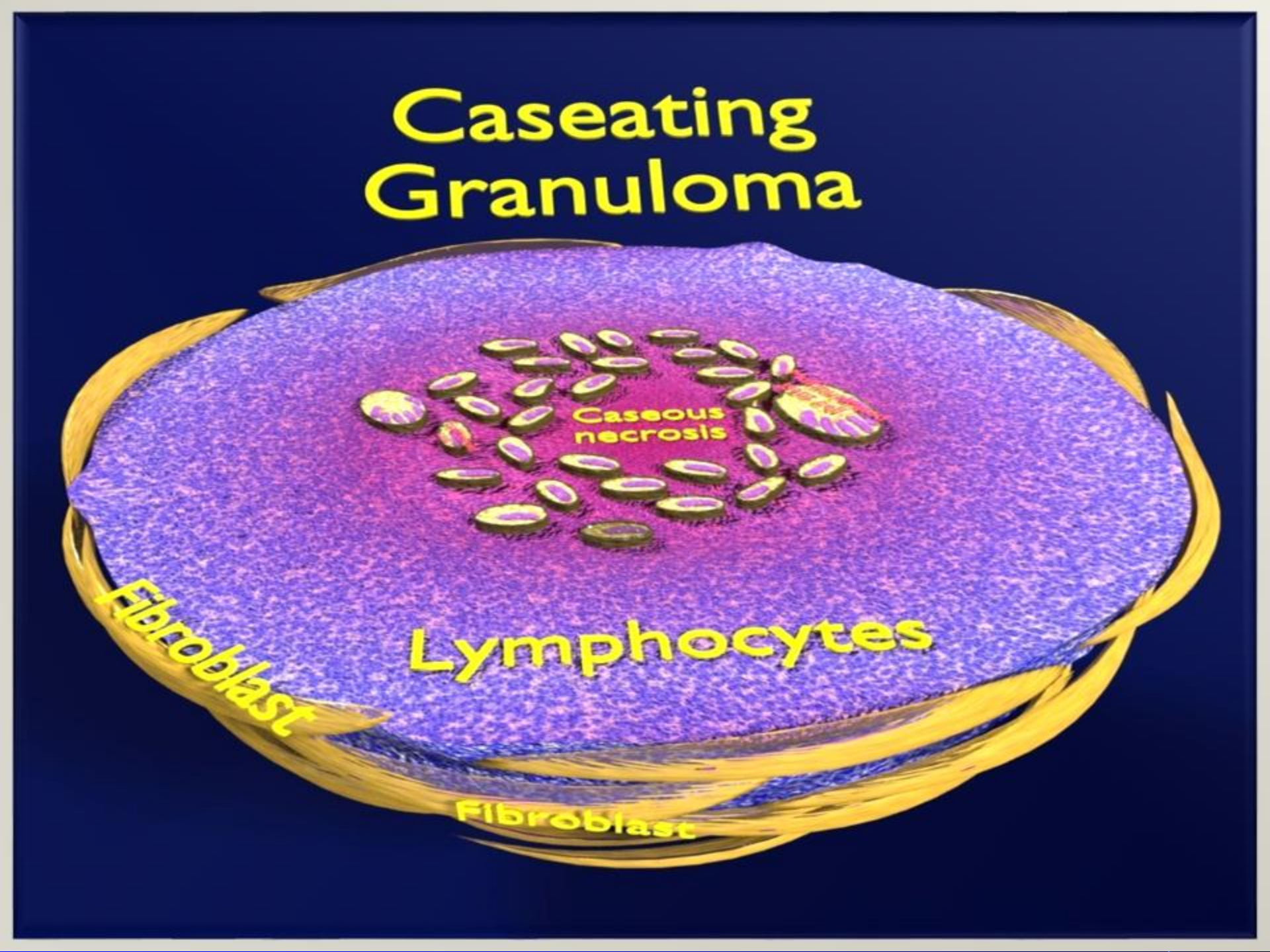

Infection with
Mycobacterium tuberculosis
Lymph node
Multinucleated giant cell
Epithelioid macrophages
Central caseous necrosis
Lymphocytes
Ghon complex



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



Shell breaks down and tubercle bacilli escape and multiply


Caseating Granuloma
Caseous necrosis
Lymphocytes
Fibroblast
Fibroblast

Normal lungs

Primary infection with Ghon focus

Post-primary immunity

2-8 weeks

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

History

Physical Exam

Sputa

Cultures

PCR

CXR

Response to therapy

Pathology

TST

Gold Standard = Culture

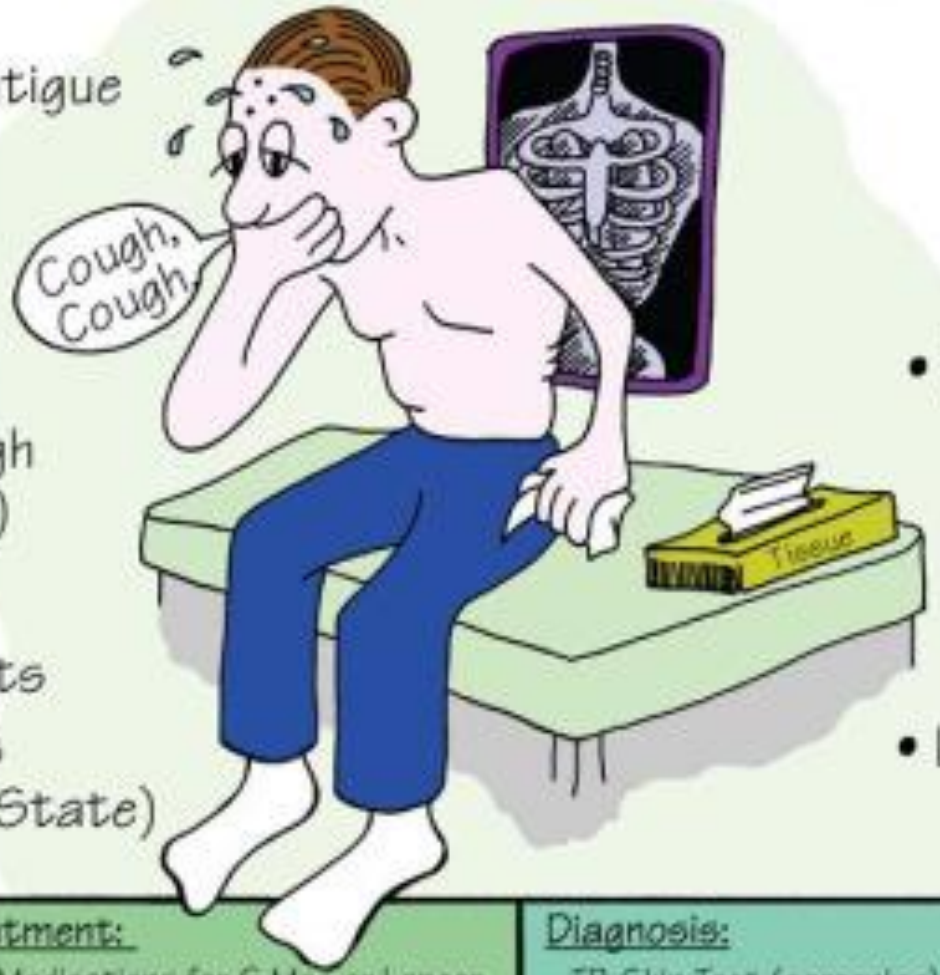
Clinical Manifestations

- *Systemic symptoms:*
  - Fever, Night sweats
  - Anorexia, Weight loss,
  - Fatigue.

- *Respiratory symptoms:*
  - Cough may vary from mild to severe, and sputum may be scant and mucoid or copious and purulent
  - Hemoptysis may be due to cough of a caseous lesion or bronchial ulceration
  - Chest pain

TUBERCULOSIS (TB)

- Progressive Fatigue
- Malaise
- Anorexia
- Wt. Loss



- Chronic Cough (Productive)
- Pleuritic Chest Pain
- Night Sweats
- Hemoptysis (Advanced State)
- Low Grade Fever

Treatment:	Diagnosis:
TB Medications for 6 Mos or Longer Decreased Activity Keep Isolation Until Negative Sputum Frequently Outpatient Treatment	TB Skin Test (screening) Chest X-Ray Sputum Studies (3 specimens collected on different days)

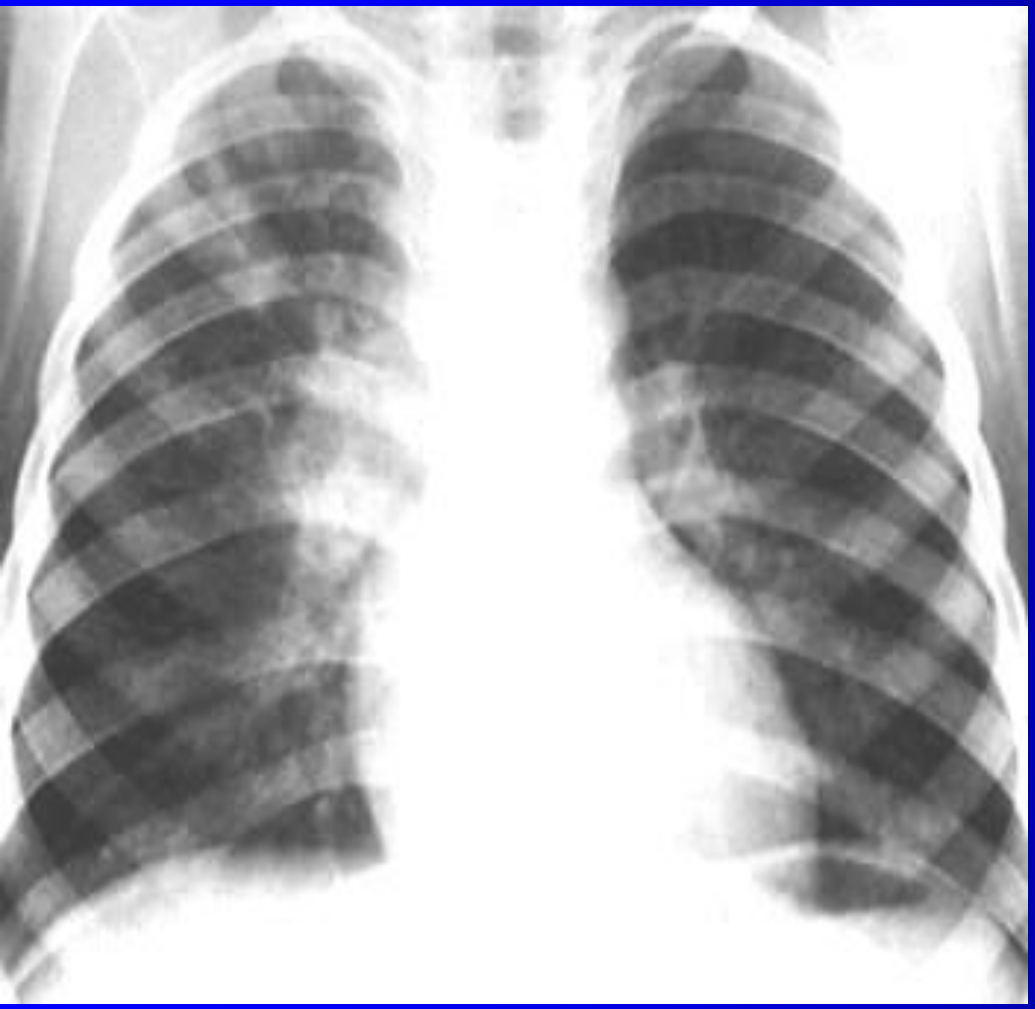
Radiology of TB

- Chest radiography is the most important method to detect TB.
- Tuberculosis is a great mimic
- TB characteristics of a chest radiograph favor the diagnosis of tuberculosis as following :

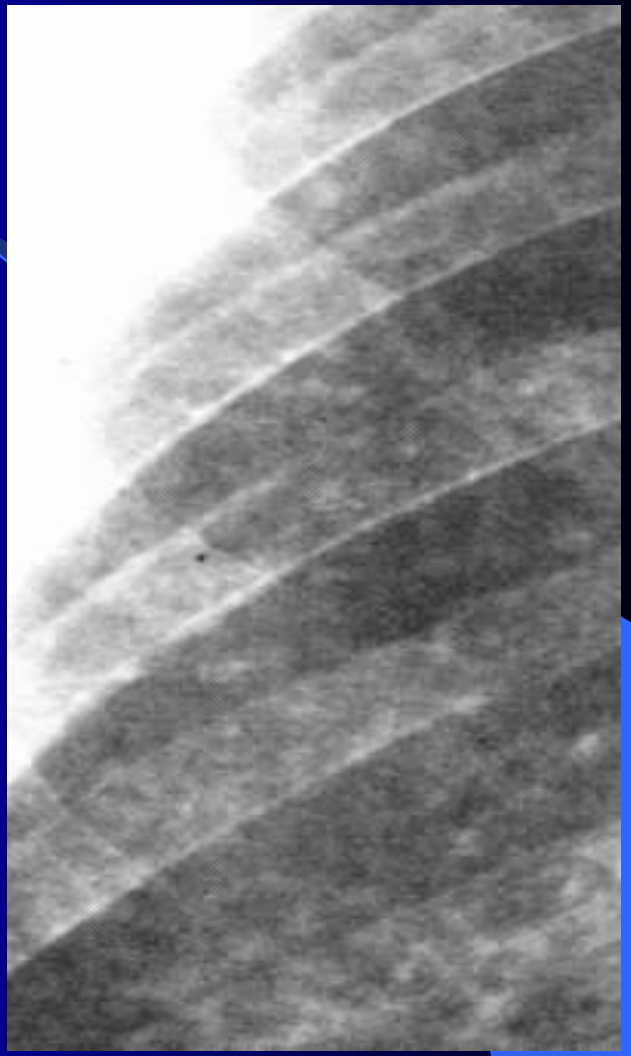
Radiology of TB

1. Pulmonary infiltration mainly in the upper zone Patchy, Nodular, or Cavitations shadows
2. Presence of calcification.
3. Persistence of the abnormal shadows after non specific treatment with antibiotics.

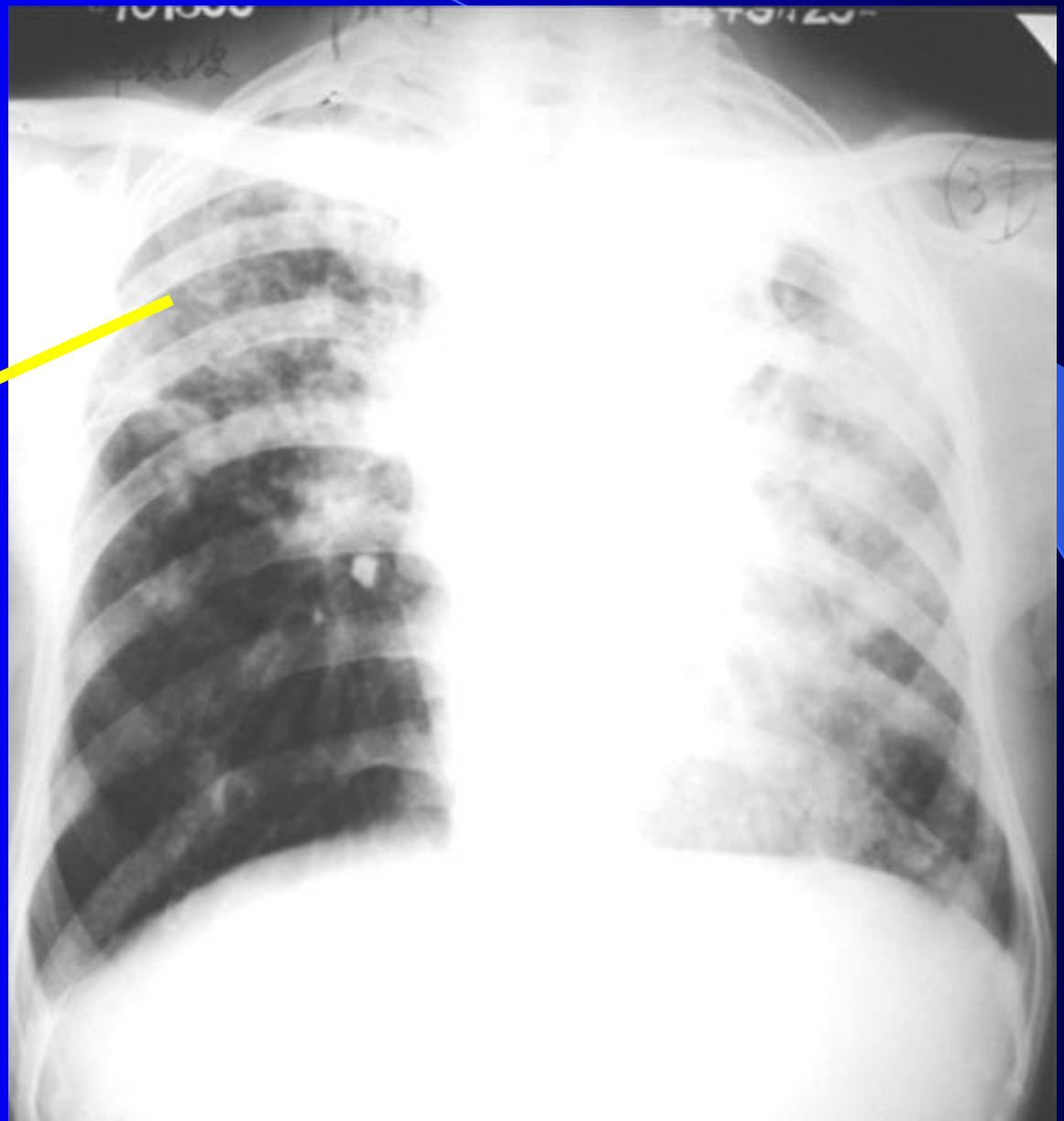
Primary complex

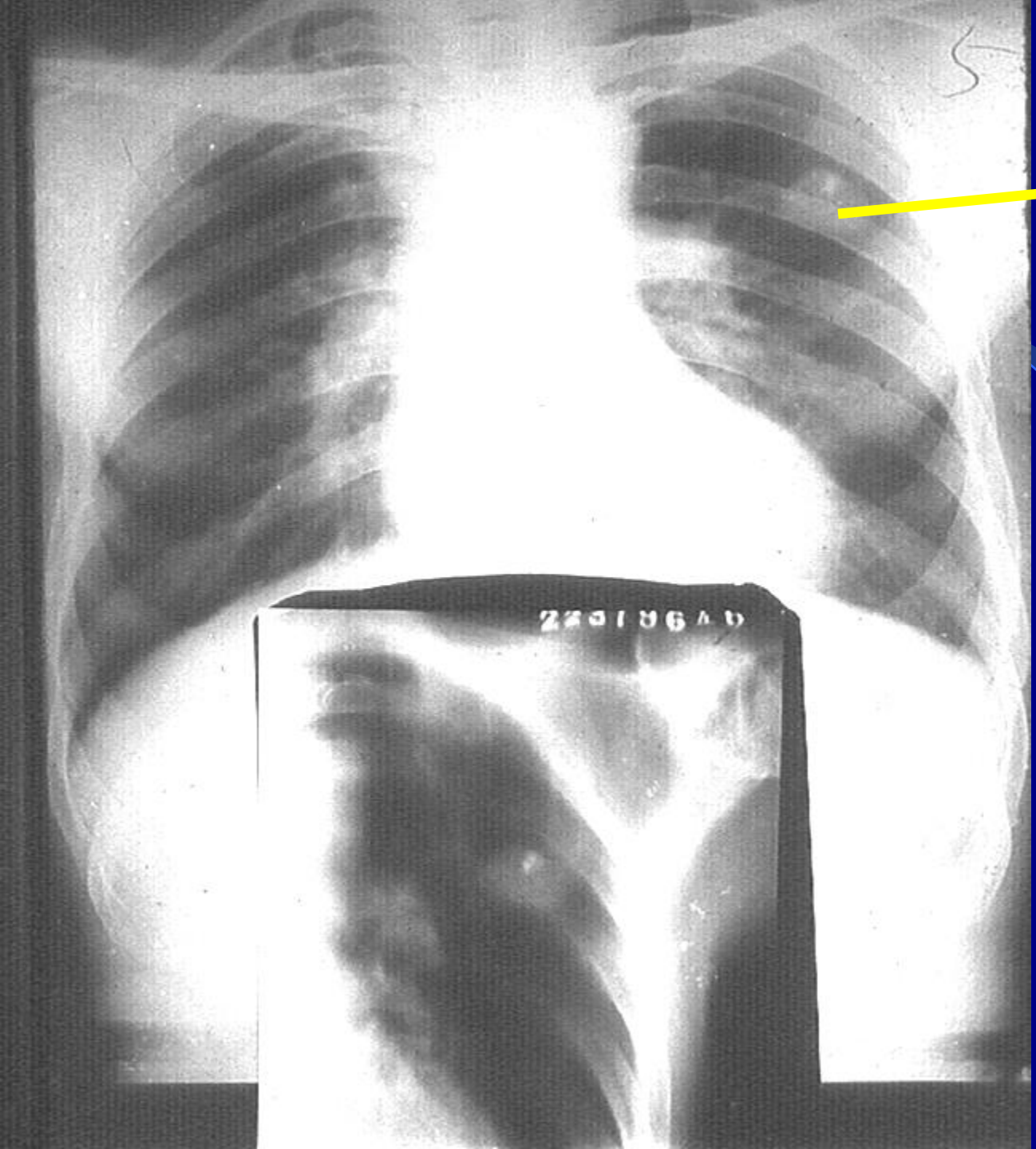


Milliary Tuberculosis



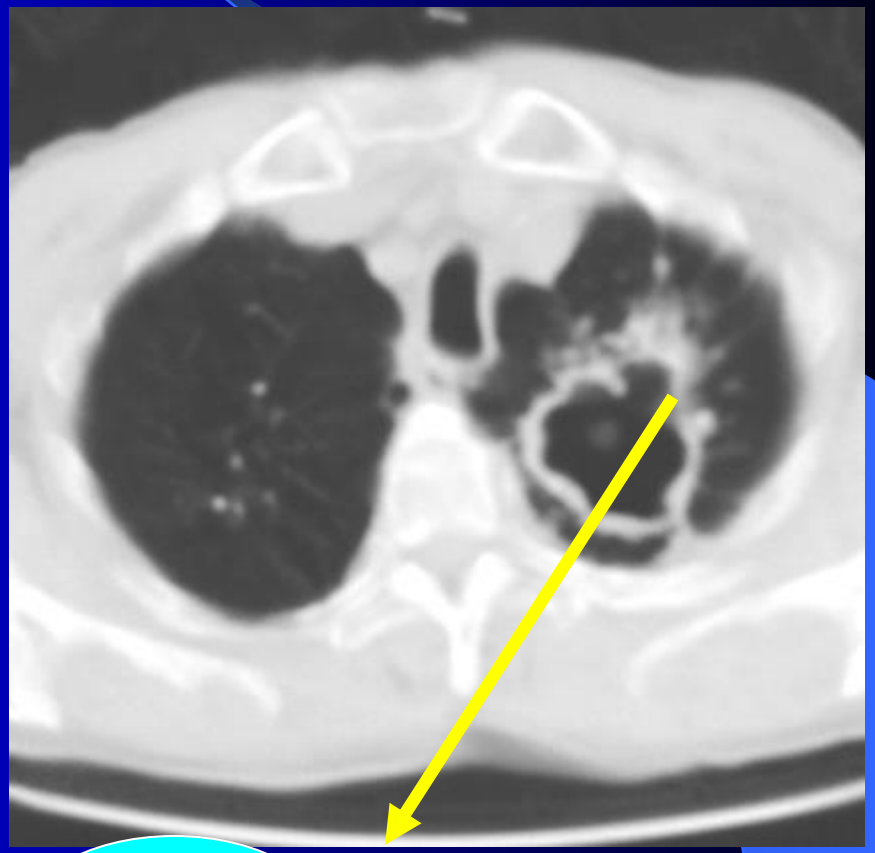
Post-primary pulmonary tuberculosis

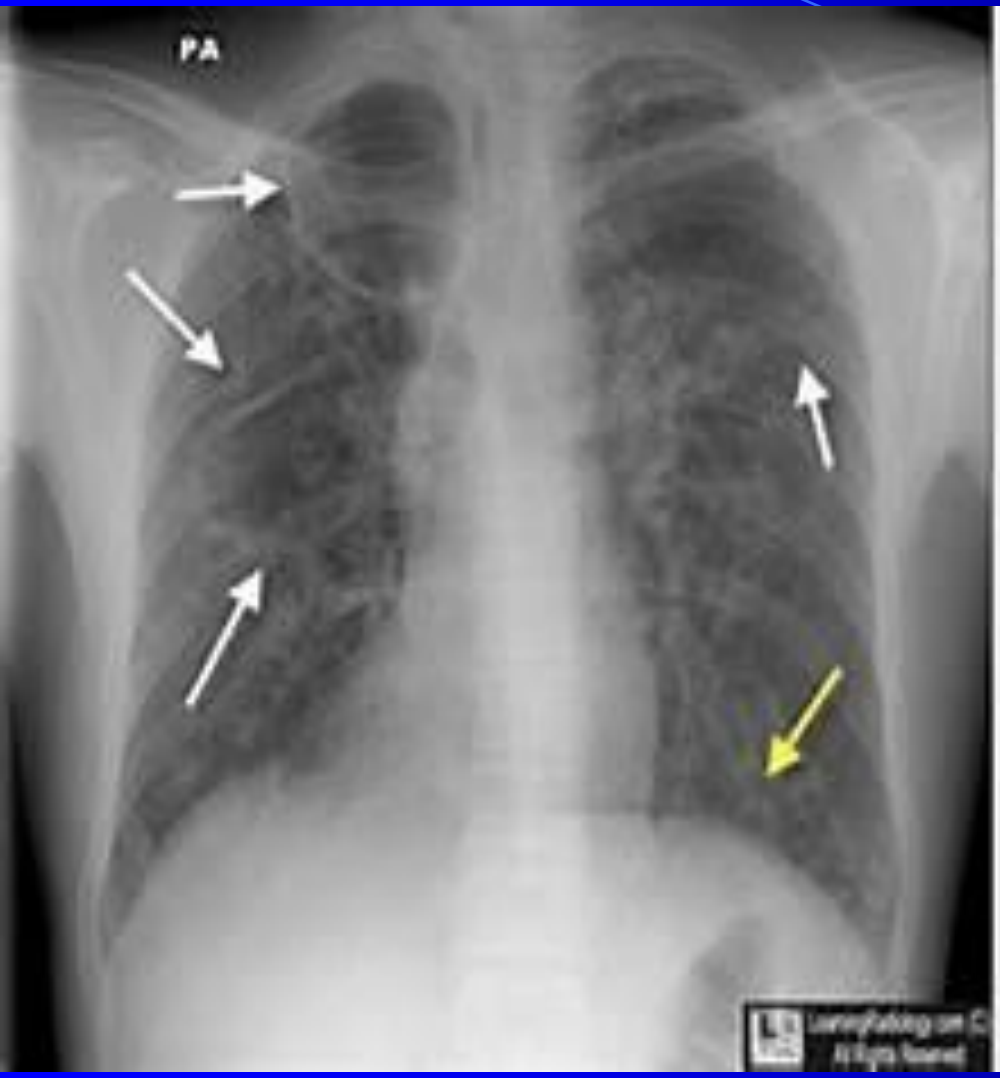




Tuberculoma

Chronic fibro-cavitary pulmonary tuberculosis

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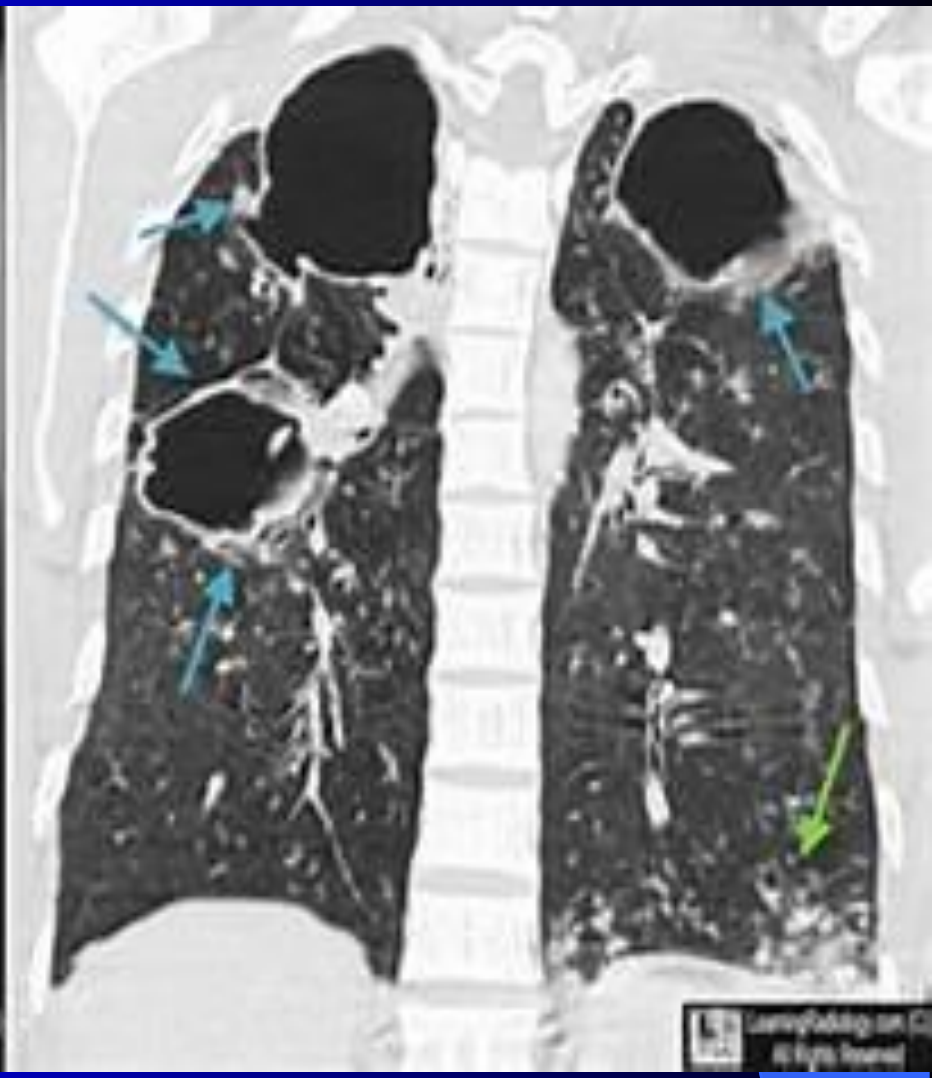

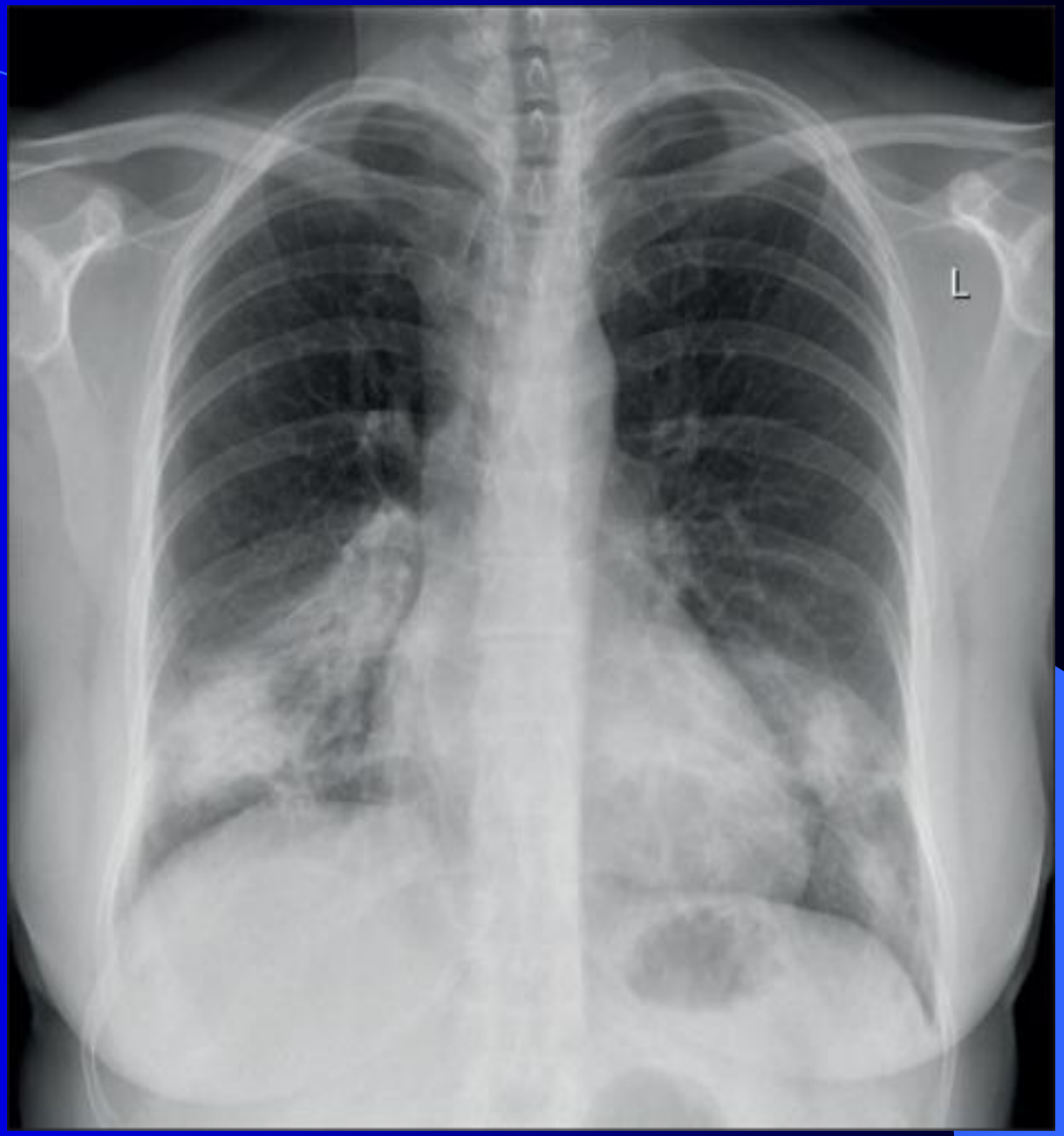
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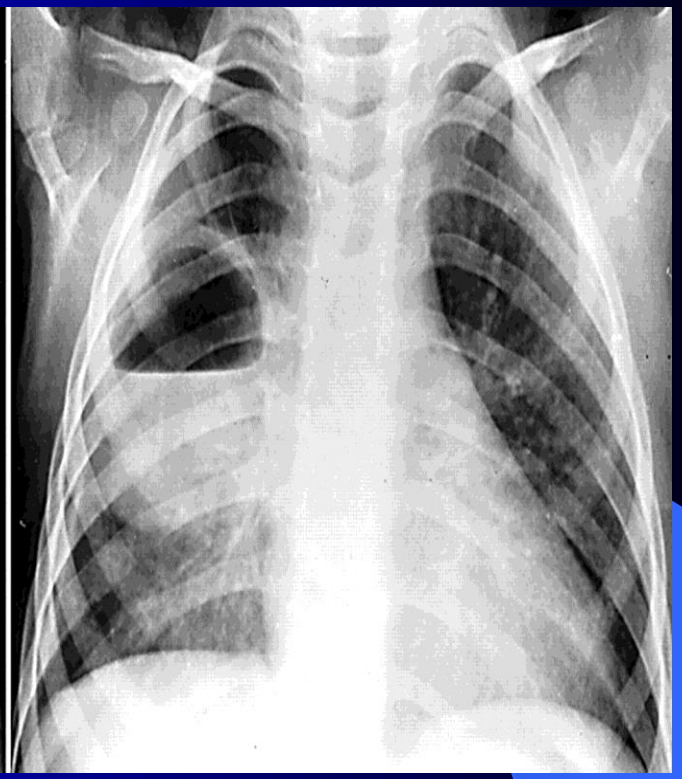


Laboratory examinations

- Specimen examination
- Tuberculin testing

Types of specimens:

- Sputum.
- BAL.
- Pleural effusions
- Blood in case of haematogenou

TB

1- Sputum smears stained by Z-N stain

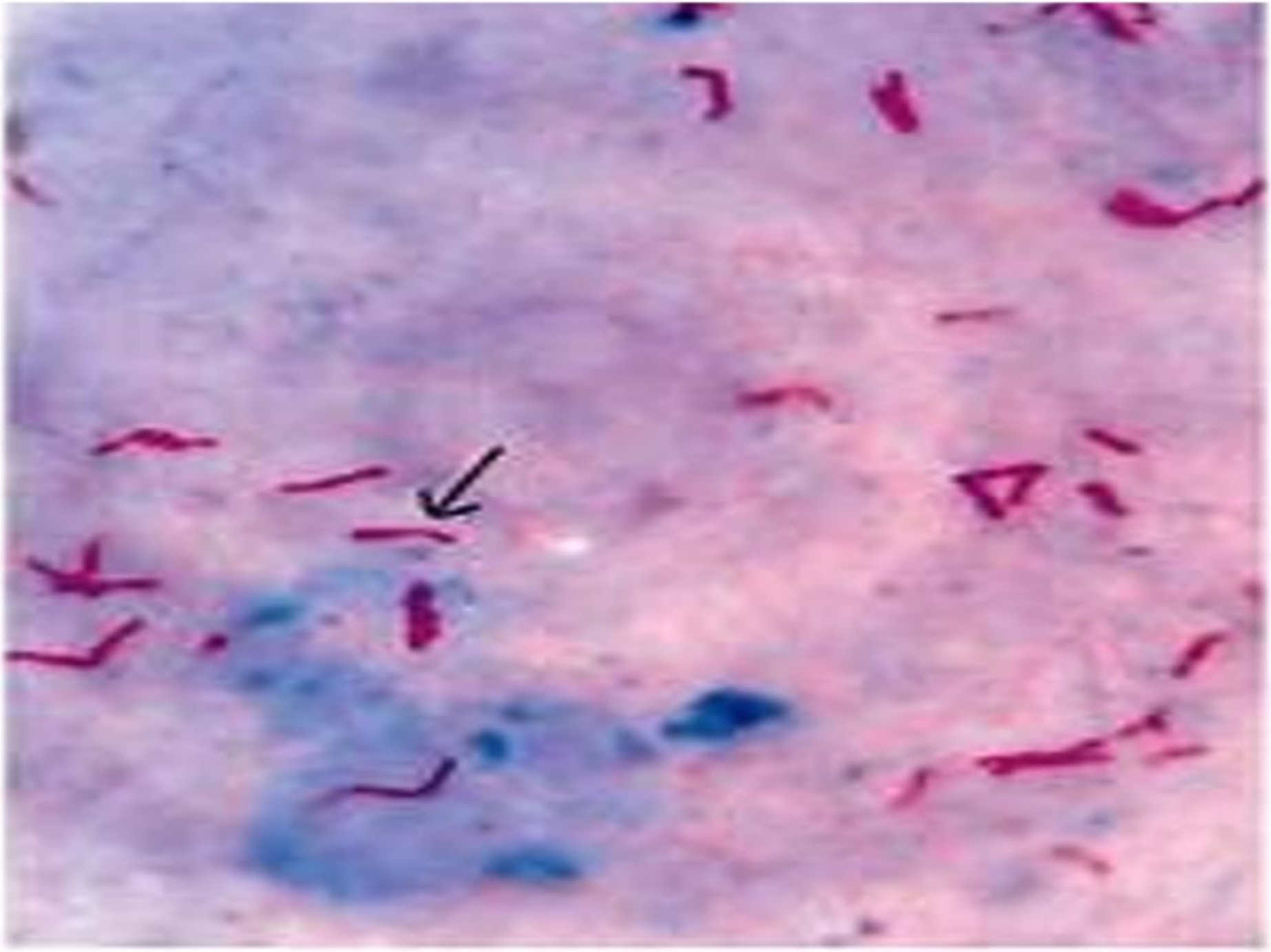
Three morning successive sputum samples are needed to diagnosis pulmonary TB.

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

Disadvantages:

- Sputum has low sensitivity (need to contain 5000-10 000 AFB/ ml.) as in non cavitary disease or low bacillary load in sputum (e.g. HIV positive patients)

-Young children & HIV infected persons may not produce sputum containing AFB.



2- Cultures on L J media

Lowenstein –Jensen medium is an egg based media

Advantages:

- **Specificity about 99 %**
- **More sensitive (need lower no. of bacilli 10-100 / ml)**
- **Can differentiate between TB complex & Non-tubercolous mycobacterium (NTM) using biochemical reactions**

- **Susceptibility tests for antituberculous drugs (St, INH, Rif., E)**

Disadvantages: Slowly growing (up to 8 weeks)

Mycobacterium tuberculosis growing on Lowenstein-Jensen (LJ) Medium

Recent Methods for Diagnosis

II-BACTEC 460 (rapid radiometric culture system)

- Specimens are cultured in a liquid medium (Middle brook7H9 broth base).
- Growing mycobacteria utilize the acid, releasing radioactive CO_2 which is measured as growth index (GI) in the BACTEC instrument.

Advantages :

- Rapid (mycobacteria can be detected within 12 days.)
- Determining drug susceptibility .
- Differentiating between TB complex & NTM by NAP test.
- Specificity is very high

Disadvantages:

- Expensive
- Hazards of using radioactive material.

INVESTIGATIONS

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

Bactec 460

Bactec9000MB

Bactec mgit960b

II-Polymerase Chain Reaction (PCR)

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

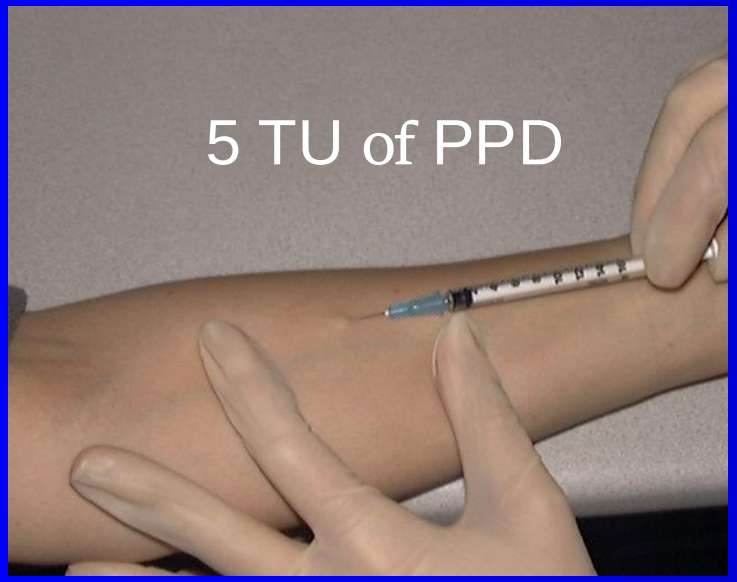
Advantages:

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

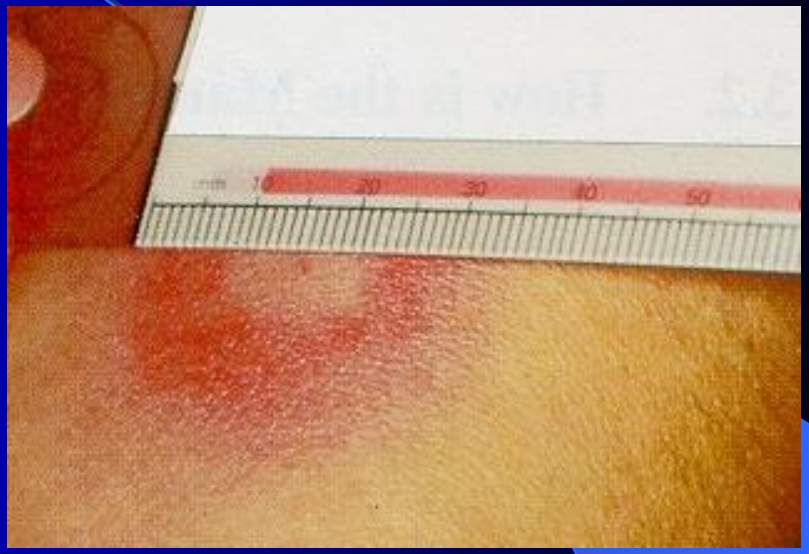
Disadvantages

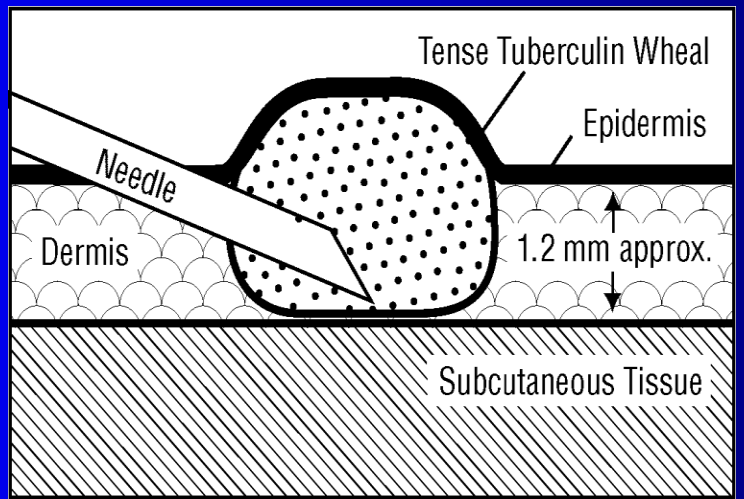
- Very expensive.
- Can not differentiate between living & dead bacilli.

Tuberculin Skin Testing
Mantoux Test



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 ⇛ Infection and Immunity

Positive Tuberculin Test

Size of induration	Considered positive in :
≥ 5 mm for	1. Close contacts of active pulmonary. 2. HIV-immunocompromised persons 3. 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 :
≥ 10 mm for	1. Persons with certain medical conditions e.g., ◦ Silicosis, ◦ Chronic renal failure, ◦ Diabetes mellitus, ◦ Some cancers, leukaemia, and lymphoma ◦ Gastrectomy/jeujunoileal bypass 2. Health care and laboratory workers. 3. Persons who have immigrated within the past 5 years from areas with high prevalence 4. Persons with prolonged stay (>1month) in areas with high TB e.g. prisons 5. Injection drug users. 6. Persons over age 70 and children < 4 years of age.
≥ 15 mm for	Considered positive in all peoples even in vaccinated persons

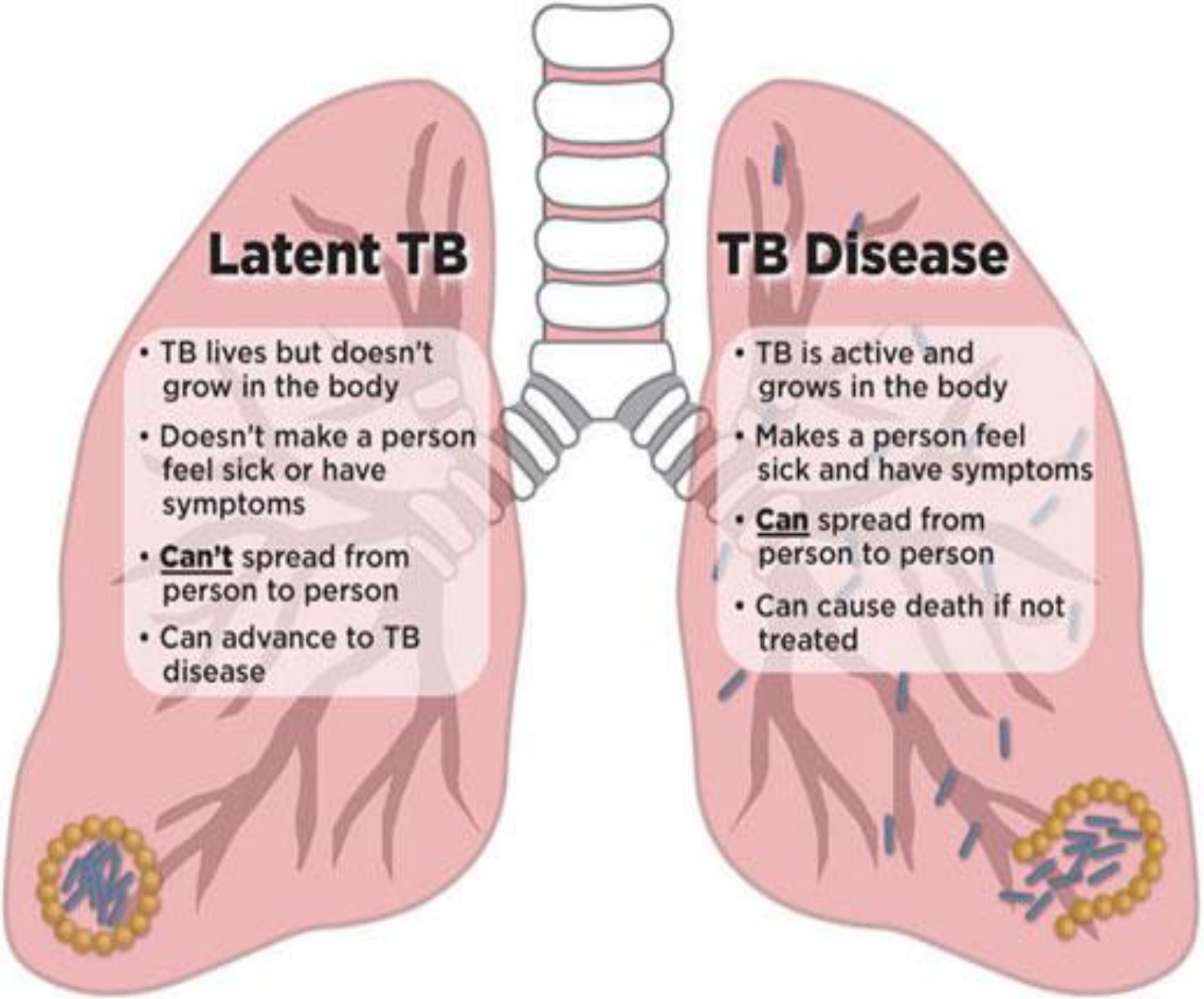
- *False negatives:*
  - Anergy (immunocompromised or malnutrition)
  - Recent TB infection
  - Very young age (< 6 months)
  - Deeper injection of TST.

- *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


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.

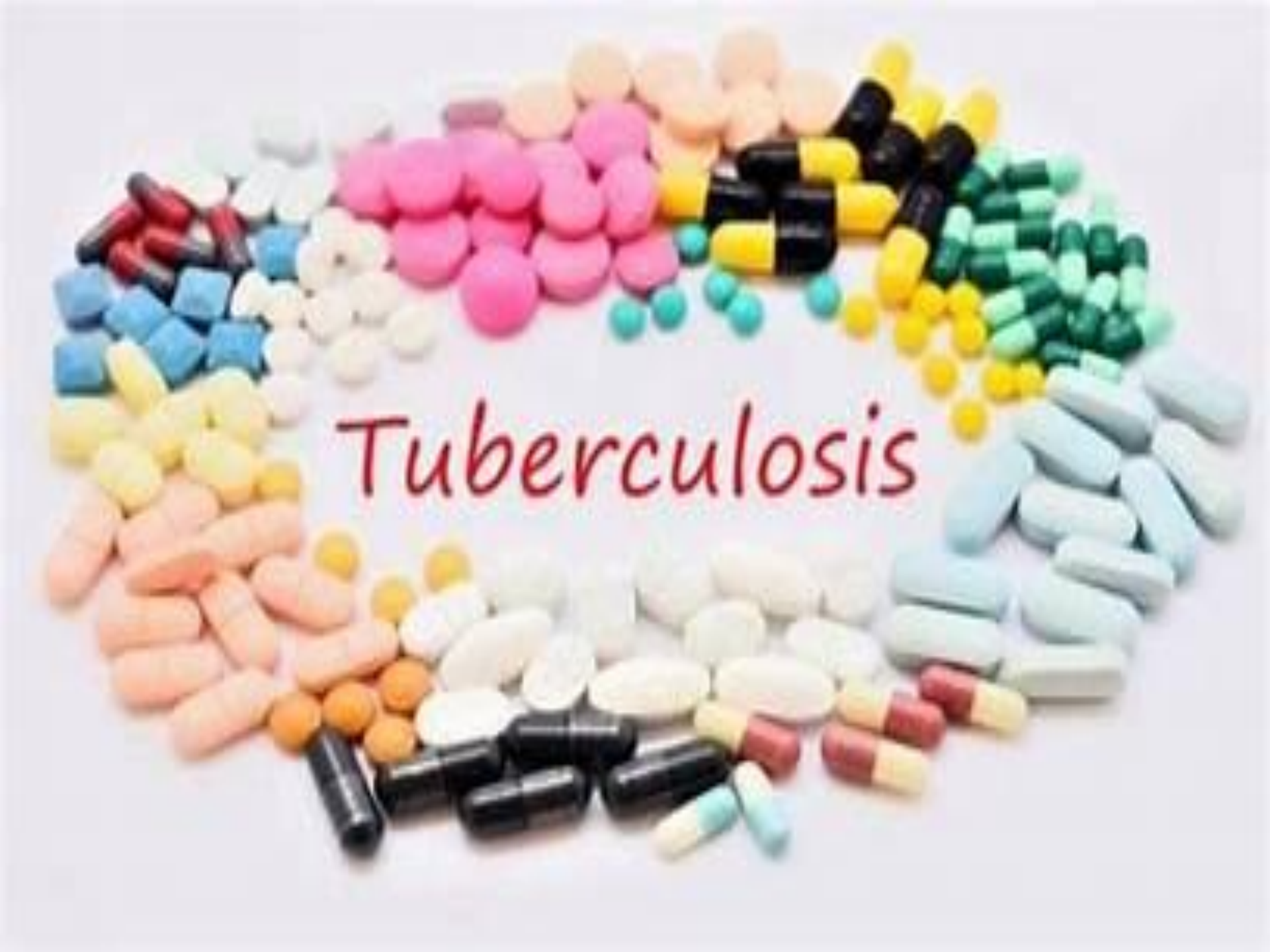
- QFT-G is an in vitro test
  - Never exposes the person to its antigenic proteins, so not generate “Booster Phenomenon”.

Differential Diagnosis

Pulmonary

Extra-Pulmonary

Anti TB Drugs


Tuberculosis

Goals of antitubercular chemotherapy

- *Kill dividing bacilli:* Drugs with early bactericidal action rapidly reduce bacillary load in the patient and achieve quick sputum negativity so that transmission of TB is interrupted. This also affords quick symptom relief.
- *Kill persisting bacilli:* To effect cure and prevent relapse. This depends on sterilizing capacity of the drug.
- *Prevent emergence of resistance:* The relative activity of the first line drugs in achieving these goals.

Basic Principles of Treatment

- Determine the patient's HIV status- this could save their life!
- 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)	**Continuation Phase** (4 months)
INH, RIF, PZA, EMB daily	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.

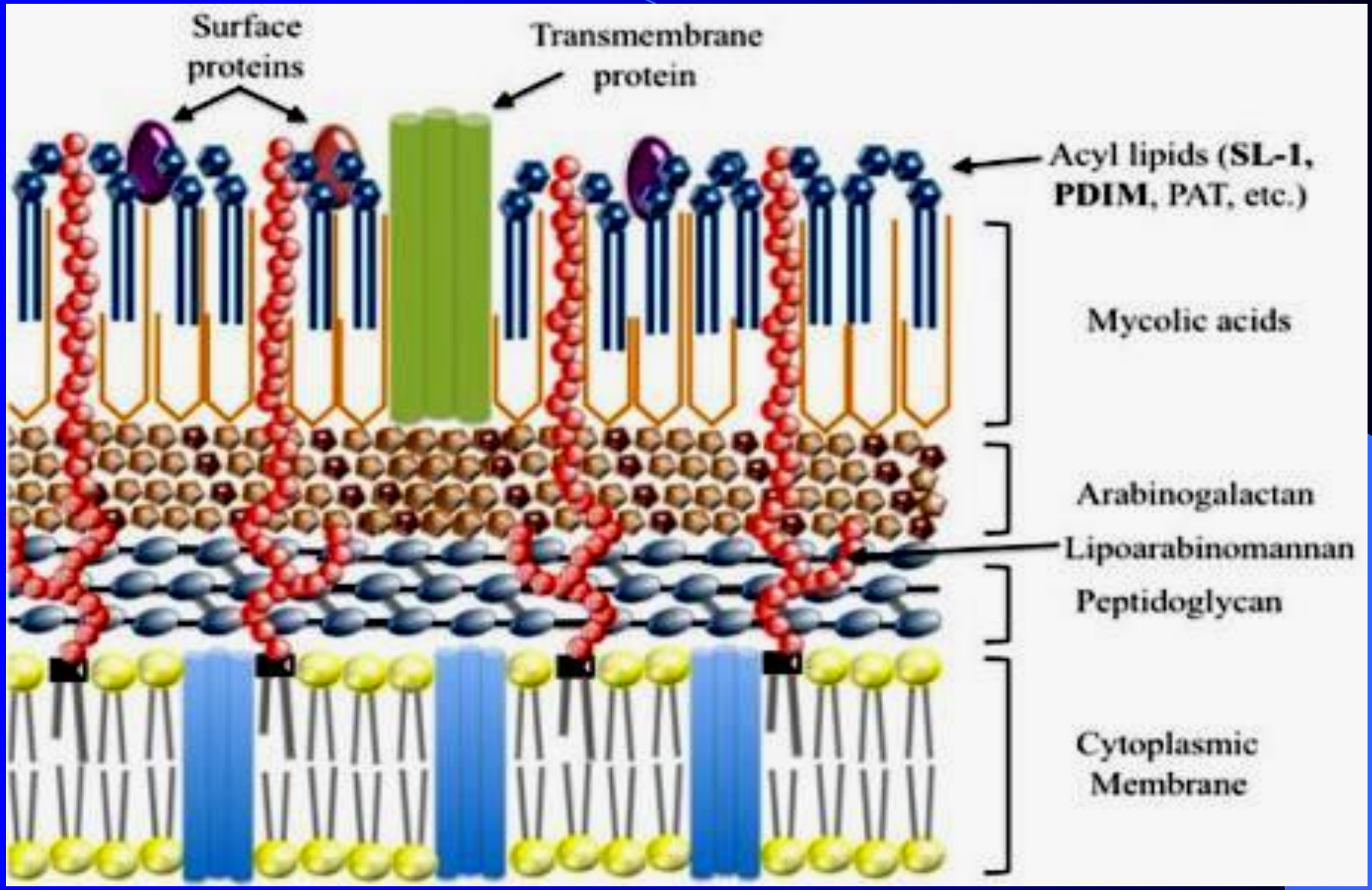
- A single dose leads to:
  - Higher peak serum concentrations
  - Potentially more effective,
  - Facilitates using DOT.

- 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	- GIT Upset - Arthralgia - Hyperuricemia	Anorexia, nausea, vomiting Joint aches Gout (rare)
Ethambutol	- Optic neuritis	Blurred vision Changed color vision
Streptomycin	-Ear damage - Kidney damage	Loss of hearing, Ringing in the ears Abnormal kidney function test

Extrapulmonary TB

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

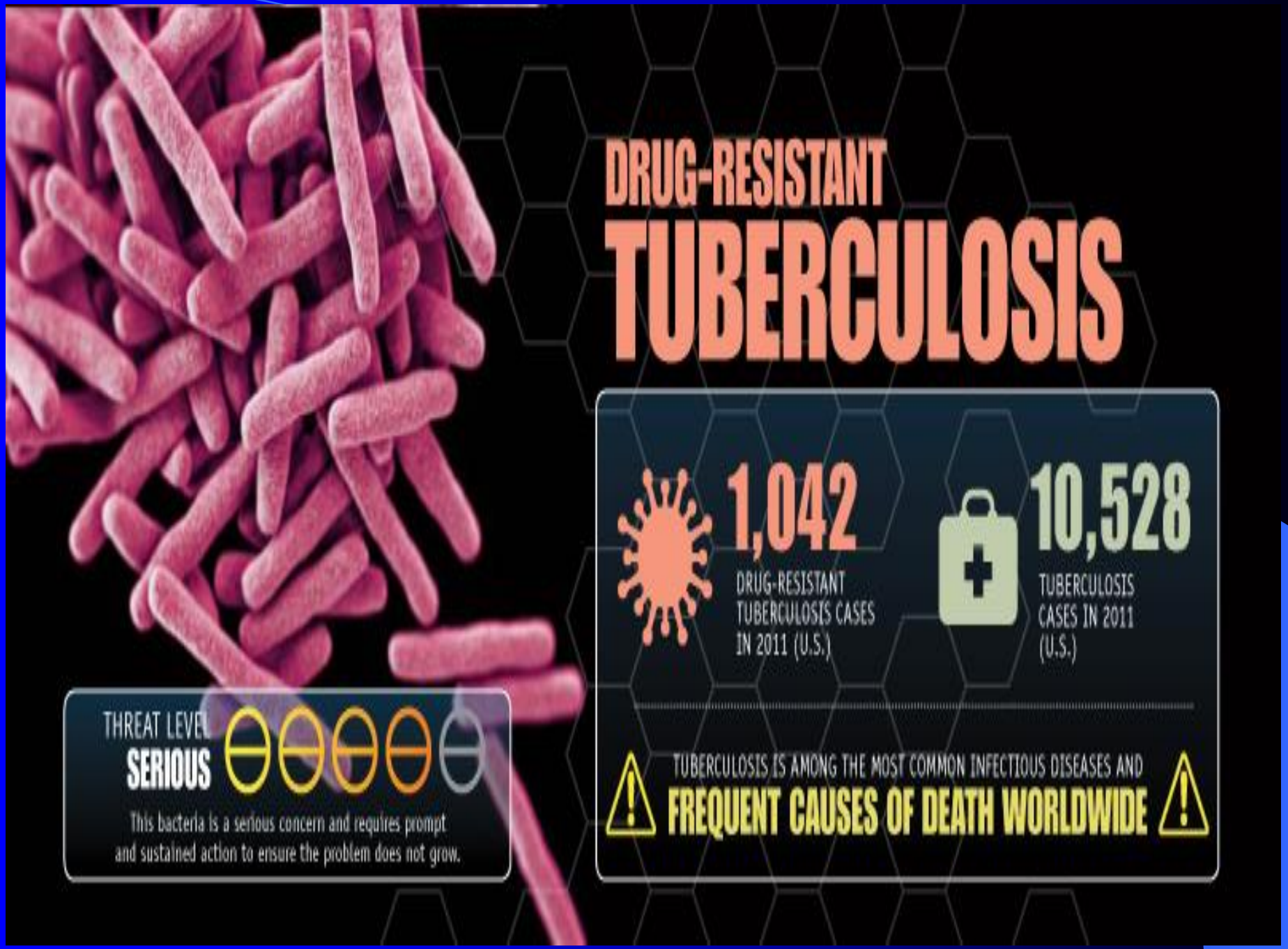
Bone and Joint TB, Miliary TB, or TB Meningitis in Children

- Treatment extended > 6 months depending on site of disease

- In TB meningitis Streptomycin replac Ethambutol

Dosing recommendations in Renal Insufficiency (CC <30ml/min) and Hemodialysis)

Drug	Recommended dose and frequency
INH	**300** mg once daily ,or 900 mg 3times/week (as)
RIF	**600** mg once daily ,or 600 mg 3times/week (as)
EMB	**15-25** mg/kg/dose 3times/week (not daily)
PZA	**25-35** mg/kg/dose 3times/week (not daily)
Levofloxacin	**750-1000** mg /dose 3times/week (not daily)
Streptomycin	**15** mg/kg/dose 2-3times/week (not daily)


DRUG-RESISTANT
TUBERCULOSIS
1,042
DRUG-RESISTANT TUBERCULOSIS CASES IN 2011 (U.S.)
10,528
TUBERCULOSIS CASES IN 2011 (U.S.)
TUBERCULOSIS IS AMONG THE MOST COMMON INFECTIOUS DISEASES AND
FREQUENT CAUSES OF DEATH WORLDWIDE
THREAT LEVEL
SERIOUS
This bacteria is a serious concern and requires prompt and sustained action to ensure the problem does not grow.

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.

Causes of MDR

HEALTH-CARE PROVIDERS: INADEQUATE REGIMENS	DRUGS: INADEQUATE SUPPLY OR QUALITY	PATIENTS: INADEQUATE DRUG INTAKE
Inappropriate guidelines	Poor quality	Poor adherence (or poor DOT)
Noncompliance with guidelines	Unavailability of certain drugs (stock-outs or delivery disruptions)	Lack of information
Absence of guidelines	Poor storage conditions	Lack of money (no treatment available free of charge)
Poor training	Wrong dose or combination	Lack of transportation
No monitoring of treatment		Adverse effects
Poorly organized or funded TB control programmes		Social barriers
		Malabsorption
		Substance dependency disorders

XDR= extensively drug-resistant TB

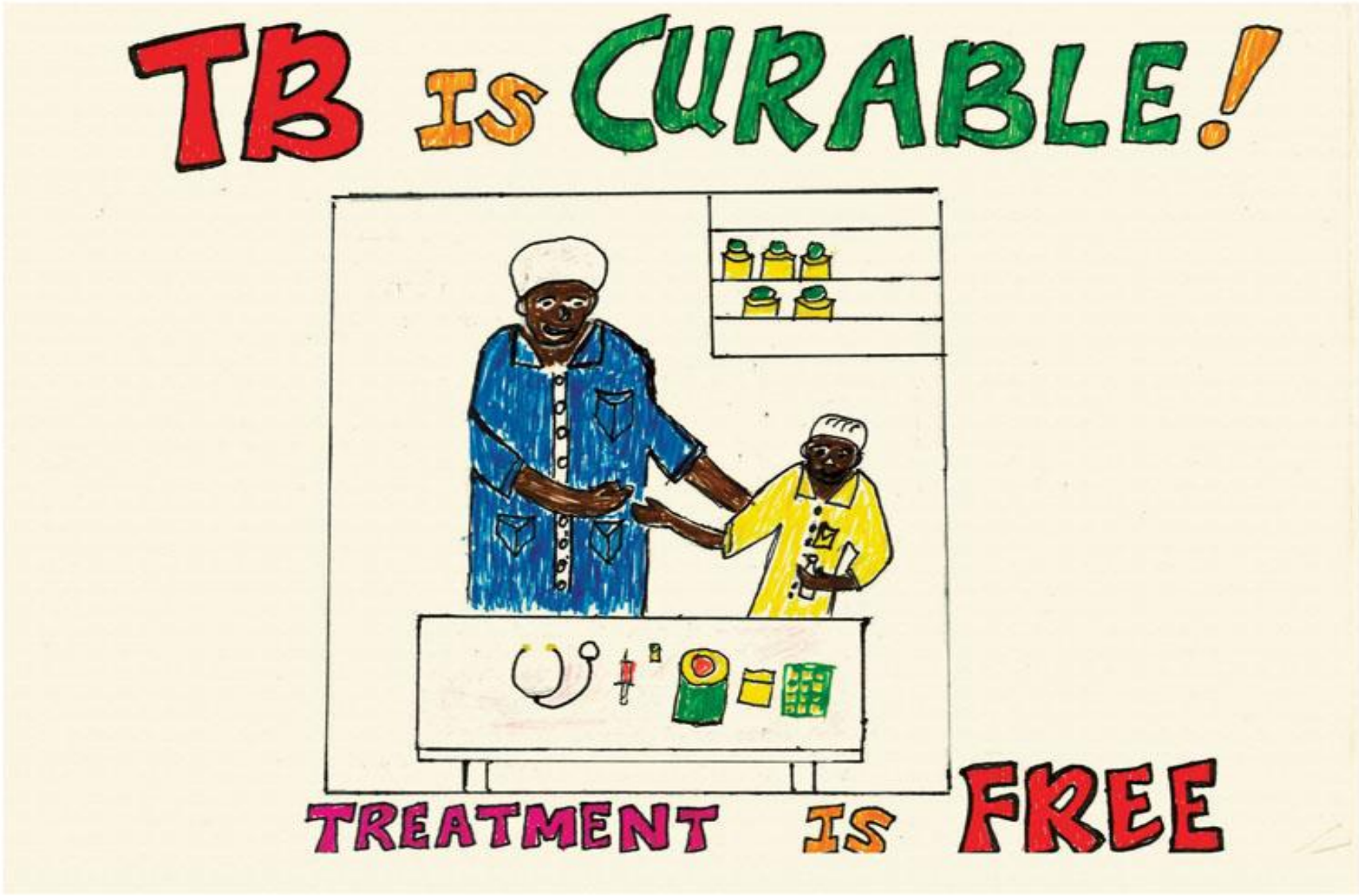
Resistance to at least Rifampicin and isoniazid, in addition to any Floroquinolones, and to at least one of the three following injectable drugs used in anti-TB treatment: Capreomycin, kanamycin and Amikacin.

Treatment Monitoring

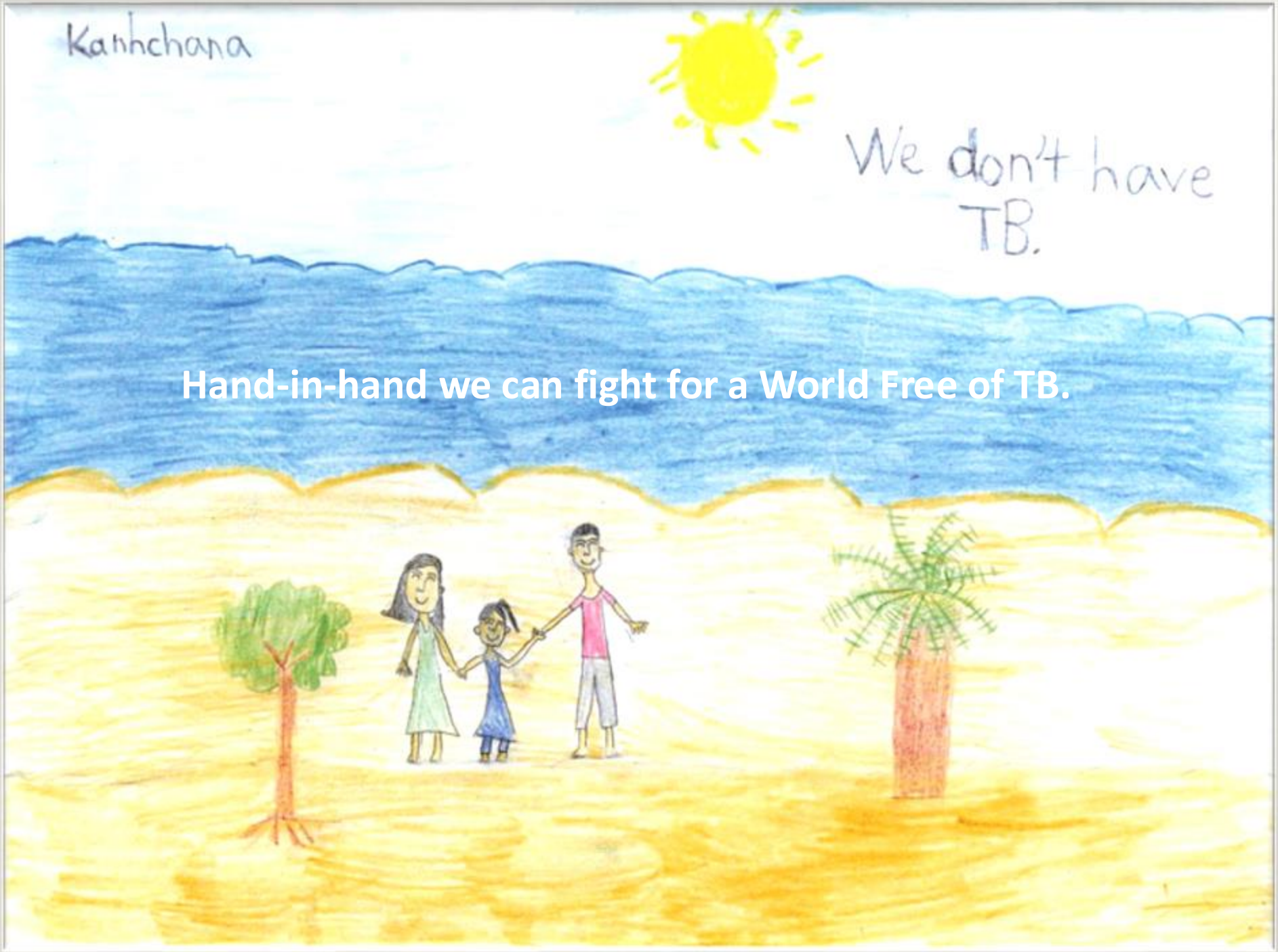
- **Sputum smear microscopy for AFB at 2 months. If positive at two months, repeat at 3 months**

- **If still smear positive at 3 months, continuation phase is still started while awaiting DST results**

Did you know that …



Papua New Guinea


Kanhchana
We don't have TB.
Hand-in-hand we can fight for a World Free of TB.

THANK YOU