TUBERCULOSIS

INTRODUCTION

HISTORY

- TB has existed since antiquity
- The oldest unambiguously detected mycobacterium tuberculosis give evidence of the disease in the remains of bison in Wyoming dated around 17.000 years ago
- TB in human can be traced back ti 9.000 years ago in Haifa archeologists found TB in remains of mother and child buried together
- Reservoi have found tubercular decay in spine of Egyptian mommies dating from 2400 to 3000 BC
- The earliest written mention TB were in India 3.300 and China 2.300 years ago
- Before industrial revolution folklore associate TB with vampries

HISTORY

Tuberculosis (TB) is one of the world's most common infectious diseases. It is caused by the bacterium Mycobacterium tuberculosis.

On March 24, 1882, Dr. Robert Koch announced the discovery of *Mycobacterium tuberculosis.*

Johann Schonlein coined the term "tuberculosis" in the 1834, though it is estimated that *Mycobacterium tuberculosis* may have been around as long as 3 million years!

Other names for tuberculosis :

- "phthisis" in ancient Greece
- "tabes" in ancient Rome
- "schachepheth" in ancient Hebrew
- In the 1700s, TB was called "the white plague" due to the paleness of the patients
- TB was commonly called "consumption" in the 1800s even after Schonlein named it tuberculosis
- Today, our names for TB tell us where TB is located (pulmonary, extrapulmonary) and how to treat it (drug-susceptible, drug-resistant, multidrug resistant, and extensively drug-resistant.)

MYCOBACTERIA GENUS

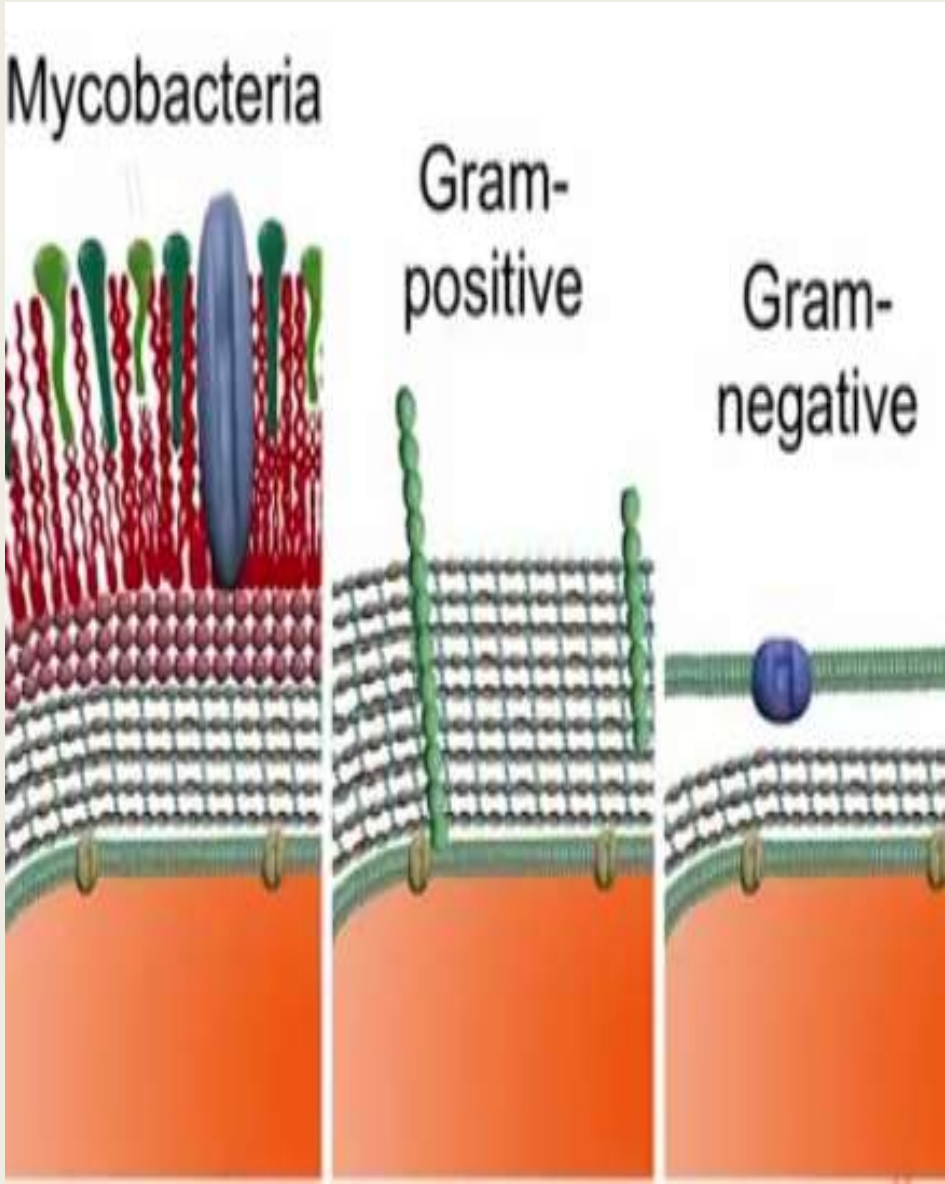
- The Mycobacterium tuberculosis complex (MTBC) refers to group of species that include (M. tuberculosis, M. canettii, M. africanum, M. microti, M. bovis, M. caprae) that are genetically very similar.
- **M. tuberculosis** is the most well known member, infecting more than one-third of the world's human population.
- **M. canettii** and **M. africanum**, can also cause human TB and are usually isolated from African patients
- **M. bovis** displays the broadest spectrum of host infection, affecting humans, domestic or wild bovines and goats.
- **M. caprae** has been isolated only from goats
- **M. microti** is a rodent pathogen that can also cause disease in immunocompromised human patients

BACTERIOLOGY

- The Cell wall consist of peptidoglycan, arabinoglycan and a waxy coat made of :
- lipoarabinomannan(LAM)
- mycolic acid
- porins and other protein

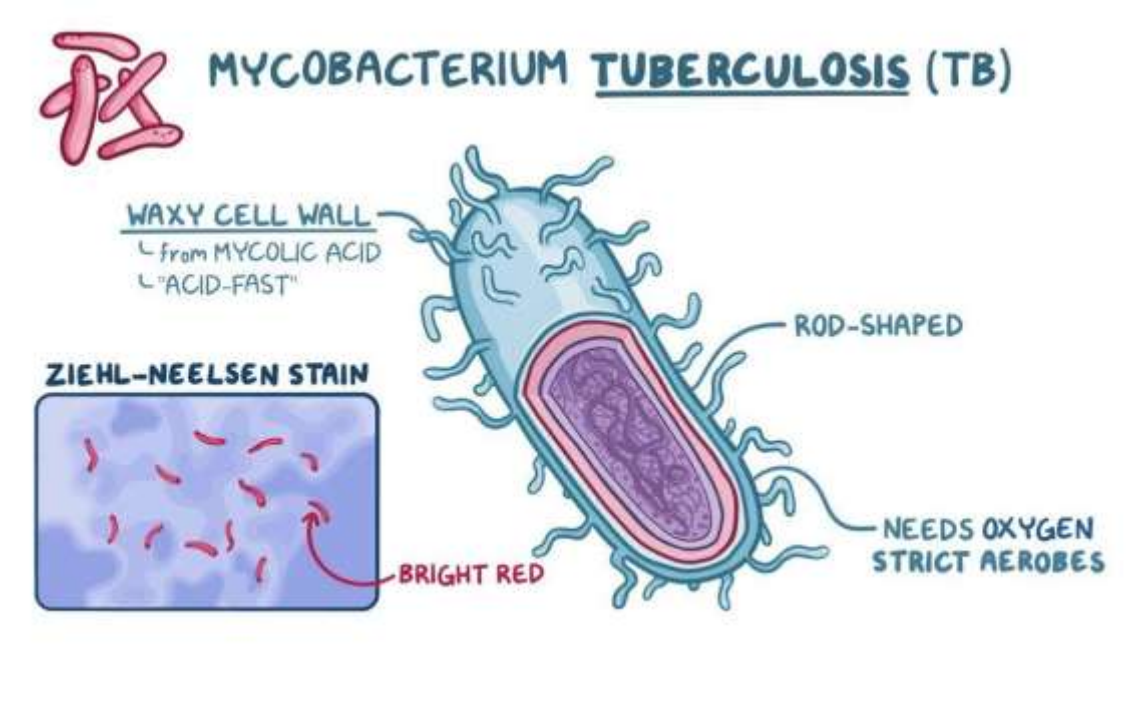
Mycobacteria, such as M tuberculosis, are :

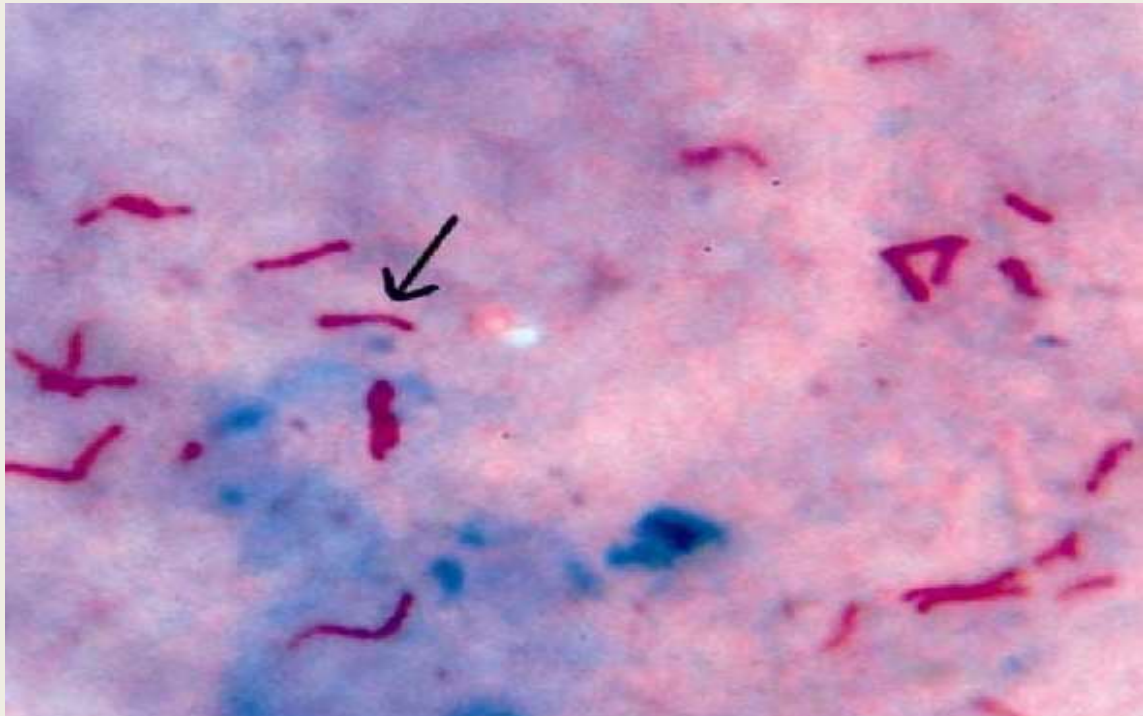
- Catalase positive
- non–spore-forming
- Nonmotile
- Obligate aerobes
- curved intracellular rods(Bacillus) measuring 0.2-0.5 µm by 2-4 µm.
- Facultative intracellular pathogen
- The incubation period may vary from about two to 12 weeks.



BACTERIOLOGY

- Nitrate reductase positive and Niacin positive
- Resistant to drying ,most common disinfectant, acid and alkaline
- Sensitive to heat including pasteurization and individual organism in droplet nuclei susceptible to inactivation by UV light
- Enhance growth in 10% of carbon diolightens relatively low PH 6.5-6.8 slowly grow bacteria
- The generation time 18-24 hours , visible colony form within 3 to 4 weeks



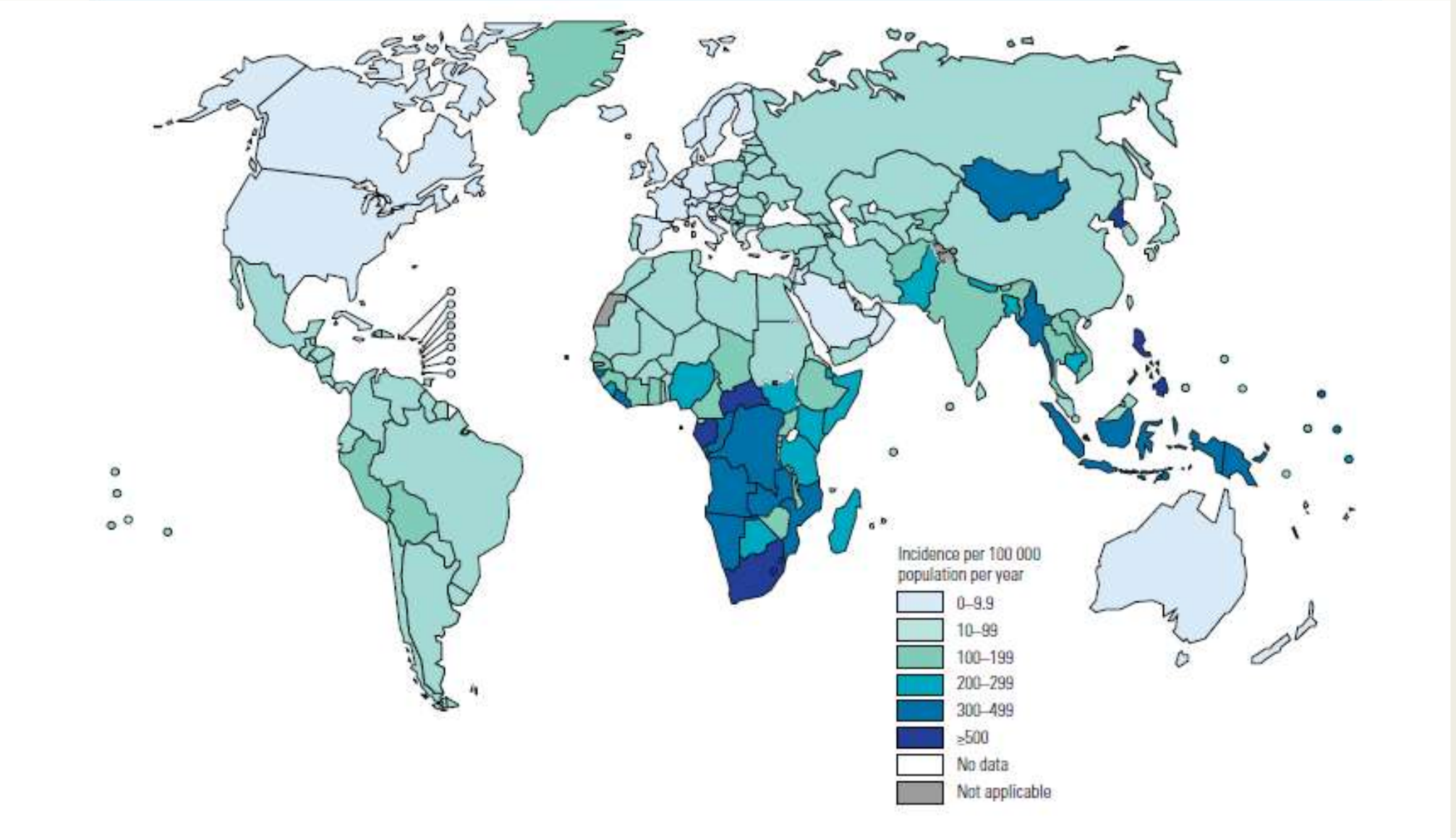


Virulence factors of mycobacteria tuberculosis

- **Trehalose dimycolate :** which is also called “cord factor” , helps evade immune response, causes granuloma formation and triggers the release of cytokines
- **Sulfatide :** is a glycoprotein on the surface of mycobacteria, inhibits the fusion of phagosomes and lysosomes
- **Catalase peroxidase :** resists host cell oxidation
- **Mycolic acid :** mycolic, acid-rich, long-chain glycolipids and phospholipoglycans (mycocides) found in the cell wall. It protects mycobacteria from cell lysosomal attack and also retain red basic fuchsin dye after acid rinsing (acid-fast stain/ Ziehl-Neelsen (ZN) stain).

EPIDEMIOLOGY

- TB is one of the top 10 causes of death and the leading cause from a single infectious agent (above HIV/AIDS).
- In 2019, an estimated 10 million people fell ill with tuberculosis(TB) worldwide. 5.6 million men, 3.2 million women and 1.2 million children. TB is present in all countries and age groups. But TB is curable and preventable.
- An estimated 60 million lives were saved through TB diagnosis and treatment between 2000 and 2019.
- TB occurs in every part of the world. In 2019, the largest number of new TB cases occurred in the WHO South-East Asian region, with 44% of new cases, followed by the WHO African region, with 25% of new cases and the WHO Western Pacific with 18%.
- In 2019, 87% of new TB cases occurred in the 30 high TB burden countries. Eight countries accounted for two thirds of the new TB cases: India, Indonesia, China, Philippines, Pakistan, Nigeria, Bangladesh and South Africa.
- The 24th of March from every year is the world Tuberculosis day



Worldwide incidence of tuberculosis
(2019). Estimated new cases (all forms) per 100 000 population.(WHO)

PATHOGENESIS

- *M. bovis* infection arises mainly by drinking non-sterilised (unpasteurized) milk from infected cows. *M. tuberculosis* is spread by the inhalation of aerosolised droplet nuclei from other infected patients.
- Once inhaled, the organisms lodge in the alveoli and initiate the recruitment of macrophages and lymphocytes. Macrophages undergo transformation into epithelioid and Langhans cells, which aggregate with the lymphocytes to form the classical tuberculous granuloma.
- Numerous granulomas aggregate to form a primary lesion or ‘Ghon focus’ (a pale yellow, caseous nodule, usually a few millimetres to 1–2 cm in diameter), which is characteristically situated in the periphery of the lung.

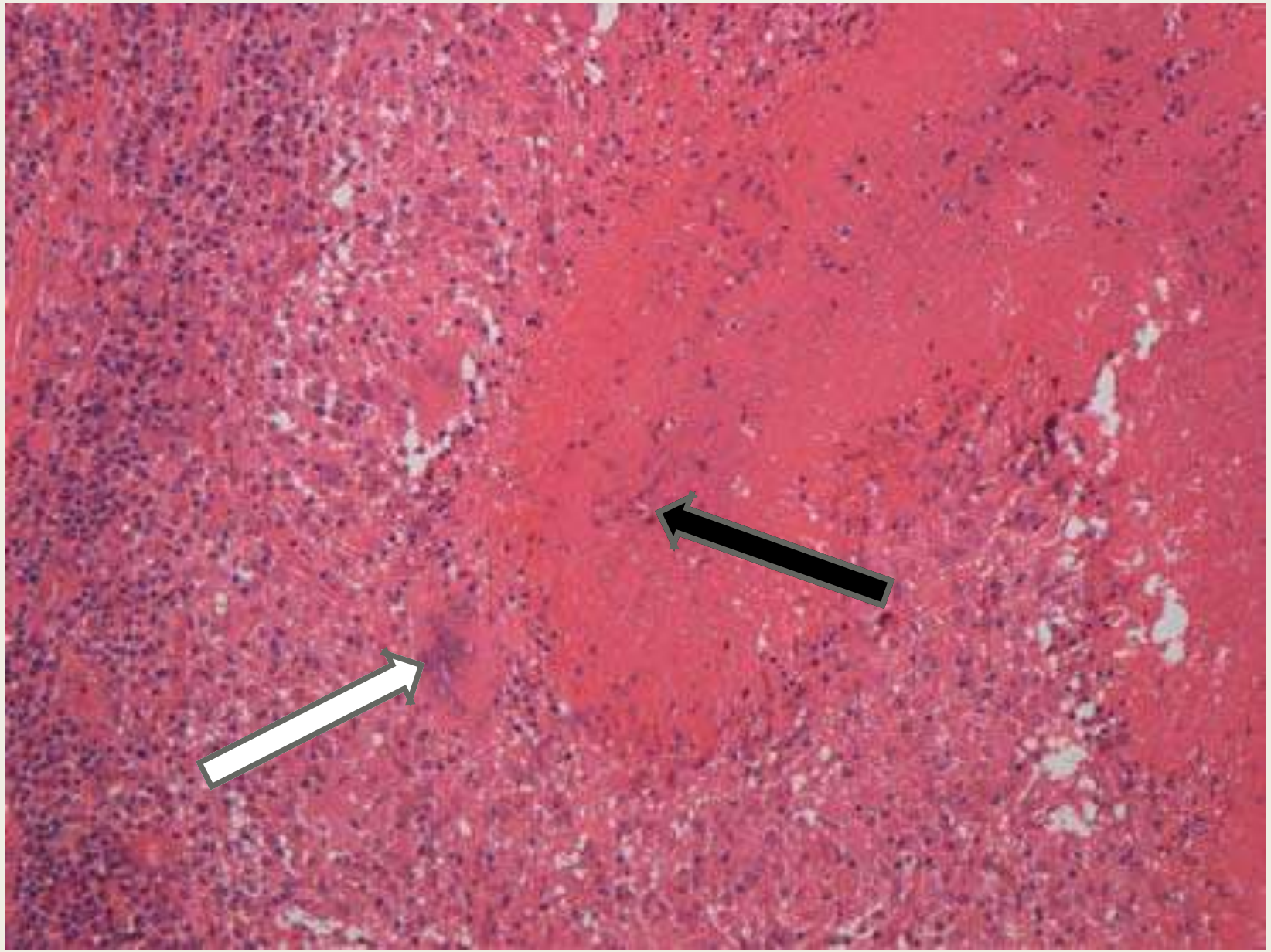
PATHOGENESIS

- Spread of organisms to the hilar lymph nodes is followed by a similar pathological reaction, and the combination of the primary lesion and regional lymph nodes is referred to as the ‘primary complex of Ranke’.
- Reparative processes encase the primary complex in a fibrous capsule, limiting the spread of bacilli. If no further complications ensue, this lesion eventually calcifies and is clearly seen on a chest X-ray.
- Lymphatic or haematogenous spread may occur before immunity is established, however, seeding secondary foci in other organs, including lymph nodes, serous membranes, meninges, bones, liver, kidneys and lungs, which may lie dormant for years.
- If these reparative processes fail, primary progressive disease ensues.

PATHOGENESIS

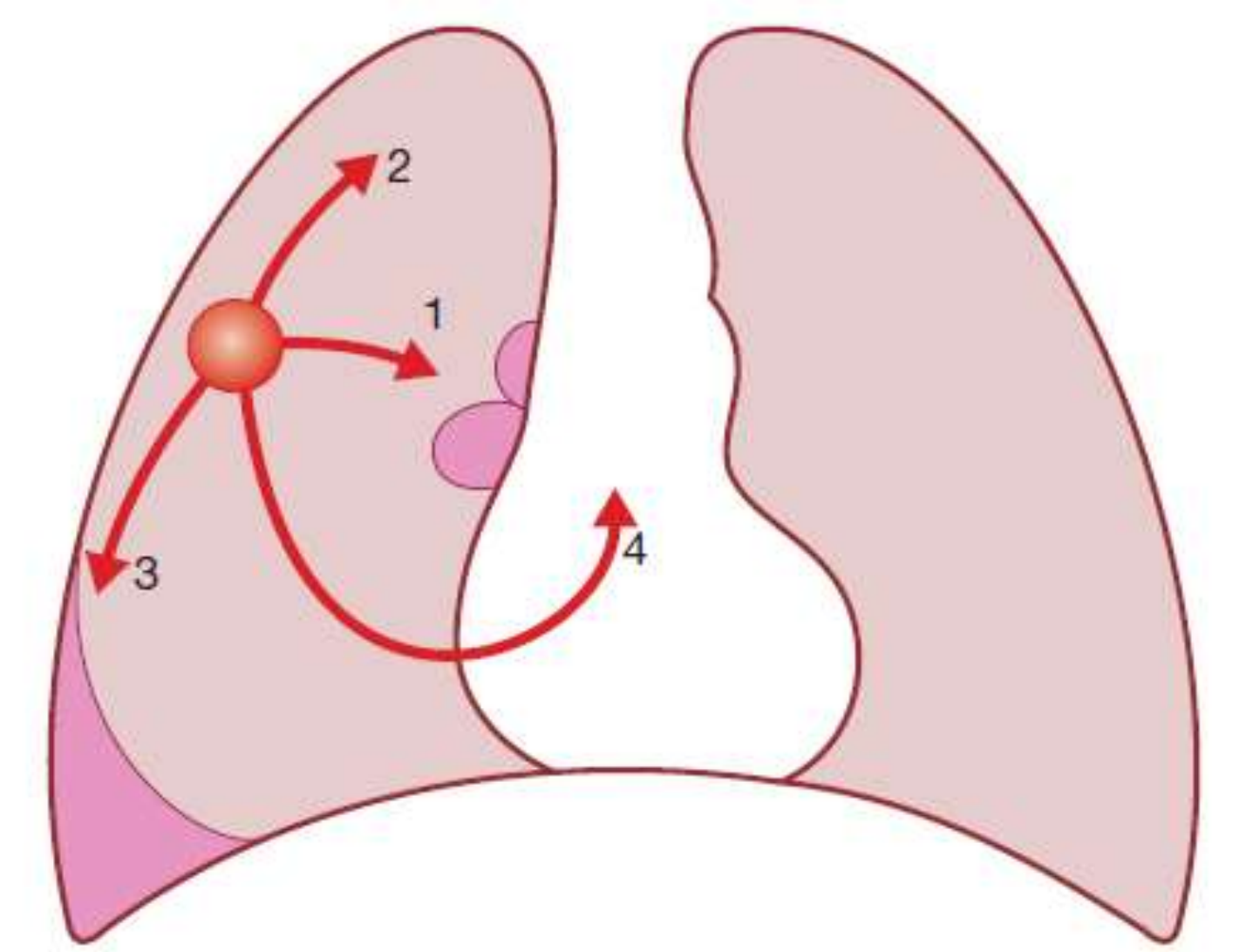
Pathogenesis of tuberculosis in the previously unexposed immunocompetent individuals :

1. Bacilli are inhaled and deposited into the lung
2. Bacilli are ingested by alveolar macrophages
3. Bacilli start multiplying inside macrophages (by preventing the fusion of the lysosomes with the phagocytes and therefore the killing of the bacteria)
4. After 3 weeks of exposure, patient develop cell mediated immunity (processed mycobacteria antigen are presented to CD4+ T cells by macrophages)
5. Activation of the CD4+ T cells and secretion of INF y
6. INF y will activate the macrophages and lead to release of a variety of mediators that lead to monocyte recruitment and differentiation into epitheliod cells and granuloma formation(caseating granuloma)



Tuberculous granuloma. Normal lung tissue is lost and replaced by a mass of fibrous tissue with granulomatous inflammation characterised by large numbers of macrophages and multinucleate giant cells (white arrow). The central area of this focus shows caseous degeneration (black arrow).

PULMONARY TUBERCULOSIS EXTENSION



(1) Spread from the primary focus to hilar and mediastinal lymph glands to form the ‘primary complex’, which heals spontaneously in most cases.
(2) Direct extension of the primary focus – progressive pulmonary tuberculosis.
(3) Spread to the pleura – tuberculous pleurisy and pleural effusion.
(4) Blood-borne spread: *few bacilli* – pulmonary, skeletal, renal, genitourinary infection, often months or years later; *massive spread* – miliary pulmonary tuberculosis and meningitis.

FACTORS INCREASING THE RISK FOR TUBERCULOSIS

Patient-related

- Age (children > young adults < elderly)
- First-generation immigrants from high-prevalence countries
- Close contacts of patients with smear-positive pulmonary TB
- Overcrowding (prisons, collective dormitories); homelessness (dosshouses and hostels)
- Chest X-ray evidence of self-healed TB
- Primary infection < 1 year previously
- Smoking: cigarettes and/or cannabis

Associated diseases

- Immunosuppression: HIV, anti-tumour necrosis factor (TNF) and other biologic therapies, high-dose glucocorticoids, cytotoxic agents
- Malignancy (especially lymphoma and leukaemia)
- Diabetes mellitus
- Chronic kidney disease
- Silicosis
- Gastrointestinal disease associated with malnutrition (gastrectomy, jejuno-ileal bypass, cancer of the pancreas, malabsorption)
- Deficiency of vitamin D or A
- Recent measles in children

NATURAL HISTORY OF TUBERCULOSIS

Time from infection	Manifestations
3–8 weeks	Primary complex, positive tuberculin skin test
3–6 months	Meningeal, miliary and pleural disease
Up to 3 years	Gastrointestinal, bone and joint, and lymph node disease
Around 8 years	Renal tract disease
From 3 years onwards	Post-primary disease due to reactivation or re-infection

ACTIVE AND LATENT TUBERCULOSIS

Latent tuberculosis

- Persons with latent TB infection do not feel sick and do not have any symptoms. They are infected with *M. tuberculosis*, but do not have TB disease.
- Persons with latent TB infection are not infectious and cannot spread TB infection to others.
- Overall, without treatment, about 5 to 10% of infected persons will develop TB disease at some time in their lives, About half of those people who develop TB will do so within the first two years of infection.
- A person with latent TB infection :

1. Usually has positive reaction to the tuberculin skin test or TB blood test
2. Has a normal chest x-ray and a negative sputum test
3. Has TB bacteria in his/her body that are alive, but inactive
4. Needs treatment for latent TB infection to prevent TB disease; however, if exposed and infected by a person with multidrug-resistant TB (MDR TB) or extensively drug-resistant TB (XDR TB), preventive treatment may not be an option

ACTIVE AND LATENT TUBERCULOSIS

Active tuberculosis(TB Disease)

- In some people, TB bacteria overcome the defenses of the immune system and begin to multiply, resulting in the progression from latent TB infection to TB disease.
- Some people develop TB disease soon after infection, while others develop TB disease later when their immune system becomes weak.
- Persons with TB disease are considered infectious and may spread TB bacteria to others.
- A person with latent TB Disease :

1. Usually has positive reaction to the tuberculin skin test or TB blood test
2. May have an abnormal chest x-ray, or positive sputum smear or culture
3. Has active TB bacteria in his/her body
4. Usually feels sick and may have symptoms such as coughing, fever, and weight loss
5. Needs treatment to treat TB disease

TYPES OF TUBERCULUSIS

A. **Pulmonary TB**, which is further divided into Primary and Secondary(Post-primary/reactivation TB).

B. **Extrapulmonary TB**, Extrapulmonary TB accounts for 20% of cases in those whoare HIV-negative but is more common in HIV-positive patients. Extrapulmonary TB include :

    1) Miliary TB
    2) Lymphadenitis
    3) Gastrointestinal tuberculosis
    4) Pericardial disease
    5) Central nervous system disease
    6) Bone and joint disease
    7) Genitourinary disease, etc.

PRIMARY PULMONARY TUBERCULOSIS

- Primary TB refers to the infection of a previously uninfected (tuberculin-negative) individual.
- Most people with primary TB are asymptomatic and don't get sick , they either clear the infection (get rid of the infection completely) or develop latent / dormant phase.
- People with primary TB will develop a lesion known as Ghon Foci (its an area of grey –white inflammatory consolidation , close to the pleura , mostly in the lower part of the upper lobe or upper part of the lower lobe) .
- When there's involvement of the lymph nodes with the parenchyma , the lesion is known as Ghon complex. Calcified Ghon complex is called Renke complex.

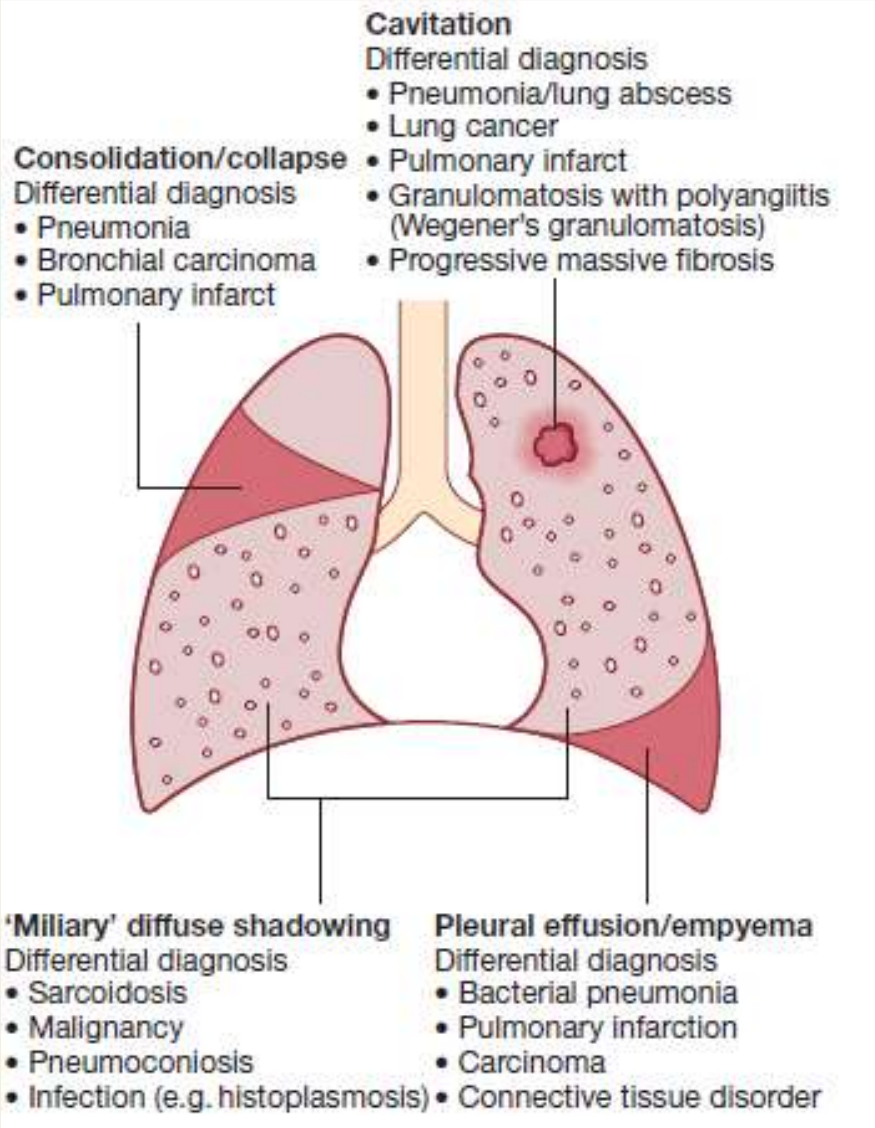
PRIMARY PULMONARY TUBERCULOSIS

- This lesion may harbor viable bacilli and thus serve as a nidus for disease reactivation at a later time if host defenses wane.
- On initial contact with infection, less than 5% of patients develop active disease. This increases to 10% within the first year of exposure.
- Progressive primary disease may appear during the course of the initial illness(usually in immunocompromised patients) or after a latent period of weeks or months.

SECONDARY PULMONARY TUBERCULOSIS

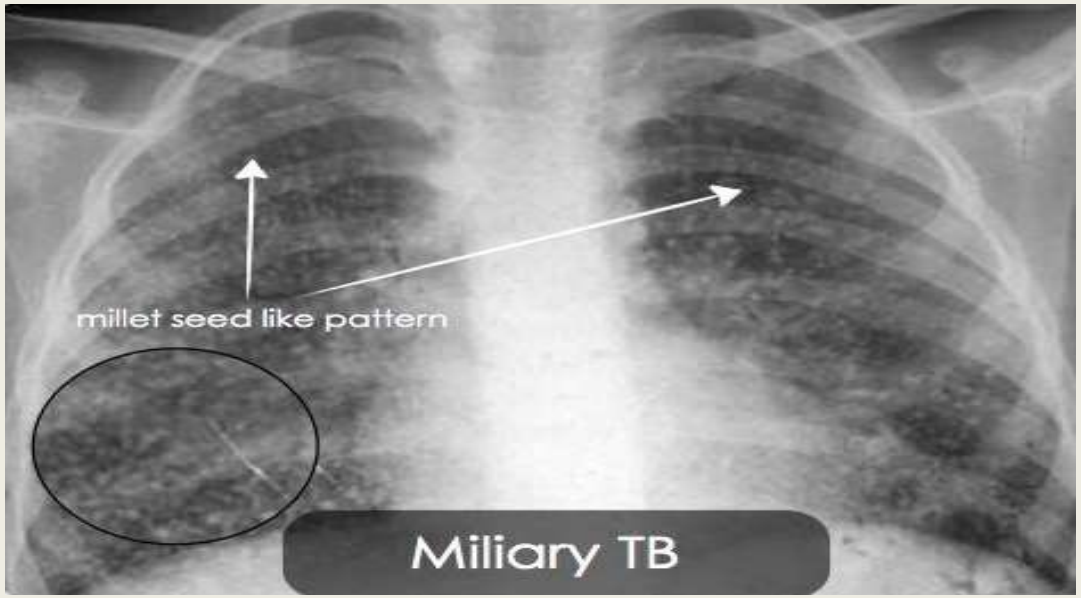
- Secondary TB refers to exogenous (‘new’ infection/reinfection) or endogenous (reactivation of a dormant primary lesion) infection in a person who has been sensitised by earlier exposure.
- Mostly in immunocompromised patient (HIV , TNF alpha inhibitors , CKD).
- The onset is usually insidious, developing slowly over several weeks.
- Systemic symptoms include fever, night sweats, malaise and loss of appetite and weight, and are accompanied by progressive pulmonary symptoms. Hemoptysis can take place when there’s erosion to the pulmonary vasculature.

SECONDARY PULMONARY TUBERCULOSIS



- Secondary TB characteristically occurs in the apex of an upper lobe, where the oxygen tension favours survival of the strictly aerobic organism. The Disease results in formation of consolidation, collapse and cavitation (caseous and liquefactive necrosis) to varying degrees.
- In extensive disease, collapse may be marked and results in significant displacement of the trachea and mediastinum.
- Occasionally, a caseous lymph node may drain into an adjoining bronchus, leading to tuberculous pneumonia.
- Secondary TB may progress to miliary TB.

MILIARY TUBERCULOSIS



17.48 Cryptic tuberculosis

- Age over 60 years
- Intermittent low-grade pyrexia of unknown origin
- Unexplained weight loss, general debility (hepatosplenomegaly in 25–50%)
- Normal chest X-ray
- Blood dyscrasias; leukaemoid reaction, pancytopenia
- Negative tuberculin skin test
- Confirmation by biopsy with granulomas and/or acid-fast bacilli in liver or bone marrow

- Blood-borne dissemination gives rise to miliary TB, which may present acutely but more frequently is characterised by 2–3 weeks of fever, night sweats, anorexia, weight loss and a dry cough.
- Hepatosplenomegaly may develop and the presence of a headache may indicate coexistent tuberculous meningitis.
- Anaemia and leucopenia reflect bone marrow involvement.
- Cryptic miliary TB is an unusual presentation sometimes seen in old age.

EXTRAPULMONARY TUBERCULOSIS

- **Tuberculous lymphadenitis**

Lymph nodes are the most common extrapulmonary site of disease. Cervical and mediastinal glands are affected most frequently involved. Seen frequently in HIV patients.

- **Pleural Tuberculous**

Involvement of pleura is common in Primary TB and results from penetration of tubercle bacilli into pleural space.

- **Gastrointestinal tuberculosis**

TB can affect any part of the bowel and patients may present with a wide range of symptoms and signs .Upper gastrointestinal tract involvement is rare.

Ileocecal disease accounts for approximately half of abdominal TB cases. Fever, night sweats, anorexia and weight loss are usually prominent and a right iliac fossa mass may be palpable.

- **Genitourinary Tuberculosis**

Accounts for 15% of all extrapulmonary TB. Haematuria, frequency and dysuria are often present. Involvement of the Epididymis(epididymitis) and Fallopian tubes(salpingitis) may result in infertility.

EXTRAPULMONARY TUBERCULOSIS

- **Pericardial disease**

Accounts for 8% of all extrapulmonary TB .Disease occurs in two forms : pericardial effusion and constrictive pericarditis.

- **Central nervous system disease**

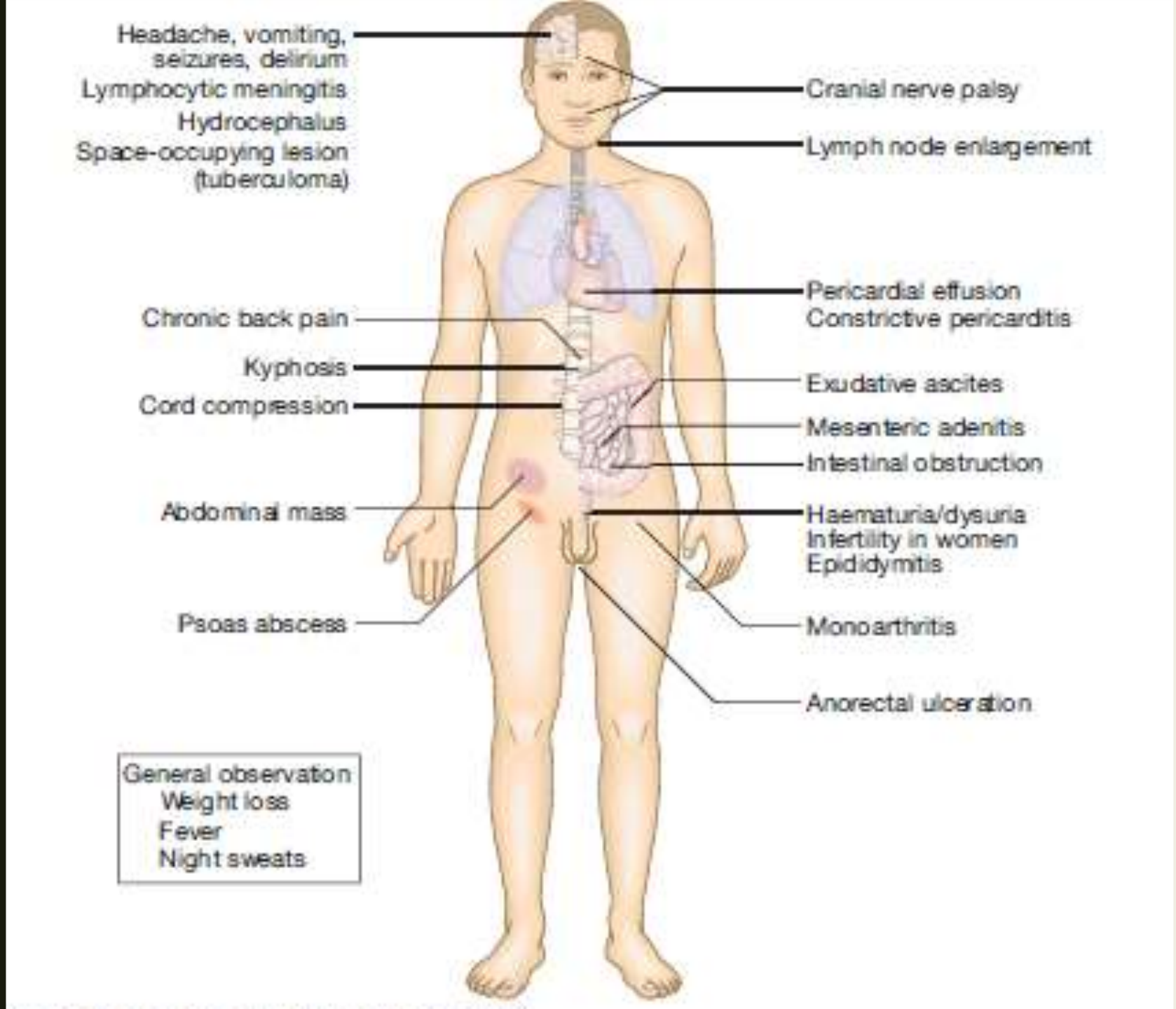
Accounts for 5% of all extrapulmonary TB .Meningeal disease represents the most important form of central nervous system TB. Unrecognised and untreated, it is rapidly fatal. Even when appropriate treatment is prescribed, mortality rates of 30% have been reported.

- **Bone and joint disease**

The spine is the most common site for bony TB (Pott's disease), which usually presents with chronic back pain and typically involves the lower thoracic and lumbar spine.

The infection starts as a discitis and then spreads along the spinal ligaments to involve the adjacent anterior vertebral bodies. Causing angulation of the vertebrae with subsequent kyphosis

Paravertebral and psoas abscess formation is common and the disease may present with a large (cold) abscess in the inguinal region. TB can affect any joint but most frequently involves the hip or knee.



Systemic presentations of extrapulmonary tuberculosis

COMPLICAIONS OF TUBERCULOSIS

- Chronic pulmonary Aspergillosis
- Hemoptysis
- Pneumothorax
- Bronchiectasis
- Broncholithiasis
- Respiratory failure
- Extensive pulmonary destruction
- Anemia of chronic disease
- Venous thromboembolism
- Malignancy(Tuberculoma)
- Secondary amyloidosis
- Septic shock

DIAGNOSIS OF TUBERCULOSIS

- Clinical manifestations
- Laboratory and radiographic examinations :

1. Chest radiography
2. Specimen examination
3. Tuberculin testing

CLINICAL MANIFESTATION

Systemic symptoms

- Unexplained weight loss
- anorexia
- Night sweats
- Fever
- Fatigue

Pulmonary Symptoms

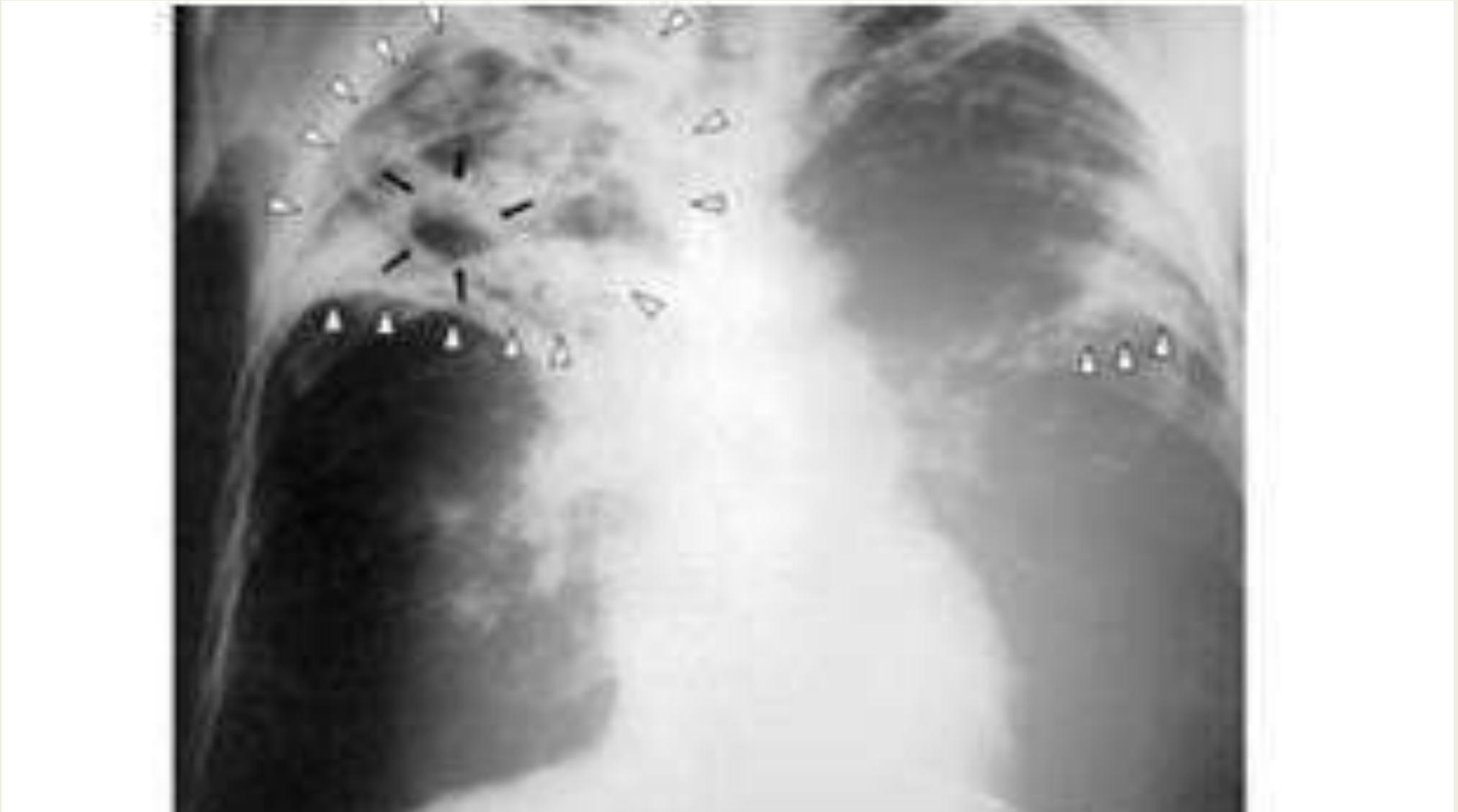
- Coughing for longer than 3 weeks. The cough may vary from mild to severe, and sputum may be scant and mucoid or copious and purulent
- Hemoptysis may be due to cough of a caseous lesion or bronchial ulceration
- Chest pain

Chest radiography

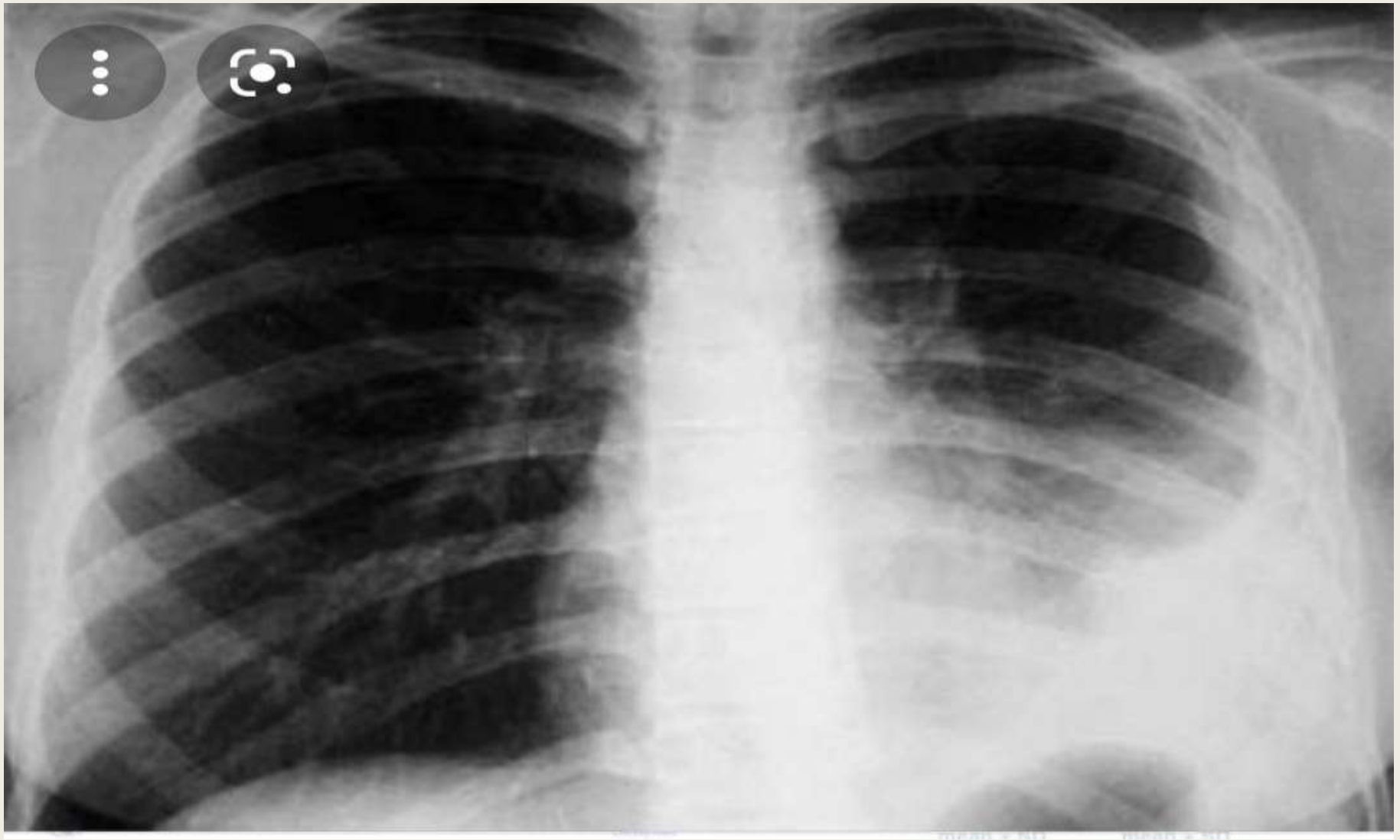
Chest radiography is the most important method to detect TB
In pulmonary TB. You will find in chest X-ray :

1. shadows mainly in the upper zone (cavitations) although these can also occur in lung abscess, carcinoma, etc
2. Diffuse shadowing (Miliary lung)
3. Plural effusion/empyema
4. Ghon complex: evidence of healed primary TB

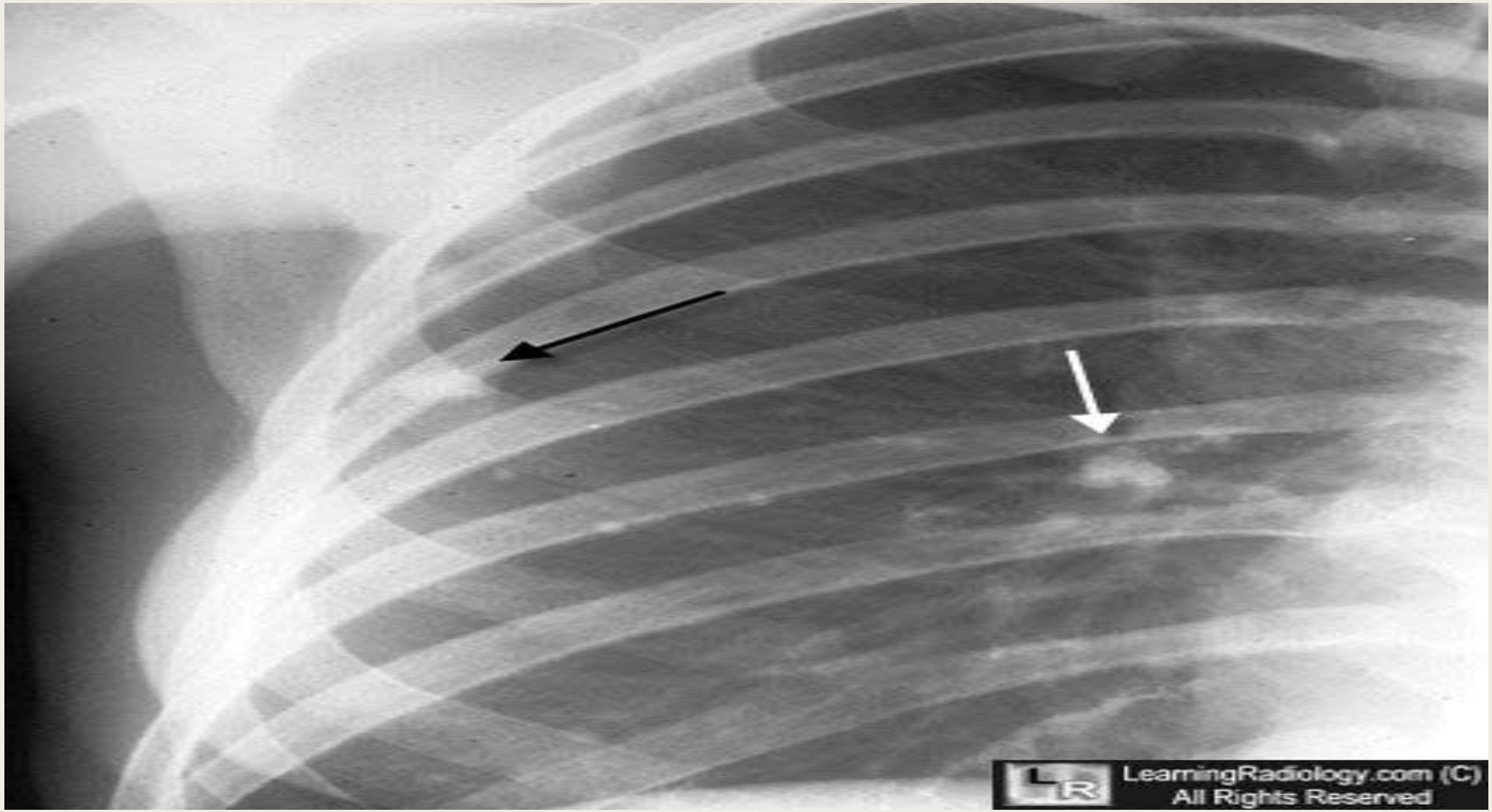
Lung cavitation

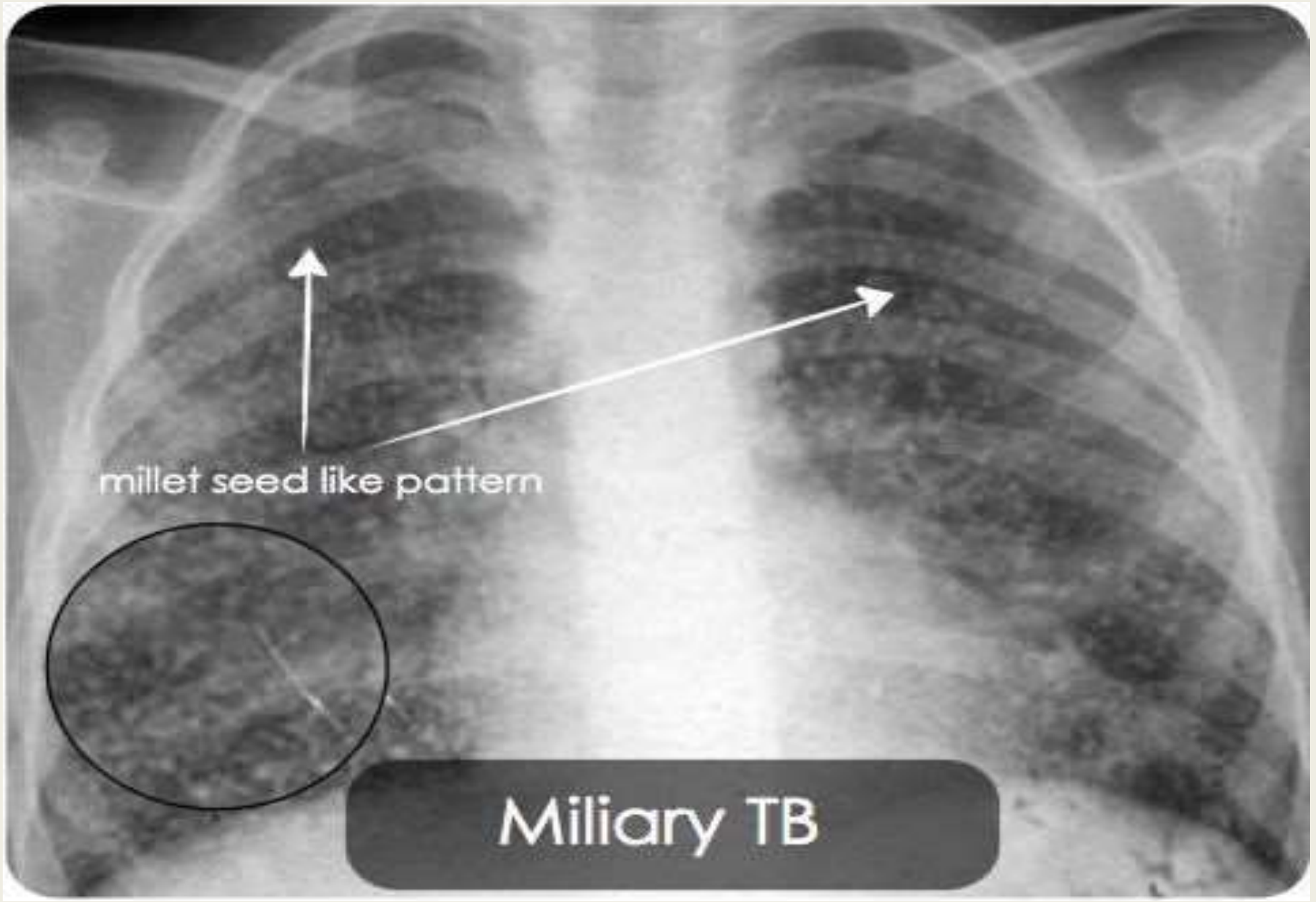


Tuberculous effusion



Ghon complex




millet seed like pattern
Miliary TB

- SPECIMENS
  take a sample from the affected organ:
  -In pulmonary TB: Take a sputum by coughing (if he can’t we take it by Bronchoscope lavage OR in children by gastric aspiration at the morning) -
  In Extra pulmonary TB: biopsy from the lesion in that organ

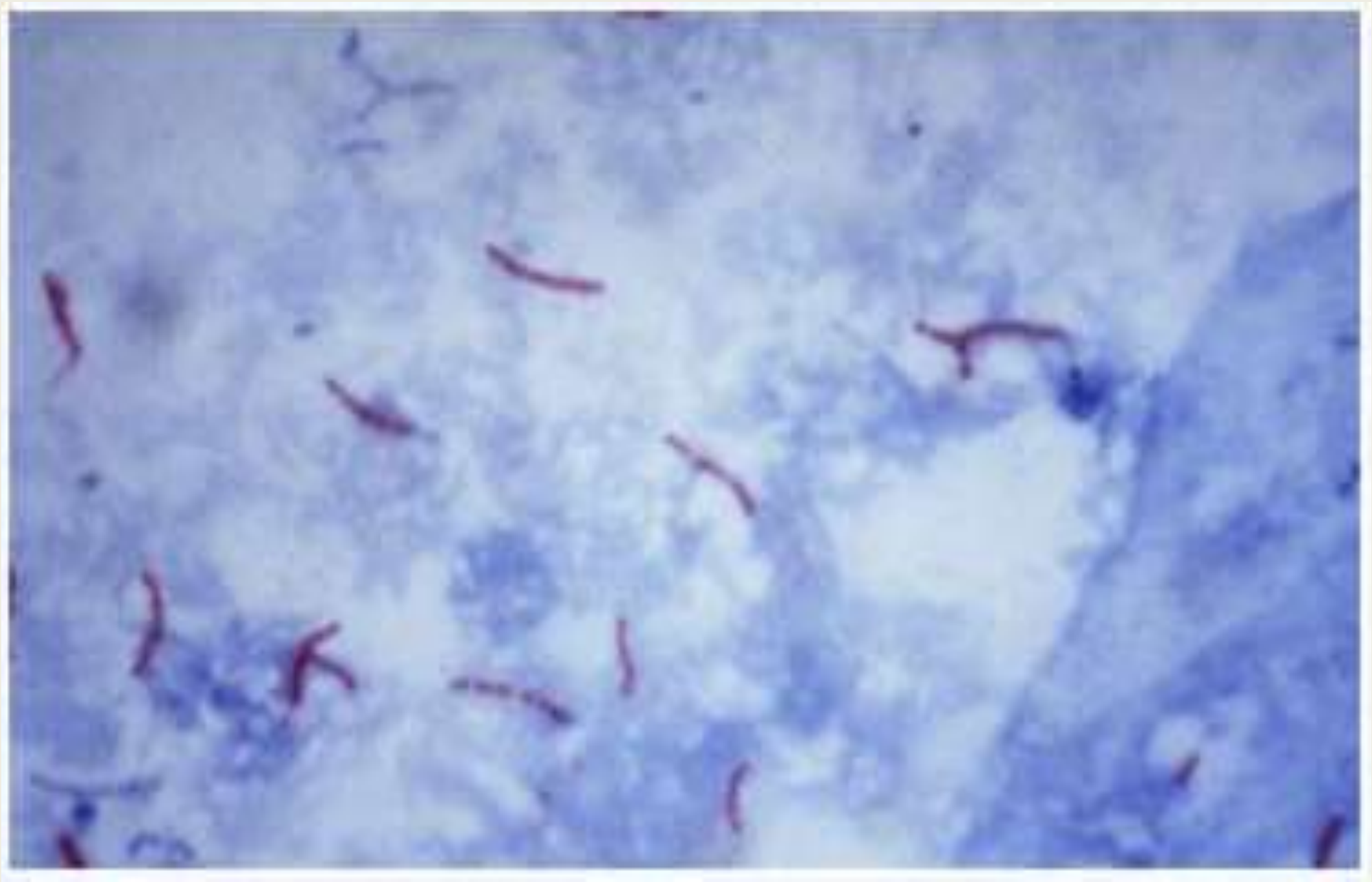
1- Sputum smears stained by Z-N stain

Three morning successive mucopurulent 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.) mainly in non cavitary pulmonary disease or low bacillary load in sputum (e.g. HIV positive patients)

-Young children, elderly & HIV infected persons may not produc



The definitive diagnosis >> Culture
may take between 4 and 6 weeks to appear on solid medium, such as **Löwenstein–Jensen(LJ) or Middlebrook media**. -The only Disadvantage : MTB grows slowly
-The important advantage : we can do antibiotic sensitivity test

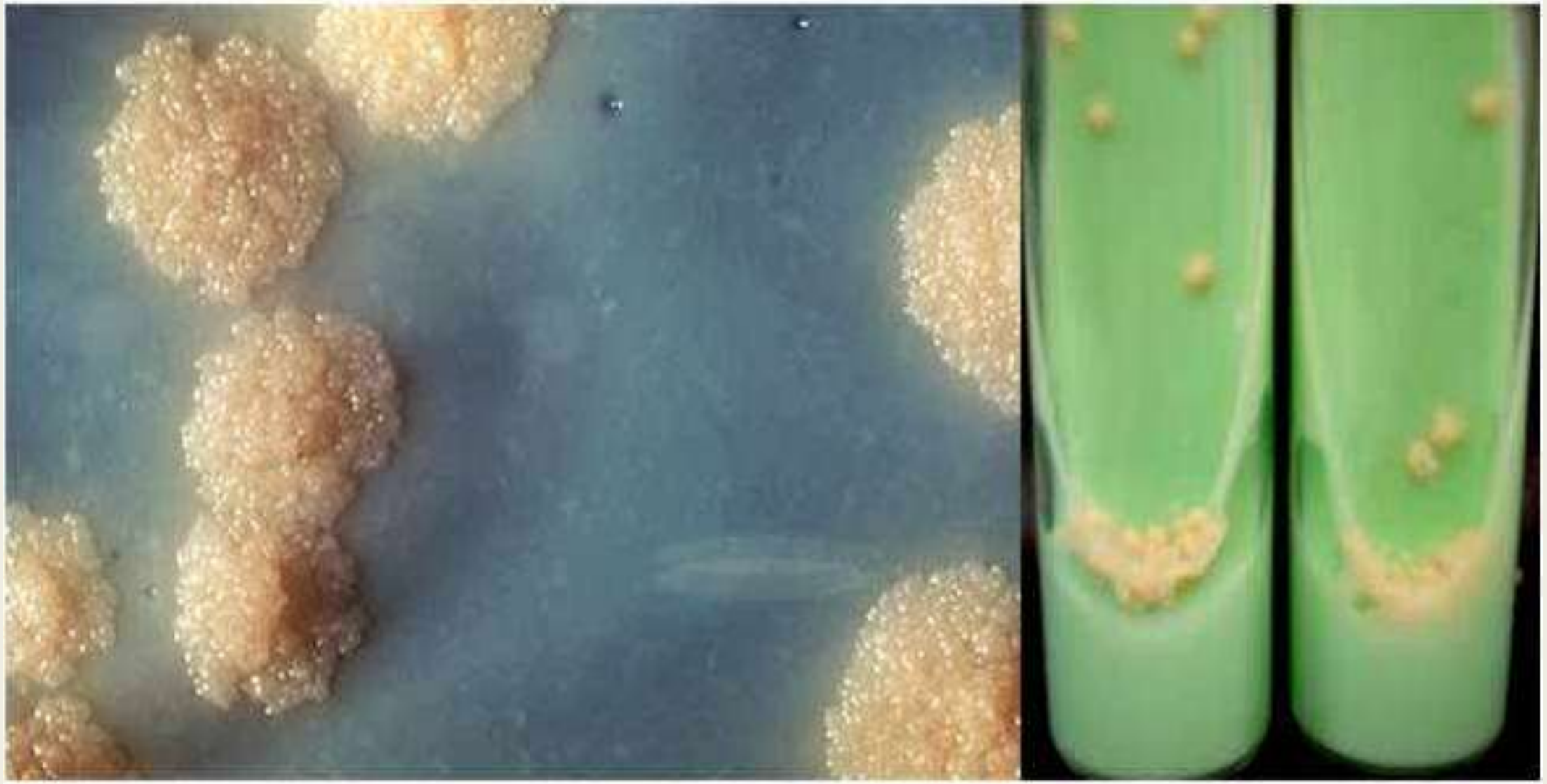


Fig: Cultural Characteristics of *Mycobacterium tuberculosis*

Recent Methods for Diagnosis

●1- BACTEC 460 (rapid radiometric culture system) ● specimens are cultured in a liquid medium ● Growing mycobacteria utilize the acid, releasing radioactive CO2 which is measured as growth index (GI) in the BACTEC instrument.

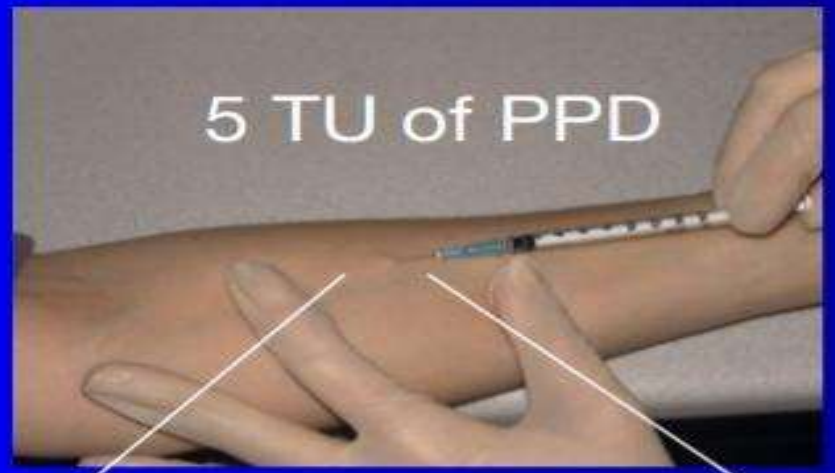
Advantages : - Rapid (mycobacteria can be detected within 12 days.) - Determining drug susceptibility . - Specificity is very high

Disadvantages: - Expensive - Hazards of using radioactive material

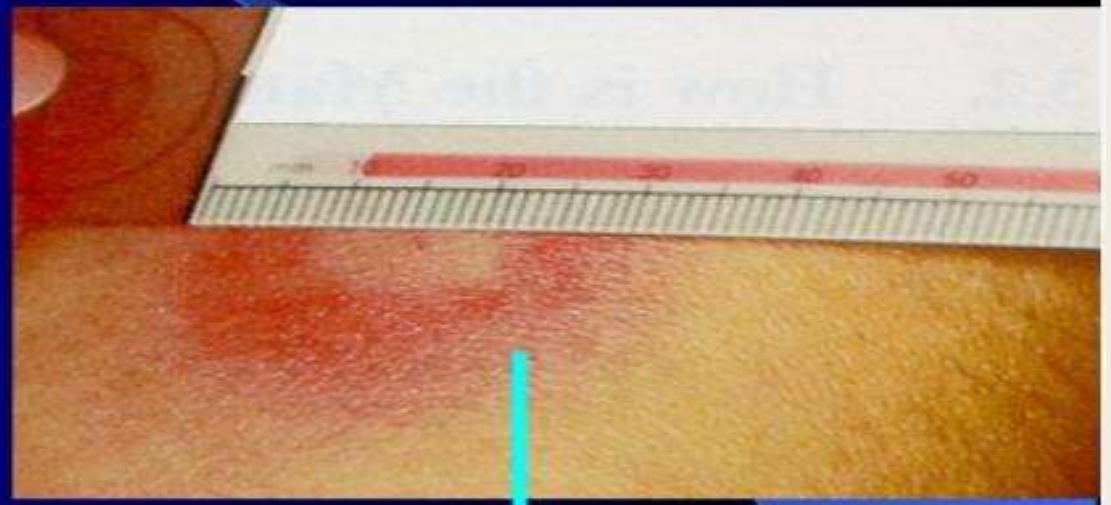
Polymerase Chain Reaction (PCR) & Gene probe

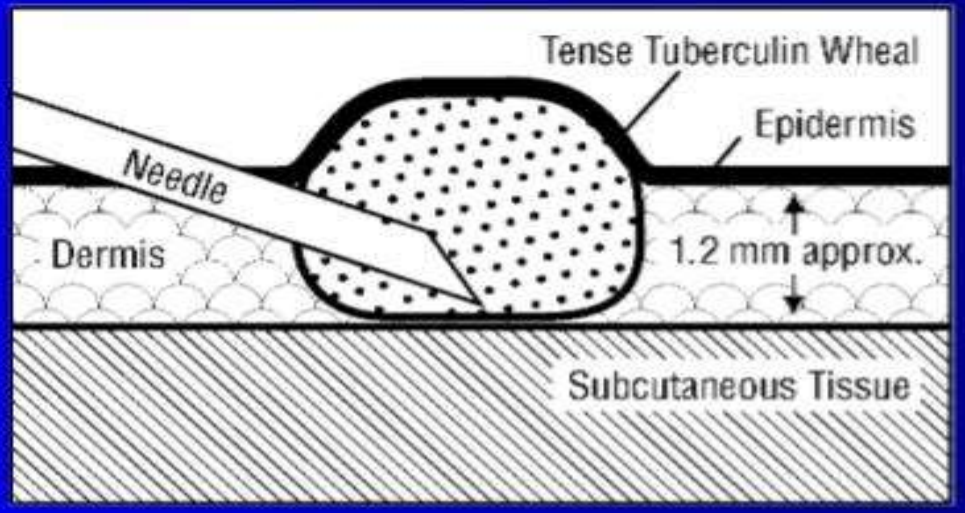
● nucleic acid amplification test in which polymerase enzymes are used to amplify (make many copies of specific DNA or RNA sequences extracted from mycobacterial cells. ● Advantages: - Rapid procedure (3 – 4 hours) - High sensitivity
Disadvantages: -Very expensive. - False positive results. - Can not differentiate between living & dead ba – can not do sensitivity test for antibiotics but there is PCR test for MTB and Rifampin resistance called Xpert MTB/RIF

Tuberculin Skin Testing
Mantoux Method



48 to 72 hours





Interpretation depends on person's risk factors

Tuberculin skin testing is the most common method used to screen for latent M tuberculosis.

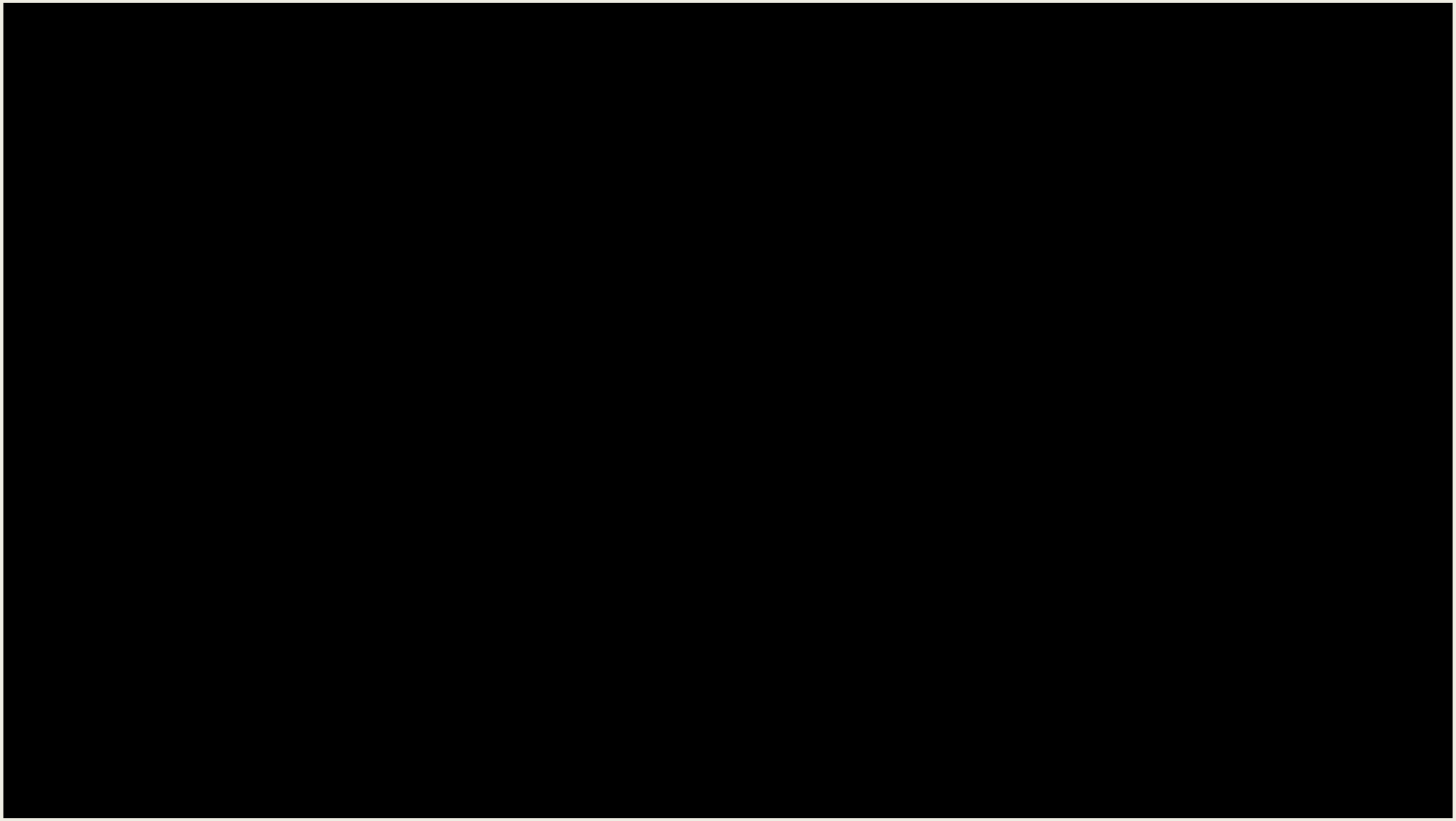
- positive tuberculin skin test indicates tuberculous infection , with or without disease

-In active infection PPD test should not be used as a diagnostic test (because false negative results in 25% of all active pt.)

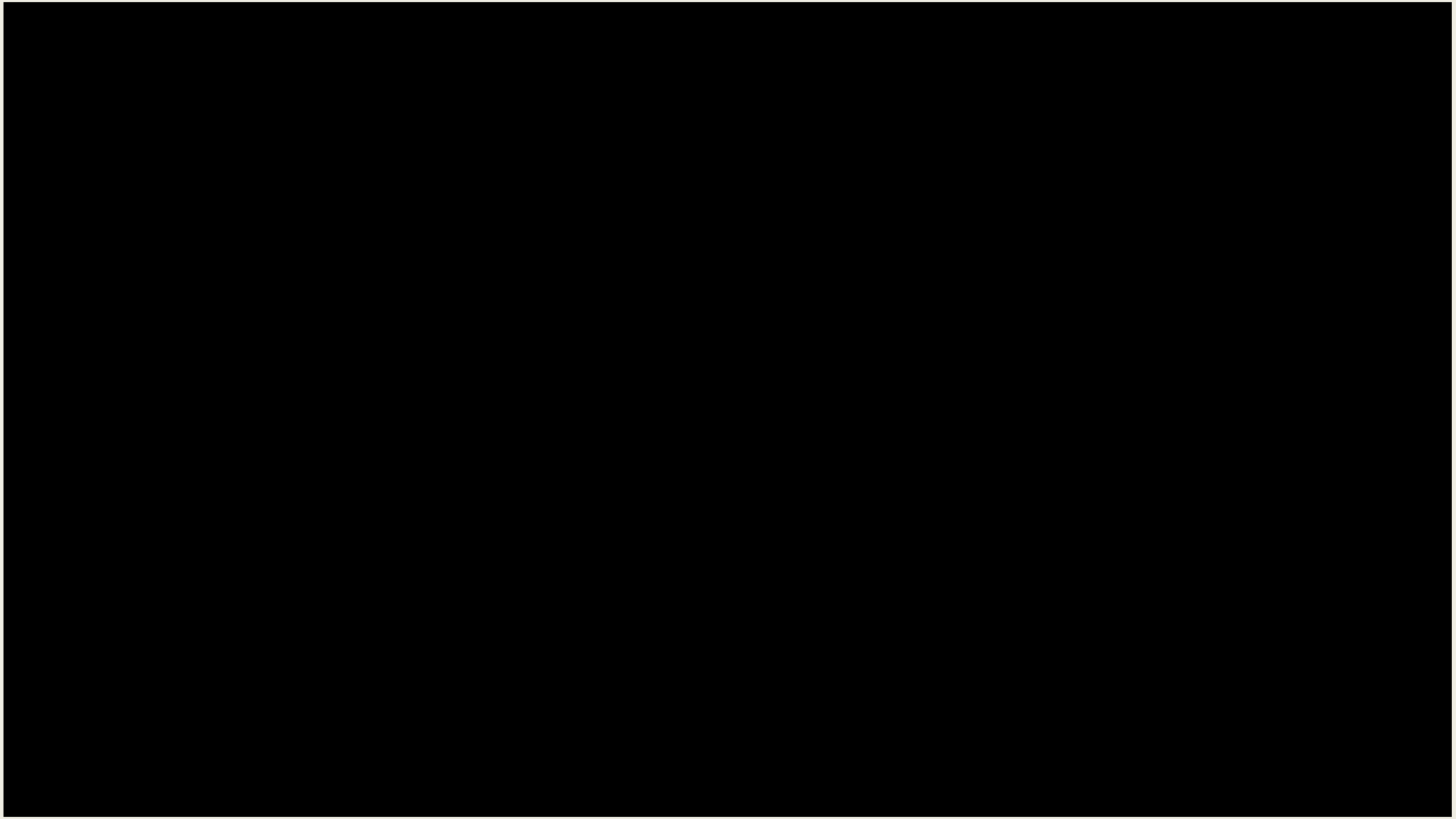
-Prior BCG strongest risk factor for positive TST among those less than age 40 with TSTs

Tuberculin skin test reaction size, (mm induration)	Situation in which reaction is considered positive
TST≥5 mm	HIV seropositive Close contact with positive AFB in the sputum Fibrotic changes on chest radiograph consistent with prior untreated tuberculosis Organ transplants and other immunosuppressed patients (e.g., persons receiving the equivalent of 15 mg/day of prednisone for at least 30 days or more)
TST≥10 mm	Injection drug use Residents and employees in high-risk settings: nursing homes, and other long-term care facilities, hospitals Persons at increased risk of developing active tuberculosis: those with silicosis, diabetes mellitus, chronic renal failure, leukemia, lymphoma, cancer of the head, neck or lung, weight loss of more than 10% of ideal body weight, gastrectomy, jejunoileal bypass Children younger than four years of age
TST≥15 mm	Persons with no risk factors for tuberculosis

Tuberculin Skin Test Procedure



Reading Tuberculin Skin Test



Treatment

The objectives of TB therapy are:

- Cure the individual patient and minimize risk of death and disability
- Reduce transmission of M. tuberculosis to other persons

Latent TB Treatment

We obviously treat Latent Tb to prevent it from progressing into –active-TB disease !

The medications used to treat latent TB infection include the following:

1. Isoniazid (INH)
2. Rifapentine (RPT)
3. Rifampin (RIF)

Most used regimens:

- Three months of once-weekly isoniazid plus rifapentine (3HP)
- Four months of daily rifampin (4R)
- Three months of daily isoniazid plus rifampin (3HR)

Those mentioned above are short-course ttt regimens and are generally preferred over the long term ones (like 6H/9H) because they have higher completion rates and are less toxic (hepatotoxicity!).

Latent TB Infection Treatment Regimens

Drug(s)	Duration	Dose	Frequency	Total Doses
Isoniazid (INH)* and Rifapentine (RPT)†	3 months	Adults and Children aged 12 years and older: INH: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum RPT: 10–14.0 kg 300 mg 14.1–25.0 kg 450 mg 25.1–32.0 kg 600 mg 32.1–49.9 kg 750 mg ≥50.0 kg 900 mg maximum Children aged 2–11 years: INH*: 25 mg/kg; 900 mg maximum RPT†: as above	Once weekly	12
Rifampin (RIF)§	4 months	Adults: 10 mg/kg Children: 15–20 mg/kg‖ Maximum dose: 600 mg	Daily	120
Isoniazid (INH)* and Rifampin)§	3 months	Adults: INH*: 5 mg/kg; 300 mg maximum RIF§: 10 mg/kg; 600 mg maximum Children: INH*: 10-20 mg/kg; 300 mg maximum RIF§: 15-20 mg/kg; 600 mg maximum	Daily	90

CDC

Active TB Treatment

A combination of drugs for a 6 or 9 months period.

Standard ttt has two phases :

- **An intensive phase**

Lasting for 2 months.

- **A continuation phase**

Lasts 4 or 7 months .

The 4-month continuation phase should be used in most patients. The 7-month continuation phase is recommended only for some groups , like :

Patients whose intensive phase of treatment did not include PZA (like pregnant women). **Patients** being treated with once weekly* INH and Rifapentine and whose sputum culture obtained at the time of completion of the intensive phase is still positive.

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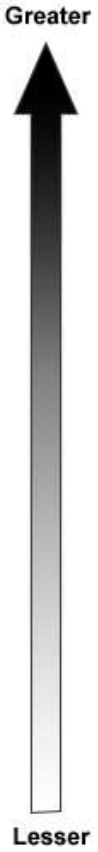
Active TB Treatment

The first line anti-TB drugs that make up the core of multiple regimens are :

- Isoniazid (INH)
- Rifampin (RIF)
- Ethambutol (EMB)
- Pyrazinamide (PZA)

	INTENSIVE PHASE		CONTINUATION PHASE				
Regimen	Drugs[a]	Interval and Dose[b] (minimum duration)	Drugs	Interval and Dose[b,c] (minimum duration)	Range of Total Doses	Comments[c, d]	Regimen Effectiveness
1	INH RIF PZA EMB	7 days/week for 56 doses (8 weeks) *or* 5 days/week for 40 doses (8 weeks)	INH RIF	7 days/week for 126 doses (18 weeks) *or* 5 days/week for 90 doses (18 weeks)	182 to 130	This is the preferred regimen for patients with newly diagnosed pulmonary TB.	
2	INH RIF PZA EMB	7 days/week for 56 doses (8 weeks) *or* 5 days/week for 40 doses (8 weeks)	INH RIF	3 times weekly for 54 doses (18 weeks)	110 to 94	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.	
3	INH RIF PZA EMB	3 times weekly for 24 doses (8 weeks)	INH RIF	3 times weekly for 54 doses (18 weeks)	78	Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance.	
4	INH RIF PZA EMB	7 days/week for 14 doses then twice weekly for 12 doses[e]	INH RIF	Twice weekly for 36 doses (18 weeks)	62	Do not use twice-weekly regimens in HIV-infected patients or patients with smear positive and/or cavitary disease. If doses are missed then therapy is equivalent to once weekly, which is inferior.	

CDC

Drug Resistant TB

Causes of drug resistant TB include :

Not completing the full course of ttt

Being prescribed the wrong dosage /length

Direct transmission from a person with resistant TB

Types :

Multidrug-resistant TB (MDR TB) is resistant to more than one anti-TB drug and at least isoniazid (INH) and rifampin (RIF).

Extensively drug resistant TB (XDR-TB): is a rare type of MDR TB that is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).

And recently : ***Total drug resistant TB (TDR-TB)***

Treating drug Resistant TB is complicated, expensive and has longer ttt course !

Adverse effects of TB drugs

Patients taking rifampin (RIF) or Rifapentine (RPT) should be informed that they will notice an orange/pinkish discoloration of urine and possibly other body fluids.

Rifampin : Thrombocytopenia

Pyrazinamide : may precipitate hyperuricaemic gout

Isoniazid : At high doses it may produce a polyneuropathy due to a B6 deficiency.

Ethambutol can cause a dose-related optic retrobulbar neuritis that presents with colour blindness for green (reversible when stopped).

They are hepatotoxic !

And for this reason consider performing frequent liver chemistry blood test esp. for older patient , those with preexisting liver disorders , postpartum period (≤3 after delivery) , HIV patients

Pregnancy

- For most pregnant women, treatment for latent TB infection can be delayed until 2–3 months post-partum to avoid administering unnecessary medication during pregnancy.
- For women who are at high risk for progression from latent TB infection to TB disease (active), especially those who are a recent contact of someone with infectious TB disease, treatment for latent TB infection should not be delayed.
- Although the treatment regimen involving first line drugs for TB cross the placenta, they do not appear to have harmful effects on the fetus.
- The following anti-tuberculosis drugs are contraindicated in pregnant women: Streptomycin, Kanamycin, Amikacin ,Capreomycin, Fluoroquinolones

Among Latent TB used regimens : 4R , 3HR , 6H or 9H with B6 supplementation

Active TB regimens :INH, RIF and EMB daily for 2 months followed by INH and RIF daily or twice weekly for 7 months

*3HP regimen and PZA are not recommended : not enough studies

PROGNOSIS

Prognosis of TB patients after treatment

- Good prognosis post-treatment and majority of patients are cured after successful completion of chemotherapy.
- There is a small risk of relapse (<5%),most relapses occur within 5 months and usually have the same drug susceptility.
- Recurrence sometimes occur due to reinfection
- Drug-resistant TB is more difficult to treat, with poor prognosis
- Risk of reactivation rises whenever immunity is suppressed
- Few patients die unexpectedly soon after commencing therapy ,it is possible that some have subclinical hypoadrenalism that is unmasked by rifampicin-induced increase in glucocorticoid metabolism.
- Pts who survived active TB after treatment might have lower life expectancy of 3-4 years , than pts with a latent infection

PROGNOSIS of TB PATIENTS WITHOUT TREATMENT :

- TB is severe and often deadly disease without any treatment, the mortality rate for TB is more than 50%

-In absence of treatment, a patient with smear-positive TB will remain infectious for an average of 2 years and 25% of untreated cases will die in 1 year.

- After 5 years without treatment, smear-positive pulmonary TB(PTB)in HIV-negative pts will have:

- 50-60% die (case fatality ratio for untreated TB)
- 20-25% are cured (spontaneous cure)
- 20-25% develop chronic smear-positive TB

-similar case fatality ratios are seen in untreated extrapulmonary TB(EPTB) and smear-negative PTB

-The case fatality ratios mentioned above, falls to less than 2-3% with ADEQUATE TREATMENT, under optimal conditions

- Untreated TB in HIV-positive patients (who are not on antiretrovirals)is almost always fatal.
- Even on antiretrovirals ,the case fatality ratio is higher than in HIV-NEGATIVE patients.

Factors affecting TB prognosis

Poor prognosis in patients with:

- HIV positive individuals (have higher mortality rate and increased risk of relapse)
- Extremes of age (elderly, infants and young children)
- Chronic comorbidities (DM,silicosis,CA)
- Pts on immunocompromising drugs
- Smoking more than one pack/day
- Drug abuse/alcoholism
- Malnutrition
- Delay in treatment
- Chronic lung disease
- End-stage renal disease
- Multidrug resistant TB(MDR-TB) &Extensively drug resistant TB(XDR-TB)-(high death rate since ttt success is often less than 50%)
- Hodgkin lymphoma
- Radiologic evidence of extensive spread
- History of previous TB infection &previous ttt. of TB
- Death is more likely in pts who are smear-positive pulmonary TB(PTB)

Vaccination

Introduction:

- The **BCG**(the Bacillus Calmette-Guerin) vaccine, is the most established vaccine for TB,discovered by Albert Calmette and Camille Guerin and it was firstly administered to humans on 1921.
- **BCG vaccine is a live attenuated vaccine ,derived from *M.bovis,*** that has lost its virulence.
- It is **injected intradermally**, usually in the left upper arm, this site is recommended so that the small scar left after vaccination could be found easily for future reference as evidence of previous vaccination
- BCG vaccine is highly immunogenic
- BCG vaccination varies from one country to another , usually given in countries with high TB prevalence, but not given in countries like USA.
- Usually targets children and high-risk individuals

Who should take the BCG vaccine?

- BCG vaccine is usually given to newborns who are 28 days old
  - *BCG vaccination should be given to children with a negative tuberculin test*
- It may also be recommended to children aged 16 and under, those with higher exposure to TB , withTB in their family history , or travelling to certain countries with high levels of TB cases , such as Africa and Indian subcontinents .
- BCG vaccine should also be given to certain adults(up till 35 y/o) like healthcare workers and veterinary staff with higher exposure to TB.
- Neonatal BCG vaccination appears to be effective in preventing disseminated diseases, it prevents meningitis TB in 70-80% of cases in childhood ,also prevents milliary TB,prevents progression of pulmonary TB in 50% of the cases.
- However , BCG vaccination does not prevent primary infection and does not prevent reactivation of latent pulmonary infection
- BCG vaccine can protect individuals for 10-15 years, those with no previous infections of TB,with an overall efficacy of 50%.

Side Effects

Mild side effects:

- soreness at site of injection
- fever
- headache
- swollen glands under armpit of injected arm
- cutaneous leisions such as hyperemia
- blister formation at injection site
- eczema vaccinatum

Serious side effects :

- local abscess formation(which requires drainage)
- bone inflammation

Side Effects

BCG lymphadenitis ,which is common after BCG vaccination(1-due to vaccine related factor as: some strains are more reactogenic than others/viability and dose of the vaccine,2-host factors as:immunocomprimised pts,HIV-positive pts)

- solated axillary or surpraclavicular/cervical LN enlargement
- history of BCG vaccination on same arm

In some rare cases :

- Disseminated BCG infection(BCG-osis) occur,it is rare but most serious complication of vaccination in immunocompromised children,pts come with systemic symptoms such as ,fever,weight loss,stunted growth AND AT LEAST TWO areas of involvement beyond site of BCG vaccination (such as LNs,skin,lungs,spleen,liver or bones)

Contraindications :

- In immunosuppressed patients like HIV pts,or individuals who are candidates for organ transplants.
- During pregnancy

BCGosis

Fig 1: Infant with BCGosis showing severe wasting and

BCG Eczema

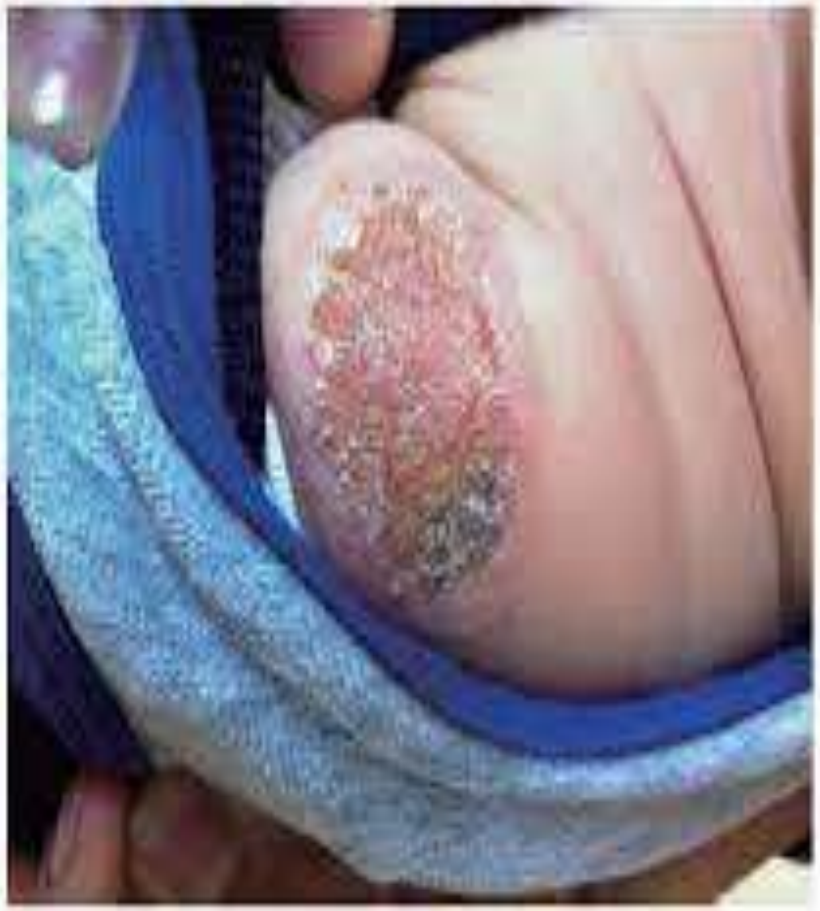
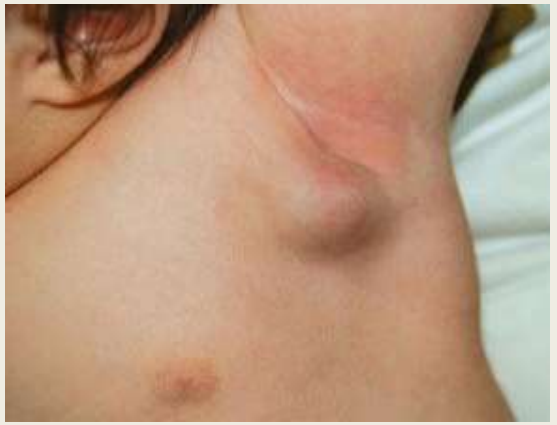
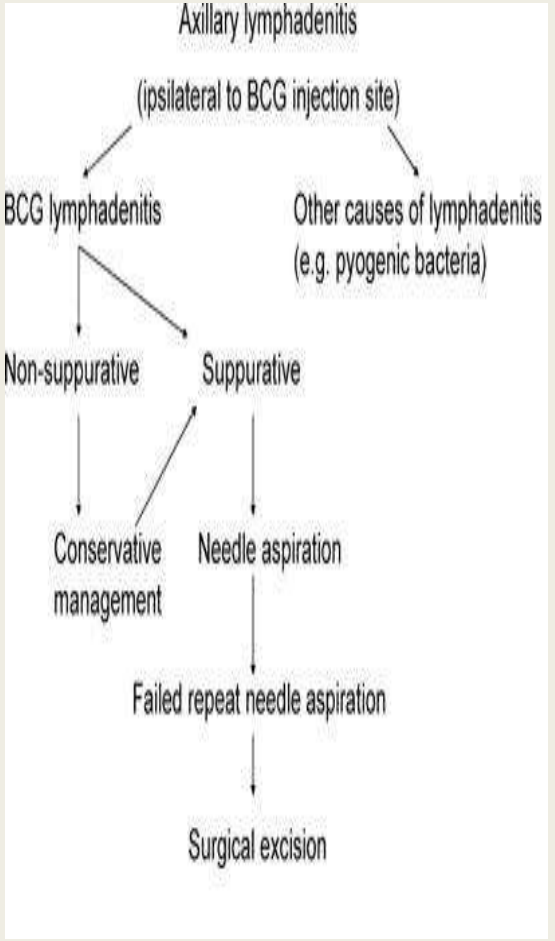


Figure 2. Eczematous locally squamous lesion at the BCG vaccination site.

BCG lymphadenitis





TB Prevention and Control

TB is preventable

TB prevention includes primary ,secondary and tertiary preventions :

- primary prevention: to prevent the development of TB in healthy individuals and includes (Vaccination and environmental controls)
- Secondary prevention :detection of TB in its early stage by screening and early intervention, and detection of Latent TB to prevent it from progressing to active TB by –Tuberculin Skin Testing ,-IGRASs that detect release of interferon gamma (more specific than skin testing)
- Tertiary Prevention: treatment of ppl who already developed TB

TB Prevention and Control

- Directly observed therapy is another method of prevention and control ,since poor adherence to therapy is a major factor in prolonged illnesses and risk of relapse.it .involves supervised administration of therapy 3 times weekly. Usually for (homeless ,alcoholics, mentally ill pts and pts with history of no compliance)

- In resources poor nations, there is a close link between HIV and TB, so it is recommended that all pts with TB should be tested for HIV

TB Control

A TB infection control program should be based on the following three levels :

1. Administrative controls
2. Environmental controls
3. Respiratory-protection controls

Administrative Controls

The first and most important level of a TB infection control program is the use of administrative measures to reduce the risk for exposure to persons who might have TB disease

Which includes :

- Health-Care Worker Education and Training
- Facility Risk Assessment :

1) • Number of patients with TB disease in the setting
2) • Evidence of transmission of M. tuberculosis in the setting
3) • Community rate of TB disease

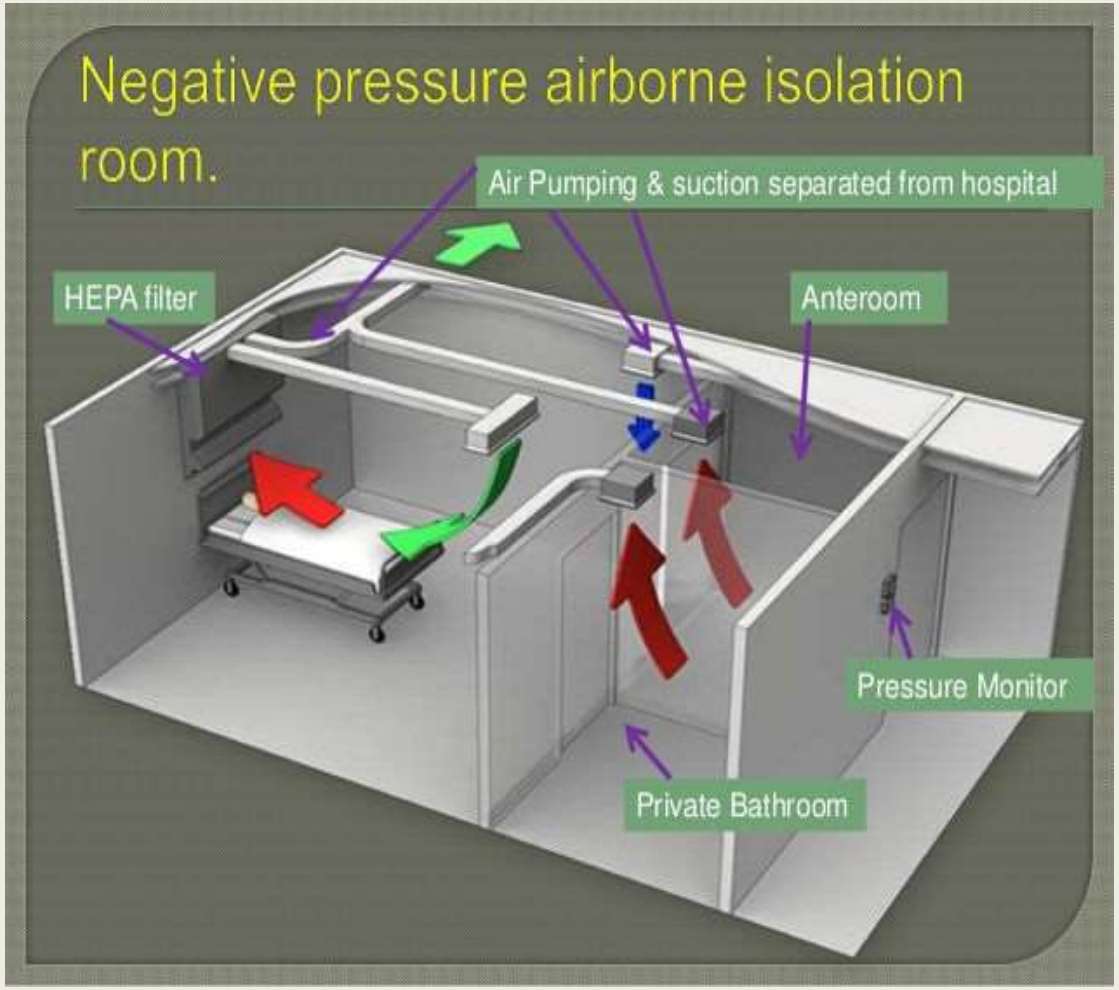
Environmental Control

The second level is the use of environmental controls to prevent the spread and reduce the concentration of droplet nuclei and include

- Primary environmental control
- Secondary environmental control

Primary Environmental Control	Secondary Environmental Control
Controls the source of infection by diluting and removing contaminated air and by using general ventilation: • Uses natural ventilation (e.g., open doors, windows) • Uses mechanical ventilation equipment to circulate and move air in a building • Uses local exhaust ventilation (hoods, tents, or booths)	Controls airflow in areas adjacent to the source and cleans air : • Controls the airflow to prevent contamination of air in areas adjacent to the source (All rooms,airborne infection isolation rooms) • Cleans the air by using high efficiency particulate air (HEPA) filtration or ultraviolet germicidal irradiation (UVGI)

Airborne Infections Isolation Rooms(AII)



- One characteristic of AII rooms is the negative pressure relative to other parts of the facility. Negative pressure allows air to flow from the corridors into the AII room.
- Air from the AII room can be exhausted directly to the outdoors, where the droplet nuclei will be diluted in the outdoor air, or passed through a special high efficiency particulate air filter that removes most (99.97%) of the droplet nuclei before it is returned to the general circulation

Respiratory Protection Control

Respiratory-protection control is the third level of a TB infection control program and consists of the use of protective equipment in situations that pose a high risk for exposure to TB disease.

1) Respirators are designed to protect health care workers and other individuals from inhaling droplet nuclei.(N95 respirators)
2) Surgical masks are designed to reduce the number of droplets being exhaled into the air by persons with infectious TB disease when they breathe, talk, cough, or sneeze.

THANK YOU!