Pediatric Tuberculosis

Dr. Abdalla S. J. Elteer

Consultant Pediatrician in infectious disease unit Benghazi children Hospital

Objectives

- **Upon completion of this session, participants will be able to:**
- Be familiar with the epidemiology of pediatric TB
- Understand the differences in pediatric TB presentations, compared to adults
- Understand transmission,pathophysiology and clinical course of TB in children
- Know the differences between patients with LTBI and active TB
- Be familiar with pediatric TB workup and management

What is tuberculosis (TB)?

TB is a chronic infection. The great majority of infections are caused by *Mycobacterium tuberculosis* (tubercle bacillus).

TB can also be caused by *M. bovis,* which is acquired by drinking unpasteurised milk from infected cows.

Global Epidemiology of TB

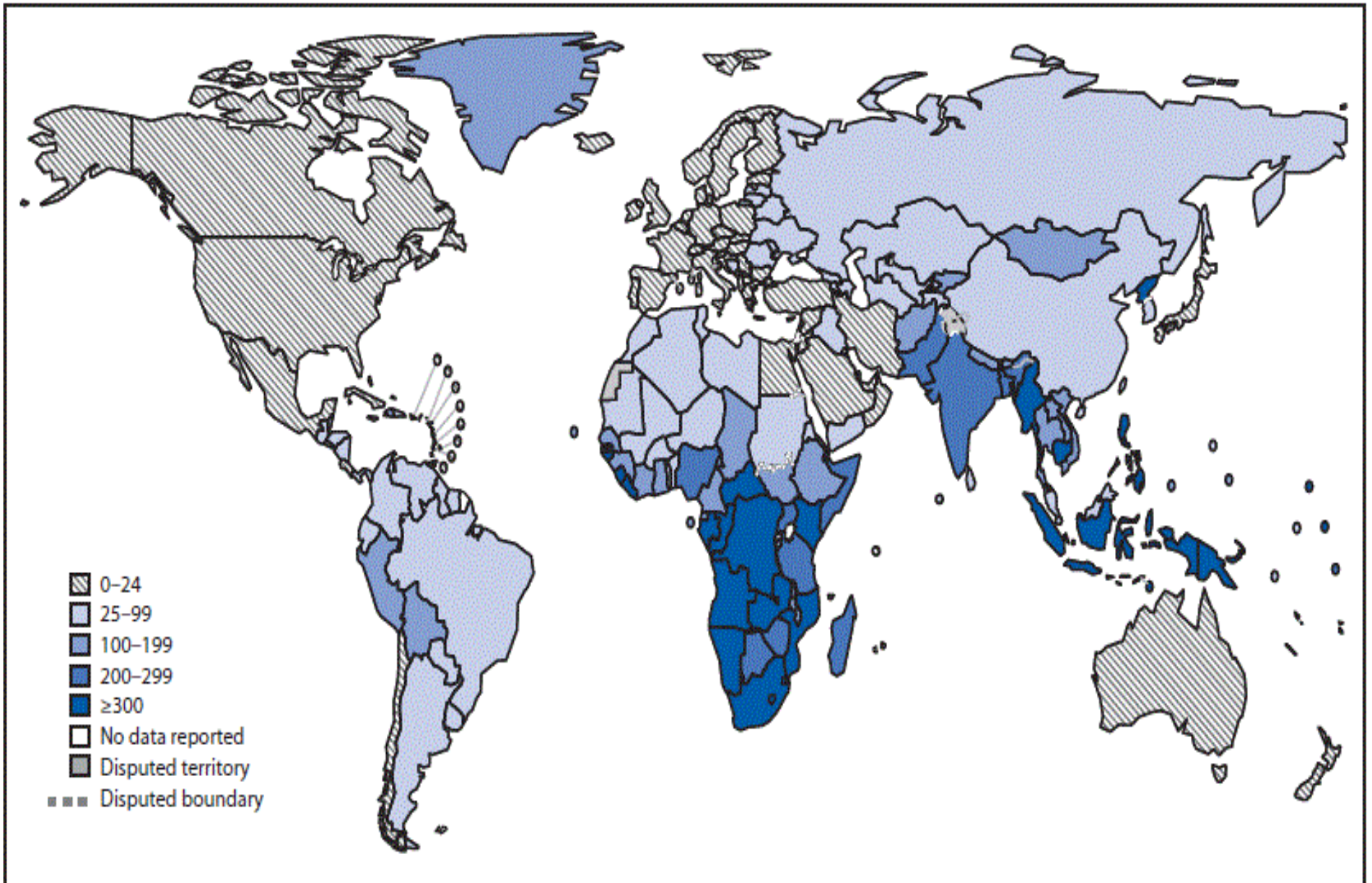
- More than **40%** of the world's population (>**2 billion** people) are infected with *M. tuberculosis*

- The global incidence of tuberculosis (TB) peaked around 2003 and appears to be declining slowly.

- 10.0 million people developed TB disease in 2017:

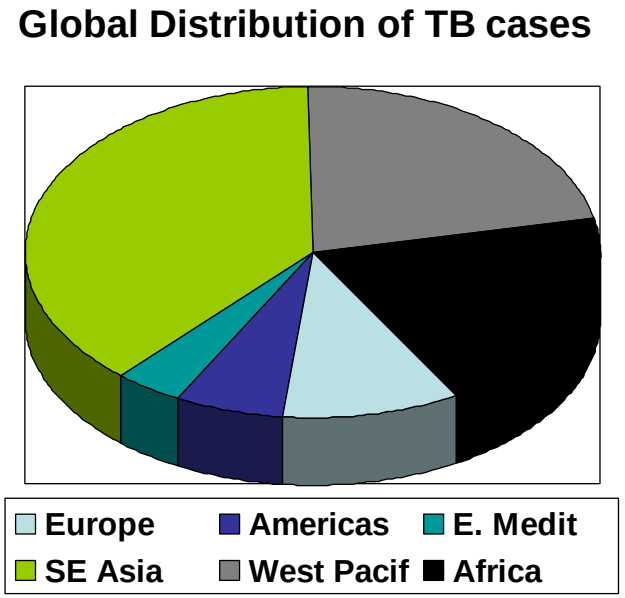
  5.8 million men, 3.2 million women and 1.0 million children.

Annual tuberculosis incidence (per 100,000 population), by region — worldwide, 2017



Where does TB occur?

- About 95% of the world's cases of TB occur in the developing countries of South East Asia, Sub-Saharan Africa and the Western Pacific.
- The highest mortality is in the Africa region, owing to the synergy with HIV.



TB in Children

- TB is more prevalent in adults
- In children, TB is more serious than in adults
- Young children, especially under the age of 4, have difficulty fighting off infections & can have serious forms of TB if left untreated
- Treating latent TB infection can prevent the child from getting active TB disease in the future

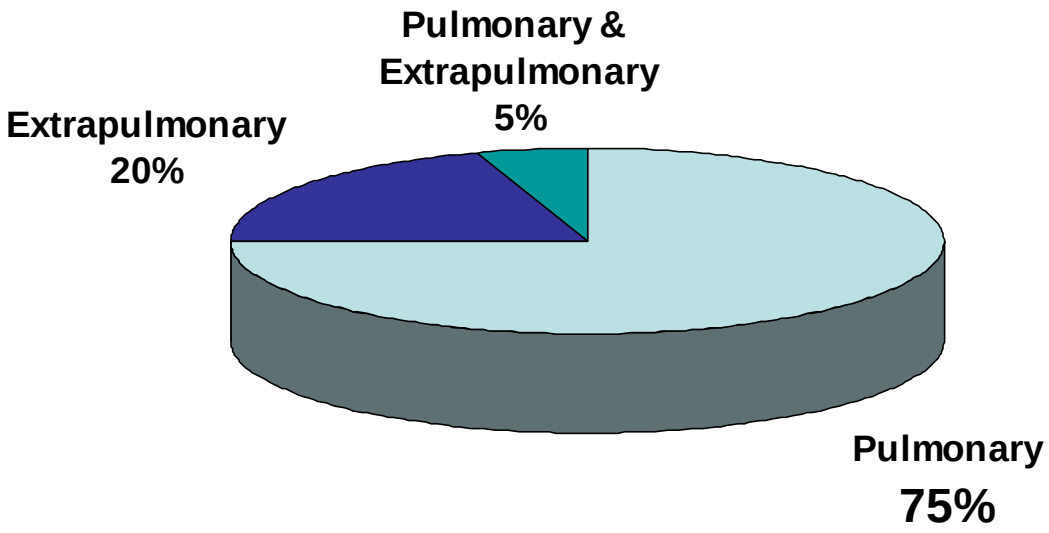
TB: adults vs children

- Compared to adults, children:
  - Tend to develop primary active TB more often after initial infection (0-4yrs)
  - Are more likely to have extrapulmonary disease, especially TB meningitis (0-4yrs)
  - Are more likely to have disseminated TB infection
  - Are less contagious
    - Paucibacillary disease (fewer organisms)
    - Cannot cough/spread infection as well
  - Are more difficult to diagnose
    - May not show typical symptoms
    - May have TB disease in unexpected places
  - Have less FDA-approved treatment meds and formulation options

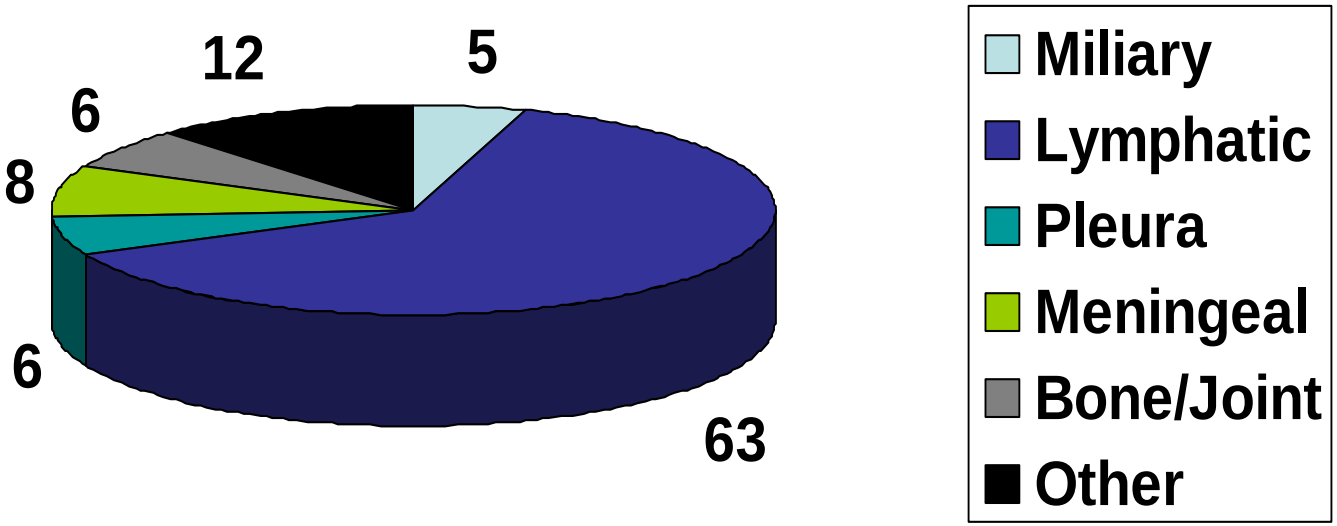
TB: adults vs children

- A child with active TB is an indicator of an unidentified contagious adult/adolescent with TB
  - Contact investigation
  - Many other children may be diagnosed this way
- A child suspected of having active TB may not yield any positive cultures/smears
- Need the adult contact's culture results for drug sensitivities and to determine treatment regimen for the child
- A thorough contact investigation is critical in the evaluation, management, and prevention of TB infection in the child.

Children <15 years with TB by Site of Disease



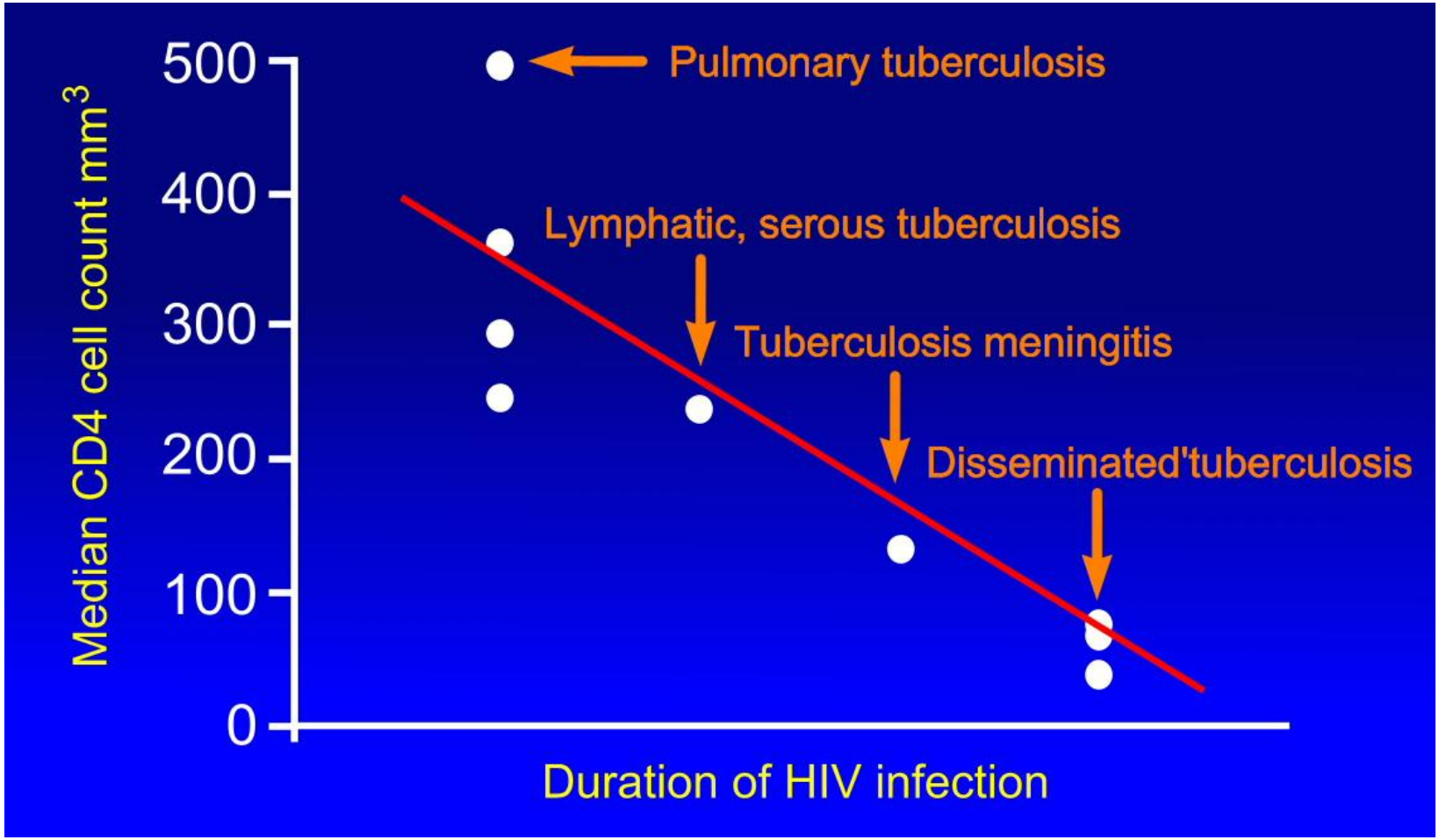
Children <15 years with TB: Extrapulmonary Disease



TB/HIV Coinfection in Children

- 11-64% of children with TB are coinfected with HIV in published studies

Clinical and immunopathological course of HIV associated TB



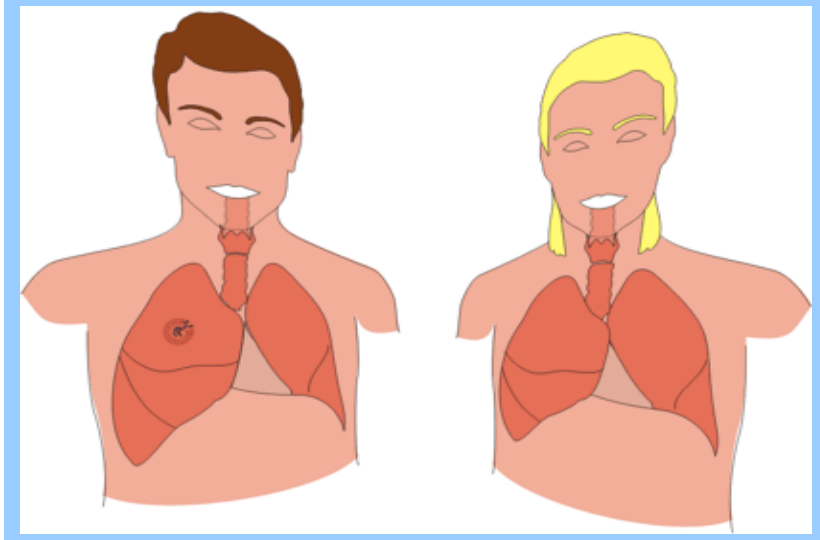
Microbiology

- ***M. tuberculosis*** is a non-motile, rod-shaped bacterium It is an obligate aerobe,
- It is a **slow growing** organism that lives within tissue **macrophages.** Humans are the only reservoir of *M. tuberculosis*. Both cows and humans serve as reservoirs for *M. bovis*.
- The organism does not have the characteristics of either Gram positive or negative bacteria. It has a peculiar cell wall it is classified as an **acid–fast** bacterium.
- The **Ziehl-Neelsen stain** is used to demonstrate the presence of the bacilli in a smear.

M. tuberculosis appearing as bright red bacilli (rods) in a sputum smear stained with the Ziehl-Neelsen stain

How is TB transmitted?

Nearly all TB infection is acquired by **inhalation of respiratory droplets** from an infectious contact.



Air droplets after coughing, sneezing, laughing, or singing by an "open" case of TB. The droplets are inhaled by a close contact. This may lead to a lung infection which then may go on to develop into disease – in the lungs(80%) and/or in other organs.

NB. **Abdominal TB** can also result from drinking unpasteurised cow's milk infected with *M. bovis.*

What happens following inhalation of *M. tuberculosis*?

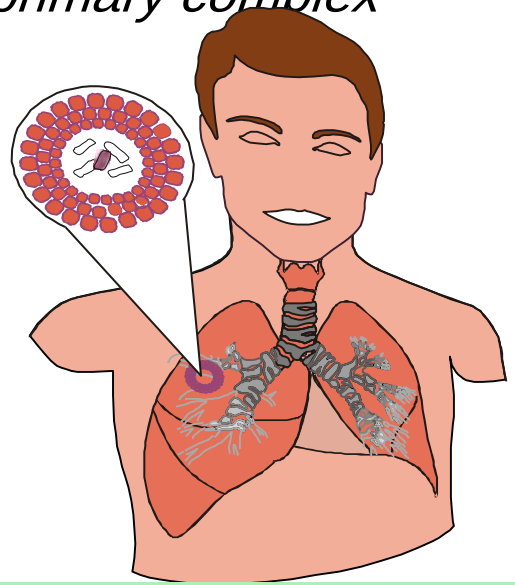
Outcome 1: *No infection*

- Between 70-90% of individuals exposed to TB will not develop any symptoms or signs of infection.

What happens following inhalation of *M. tuberculosis*?

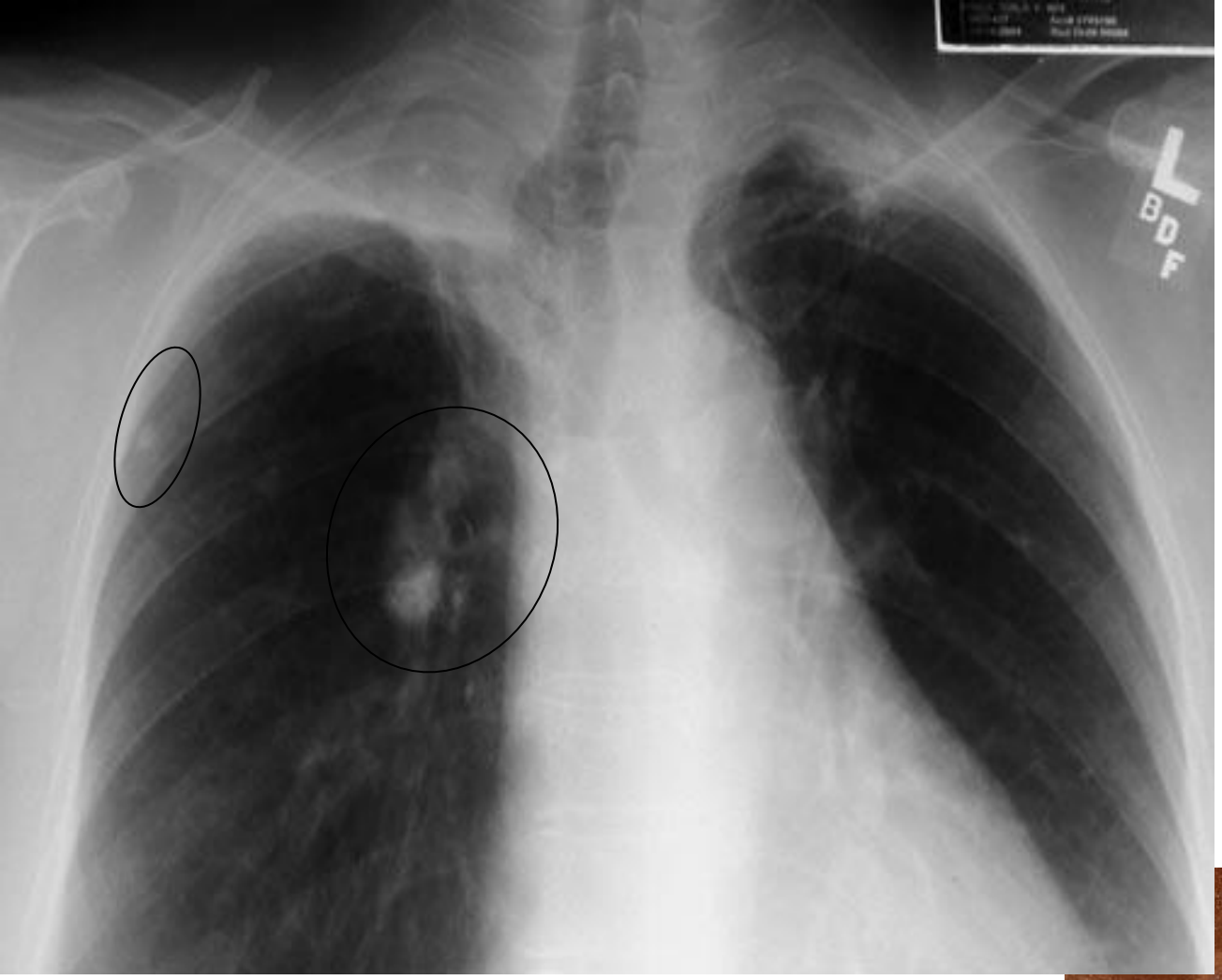
Outcome 2: *Infection with formation of a primary complex*

- Following inhalation, TB bacilli settle in the alveoli. This results in a small focus of local inflammation in the lung (**primary focus)** More than one focus may occur in the same patient.
- The organisms then spread via the local lymphatics to the nearest **hilar lymph nodes**, which may then enlarge.
- The primary focus and the enlarged regional lymph nodes form the **primary complex** or **"Ghon complex".**
- What happens next depends on the size of the infecting dose and the resistance of the host. Most commonly, the primary focus is "walled-off" by the immune system and lies dormant for years. The infection may be reactivated years later if the immune system of the host becomes weakened.

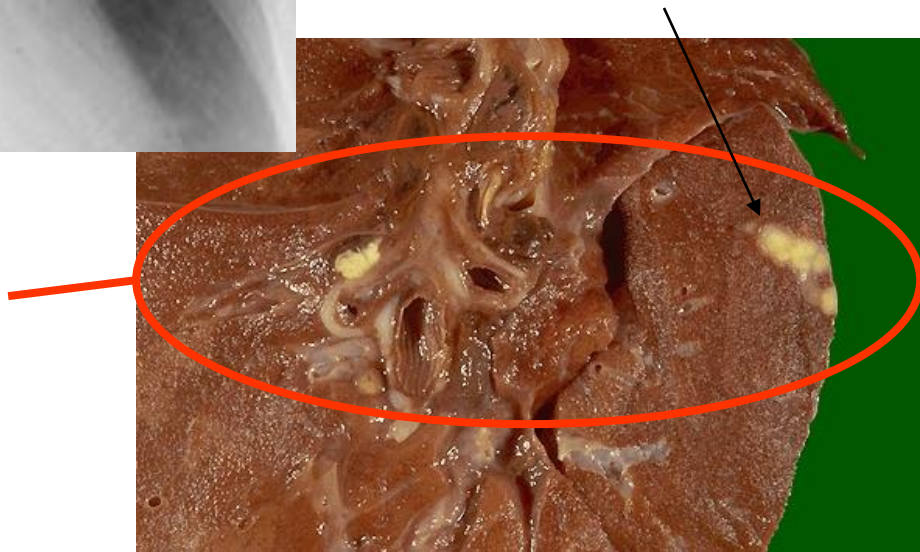


Primary focus successfully contained by the host immune system

The infected person does not have TB disease and cannot spread TB. However, an immune response to *M. tuberculosis* will have developed – and can be demonstrated by a positive Mantoux test.



– Ghon Complex

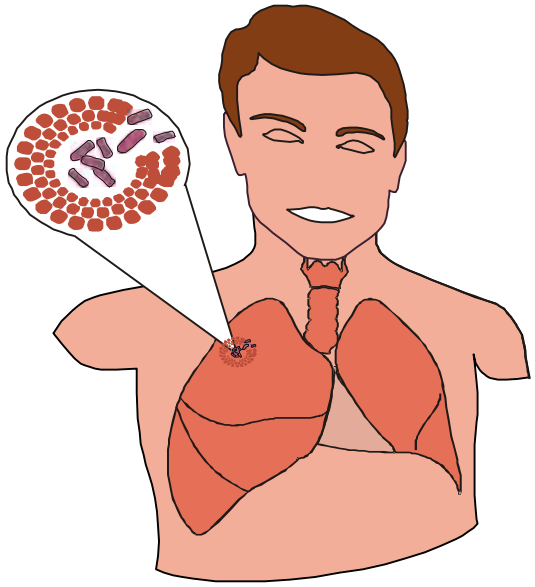


– Primary Complex

What happens following inhalation of *M. tuberculosis*?

Outcome 3: *Pulmonary disease*

- The primary focus is not contained and lung disease may develop in **several ways:**
- The primary focus enlarges and undergoes central necrosis to form a **cavity**
- The infection can spread locally and result in **tuberculous bronchopneumonia**
- Marked swelling of the mediastinal lymph nodes may compress large bronchi and result in **lobar collapse**
- The enlarged lymph node may act like a one-way valve causing **hyperinflation** of a lung or lobe
- The adjacent pleura can become infiltrated by *M. tuberculosis* resulting in a hypersensitivity reaction characterised by **granulomas** composed mainly of lymphocytes
- Pleural infiltration may result in a **pleural effusion** which is rich in lymphocytes – a useful pointer to the diagnosis when pleural fluid is aspirated and analysed
- Long term complications of the damage to lung tissue include **emphysema and bronchiectasis**



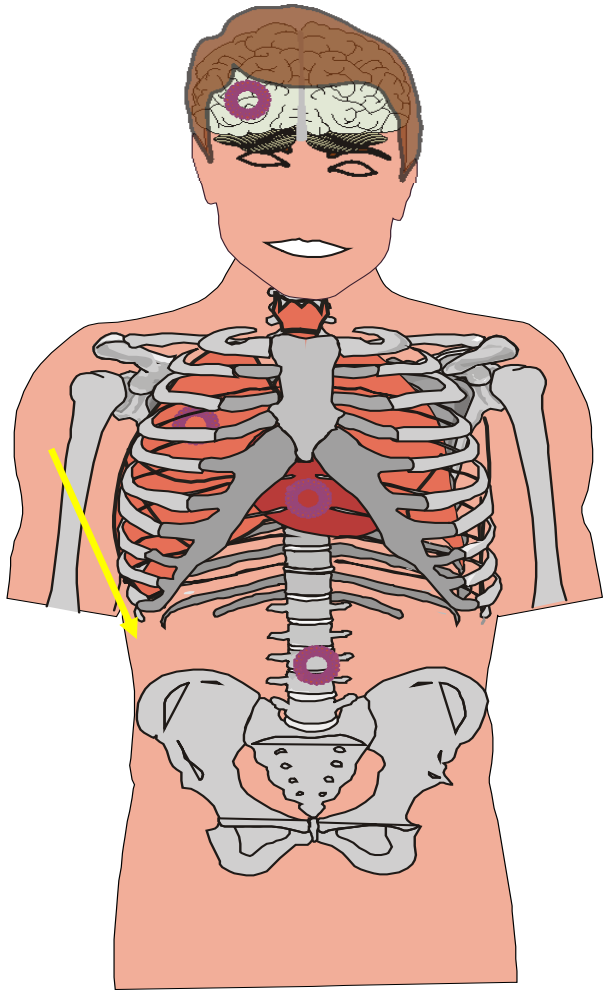
Infection not successfully contained by the immune system. Person develops lung disease.

What happens following inhalation of *M. tuberculosis*?

Outcome 4: *Systemic disease*

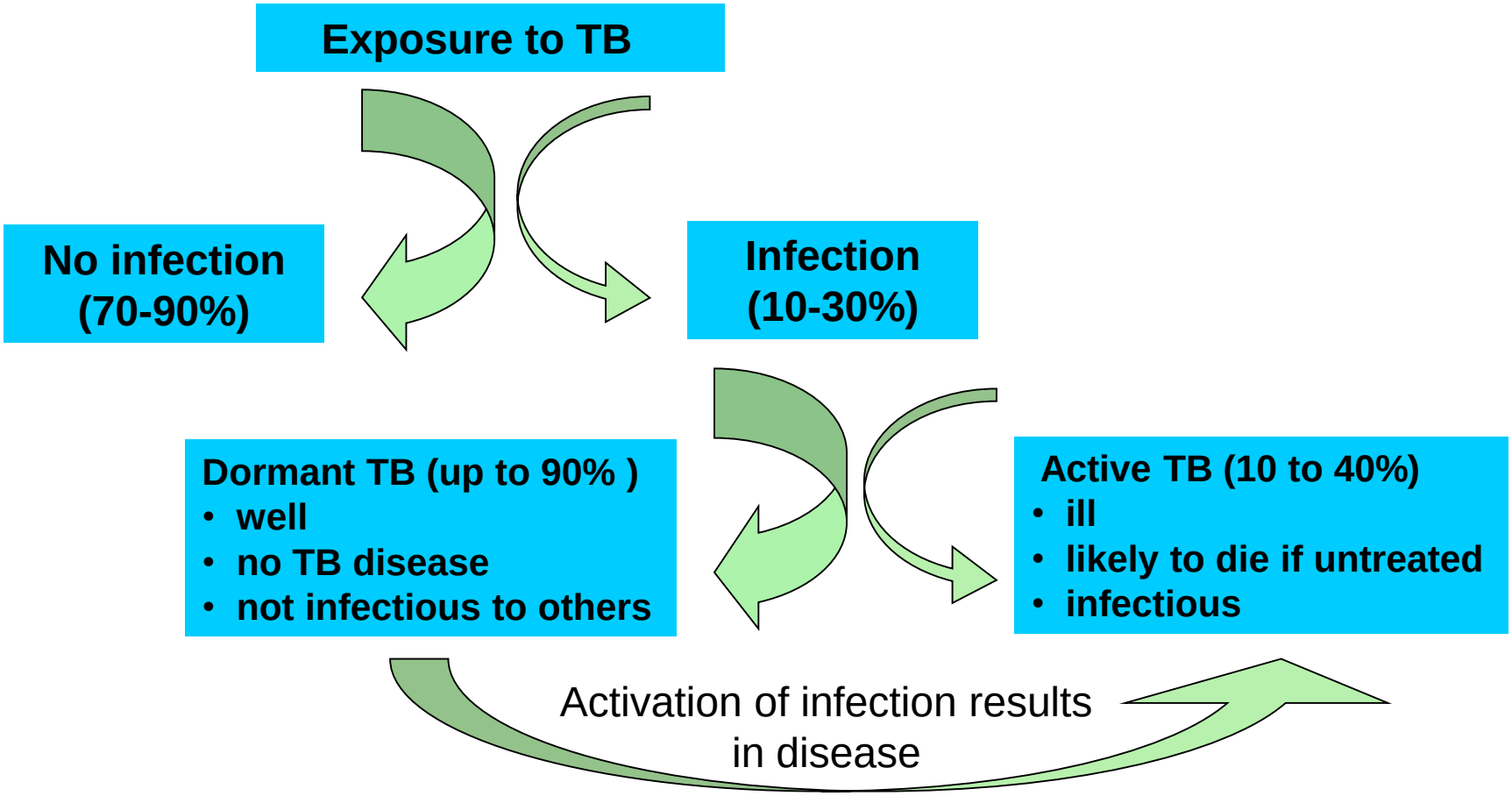
- Haematogenous dissemination of *M. tuberculosis* leads to granuloma formation in many organs. Examples include:
  - Diffuse infection of the lungs: "**miliary" TB**
  - Brain: TB **brain abscess**
  - Meninges: **TB meningitis**
  - Bones: **TB osteomyelitis** – commonly affects the spine and is then called "Potts' disease"
  - Pericardium; **TB pericarditis** and pericardial effusion

- **Disseminated disease** is most likely to occur in the **immunocompromised** patient (e.g. HIV/AIDS, malnutrition) and at extremes of age.



Summary (1): natural history following TB exposure

What are the likely outcomes following exposure to open TB?



Disease

- Risk of developing TB disease is highest during 6 months following infection
- Risk remains high for 2 years
- Many years can elapse from infection to disease
- untreated infants with LTBI have up to a 40% chance of development of tuberculosis disease

Risk factors : infection to disease

- **HIV**
- **Malnutrition**
- **Recent exposure**
- **Young age**
  - Short incubation period
  - More severe
  - Highest risk
  - More difficult to diagnose

What are the symptoms and signs of TB?

1. Primary infection with no spread of the disease

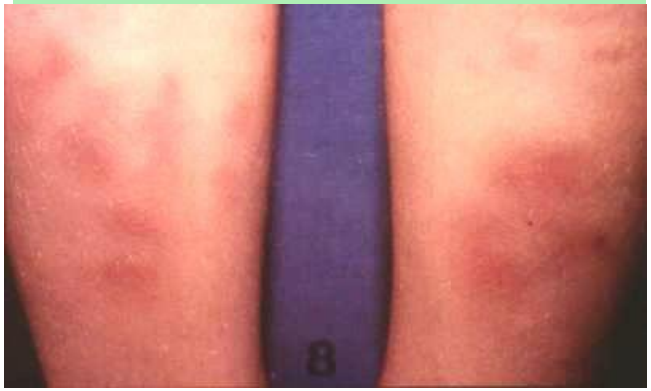
Individuals with primary infection do not usually have any symptoms or signs of ill health although some people develop a minor flu-like illness.

The response of the immune system to the infection may result in clinical signs of hypersensitivity to *M. tuberculosis* in a minority of people, for example:

- **erythema nodosum**
- **phlyctenular keratoconjunctivitis**

They will also have a positive Mantoux test.

Erythema nodosum: ecchymotic papules found along the shin or on the flexural surfaces of the limbs



Phlyctenular keratoconjunctivitis: raised, yellowish nodule at the corneoscleral junction. Small blood vessels are seen radiating from the nodule

What are the symptoms and signs of TB?

2. Active infection: symptoms

Symptoms of TB can be divided into **general symptoms** and those **specific** to the organ infected.

TB symptoms depending on which **organs are involved** and how their **function** is affected.

The **lung** is the predominant organ affected, being involved in over 75% of cases.

Commonly affected organs following haematogenous spread from the lung are the **abdomen, lymph nodes, spine, meninges, kidneys, bone , and reproductive organs.**

General symptoms:

- Loss of weight
- fever / Night sweats
- Malaise
- Anorexia

Organ specific - examples include:

Lungs

- Cough – usually chronic
- Productive of whitish or mucoid sputum in adults but usually unproductive in children
- Haemoptysis

Central Nervous System – may present as

- TB meningitis
- Tuberculoma, with the classical features of a space-occupying lesion simulating a brain tumour

What are the symptoms and signs of TB?

2. Active infection: signs

General examination - *look for:*

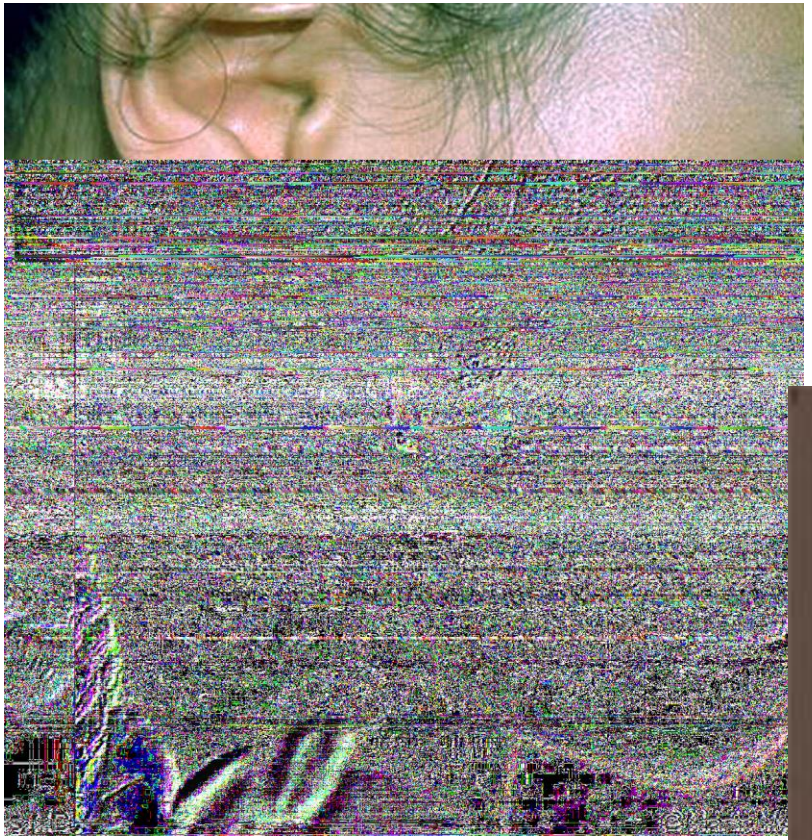
- signs of **malnutrition** signifying a chronic illness
- **fever**
- enlargement of the **peripheral lymph nodes**
- digital **clubbing** as a consequence of chronic infection/inflammation in the chest or abdomen

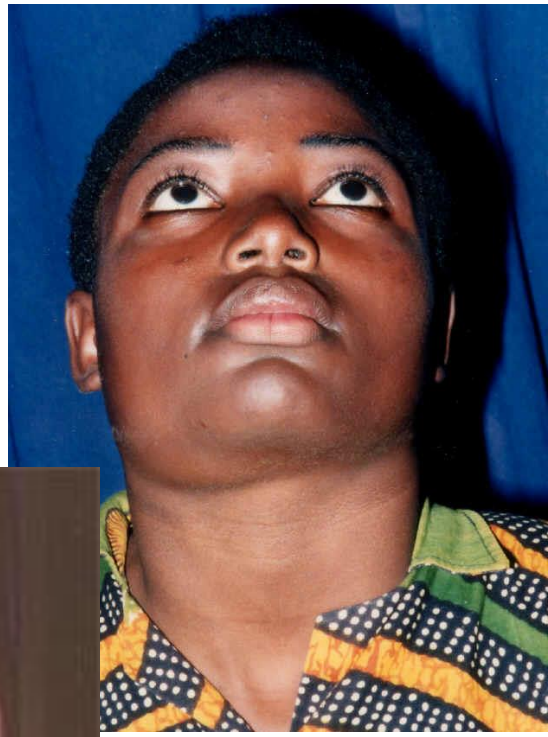
TB lymphadenitis presents as **painless** enlargement of the **superficial lymph nodes**. The **neck** is the commonest site involving the cervical, submandibular, pre and post- auricular lymph nodes. The lymph nodes are **non-tender, matted together and rubbery** in consistency. It is common for enlarged lymph nodes to **ulcerate and discharge.**

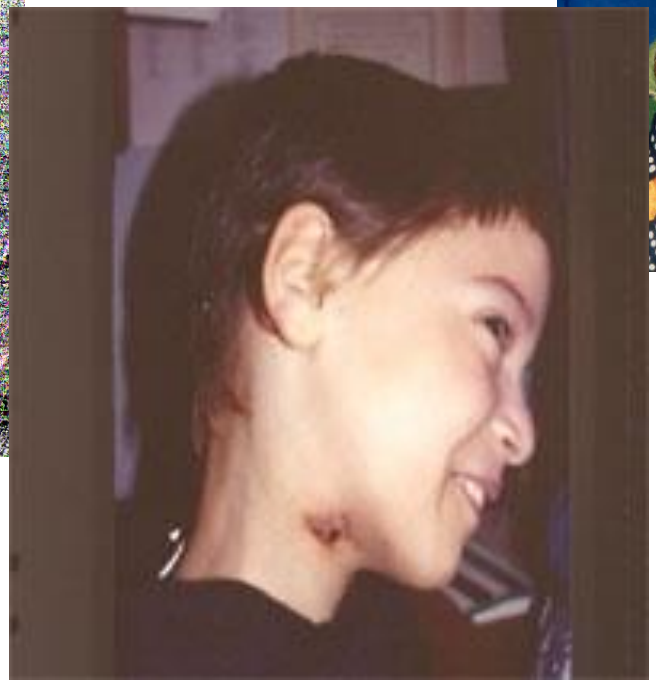
Look at this picture of a 4 year old boy Note that he is generally **wasted** and has marked enlargement of the **cervical lymph nodes** – especially on the right side.

Scrofula

Primary Disease of Cervical Lymph Nodes







What are the symptoms and signs of TB?

3. Pulmonary and abdominal TB

Pulmonary TB (PTB)

Pulmonary lesions may involve any part of the lung in infancy and childhood. The apical region is the most commonly affected in adults.

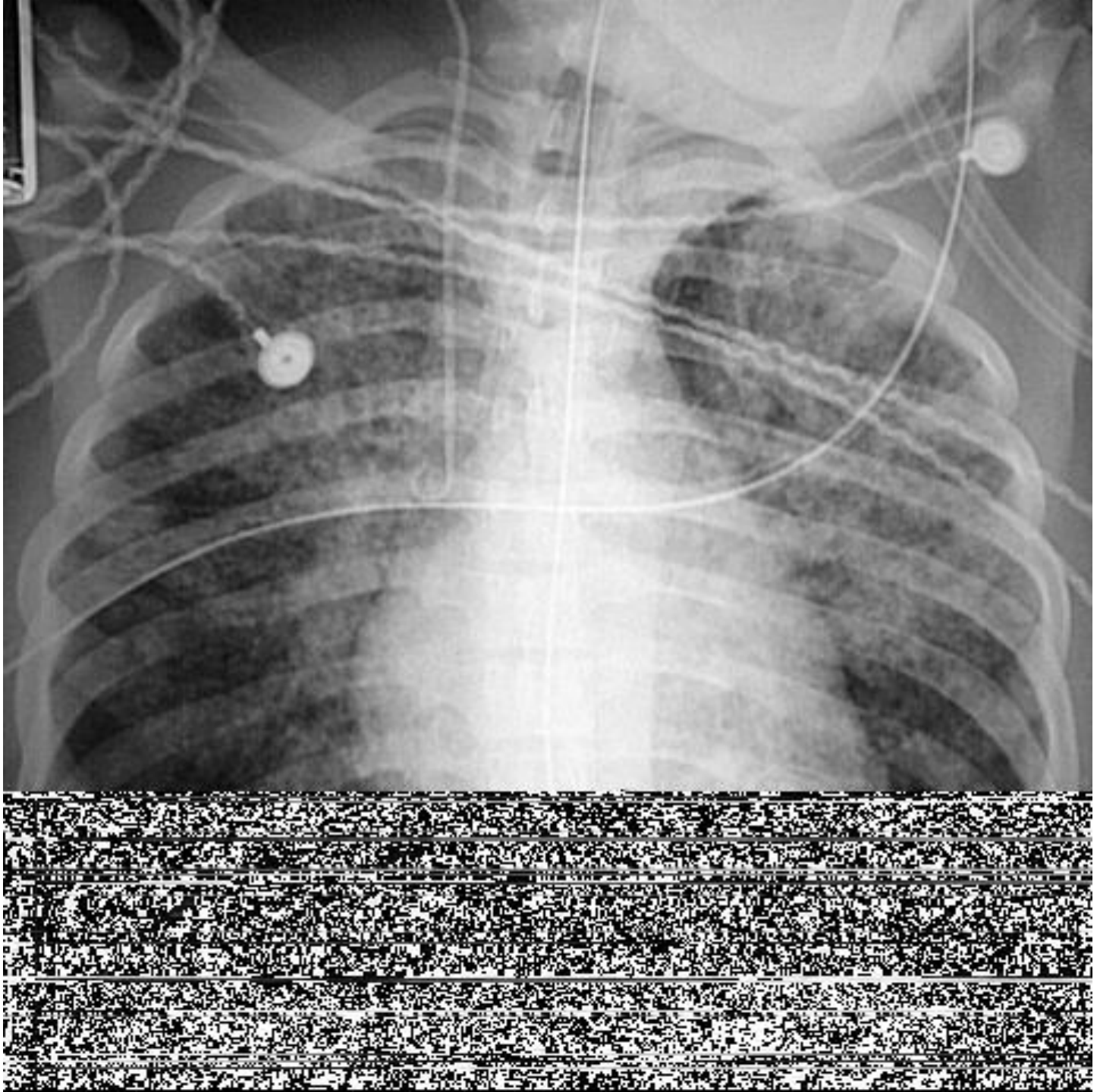
Examination of the respiratory system may be completely normal even in active disease. Abnormalities which may be detected clinically include signs of consolidation, collapse, pleural effusion and fibrosis.

Abdominal TB

Pathology affects the **mesenteric and the retroperitoneal glands**, the **omentum and the gastrointestinal tract.** Patients may present with weight loss, diarrhoea or constipation, abdominal distension (from ascites) or chronic intestinal obstruction. Enlarged mesenteric lymph nodes may be palpable as multiple intra-abdominal masses.

Miliary TB

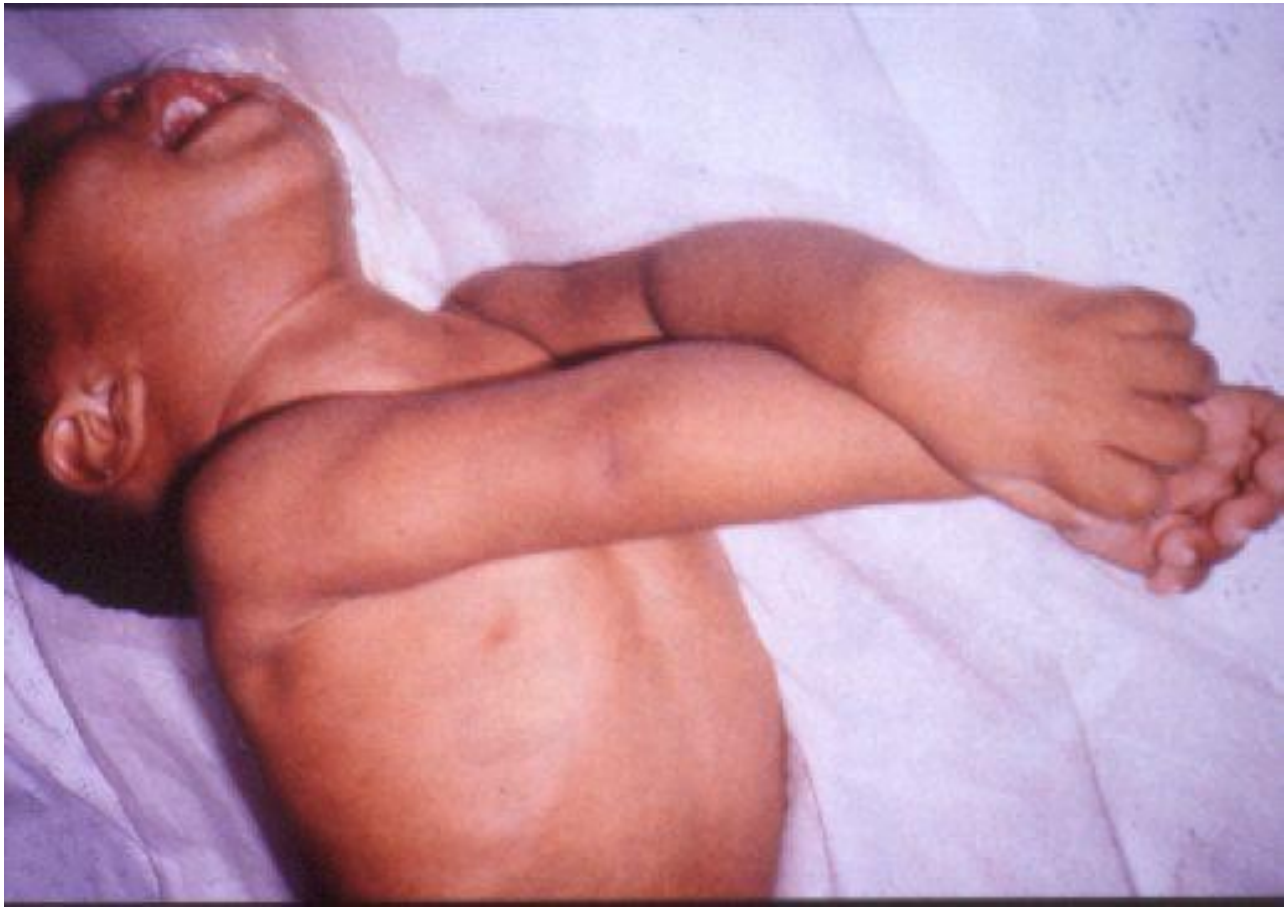
- Massive number of T.bacilli released into blood stream ,disseminated to distant sites (liver,spleen,skin and lungs).
- Usually complicate the primary infection 2-6 months of initial infection
- Most common in infants and young children, it is also found in adolescents and older adults
- Most common in malnourished and immune compromised
- Onset is insidious ,fever,anorexia ,wt loss ,generalized lymphadenopathy ,hepatosplenomegaly, late pulmonary signs
- Radiological findings are diagnostic
- 20-40% may have meningitis
- Tuberculin test is negative in 40 % of cases

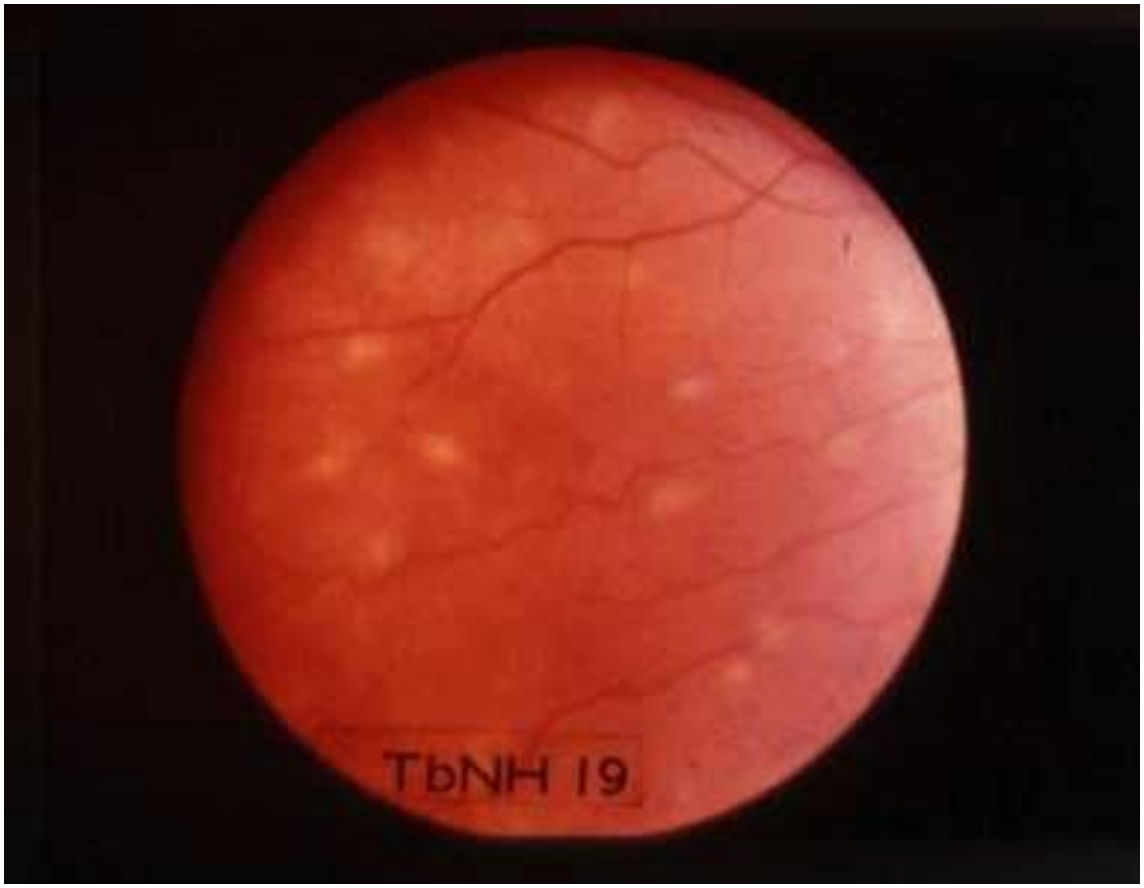


TB meningitis

- The most serious complication of TB,it is fatal without treatment
- Age : Most common age - 6 months to 4 years.
- Insidious in onset, but may be acute
- Presents with fever ,headache ,irritability ,drowsiness nuchal rigidity ,convulsion ,hypertonia ,cranial nerve palsy ,communicating hydrocephalus ,coma
- Tuberculin test negative in 50% ,CSF protein is high with low CSF sugar,↑cells mainly lymphocytes.

TB Meningitis





- **optic funds shows patches due to localised tuberculous lesions in the choroid.seen in cases of TBM and miliary TB.**

Tuberculosis of the spine – "Pott's disease"

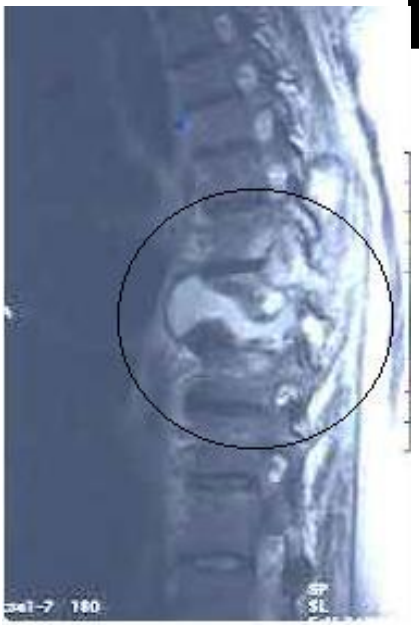
TB commonly affects the spine, especially in young children, and usually presents as a **swelling** on the back.

The **lower thoracic** and the **upper lumbar vertebrae** are the usual sites, however any vertebra can be affected.

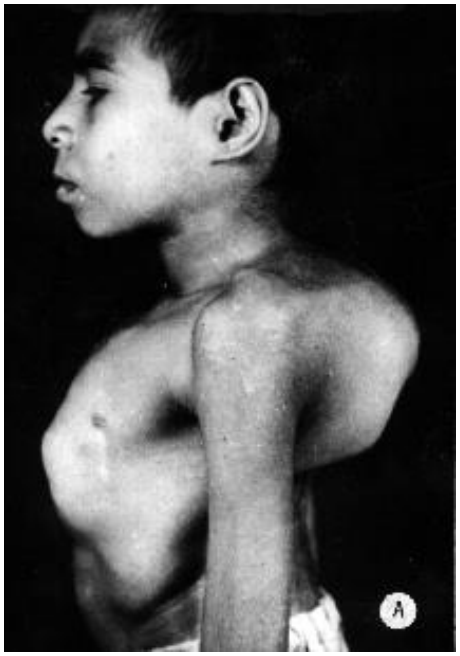
The patient may also present with **kyphosis, scoliosis, kyphoscoliosis**, or features of spastic paraparesis. There may be a sharp angulation of the spine caused by collapse of a vertebra – referred to as a **"gibbus"**

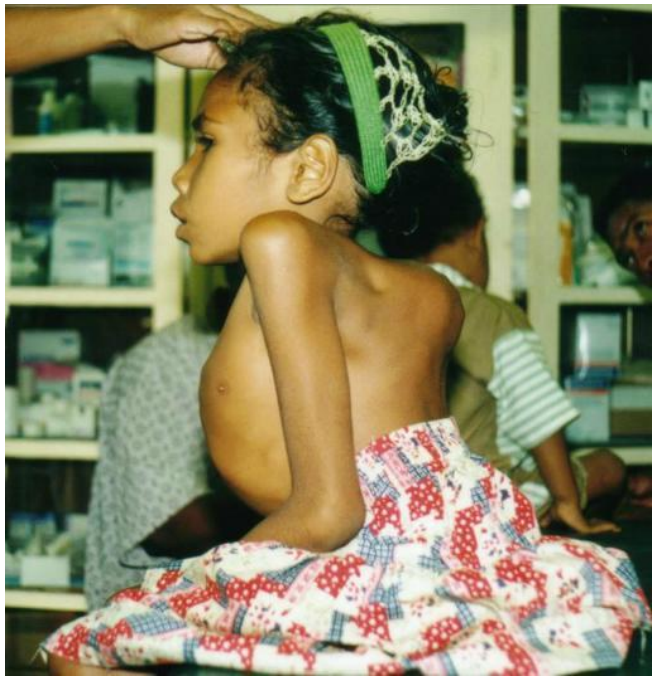
A young child with swelling over the lower thoracic vertebrae.

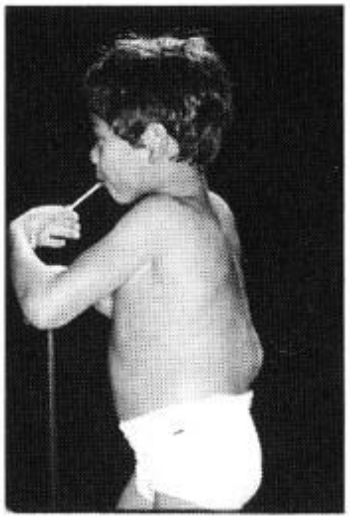
Pott's disease



Destroyed vertebrae with Cold Abscess

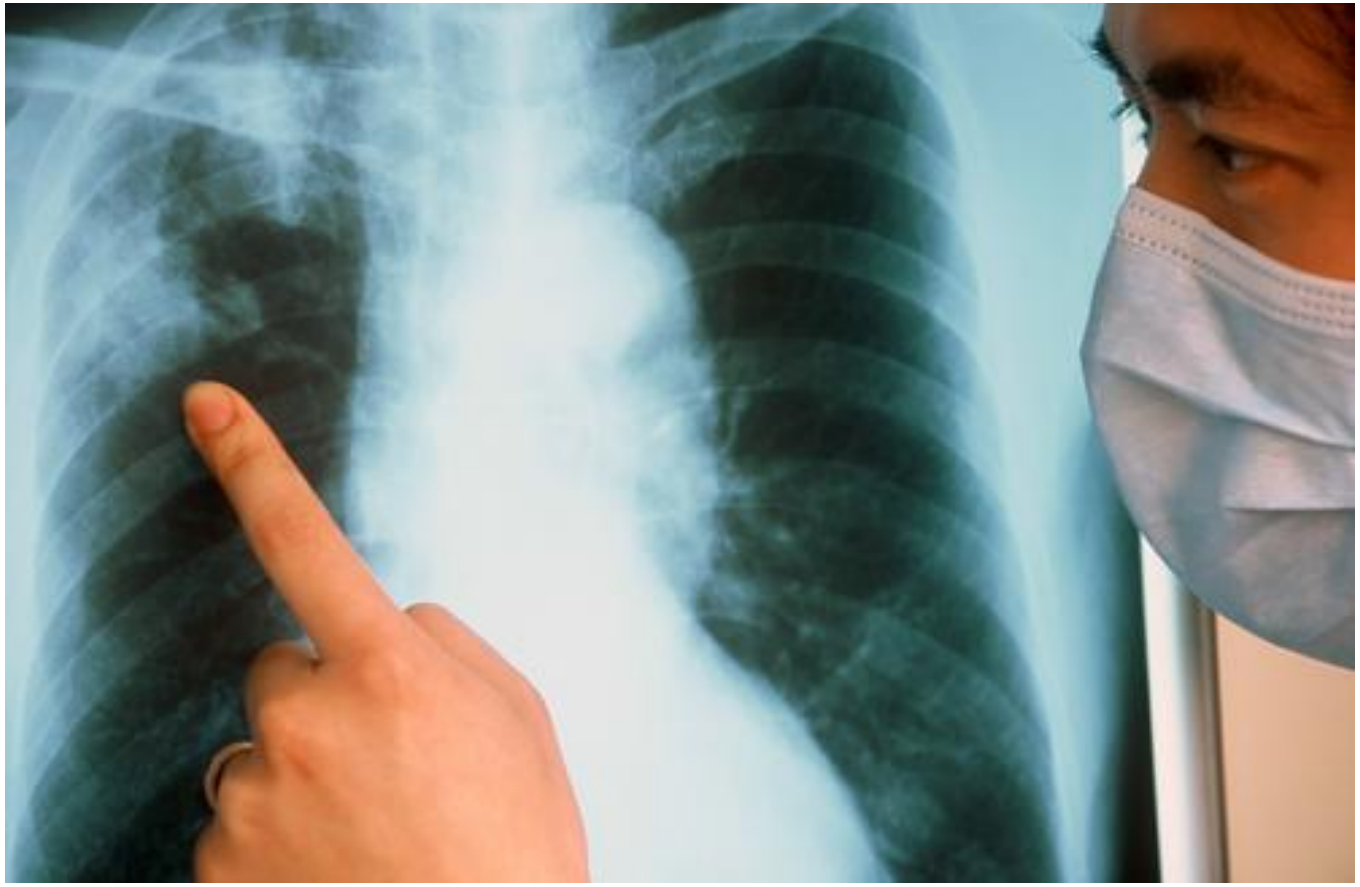




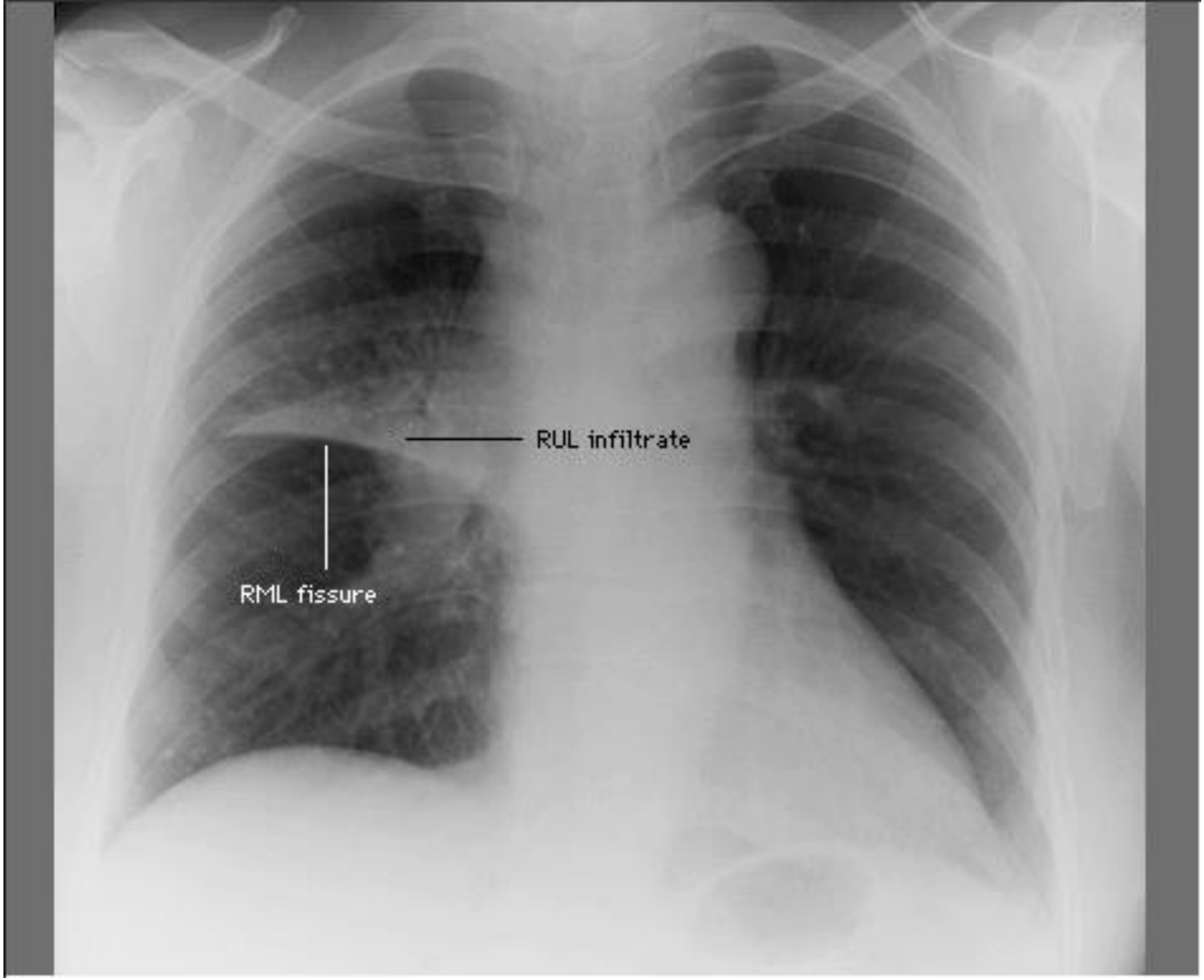


Post-primary TB / Secondary TB

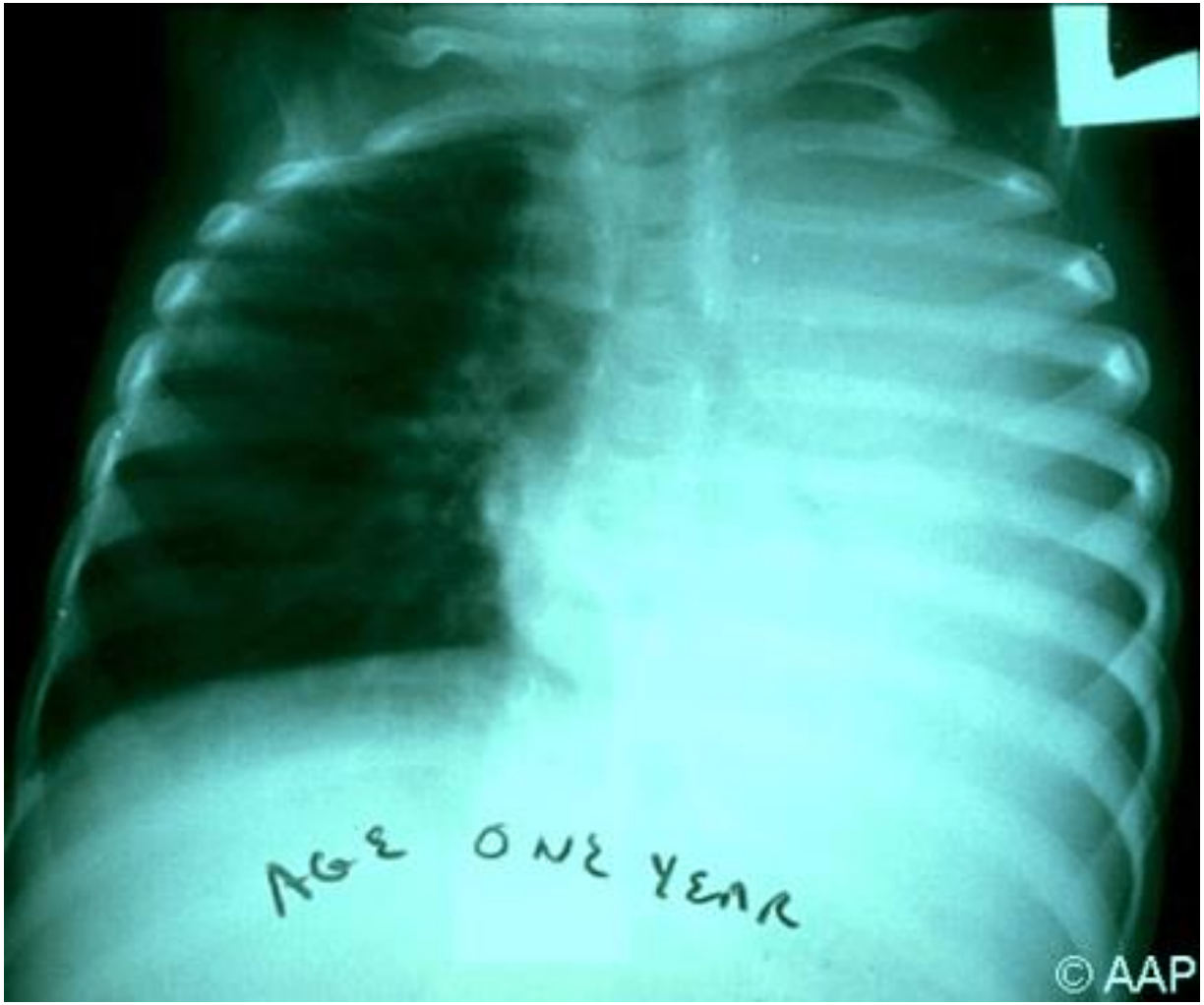
- Post-primary TB is the pattern of disease that occurs in a **previously sensitised host**, uncommon in children (usually adult or sometimes older children). It occurs after a latent period of months or years after primary infection. It may occur either by reactivation of latent bacilli or by reinfection.
- In a small number of cases it occurs as a progression of primary infection. Following primary infection, rapid progression to intra-thoracic disease is more common in children than in adults.
- Post-primary TB **usually affects the lungs** but can involve any part of the body. The characteristic features of post-primary PTB include **upper lobe involvement with cavitation** and extensive lung destruction. Sputum smears are usually positive and there is usually no intrathoracic lymphadenopathy.

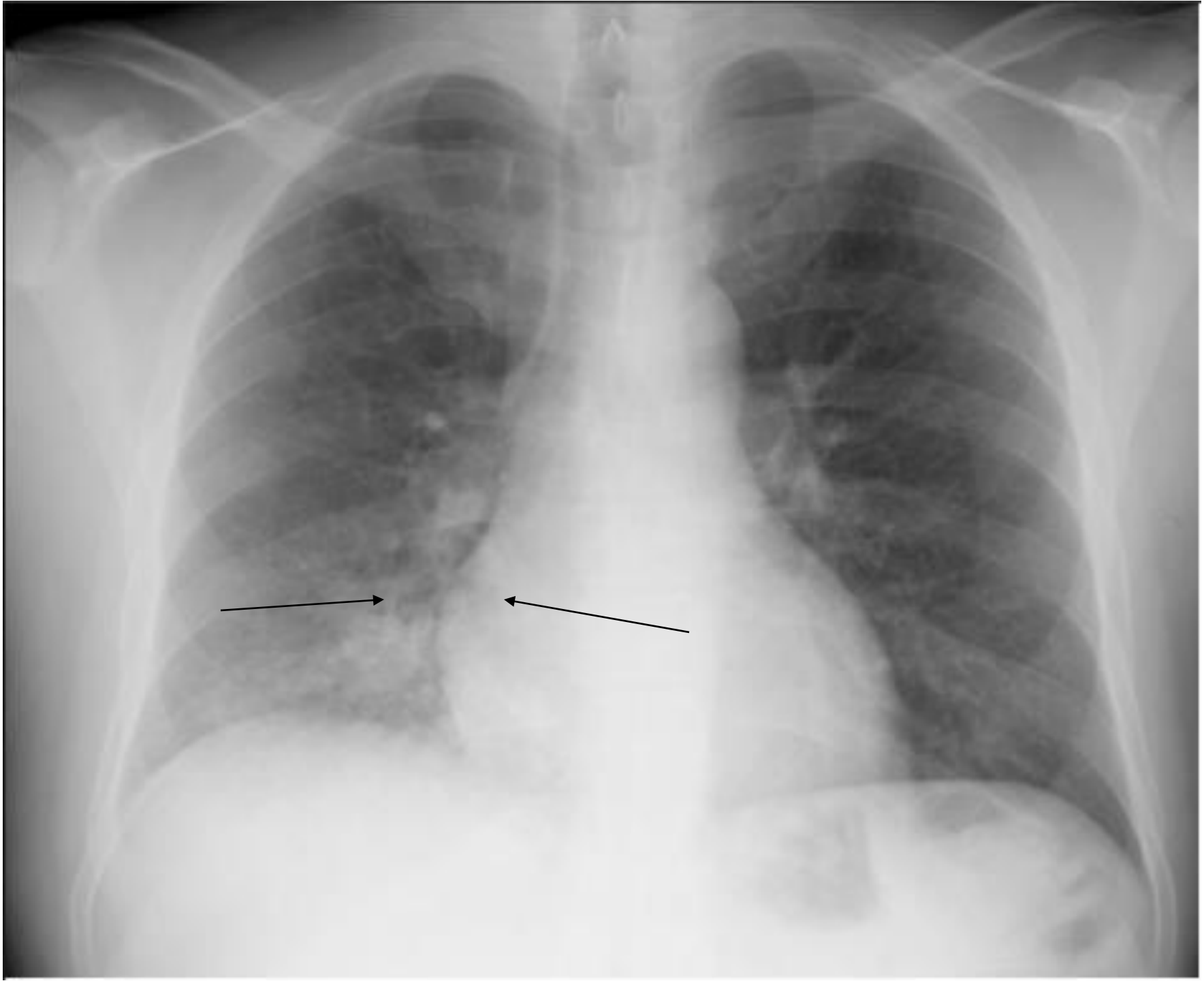


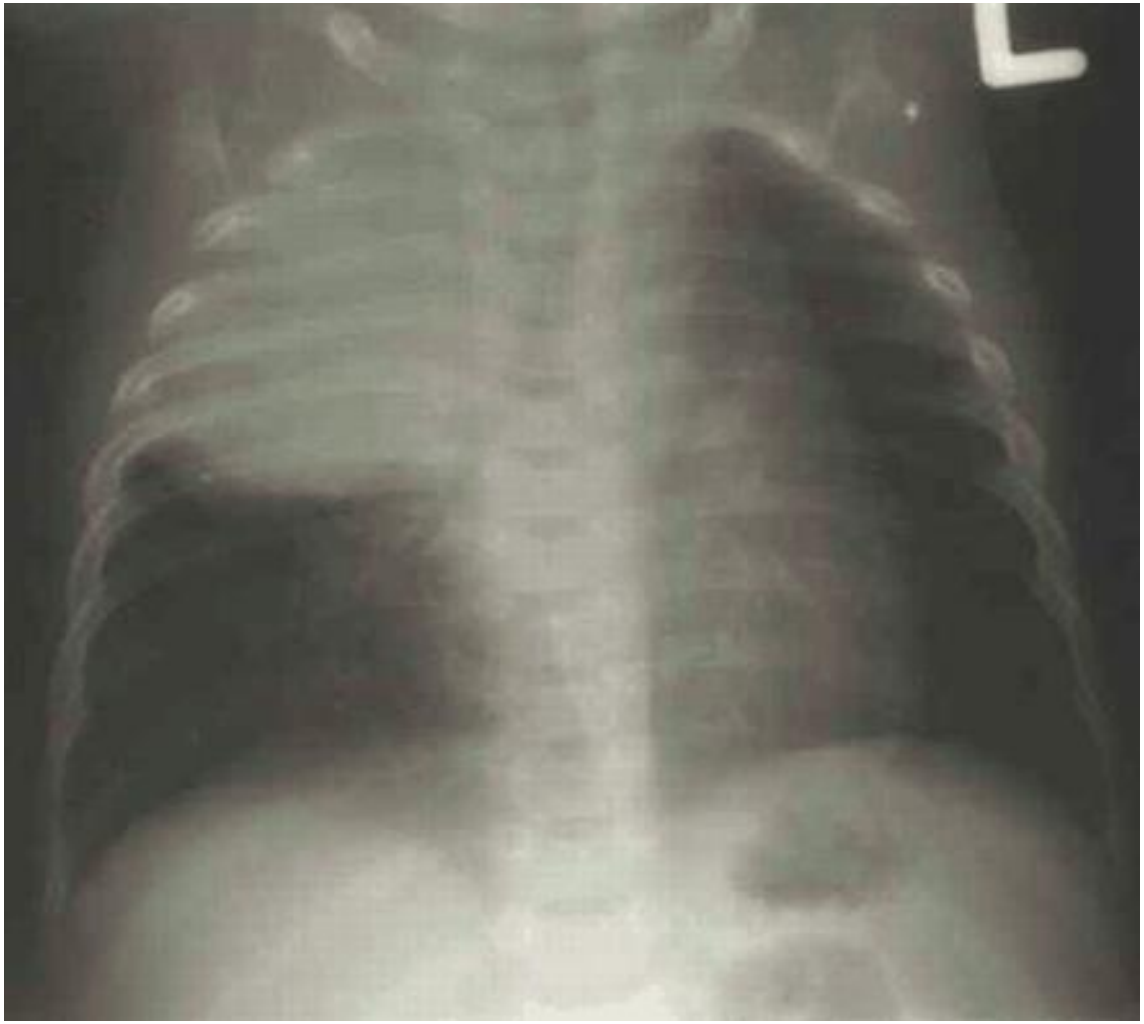
Upper lobe changes on CXR


RUL infiltrate
RML fissure

A 1-year-old with endobronchial TB with pulmonary consolidation.

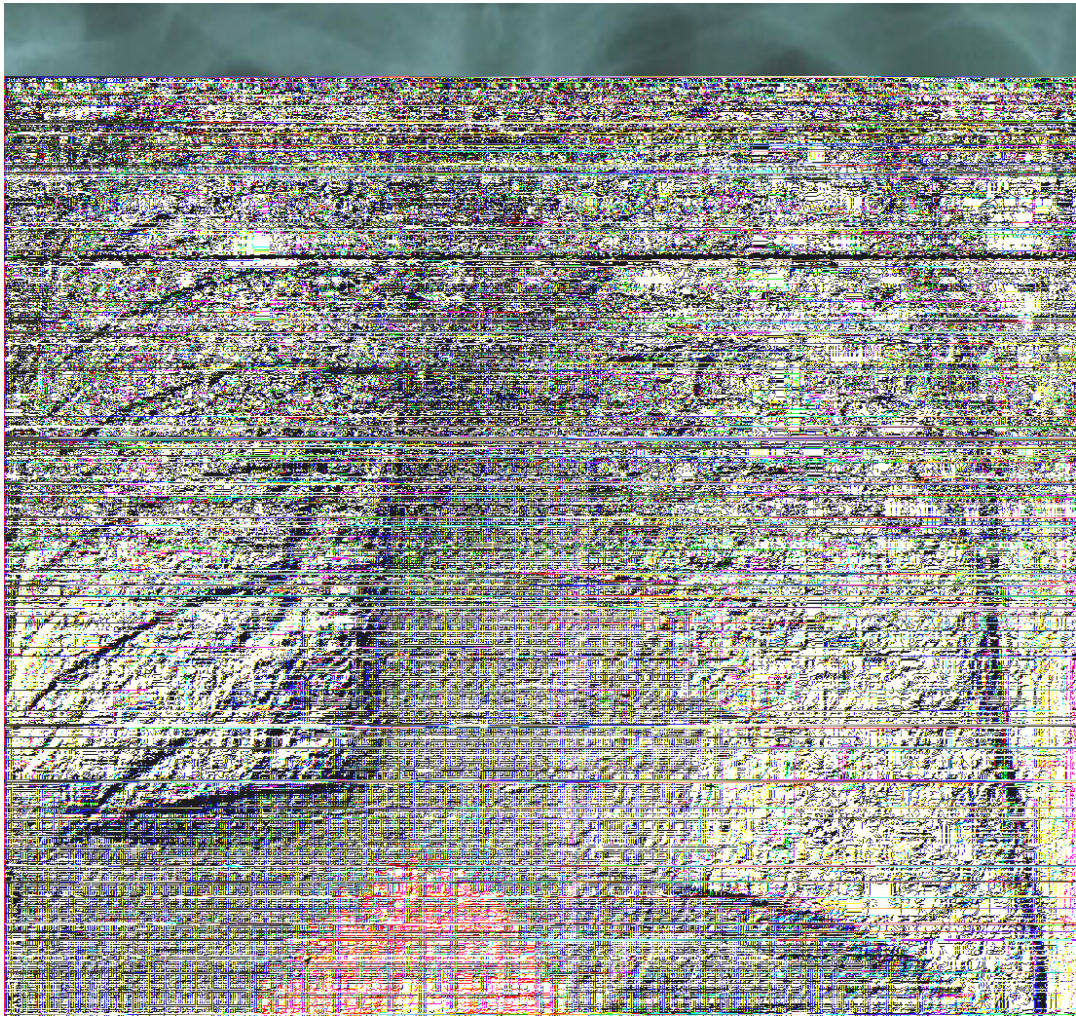






3 mo old with TB. CXR—RUL consolidation..

Primary pulmonary TB with pleural effusion (right lung). The possibility of TB should routinely be considered in children with a pleural effusion



Pericardial Disease

- The most common form of cardiac TB.
- symptoms are nonspecific, including :

✓ low-grade fever,

✓ malaise,

✓ weight loss.

Diagnosis

- **Childhood TB diagnosed by Combination of :**
  - **Contact with infectious adult case**
  - **Symptoms and signs (may be absent)**
  - **Suspicious CXR**
  - **Positive tuberculin skin test.. ±**
  - **Bacteriological confirmation**
  - **Molecular diagnosis**
  - **Others**

Diagnosis: Skin tests
Mantoux test & c-TB test

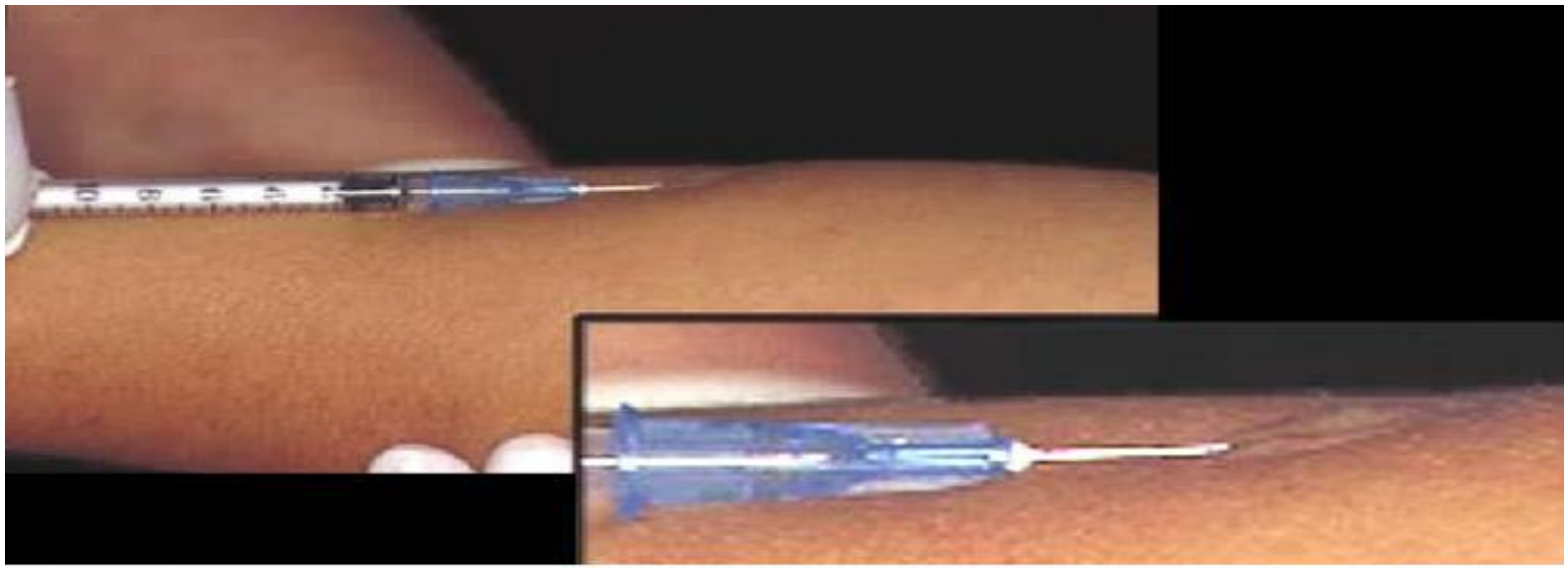
Mantoux test

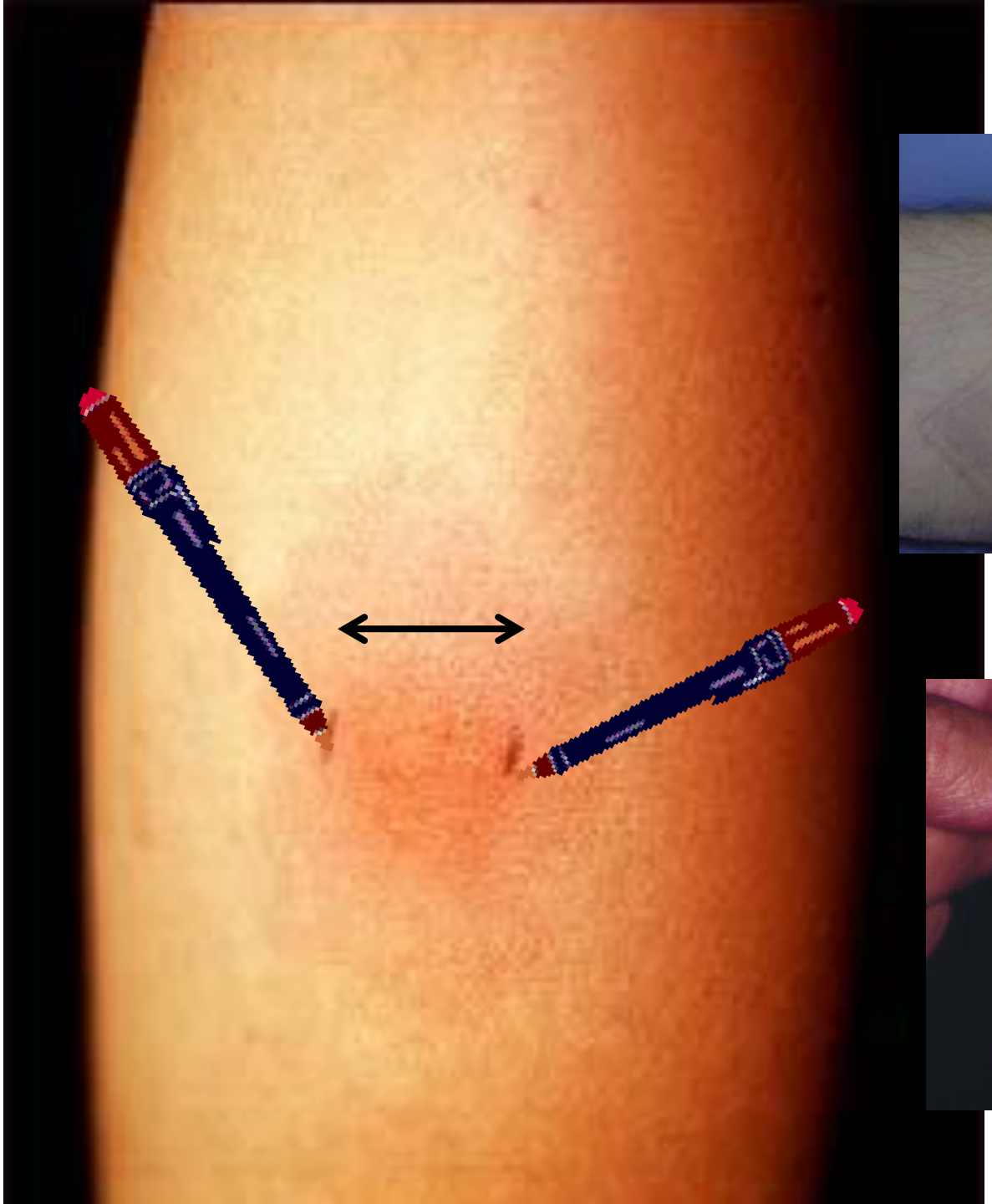
- This test detects a delayed hypersensitivity, cutaneous reaction to a **purified protein derivative (PPD) of *M. tuberculosis***
- PPD is injected **intradermally**
- the reaction is read at **48-72 hours**
- **erythema and induration** at the injection site signifies previous exposure to mycobacteria
- A positive test signifies that the individual has been **exposed to mycobacteria** but does **NOT necessarily mean TB disease**.
- In general, the greater the degree of erythema and induration, the more likely the patient has TB disease.
- A common difficulty is the **interpretation** of the degree of **erythema and induration**t

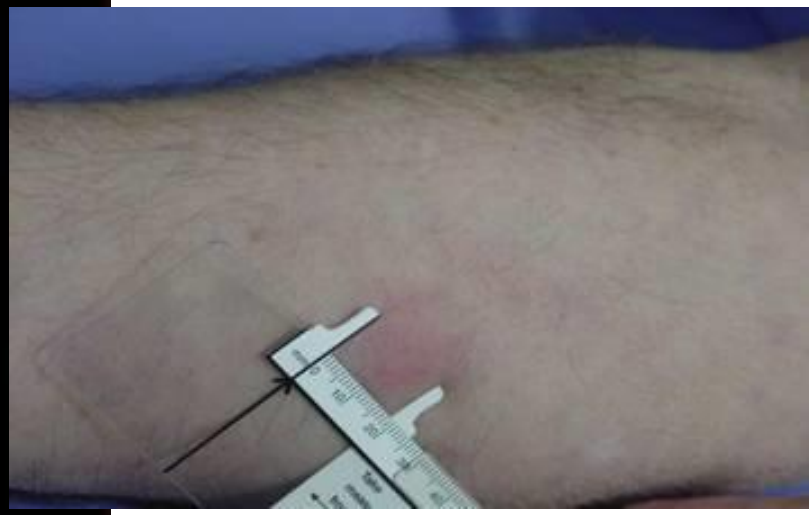
Diagnosis: Tuberculin Skin Test (TST)

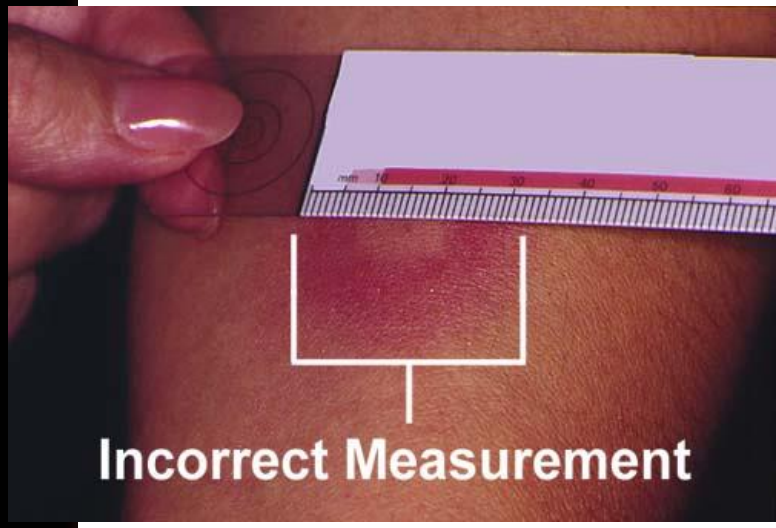
- 5 tuberculin units of purified protein derivative (PPD)

intradermally on the volar surface








Incorrect Measurement

Diagnosis: TST interpretation

- Read induration (not erythema) at 48-72^{o}
  - transverse to the long axis of the arm
- Measure only induration
- Record reaction in millimeters
- Self interpretation is unacceptable
- + tests sometimes persist for several wk

Positive PPD defined (infants, children, adolescents)

- **Induration ≥ 5 mm**
  - Children in **close contact** with known/suspected case of TB
  - Children **suspected** to have TB
    - CXR findings
    - Clinical findings c/w TB
  - Children receiving immunosuppressive Tx or with immunosuppressive conditions (e.g. HIV)

Positive PPD defined (infants, children, adolescents)

- **Induration ≥ 10 mm**
  - Children at inc. risk of disseminated Dz
    - < 4 y/o
    - Those with Hodgkin's, lymphoma, DM CRF, malnutrition
  - Children w/ increased exposure (travel, country of origin, exposure to high-risk adult)

Positive PPD defined (infants, children, adolescents)

- **Induration ≥ <u>15 mm</u>**
  - Children > 4 y/o with no risk factor (i.e. all patients)

Diagnosis: TST interpretation (negative test)

- Negative TST does not r/o TB
  - 10% of normal children with culture confirmed TB do not initially react

Factors that May Affect the Skin Test Reaction

Type of Reaction	**Possible Cause**
False-positive	Nontuberculous mycobacteria
	BCG vaccination
False-negative	Recent TB infection
	Very young age (< 6 months old)
	Live-virus vaccination
	HIV infection, malnutrition and also overwhelming TB

Interferon-γ Release Assays (T-SPOT.TB & QuantiFERON TEST)

The QuantiFERON-TB Gold test (QFT-G) and T-SPOT.TB are whole-blood test for use as an aid in diagnosing *Mycobacterium tuberculosis* infection, including latent tuberculosis infection (LTBI) and tuberculosis (TB) disease.

Advantage

- Requires a single patient visit to draw a blood sample.
- Results can be available within 24 hours.
- Is not subject to reader bias that can occur with TST.
- higher specificity compared with the TST , **not affected by prior BCG vaccination, or Nontuberculous mycobacterial** disease

Obtaining Clinical Samples

- Sputum samples rarely can be produced below 8 years old
- First morning gastric aspirates x 3

Diagnosis: Sputum examination

- **Gastric washings examined for AFB:** Carried out in children as they swallow rather than cough-up sputum. The test aims to recover the swallowed AFB from the stomach. Test positive in only about one third of children with TB.

- **Sputum microscopy**: Smear stained with the Ziehl-Nielsen stain to demonstrate the presence of the acid and alcohol fast bacilli (AFB). When positive, patient is referred to as “smear-positive” or “open TB” and risk of transmission of infection to others is very high. However, the test often negative in patients with TB. Yield is higher in patients with lung cavities.

- **Sputum culture**: Takes about 6-8 weeks and so is of limited use in clinical diagnosis. *M. tuberculosis* grows on a special medium.

- **Molecular testing ,** quick and accurate diagnostic test with better sensitivity for the diagnosis of pulmonary tuberculosis in children

Molecular testing

-polymerase chain reaction [PCR])

- The sensitivity varied from 25-83%, and specificity has varied from 80-100%.
- A negative PCR result never eliminates the diagnosis of tuberculosis, and the diagnosis is not confirmed by a positive PCR result (false positive)

-Xper MTB / RIF (GeneXpert)

Diagnosis: Other investigations

Other investigations are indicated depending on the organs/ systems affected by the disease

- Lymph node aspirate or biobsy (microscopy **,** GeneXpert , culture , cytology or histology)
- Lumbar puncture for cerebrospinal fluid analysis in TB meningitis (microscopy, GeneXpert biochemical analysis and culture)
- Spinal radiographs in Pott’s disease

Definitions

- TB exposure: a child with a negative PPD or interferon gamma release assay (IGRA), negative CXR, and normal exam who has been in contact with an adult with contagious TB
- (Latent) TB infection (LTBI): positive TST or IGRA in a child with a negative CXR and normal physical examination
- TB disease:

[Contagiousness/Isolation]

- Children < 12 years are rarely contagious
  - Pulmonary lesions are small
  - Cough is not productive
  - Little expulsion of bacilli

Therapy for:

- Latent TB infection (LTBI)
- TB disease
  - Pulmonary Disease
  - Extrapulmonary
  - Meningitis

Directly Observed Therapy (DOT)

- DOT is the watching of the ingestion of anti-TB medications by a trained outreach worker or healthcare worker
- DOT **cannot** be administered by a family member
- 2 *or* 3 x weekly regimens are employed:
  - Doses for all medications are higher than for daily dosing regimens

LTBI treatment

- **Isoniazid alone, daily for 6 or (9) months** .
- 3-months regimen of weekly rifapentine plus isoniazid
- 3–4 months of daily isoniazid plus rifampicin
- 3–4 months of rifampicin alone

TB Treatment

- If TB is suspected, prior to receiving TB culture results, treatment must be initiated
- There are four first-line TB drugs, start with 3 or 4 drugs:
  - Isoniazid (INH)
  - Rifampin (RIF)
  - Pyrazinamide (PZA)
  - Ethambutol (EMB)
- Adjust regimen when drug susceptibility results are Known

Drug Doses

- isoniazid (H) – 10 mg/kg (range 10–15 mg/kg); maximum dose 300 mg/day
- rifampicin (R) – 15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/day
- pyrazinamide (Z) – 35 mg/kg (30–40 mg/kg)
- ethambutol (E) – 20 mg/kg (15–25 mg/kg)

Pulmonary TB

- 6 mo duration is now standard
  - 2 mo of INH + Rif + PZA ± EMB ----followed by
  - 4 mo of INH + Rif
    - Treatment is daily { or daily for 2 wk-2 mo and then 2-3x weekly **(by DOT only)}**

Treatment

Treatment should be started with a four-drug regimen in :

- High HIV prevalence area.
- High isoniazid resistance area
- extensive pulmonary disease

Treatment

Treatment can be started with a three-drug regimen in :

- Settings with low HIV prevalence ,and
- low resistance to isoniazid,and
- Children who are HIV-negative

Extrapulmonary TB

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

- **Bone and Joint TB, Miliary TB, or TB Meningitis** in Children **Treat for 12 months** with a **four-drug** regimen (HRZE) for 2 months, followed by a two-drug regimen (HR) for 10 months

Usual Pediatric Treatment Regimens

Diagnosis	Treatment
TB Infection	**INH – 6 Months**
TB Disease **3 or 4 drugs**	**First 2 months – INH, RIF, PZA± EMB** **Next 4 months – 2 most effective sensitive drugs (INH & RIF in pansensitive cases)**

Adjunctive therapy [Corticosteroids]

- **Indicated in TB meningitis** (↓ mortality and sequelae)
- Consider for pleural, pericardial effusions, miliary disease, endobronchial disease

- Prednisone 1-2mg/kg/day [or its equivalent] (max 60 mg/kd/day)

  x 6-8 wk

Prevention and Control

TB Control Strategies include –

- **Case finding:** aims to identify TB cases promptly and treat them with effective drugs.
- **Contact tracing:** Close contacts of TB cases are screened for evidence of infection. Mantoux positive cases are treated to prevent them from developing the disease.
- **BCG vaccination:** Although the efficacy of BCG vaccination in protecting against TB is controversial, it is generally accepted that BCG is more effective in preventing disseminated disease and death, than pulmonary TB.

Current WHO recommendations

- All children irrespective of age need to be screened for TB disease after exposure to an infectious case of drug susceptible or drug resistant TB.
- If TB disease is excluded, all child TB contacts of less than 5 years of age receive prophylactic therapy with regular follow-up
- If TB disease is excluded, all HIV-infected child TB contacts irrespective of age should receive prophylactic therapy with regular follow-up

Summary

- TB infection in a child can progress rapidly to TB disease
- Diagnosing TB, particularly PTB, in children is difficult and should include the diagnostic elements discussed
- Not all children with TB disease have a positive TST and not all children with a positive TST and radiographic abnormalities have TB disease
- Attempts should be made to obtain and send sputum and/or other sample for AFB smear ,TB culture and molecular assay on children with suspect TB

Summary:

- The diagnosis of intrathoracic TB in symptomatic children with negative sputum smears should be based on:
  - A history of exposure to an infectious case
  - The presence of abnormalities consistent with TB on chest radiography
  - Evidence of TB infection (positive tuberculin skin test or interferon gamma-release assay), and
  - Clinical findings suggestive of TB

- Contact investigation is importance

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