Respiratory System Module
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Tuberculosis

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General characteristic of *M. tuberculosis*

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).

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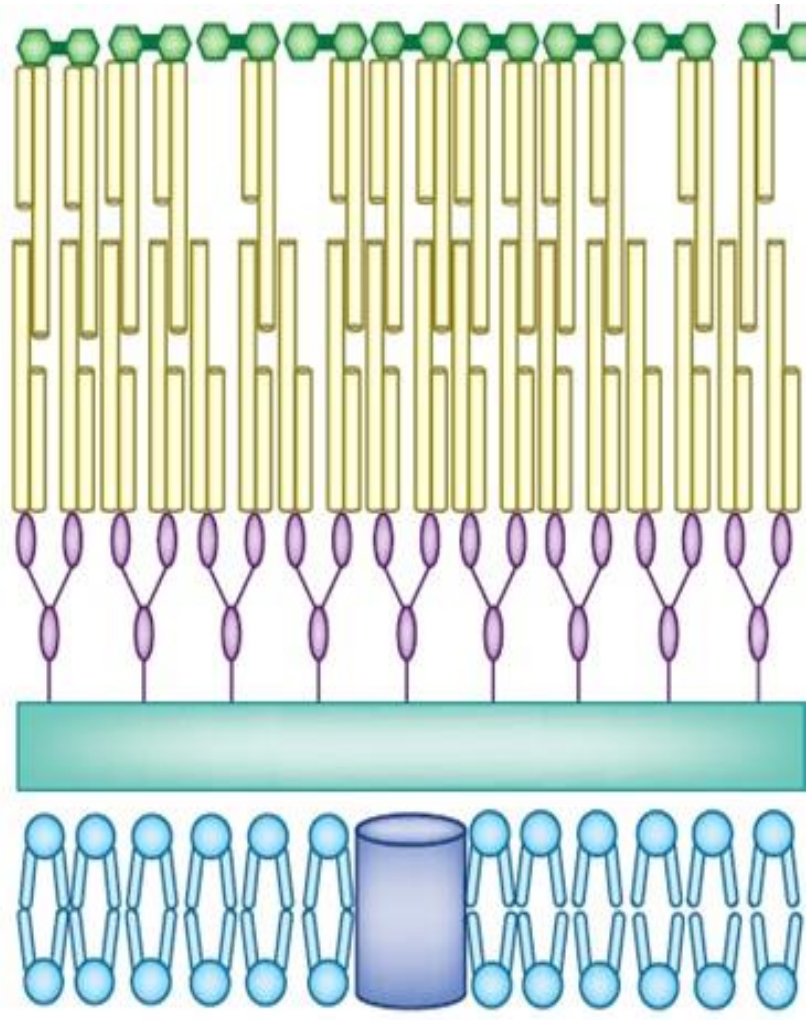
General characteristic of *M. tuberculosis*

Antigenic structure



Mycolic acid: It confers very low permabilty to antibiotics and responsible for acid fastness

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

Peptidoglycan: maintains the regigidity of the cell wall

Plasm membran

Pathogenesis

Source of Infection:

- Human (e.g. cases of pulmonary tuberculosis)
- Bovine (e.g. consumpion of unpasturized milk)

Mode of infection

1. **Inhalation mode:** tuberculosis is an airborn disease transmitted by inhilation of droplet nuclei while coughing and sneeezing, or spaking of infectd patients. The tiny dry droplets that contains bcateria (<5 µm in diameter) may remains suspended in the air for several hours.
2. **Inoculation mode:** the trasmission through direct skin contact with a infectd patiens is uncommon.

Risk factors

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

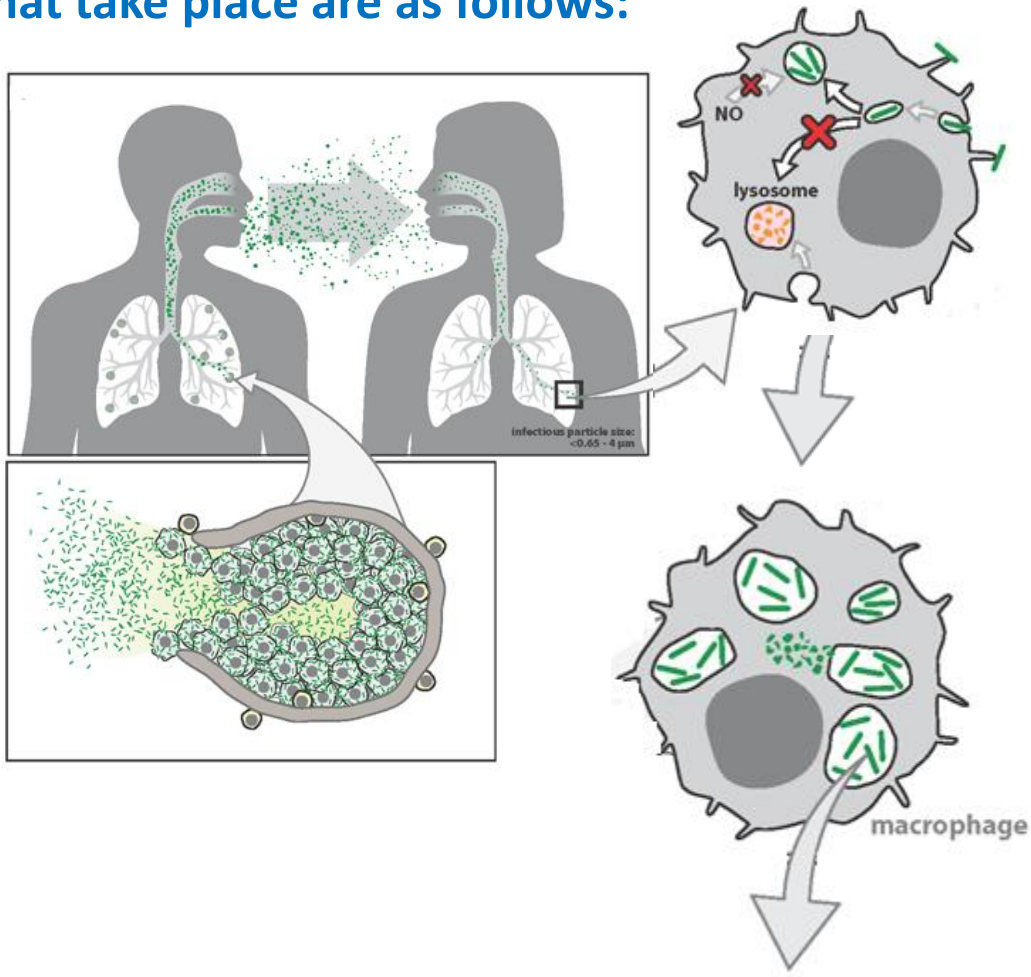
Epidemiology of tuberculosis

- 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**.

Sequence of pathogenic infection

The sequence of pathogenic events that take place are as follows:

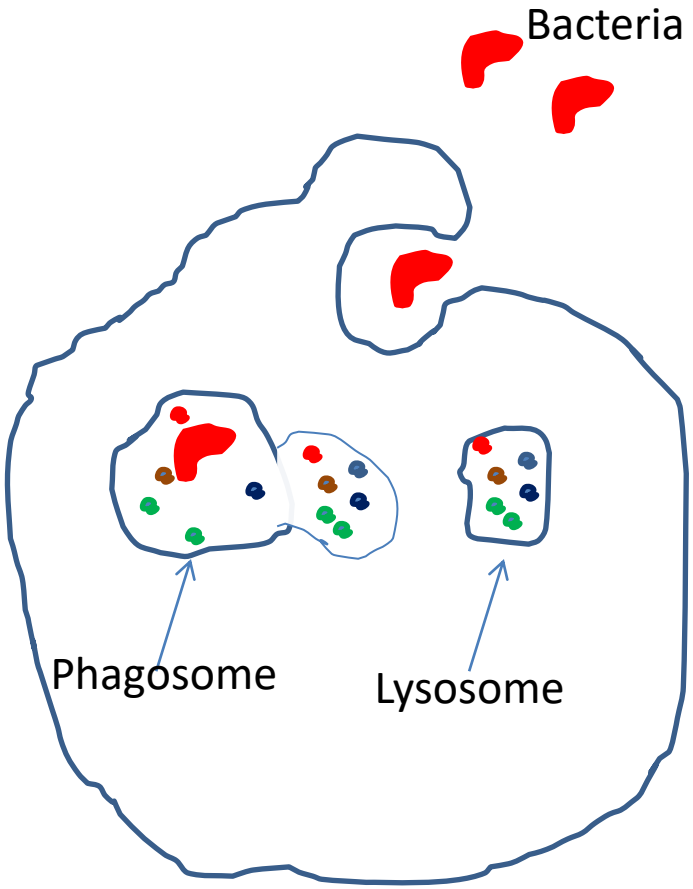
1. **Droplet nuclei**: containig tubrcl bacilli from the infcted patients are inaled
2. **Adhesion to macrophages:** Mycobacterial surface Lipoarabinomannan (LAM) binds to complement receptor and mannose receptor on the surface of macrophages which leads to internalization of bacilli
3. **Survival inside macrophages**: this is due to LAM which inhibits the phagosome lysosome fusion by inhibiting increase in the cellular calcium levels.
4. If the bacilli are succssfull in arestig phagosome lysosome fusion, then they are happyly replicate inside macrphages which ventually rupturs and infect other macrophages.

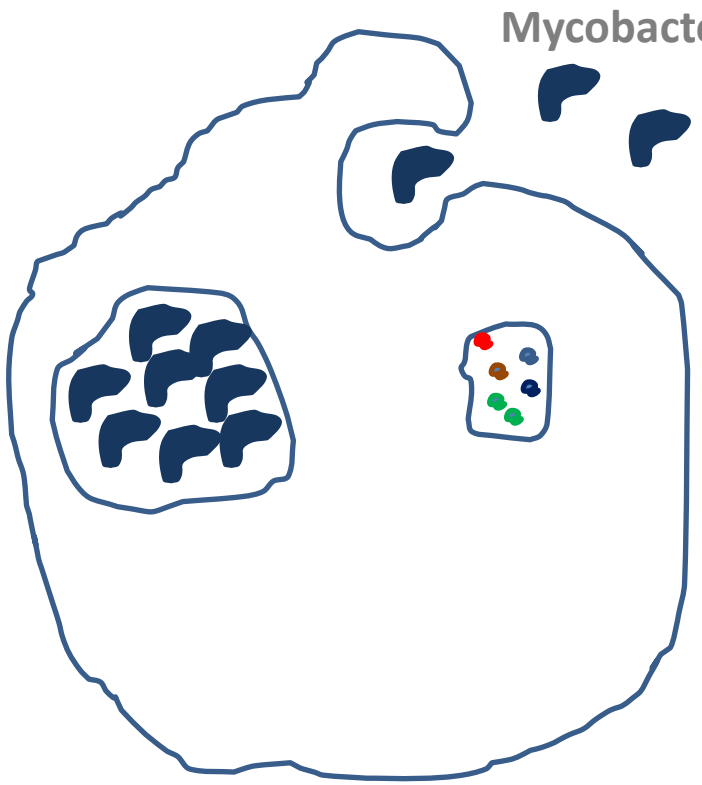


Rupturs and infect other macrophages.

Pathogenesis of TB

Q: Why Mycobacteria are can survive inside macrophages



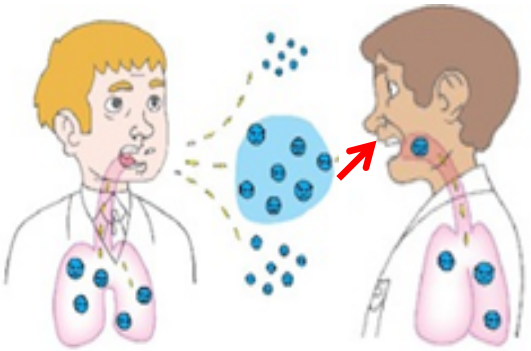


- Mycobacteria inhibits phagosome lysosome fusion
- Bacteria will multiply
- Macrophage will burst
- Proteolytic enzymes will released outside causing tissue destruction

Pathogenesis of TB

Classification of tuberculosis

Exposure



1° infection

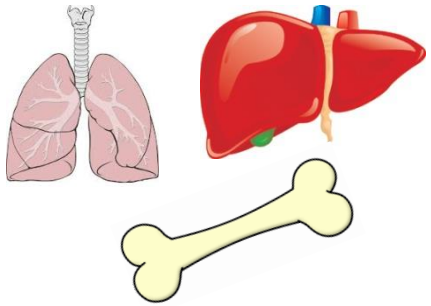
95%

Healing

5%

Local pulmonary progression

Miliary TB



5% undergo 2° TB (reactivation)

Due to

- HIV
- Transplantation
- DM
- Smoking
- Others

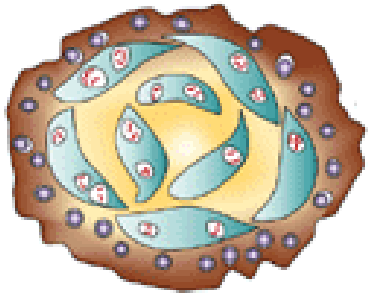
Pathogenesis of TB

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 **nonspecifically activated** 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

Pathogenesis of TB

Primary TB



Types of granulomas:

A. **Hard tubercles**: tubercles are initially hard, composed of a central zone of activated macrophages (epitheloid and giant cells) and peripheral zone of lymphocytes and fibroblast

B. **Soft tubercles**: later the central part of the lesion undergoes caseous necrosis, and in contains necrotic tissues resembling soft cheese

Growth of the *M .tuberculosis* is inhibited within this necrotic environment because of low oxygen tension and low pH. Eventually the lesion heals and calcifies. The viable bacilli may remain dormant within the macrophages or within necrotic material for many years without causing further tissue destruction

In a minority of cases, especially associated with the risk factors the macrophage activating response will be weak and the bacilli will be more virulent leading to secondary and reactivation infection.

Pathogenesis of TB

Primary TB

Manifestations of Primary TB

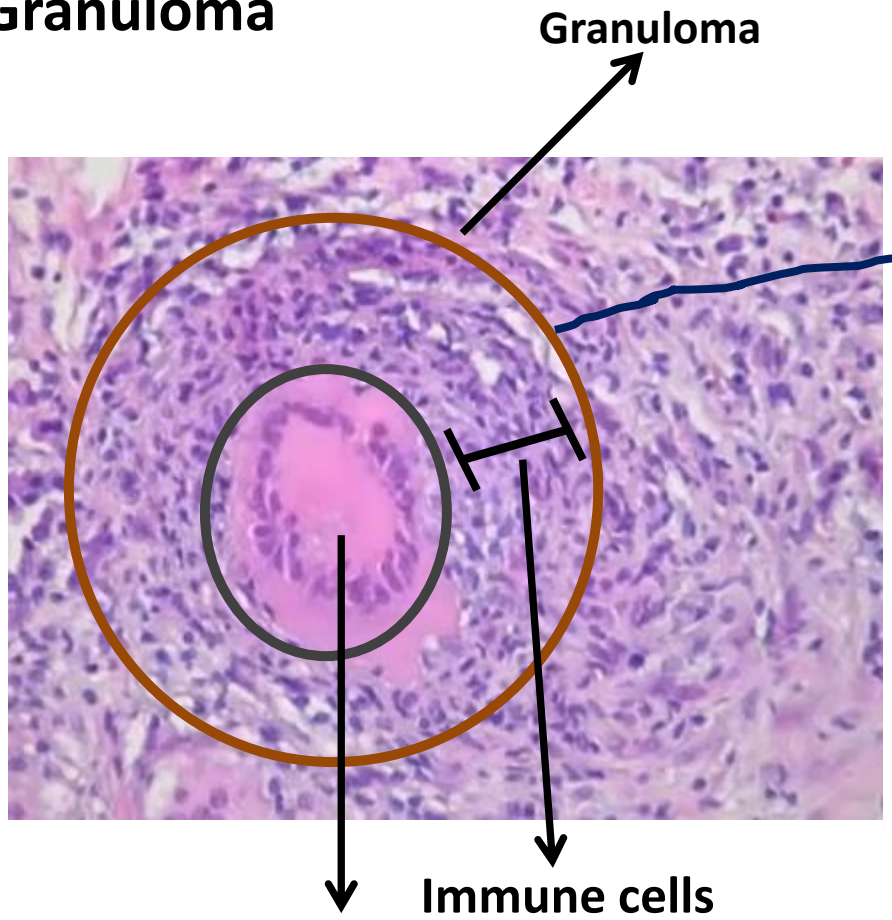
- The primary stage of the disease may be symptom-free, or the individual may experience a flu-like illness.
- Patients develop flu like illness (cough, fever, night sweats, weight loss etc). This can lead to delays in seeking care, and results in transmission of the bacteria to others.
- **Healing in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

Primary TB = Latent TB

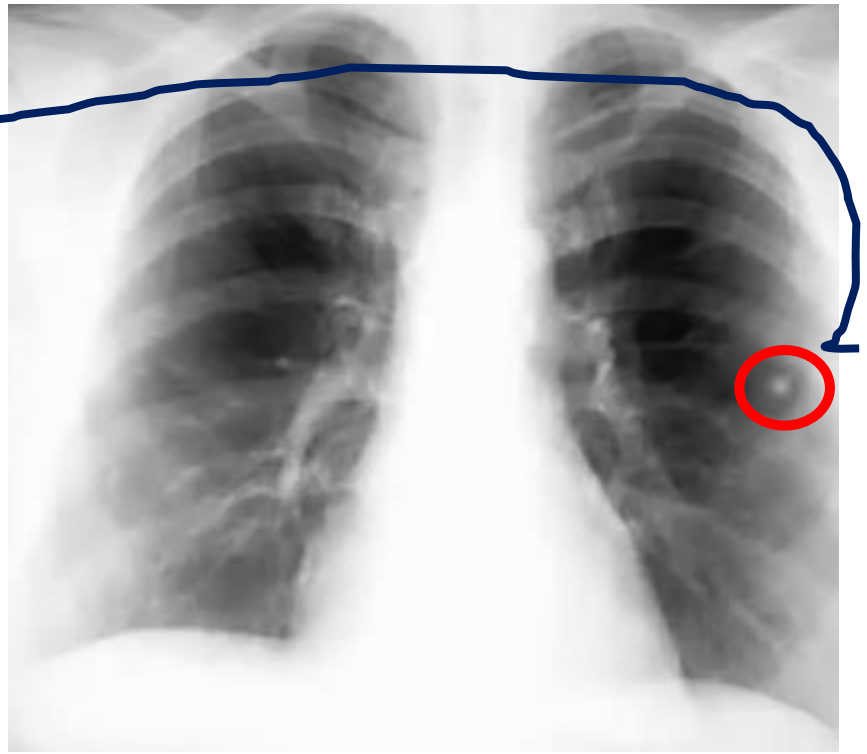
Pathogenesis of TB

Primary TB

Granuloma



Necrosis (dead macrophages and cells)



Calcified granuloma

Healthy immune system

Latent infection (primary)

Altered immune system

Latent infection (primary)

Reactivation

Pathogenesis of TB

Secondary (reactivation) tuberculosis

1. Occurs in 5% 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.

Pathogenesis of TB

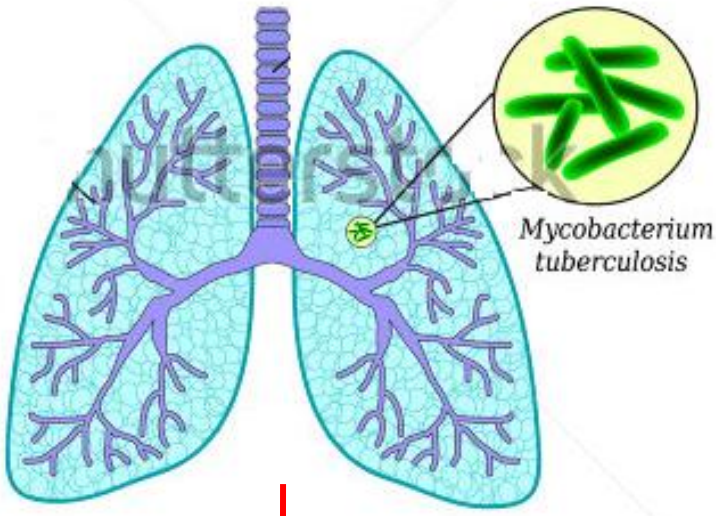
Secondary (reactivation) tuberculosis

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

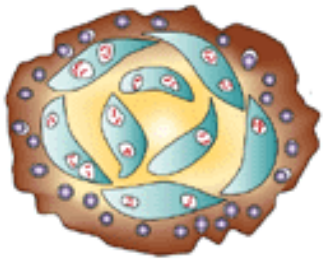
5. The lesions show spreading and resulting in a large pulmonary cavity and bronchial spread

Primary vs. Secondary tubrculosis



Infection (primary)

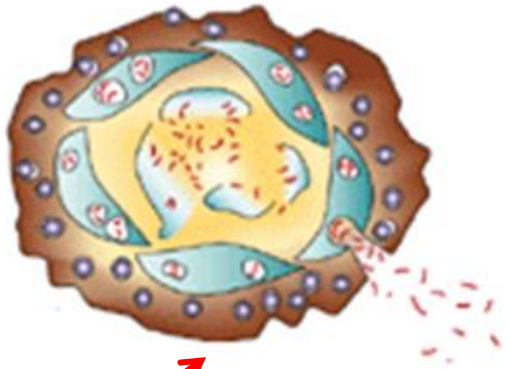
healing



Granuloma

Ractivation (secondary)
(5%)

Dissemination transmission



Pathogenesis of TB

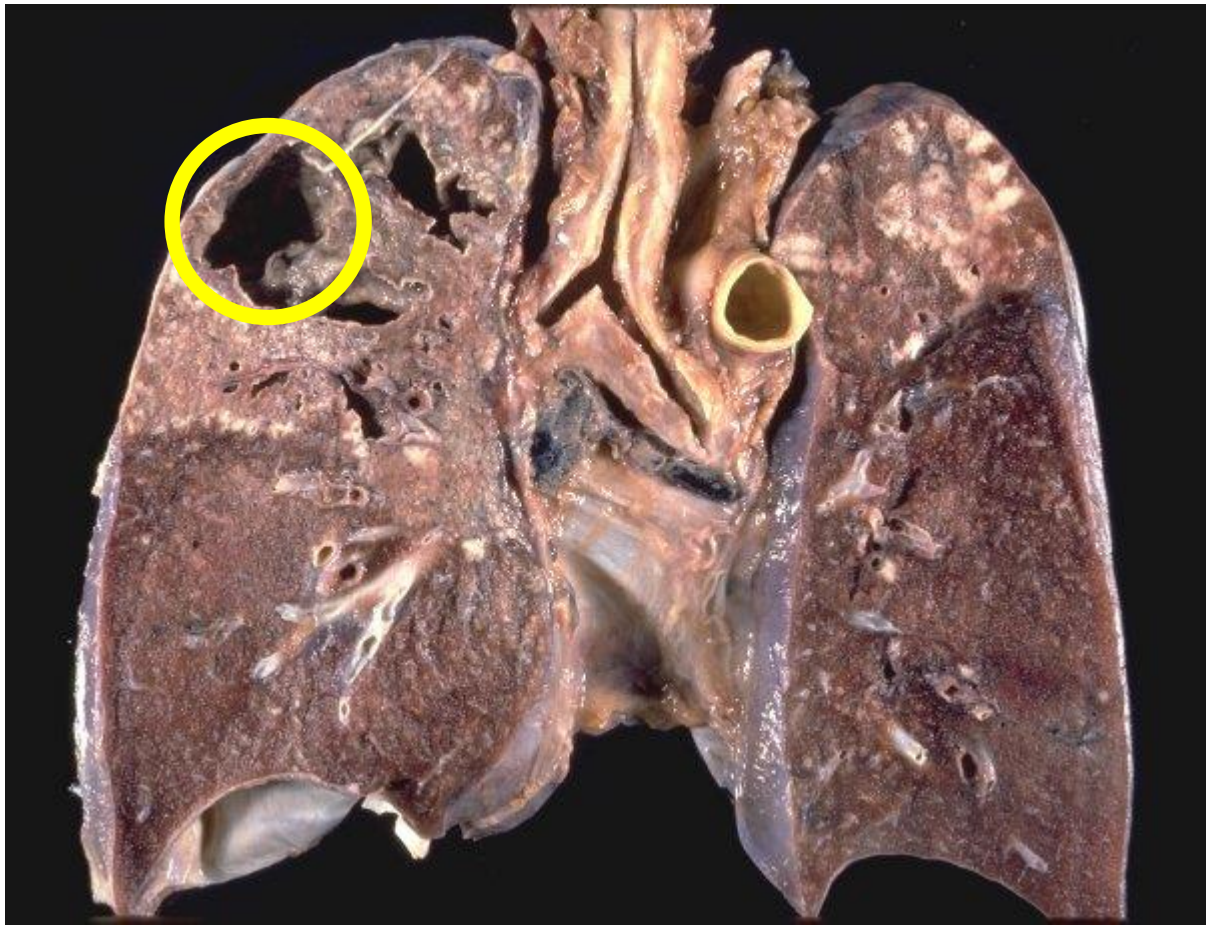
Secondary (reactivation) tuberculosis

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.

Pathogenesis of TB

Secondary (reactivation) TB



Pathogenesis of TB

Local Progressive Pulmonary TB

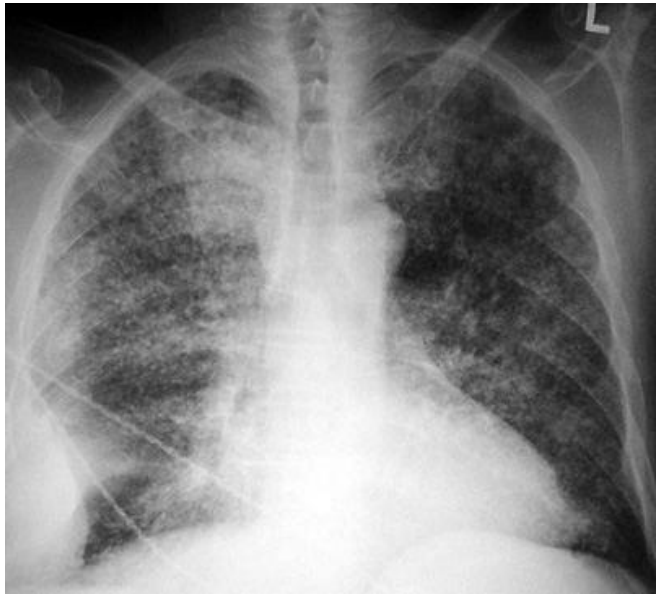
1. This can occur after primary or secondary TB
2. Occurs by the local extension to an entire lobe or segment

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 .

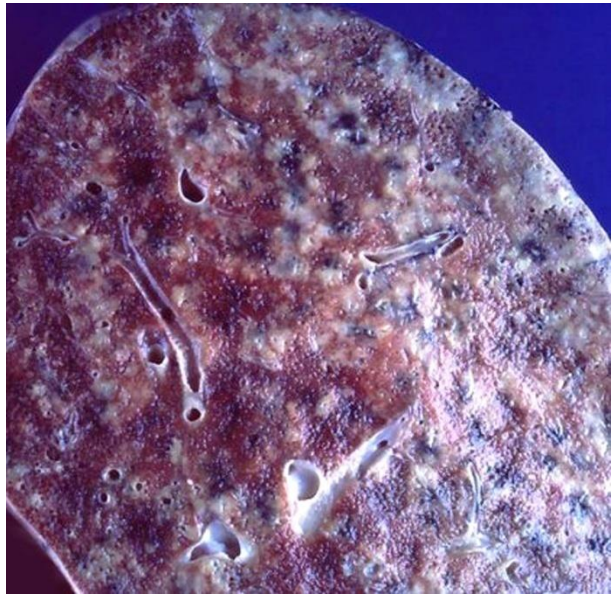
Pathogenesis of TB

Miliary TB



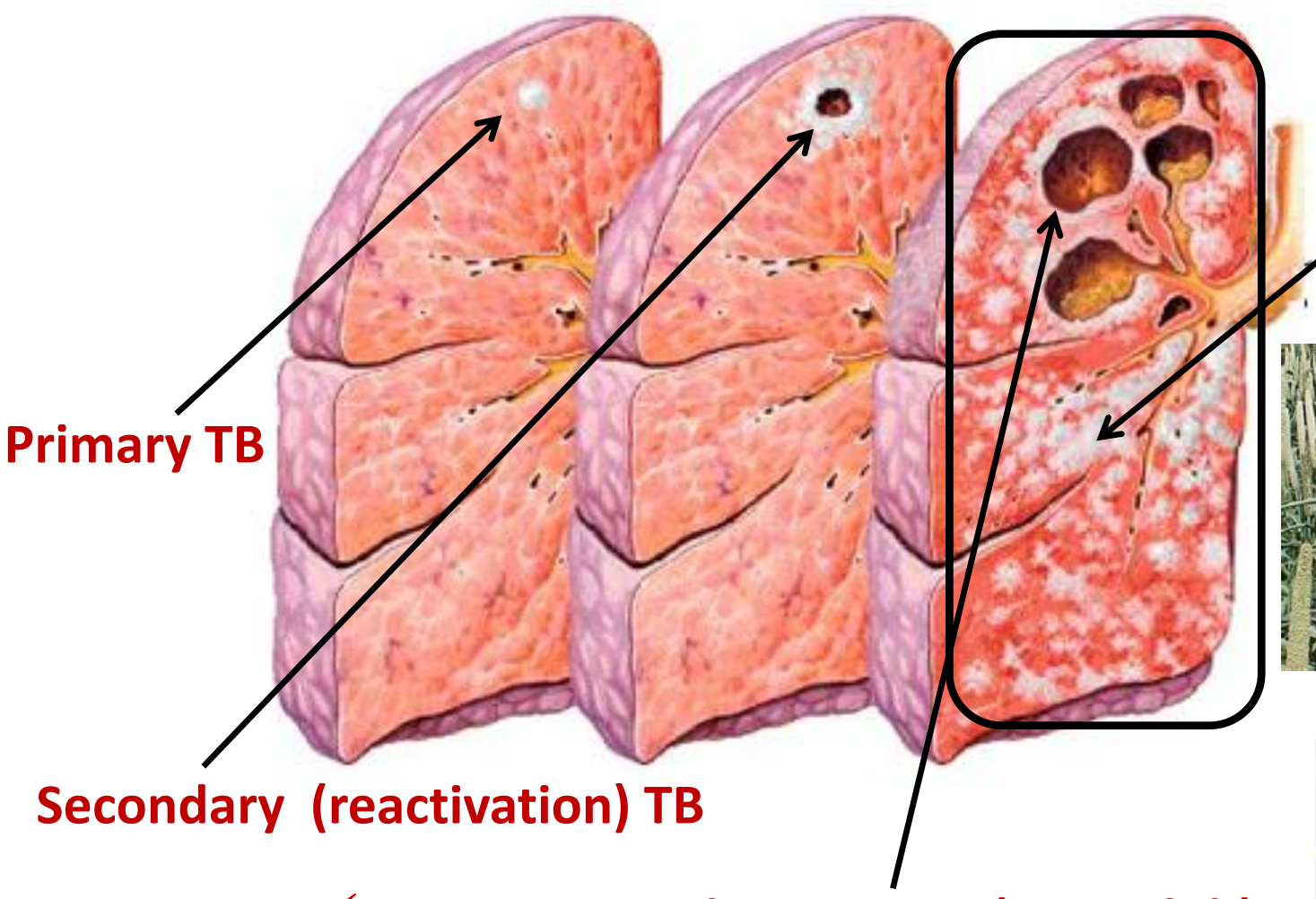
X-ray of lung with miliary TB

CT scan of lung with miliary TB



Lung miliary TB

Pathogenesis of TB



Primary TB

Miliary TB

Secondary (reactivation) TB

✓Progressive Pulmonary TB (entire lob)

Millet

Millet seeds

Who is a TB Suspect?

"Any person who presents with symptoms or signs suggestive of TB, in particular cough of long duration (more than 2 weeks)."

Diagnosis

Diagnosis of active Tuberculosis

Diagnosis of latent Tuberculosis

Diagnosis

Diagnosis of active Tuberculosis:

Specimen collcetion:

1. In pulmunary tuberulosis:

a. specimen is collected in a widemouth container, two specimens

- ✓ Sample collected at the same day
- ✓ Sample collected on the next day (early morning)

b. Laryngeal swabs or brochial washing

c. In children, gastric aspirate my be used as they tend to swallow sputum

2. In extrapulmonary tubeculois (depending on te site of infection):

- ✓ Lymph node aspirate
- ✓ Pleural fluid
- ✓ Urine
- ✓ Synovial fluid
- ✓ CSF
- ✓ Pus

Diagnosis

1- Diagnosis of active Tuberculosis (Explained in the lab):

2- Diagnosis of latent Tuberculosis (tuberculin test):

Principle

Latent tuberculosis is diagnosed by demonstration of type IV (delayed) hyoersensitivity rection against the tubercule bacllic 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

Dosage

It is expressed in tuberculin unit (TU). One TU is equal to 0.01 ml of 0.00002 mg of PPD

Procedure

Mantoux test: 0.1 ml of PPD containing 1 TU is injected intradrmally into the flexor surface of the forearm.

Reading

It is taken afetr 48-72 hours. At the site of inoculation, and induration surrounded by erythema is produced. If the width of induration is:

≥ 10 mm: Positive (tuberculin reaction)

6-9 mm: Equivocal/ doubtul reaction

< 5 mm: Negative reaction

Diagnosis

Mantoux test

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

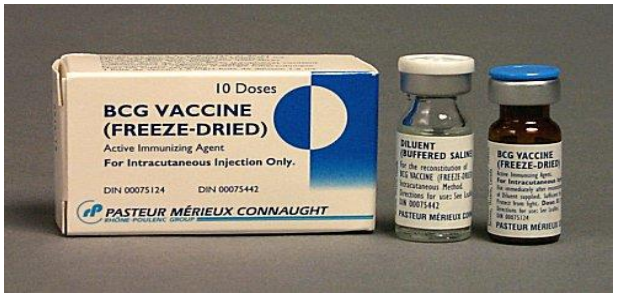
Prevention

1. prompt detection of infectious patients
2. **Stay home : E**specially in the first few weeks of treatment for active tuberculosis
3. airborne precautions
4. treatment of people who have suspected or confirmed TB disease.
5. **Wear a mask (N95)**
6. **Vaccinations**

Prevention

Vaccinations

1. **The only available vaccine is bacillus Calmette-Guérin (BCG).**
2. **Bacillus Calmette-Guérin** (**BCG**) is a live attenuated strain of Mycobacterium bovis.
3. M. bovis is most commonly found in cattle and other animals such as bison, elk, and deer
4. **BCG vaccine :**
   - It is a live freeze-dried vaccine which must be reconstituted
   - Administered intra-dermally at the deltoid region on the left side
   - Dose: 0.05 ml
   - should immunize infants and under 5 years with single dose of BCG



Treatment

Treatment of latent TB :

- Isoniazid for 9 months .
- Rifampin for 4 months .

Treatment of Active TB :

- Isoniazid + Rifampin for 9 months .
- pyrazinamide + levofloxacin for 6-12 months .
- Rifampin + pyrazinamide for 2 months .

Interpretation of x-ray and skin test results

	X-ray	Mantoux test	Interpretation	
Sick patient suspected of having TB: ➢Fever ➢Hemopt-ysis ➢Other symptoms	Positive	Positive	Mostly have TB	**All should be confirmed by lab investigations**
	Positive	Negative	Negative skin test due to: 1. Not caused by TB 2. False negative test due to • personal error • False procedure	
	Negative	Positive	Negative x-ray might be due to extrapulmonary TB	

Case study

23-year-old man presented with a **4-weeks history of coughing**, **Shortness of breath** and **malaise**. He had lost **4kg in weight**, had **history of night sweating and haemoptysis.**

On examination

- 37.8°C but had
- No signs of nasopharyngeal infection
- Clear Lung sounds. No other physical signs.
- Chest X-ray showed bilateral upper- and middle-lobe shadowing

Lab tests

- High CRP
- Sputum was found to contain acid-fast bacilli and M. tuberculosis was subsequently cultured.

Diagnosis

- A diagnosis of *pulmonary tuberculosis* was made.
- The patient was treated with specific antibiotics