TB in Children

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Block 10 Lectures

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Contents

- Epidemiology
- Transmission and pathogenesis
- Diagnosis of TB
- TB and HIV
- Management

Epidemiology

- The year 2000
  - 8.3 million new TB cases diagnosed
    - 11% (884 019) were children
  - Prevalence of TB varies greatly between countries
  - 75% of all diseased children reside in 22 high burden countries

BJ Marais, Intrathoracic Tuberculosis in children, Arch Dis Child Educ Pract Ed 2006;91:ep1-ep7.doi:10.1136/abc.2005.072876

Epidemiology

1.1 Global epidemiology and burden of disease

TB is still a major cause of death and disease worldwide with estimates[1] of 9.2 million new TB cases in 2006 and 1.7 million deaths, including 200,000 in clients co-infected with HIV. Even though the global epidemic is in decline with decreasing global TB prevalence and death rates, the total number of new TB cases is still rising due to population growth.

Africa is the only region to show huge increases in TB, from an estimated 162 per 100,000 population in 1990 to 363 per 100,000 population in 2006. Factors contributing to the increasing TB burden include:

- Poverty and rapid urbanisation.
- The impact of the HIV-pandemic.
- Poor health infrastructure.
- Poor programme management with inadequate case detection, diagnosis and cure.

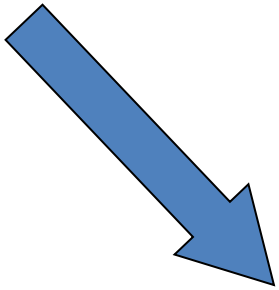
Amongst the 202 countries that report to the World Health Organisation (WHO), the 22 high burden countries accounted for 80% of TB cases. The average estimated incidence[1] of TB in the high burden countries in 2006 was 177 cases per 100,000 population compared to a global figure of 139 cases per 100,000 population. The TB incidence in Africa was higher, at 363 cases per 100,000 population and in South Africa it was a massive 940 per 100,000 population.

1.2 TB control in South Africa

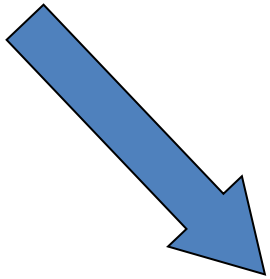
According to the WHO Global Tuberculosis Report 2008[1], South Africa had the highest TB incidence in the world, at over 5 times the average incidence rate found in the 22 high-burden countries. It had the 4th highest estimated total burden of TB for 2006, behind only India, China and Indonesia, countries with much larger populations. In 2006, South Africa with only 0.7% of the world's population had an estimated 28% of HIV positive adult TB cases reported globally. On a more positive note, revised estimates suggest that the 70% case detection rate target was reached in 2006.

National TB Control Programme data shows that over the last five years TB case notification has increased by a massive 81%, from 188,695 cases in 2001 to 341,165 in 2006. In 2006, Kwa-Zulu Natal had the highest total TB caseload accounting for 31% of all TB cases nationally.

Exposure



Infection



Disease

How does tuberculosis enter the body and cause disease?

- You breathe it in *(exposure);*
- It sticks in your lungs;
- It starts to grow *(infection);*
- It spreads to the lymph fluid and blood;
- It settles in other parts of the body;
- It goes to sleep;
- It reawakens *(disease).*

TB Terms

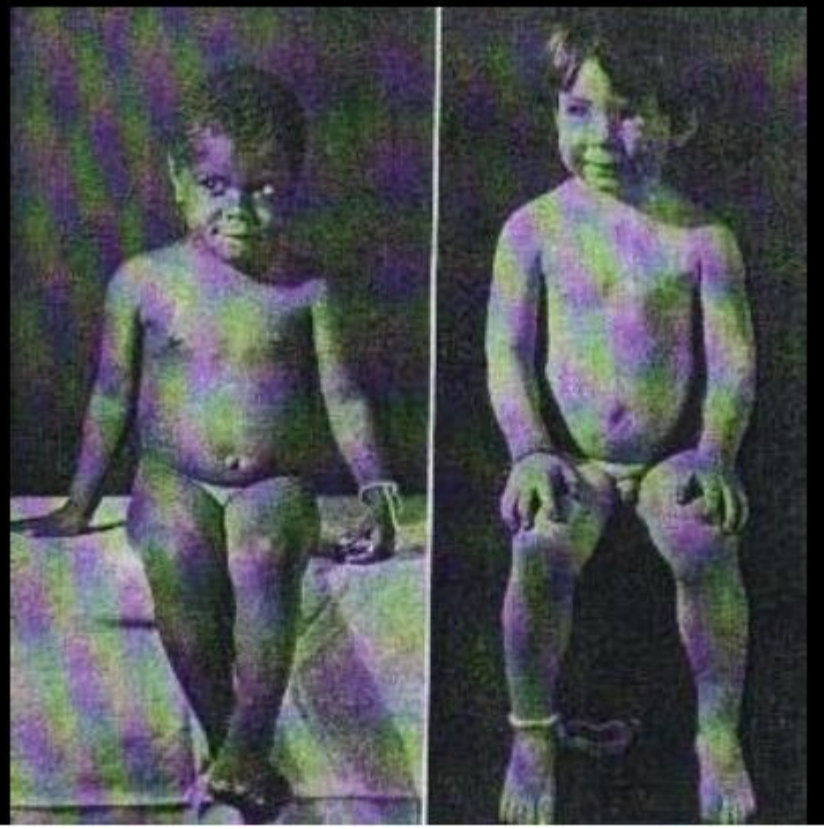
- TB Infection
  - Child inhales TB organism.
  - Diagnosed when TST is positive & child asymptomatic
  - Not all cases of exposure will result in disease

11.1.1 Diagnosis of tuberculous infection

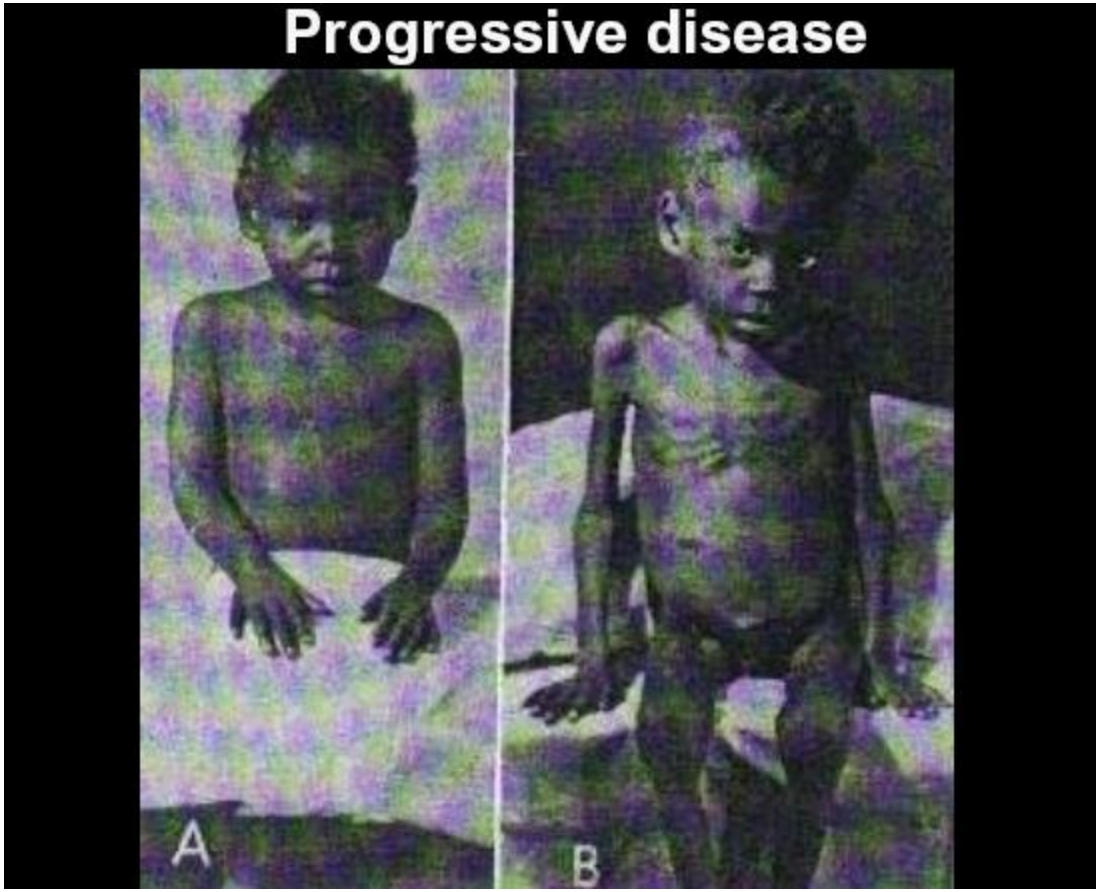
A child that has been infected by TB develops a positive tuberculin skin test (TST). It takes between 6 weeks and 3 months after exposure for a positive TST to develop. Children with tuberculous infection are asymptomatic. Most children have an immune system that is strong enough to prevent the infection from progressing to disease.

The TST measures the hypersensitivity to tuberculin purified protein derivative (PPD). A positive tuberculin test does not indicate the presence or extent of tuberculosis disease; it only indicates TB infection.

Infection without disease



Progressive disease

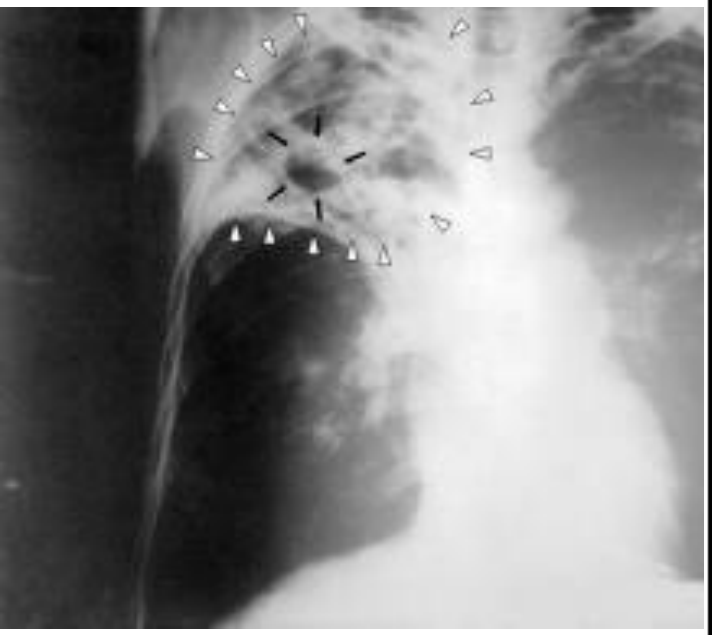


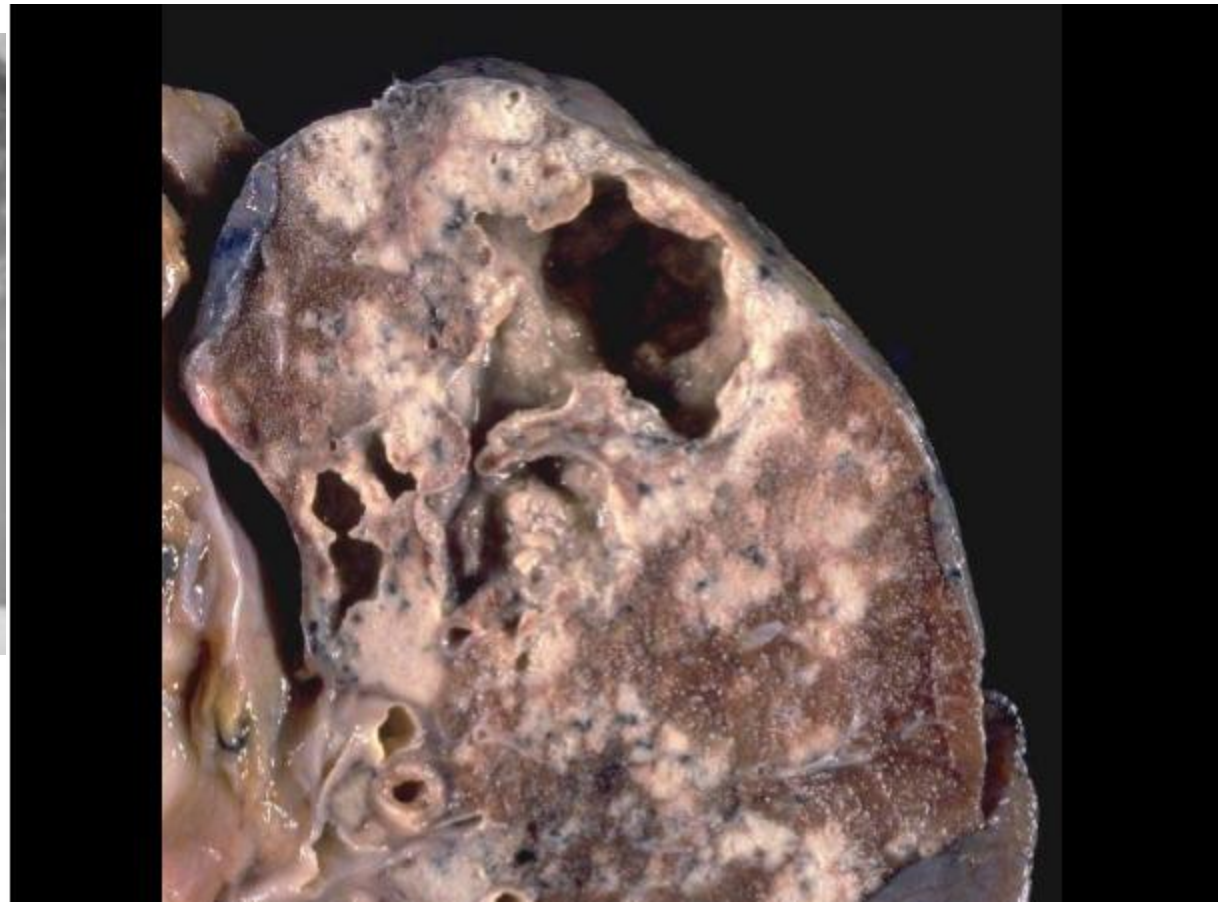
Transmission

- Droplets
- Aerosols
  - 1 – 5 um
- Needs to reach the alveoli…

Contact

- Adult who is sputum AFB positive

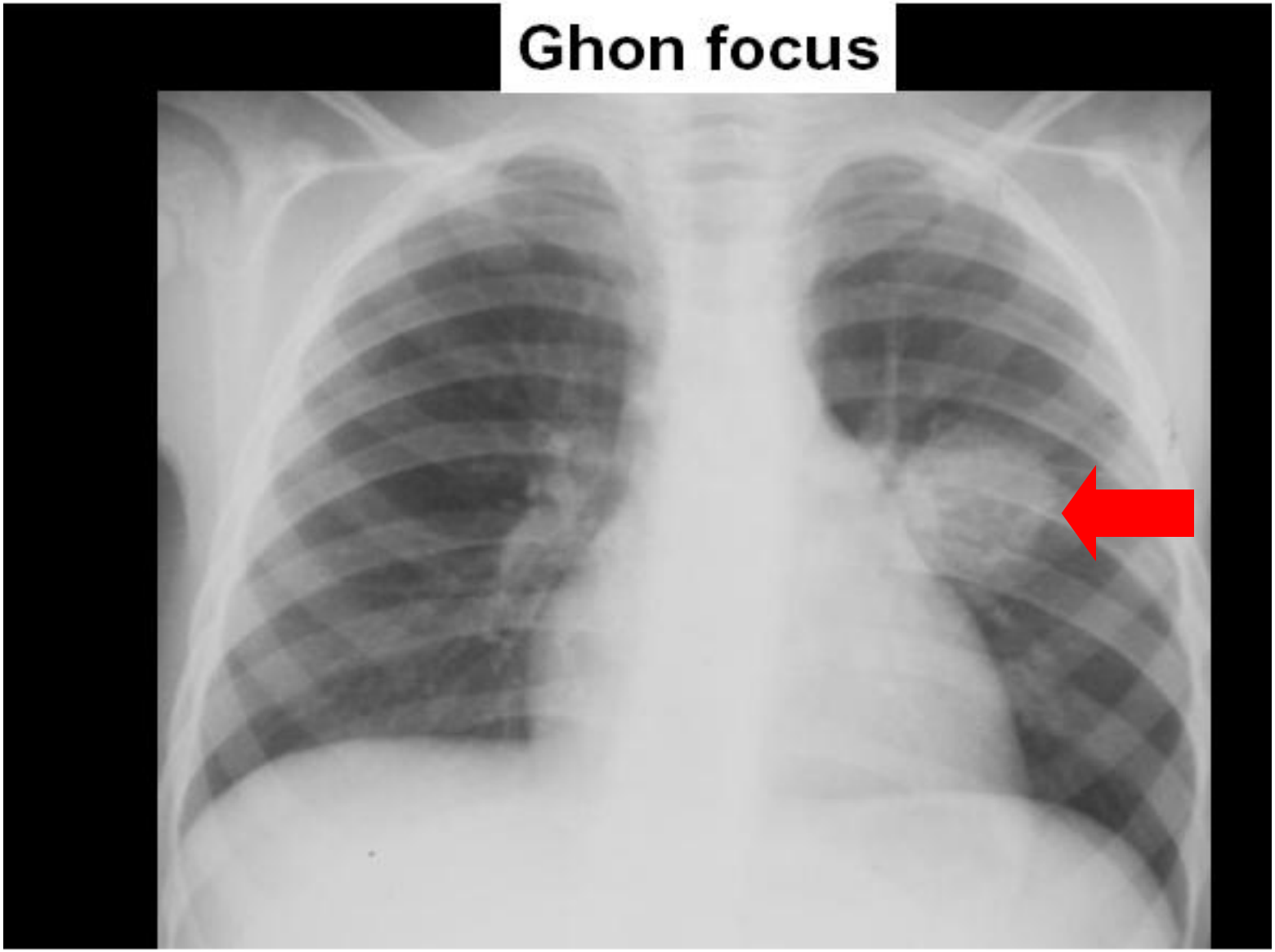




Pathogenesis

- Uninfected person inhales an infectious droplet
- Ghon Focus: Primary pulmonary infection (localized pneumonic process)
- Bacilli drain via local lymphatics to regional lympnodes. (GF + pleural reaction + local lymphangitis + regional LN involvement)
- Primary Ghon Complex (Latent)

Ghon focus



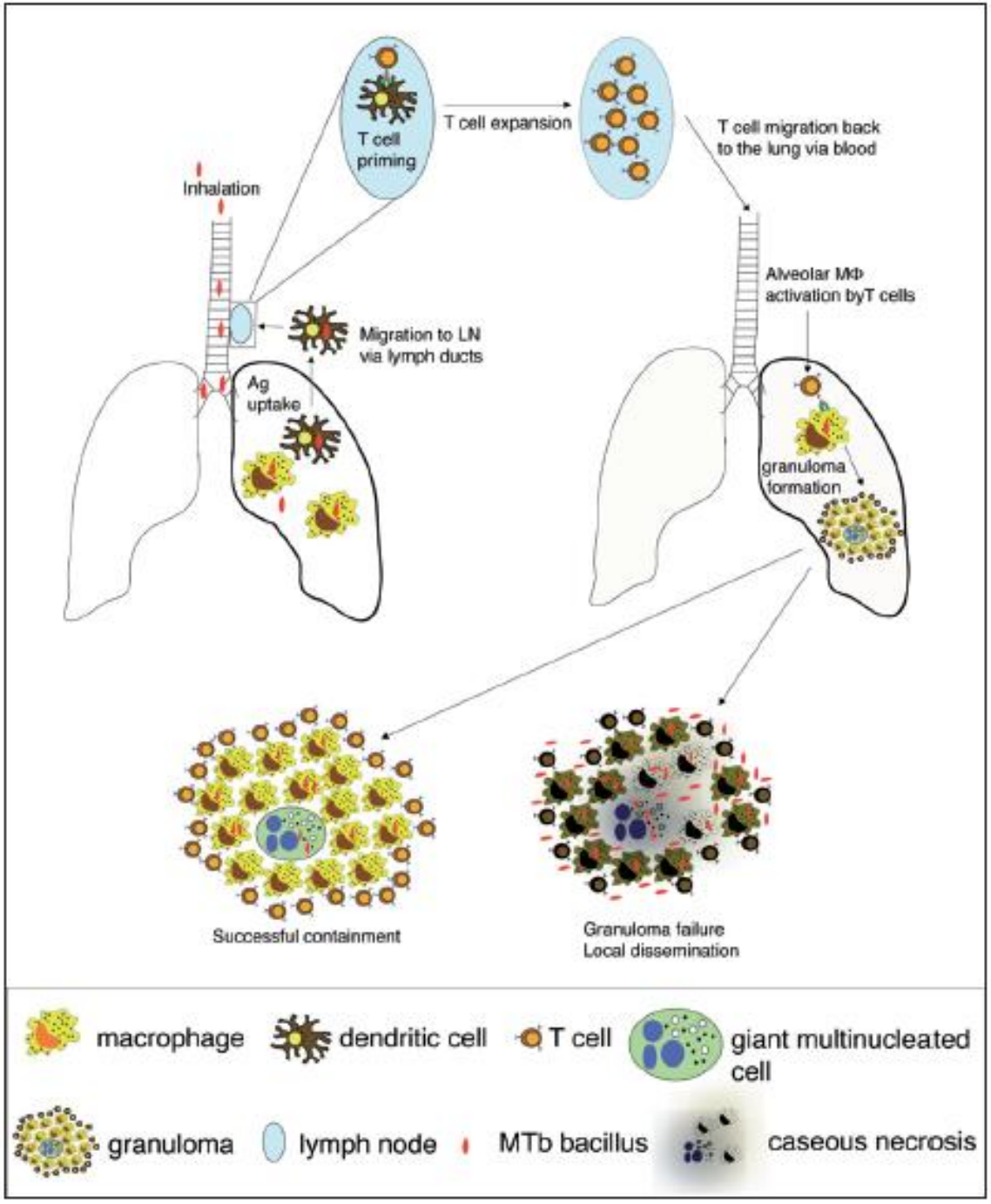


Fig. 1. Events that follow infection with M. tuberculosis. Following inhalation of the bacillus, alveolar macrophages ingest the pathogen. Dendritic cells ingest M. tuberculosis either directly or via ingested dying, infected macrophages. Activated dendritic cells migrate to the draining lymph nodes where naïve mycobacteria-specific T cells are primed to differentiate into antigen-experienced cells. These T cells expand and migrate to the site of infection, the lung, via the blood. In the lung, T cells further activate macrophages and induce the formation of granulomas. Successful granuloma formation and maintenance result in containment of the pathogen. Defective granuloma formation allows mycobacterial growth, and leads to cell death (caseous necrosis), permitting dissemination of bacilli.

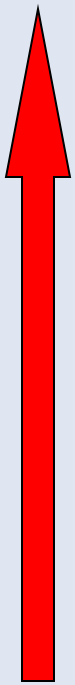
Infection

- The risk of infection increases with:
  - Long duration of exposure to infectious case
  - High intensity of exposure
    - Smear positive are the most infectious
    - Smear negative but culture positive are less infectious
    - Extrapulmonary cases are usually not infectious
  - Close exposure, where the mother or caregiver has active TB
  - Young Children
  - HIV infected children

Table I. Age-specific risk to progress to disease following primary infection with *M. tuberculosis* in immune-competent children*

Age at primary infection	Risk to progress to disease	
< 1 year	No disease	50%
	Pulmonary disease	30 - 40%
	Disseminated (miliary) disease or TBM	10 - 20%
1 - 2 years	No disease	75 - 80%
	Pulmonary disease	10 - 20%
	Disseminated (miliary) disease or TBM	2 - 5%
2 - 5 years	No disease	95%
	Pulmonary disease	5%
	Disseminated (miliary) disease or TBM	0.5%
5 - 10 years	No disease	98%
	Pulmonary disease	2%
	Disseminated (miliary) disease or TBM	< 0.5%
> 10 years	No disease	80 - 90%
	Pulmonary disease	10 - 20%
	Disseminated (miliary) disease or TBM	< 0.5%

*Adapted from Marais *et al.*[2]
TBM = tuberculous meningitis.



Disease

- TB disease
  - 10% of children who have been infected, will develop active disease
  - Present with symptoms

Disease

SYMPTOMS

- The commonest symptoms are chronic unremitting cough, fever, weight loss and unusual fatigue.
  - Chronic cough is a cough that has been present for more than 14 days and that is not improving, especially if the child fails to respond to a course of antibiotics (amoxycillin).
  - Fever of greater than 38^{0}C for 14 days after common causes like malaria or pneumonia have been excluded.
  - Children with weight loss, especially when documented on the "Road to Health" card should be investigated for TB. A child in a nutrition programme who fails to gain weight should also be investigated for TB.
  - Unusual fatigue: The child becomes less playful or complains of feeling tired.

Signs

Signs suggestive of TB disease:

- Fever, especially if present for more than 14 days without an obvious cause (such as malaria).
- Painless enlarged lymph glands, most commonly in the neck, that do not respond to a course of antibiotics.
- Other non-specific signs including night sweats, breathlessness (due to pleural effusion), peripheral oedema (due to pericardial effusion) or painful limbs and joints (due to erythema nodosum or dactylitis/inflammation of digits).

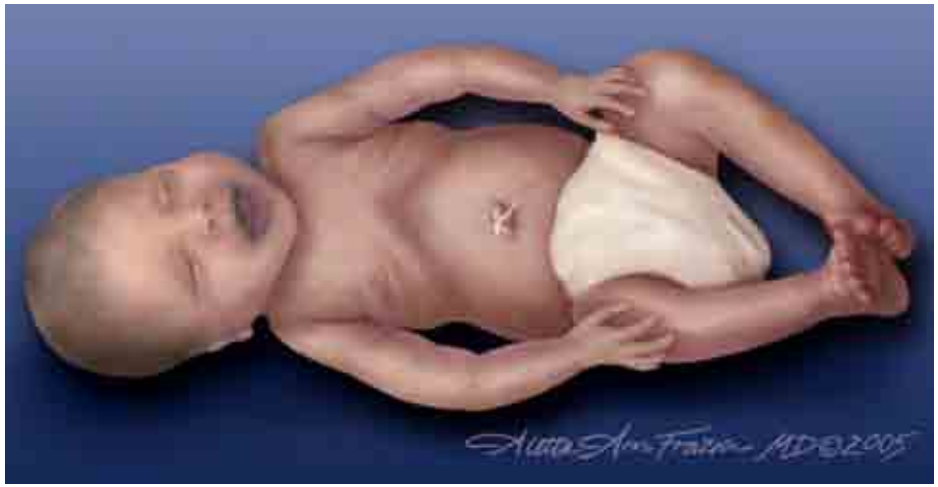
Danger Signs

Although TB in children is a chronic disease, there are **danger signs** that require immediate referral to hospital as they indicate serious, life-threatening forms of TB:

- Headache (especially if accompanied by vomiting), irritability, drowsiness, neck stiffness and convulsions (signs of TB meningitis)
- Meningitis not responding to treatment, with a sub-acute onset or raised intracranial pressure
- Big liver and spleen (signs of disseminated TB)
- Distended abdomen with ascites
- Breathlessness and peripheral oedema (signs of pericardial effusion)
- Severe wheezing not responding to bronchodilators (signs of severe bronchial compression)
- Acute onset of angulation (bending) of the spine.

Chronic Cough

"Don't step on it . . . it makes you cry."



Existing methods - Diagnosis PTB in children

- Difficult
- Clinical
- Radiological
- Immune diagnosis
  - Skin testing
- Culture confirmation

Clinical diagnosis PTB in children in high burden area

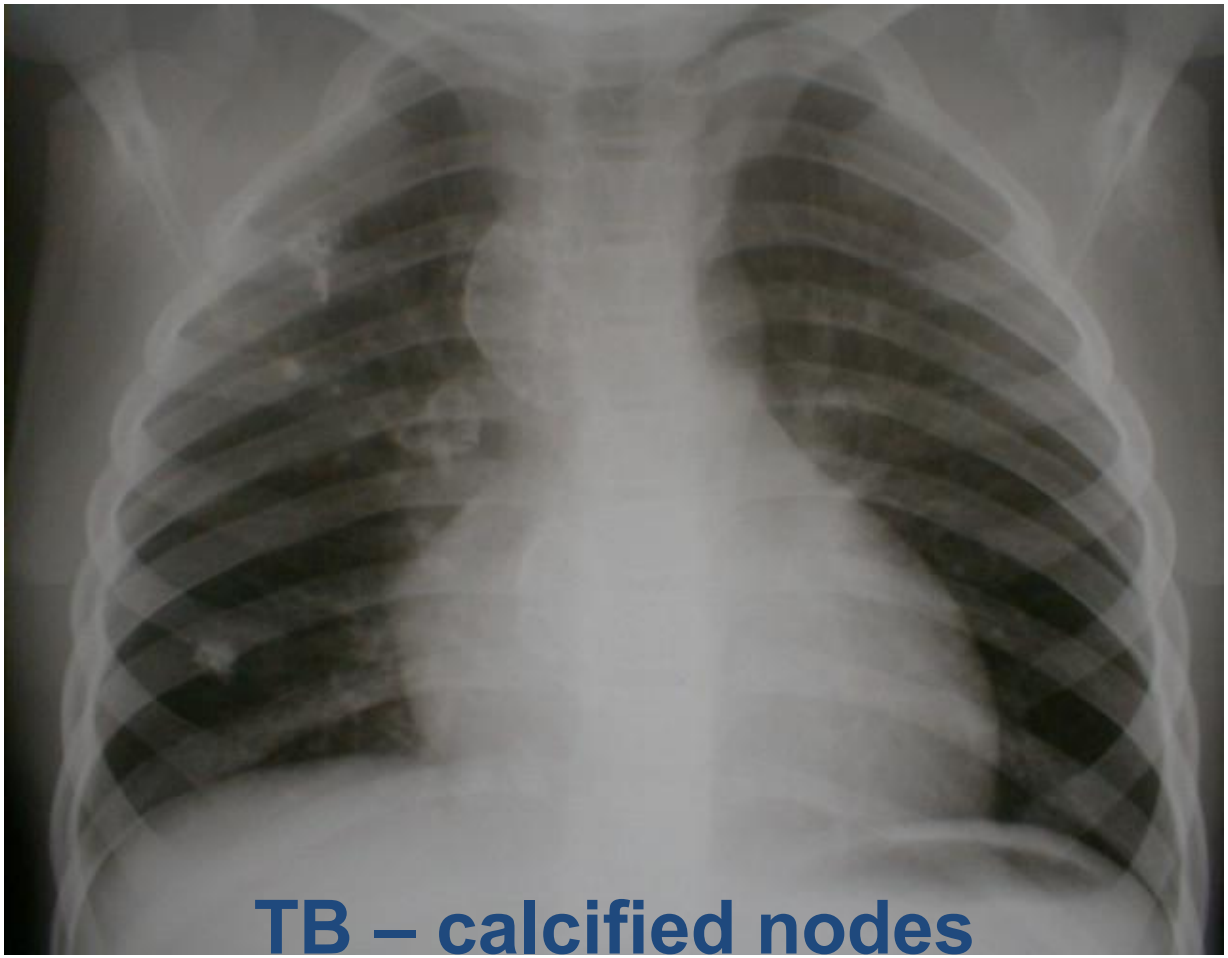
- Symptom based approach
  - Persistent, continuous cough > 2 weeks
  - Weight loss over preceding 3 months
  - Fatigue
  - Fever present for more than 14d
- Reasonable performance in HIV-uninfected, older than 3 yrs

Marais et al Pediatr 2006:118

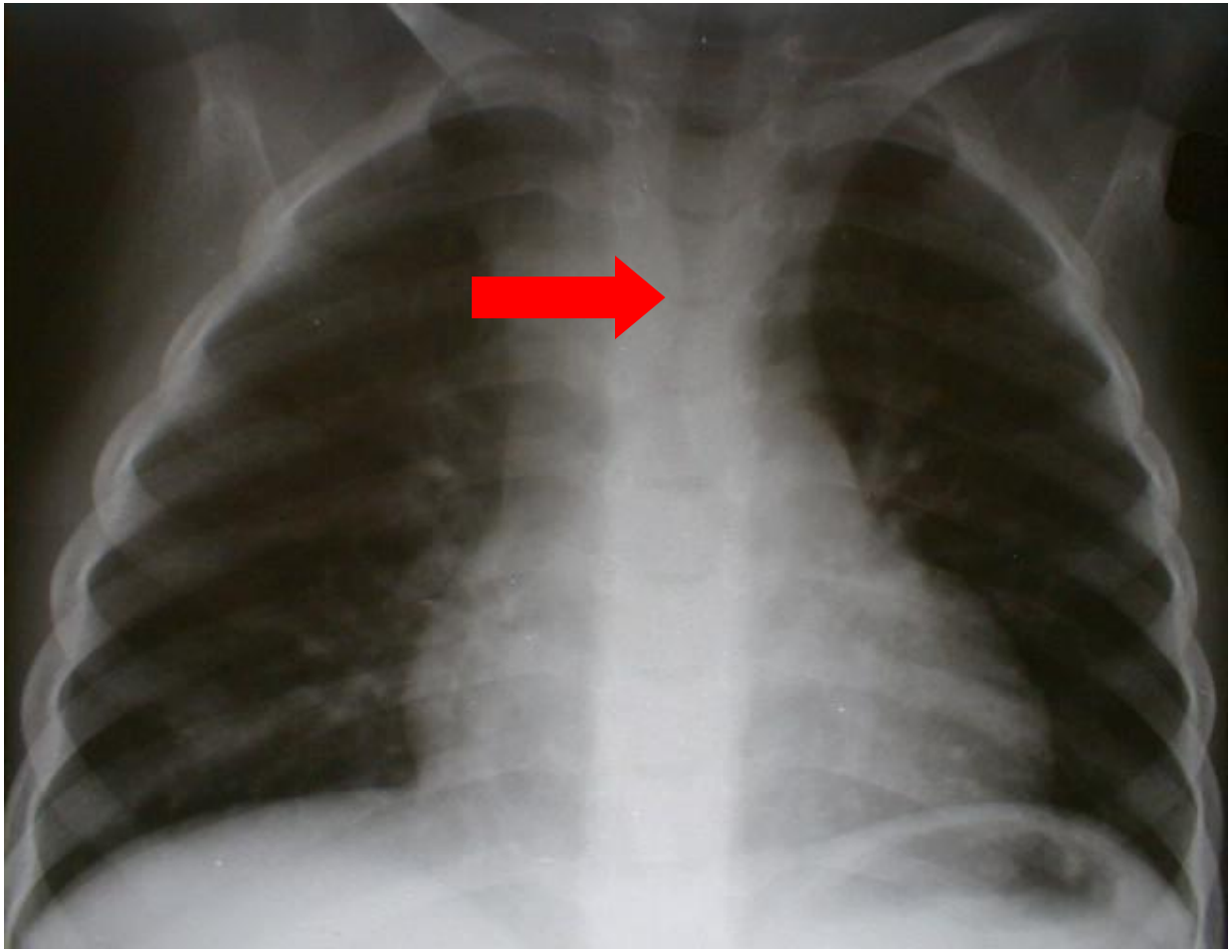
Radiological diagnosis

- Non-specific
- Suggestive – miliary pattern, hilar adenopathy, chronic consolidation, bronchial compression
- Hilar adenopathy – wide inter and intra-observer variation

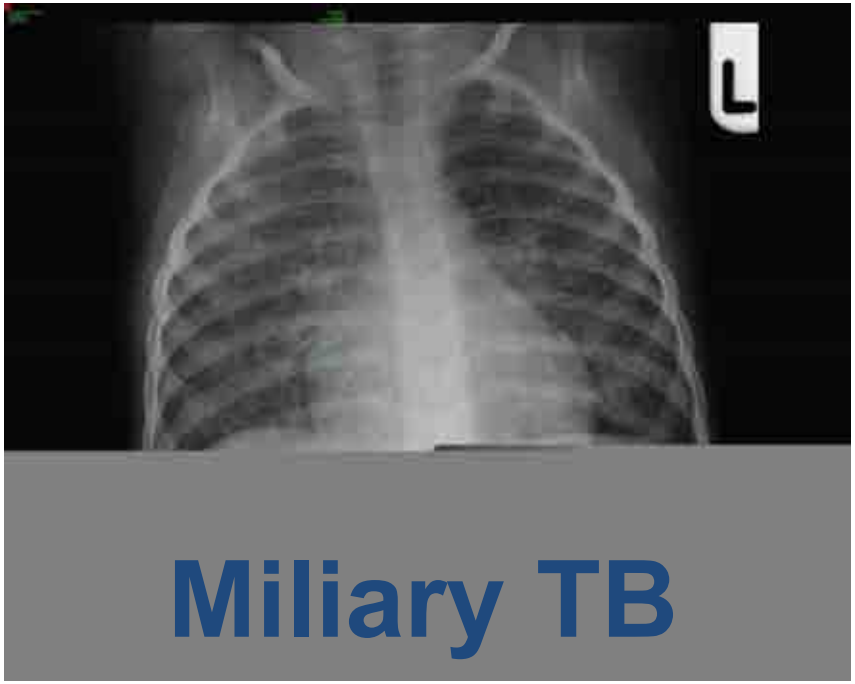
Radiological findings in TB

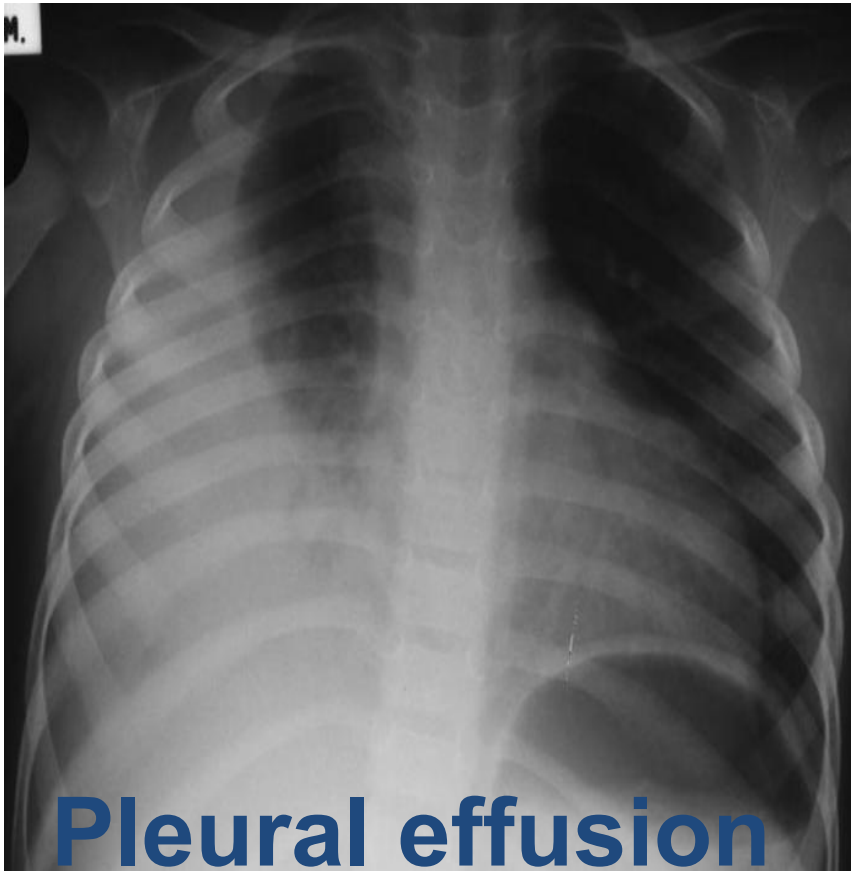


Tracheal compression by TB lymphadenopathy

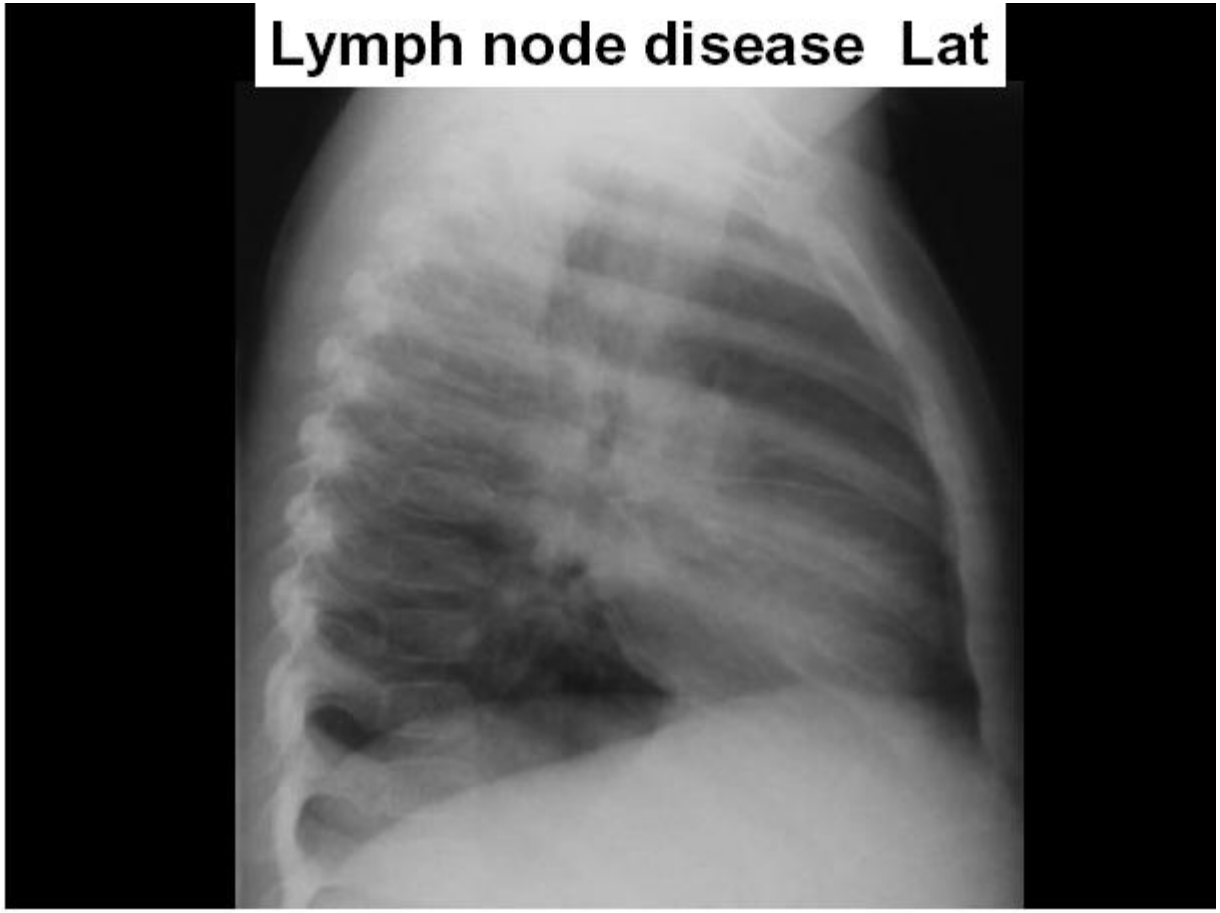


Radiological findings of TB

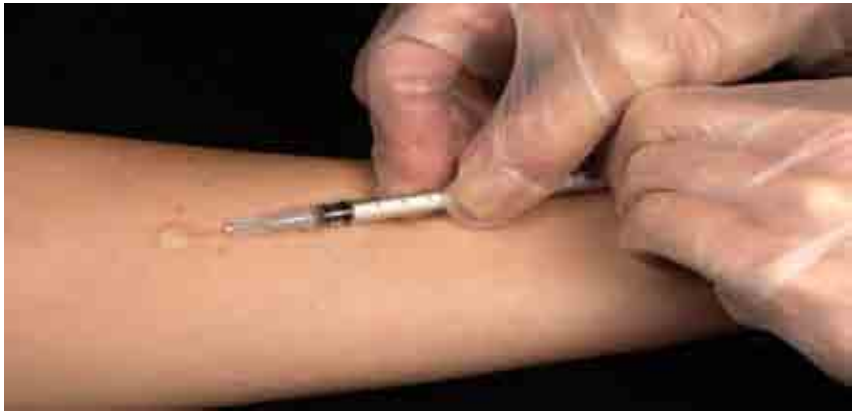




Radiological Findings of TB



Tuberculin Skin Test



Left forearm

2 IU PPD

0,1ml PPD

INTRADERMALLY

- Read after 48-72h

Turberculin Skin Test

Table I. Causes of false-positive or false-negative tuberculin skin tests (TSTs) in children[5]

False-negative TST	False-positive TST
Improper placing/interpretation	Improper interpretation
HIV infection	BCG vaccination
Malnutrition or low-protein states	Non-tuberculous mycobacteria
Severe TB	
Improper storage of tuberculin	
Viral infections	
Bacterial infections	
Live viral vaccines (within 6 weeks)	
Immunodeficiencies (other than HIV)	
Neonates	

Management of the child with TB infection

- INH 10mg/Kg for 6 months

11.1.3 Management of children with tuberculous infection

After exclusion of TB disease, INH prophylaxis should be given to:

- All children under 5 years of age and HIV-infected children (irrespective of age) in contact with an infectious case of TB (drug susceptible TB and MDR-TB)
- All children under 5 years of age with a positive Mantoux (10 mm in diameter or greater)
- All HIV-infected children, irrespective of their age, with a positive Mantoux (5 mm in diameter or greater)

Microbiological confirmation PTB

- Difficult in children
- Specimens for AFB staining, culture
  - gastric lavage
  - induced sputum
  - BAL
  - others – ear swabs, blood, fine needle aspiration
- Yield depends on intrathoracic disease

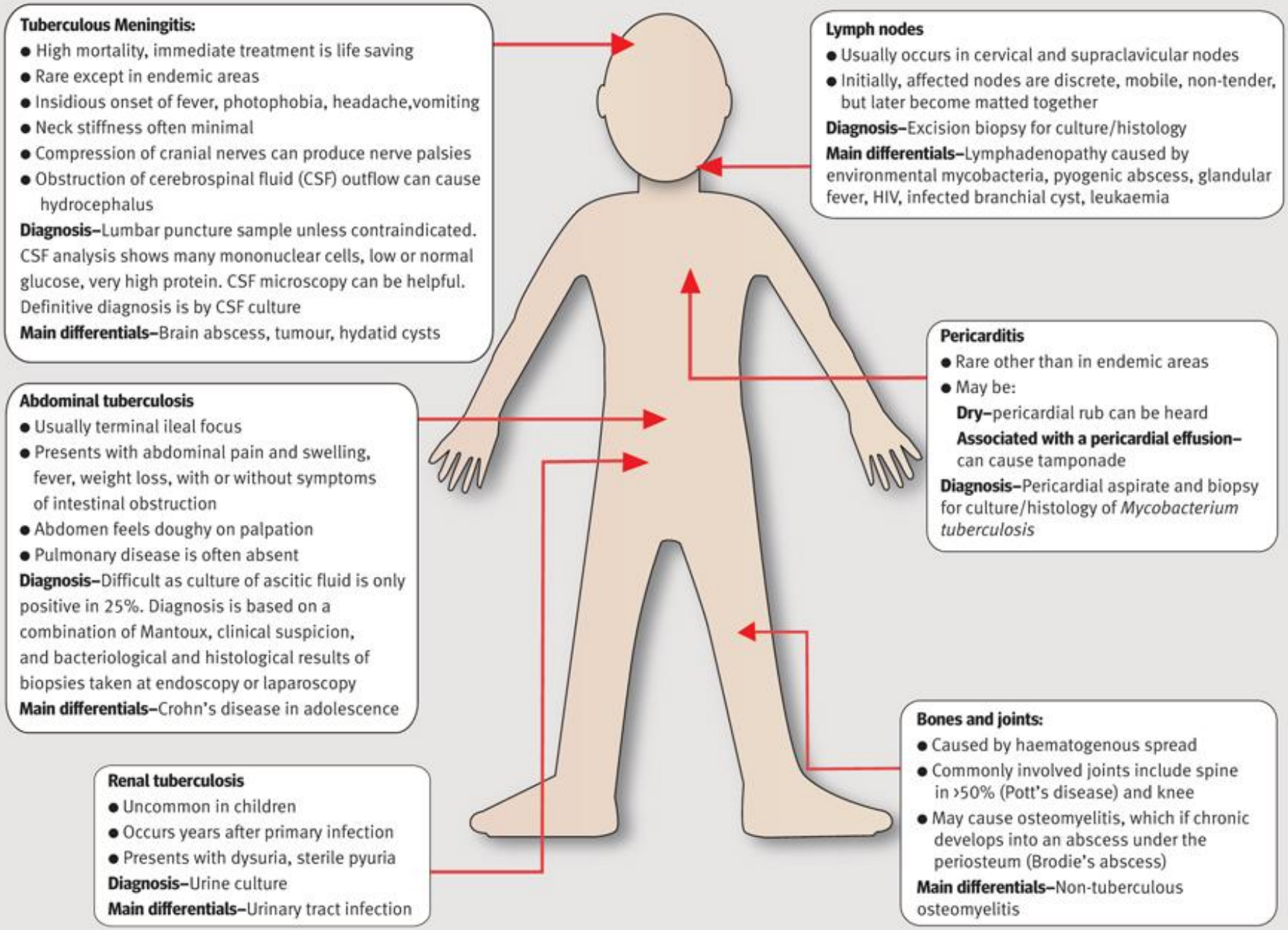
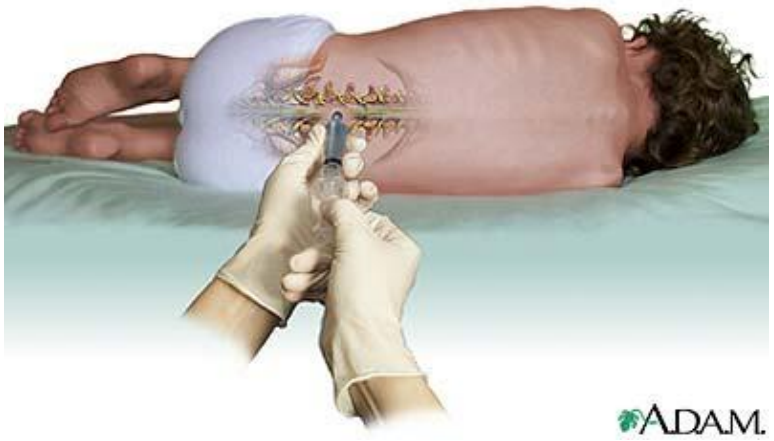
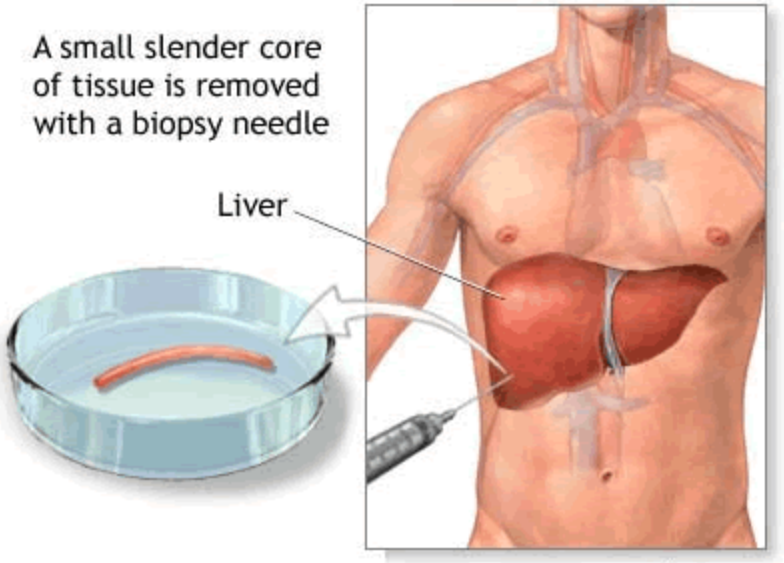


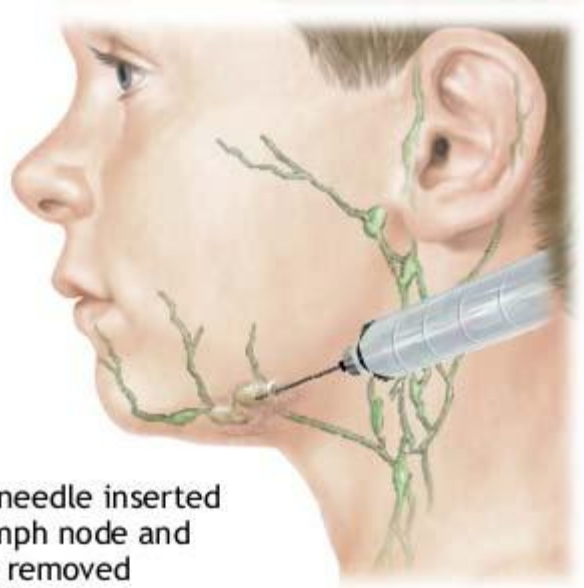
Fig 3 | Tuberculosis can effect almost any organ

Cerebrospinal fluid drawn
from between two vertebrae



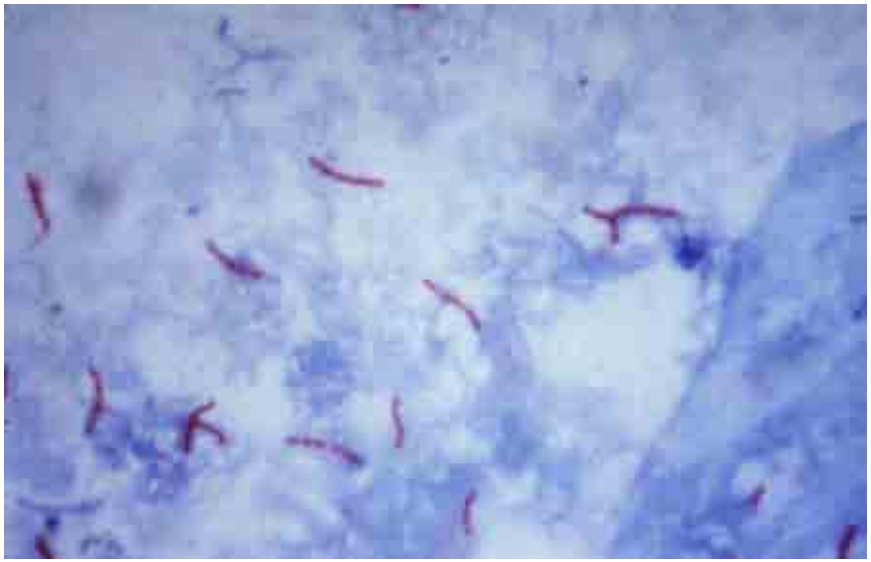
A small slender core
of tissue is removed
with a biopsy needle





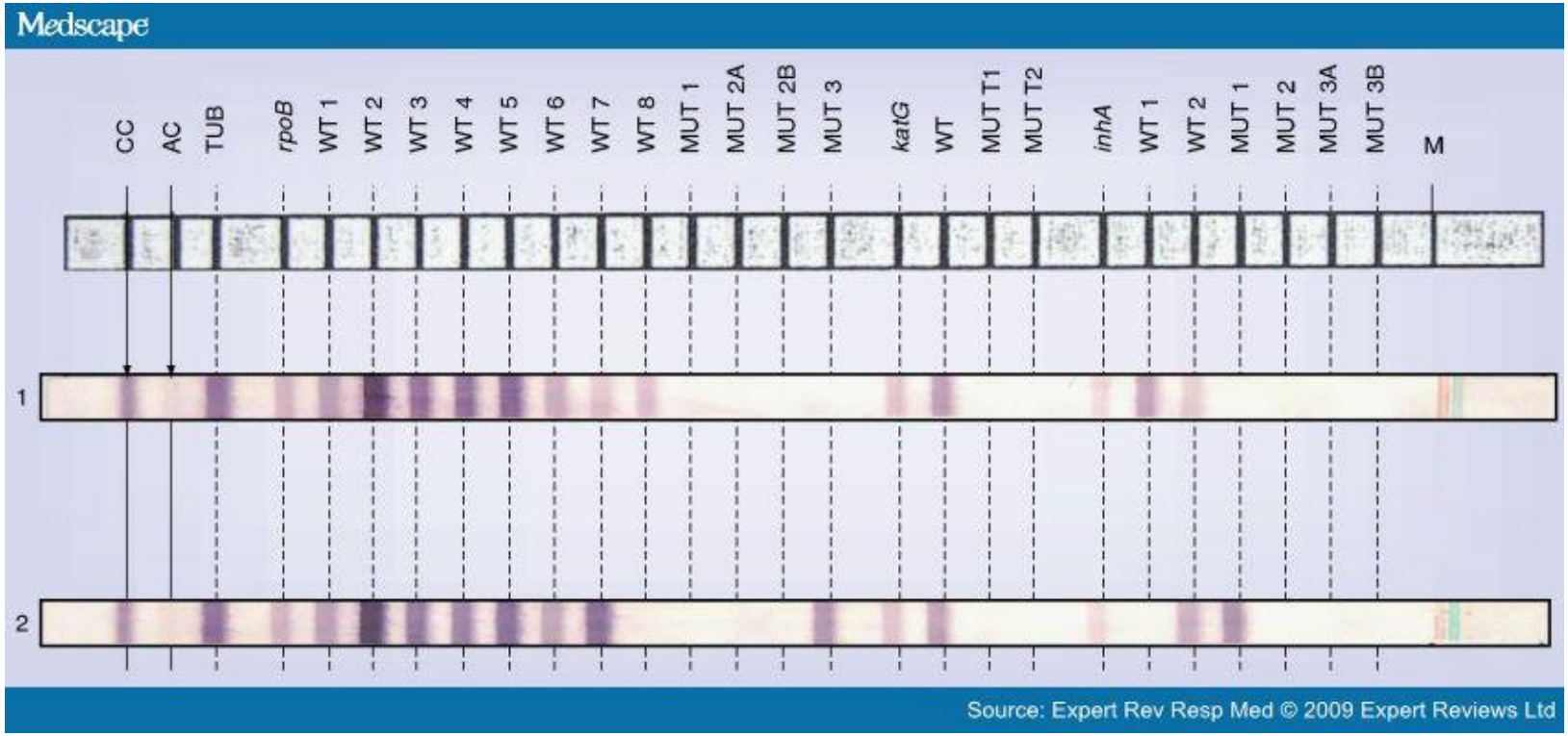
Biopsy needle inserted
into lymph node and
sample removed

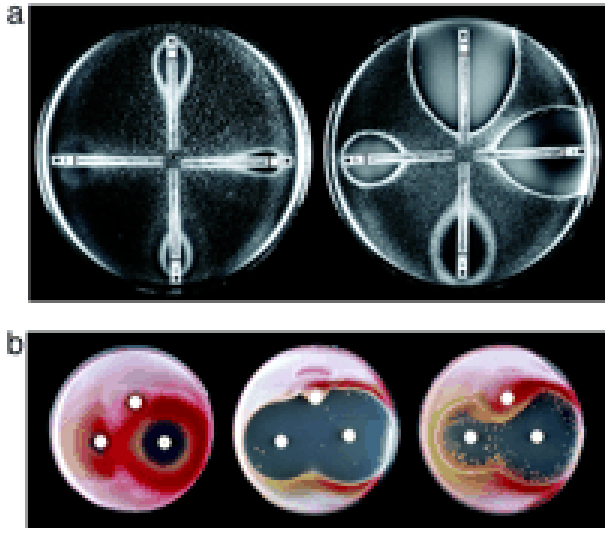
A.D.A.M.



MICROSCOPY

CULTURE





SENSITIVITY

Diagnosis of extra-pulmonary TB

Peripheral LN	FNA, LN biopsy
TBM	LP
Pleural effusion	Pleural tap for chemistry and culture
TB Abdomen	Ascitic tap
Osteoarticular TB	Joint tap, synovial biopsy
Pericardial	Pericardial tap

TB

- Complicated TB
- Extrapulmonary
  - TBM
  - BONE
  - ABDOMINAL
  - Miliary

  - 4 TB drugs

- Uncomplicated TB
  - Pulmonary
  - TB pericarditis
  - TB lymphadenitis

  - 3 TB drugs except sputum positive AFB

ONCE CONFIRMED NOTIFY!!!!!!!!

AND TRACE THE ADULT CONTACT!!!!

But what about HIV

- More difficult because of the following:

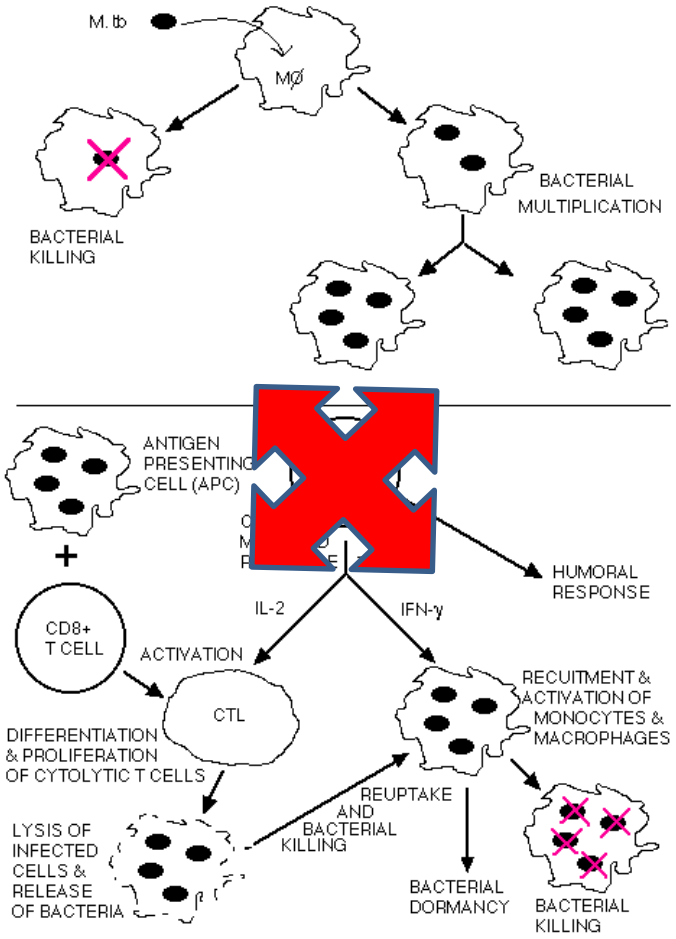
11.7.1 TB diagnosis in HIV positive children

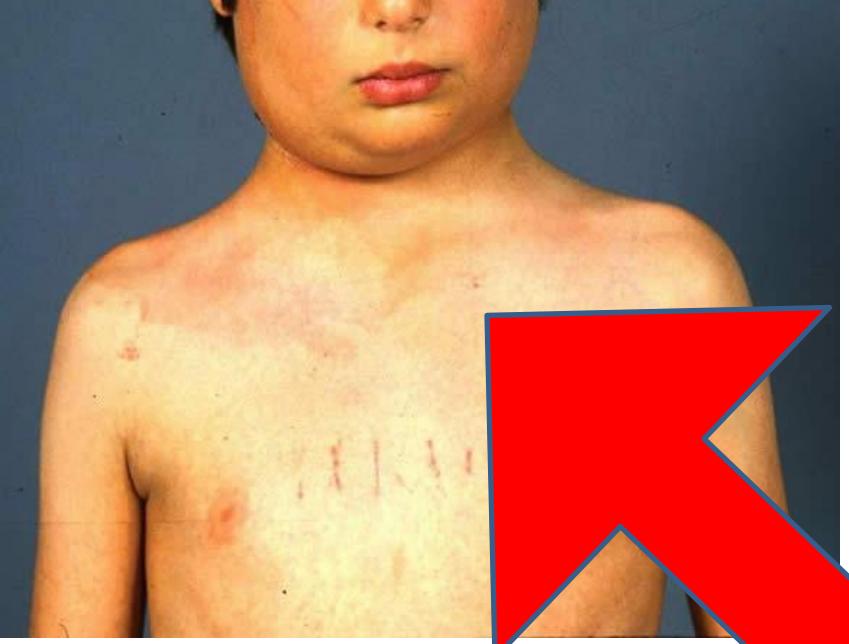
In HIV positive children the diagnosis of tuberculosis is more complex because:

- The symptoms and signs of tuberculosis and those of other HIV related lung diseases could be indistinguishable. Symptoms such as chronic cough, weight loss and persistent fever are common to both HIV related lung disease and TB.
- The Mantoux skin test is frequently negative even though the child may be infected with TB or has TB disease.
- Although the radiological features are usually similar to that found in HIV-negative children, the picture could also be atypical. Radiological changes of HIV related lung diseases are confused with those caused by tuberculosis e.g. LIP may look very similar to miliary TB.
- The differential diagnosis of pulmonary TB in HIV-infected children is much broader and includes: bacterial pneumonia, viral pneumonia, fungal lung disease, pneumocystis jiroveci pneumonia (previously known as PCP), pulmonary lymphoma and Kaposi's sarcoma.

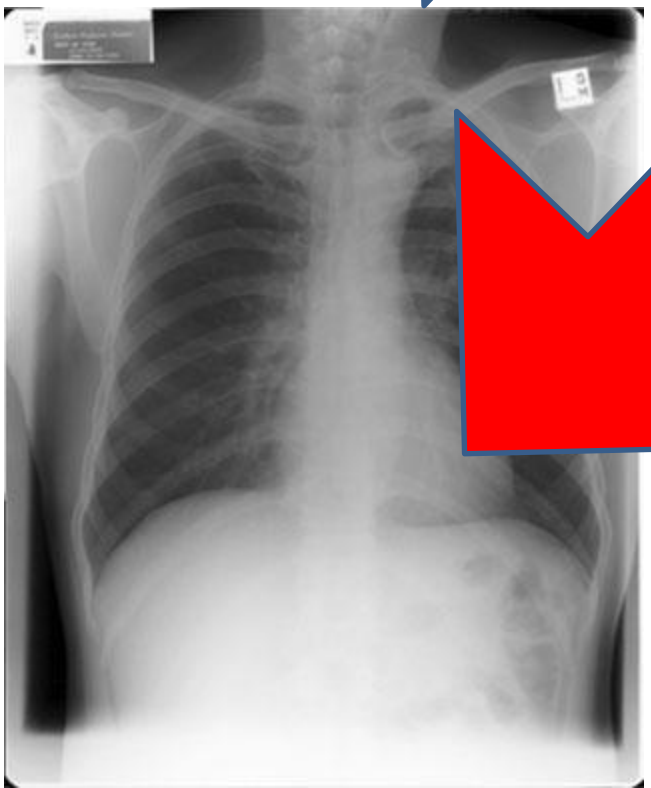
HIV infection and TB

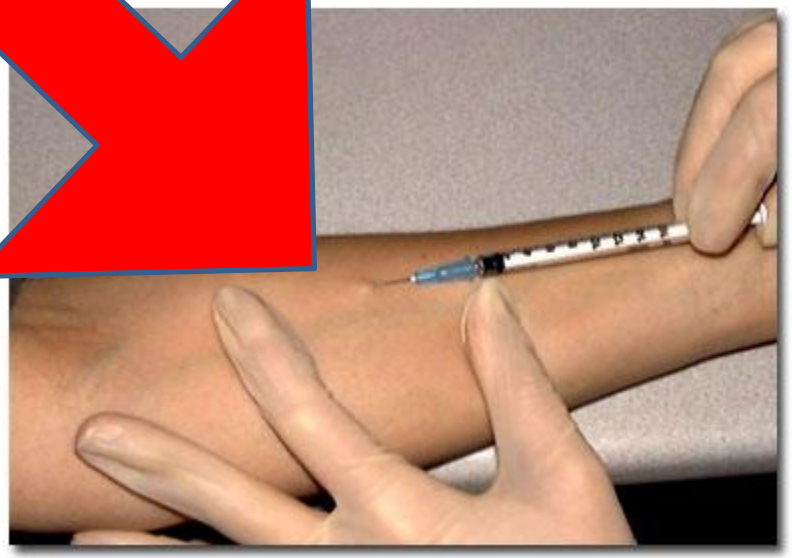
- Pathogenesis





ure-1: Massive hepatosplenomegaly.





Diagnostics

- Remains the same…
- Do HIV staging… WHO 3 or 4
- Remember Co-trimoxazole prophylaxis
- Wait at least 2 weeks after TB medication initiation prior to start of ARV's

ALL CHILDREN WITH TB MEET CRITERIA FOR ARV INITIATION

When to start HAART in relation to TB Rx

TB newly diagnosed: New HIV-diagnosis/Not on HAART

- TB treatment is the priority
- Recent data shows benefit starting HAART early in ALL TB cases. Urgent in stage 4 disease and in MDR-TB cases – in these cases start HAART within 1-2 weeks of starting anti-TB Rx
- In all other cases start within two weeks to eight weeks (to prevent majority of overlapping drug toxicities and IRIS)

Criteria for ARV initiation

Confirmation of diagnosis of HIV infection AND:	
Age	**Eligibility for Treatment**
Child less than 1 year	All children should be started on ART
1 – 5 years	Symptomatic (stage III or IV) or CD4 ≤ 25 % or absolute count < 750 cells/mm^3
≥ 5 years	Symptomatic (stage III or IV) or CD4 < 350 cells/ mm^3

IRIS

Immune Reconstitution Inflammatory Syndrome (IRIS)

- Can occur when introducing ARVs (unmasking TB-IRIS) or when introducing ARVs soon after initiating anti-TB Rx (paradoxical TB-IRIS)
- Unmasking IRIS: aggressive onset of TB in previously undiagnosed case
- Paradoxical IRIS: Temporary exacerbation of symptoms (e.g. fever), signs (e.g. lymph node enlargement) or XR-appearance
- Can be severe. Mostly subsides spontaneously, not Rx failure. Severe cases may need steroids
- Distinguish from MDR-TB

New ARV regime

- First Line Regime for ART initiation

<3years &<10Kg	>3years &10Kg
Abacavir (ABC)	Abacavir
Lamivudine (3TC)	Lamivudine
Lopinavir/Ritonavir (Kaletra)	Efavirenz

TB Rx & ART

- Drug toxicity
  overlapping side-effect profile
  increased toxicity of drug combinations
- Drug interactions

NB!! RMP stimulate liver enzymes

  decrease levels of NNRTI's and PI's

- Increased drug burden – adherence
- Immune reconstitution inflammatory syndrome (IRIS)

TB Rx as discussed – initiate when Dx made

* Newly Dx HIV-infection – initiate ART after first 2/52 of TB Rx (earlier if required)

Retain 2 NRTI backbone - adjust third drug

<3yrs or <10kg

- If on Kaletra® – boost with additional RTV continue 1-2 /52 after TB Rx stopped

≥3yrs and ≥10kg

- If on NVP or Kaletra® – switch to EFV

Monitoring TB Rx / ART

- ALT at baseline, 2 & 4 weeks
- Clinical FU monthly
- Adjust drug dosages with wt gain

Overlapping Toxicities

Side Effects	Anti-TB Drugs	ARV Drugs
Skin rash	PZA, RMP, INH	NVP, EFV,ABC
Nausea, vomiting	ETH, EMB, PZA, RMP, INH	AZT, RTV, Kaletra
Hepatitis	PZA, RMP, INH, ETH	NVP, all PIs, EFV paradox reactions
Leukopenia, anemia	INH, RMP	AZT
Peripheral neuropathy	INH	d4T, ddI

Management of TB

The aims of TB treatment are to:

1. Cure the client of TB
2. Decrease transmission of TB to others
3. Prevent the development of acquired drug resistance
4. Prevent relapse
5. Prevent death from TB or its complications

Table 7.1: Properties of TB Drugs

Drug	Drug Property	Target Bacilli	ph	Site of Action
Isoniazid (H)	Bactericidal after 24 hours. High potency: kills >90% bacilli in first few days of treatment.	Rapid and intermediate growing bacilli	Alkaline and acid media.	Intracellular and extracellular.
Rifampicin (R)	Bactericidal within 1 hour. High potency. Most effective sterilising agent.	All populations including dormant bacilli.	Alkaline and acid media.	Intracellular and extracellular.
Pyrazinamide (Z)	Bactericidal with a low potency. Achieves its sterilising action within 2-3 months.	Slow growing bacilli.	Acid medium.	Intracellular bacilli only (macrophages).
Ethambutol (E)	Bacteriostatic. Low potency. Minimises the emergence of drug resistance.	All bacterial populations.	Alkaline and acid media.	Intracellular and extracellular.
Streptomycin (S)	Bactericidal with a low potency.	Rapidly growing bacilli.	Alkaline medium.	Extracellular bacilli

TB Treatment

- Anti-tuberculostatics:
  - 2 Phases: intensive phase 2mo and continuation phase 4mo (regime 3)
  - Smear positive TB: 4 drugs required in intensive phase and 2 drugs in the continuation phase (regime 3B)
  - >8years treat as adult with regime I for newly diagnosed TB and regime II for retreatment cases
- Directly observed therapy (DOTS)

Treatment of uncomplicated TB smear negative TB

- Pulmonary TB
- EPTB such as LN TB and TB pleural effusion
- Treat with regime 3 for 6mo
  - Rifampicin, INH, Pyrazinamide (initiation 2mo phase)
  - Rifampacin and INH for 4mo (continuation phase)

Complicated TB < 8years

REGIMEN 3 B: FOR NEW CASES - WITH ETHAMBUTOL

Body weight (kg)	Intensive Phase (2 months) Treatment given 7 days a week			Continuation Phase (4 months) Treatment given 7 days a week	
	RHZ (60, 30, 150)	E (100mg)	RHZE (150, 75, 400, 275)	RH (60, 30)	RH (150, 75)
5 – 7.9	1	1		1	
8 – 14.9	2	2		2	
15 – 19.9	3	3		3	
20 – 29.9			2		2

Uncomplicated < 8years

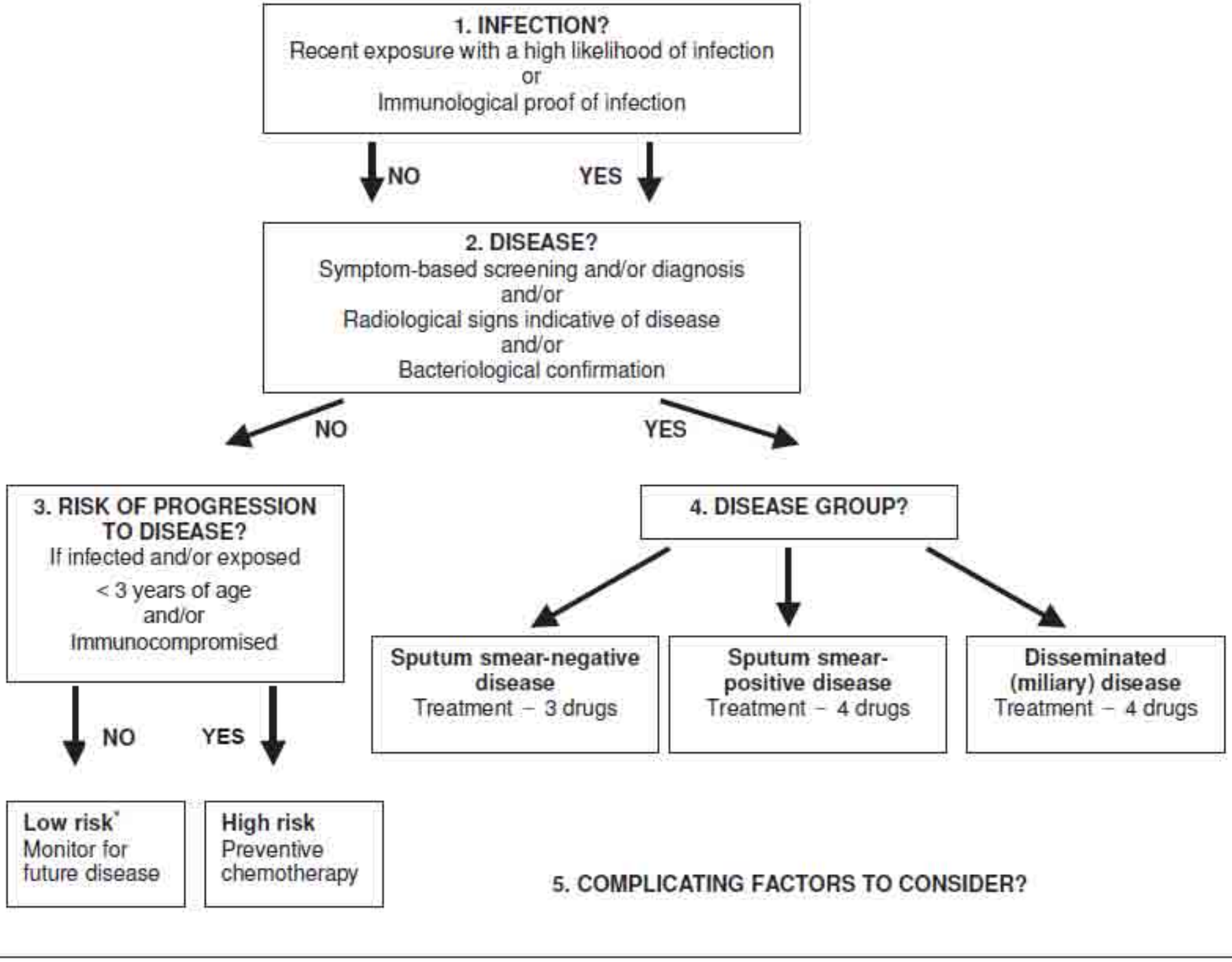
REGIMEN 3 A: FOR NEW CASES - WITHOUT ETHAMBUTOL

Body weight (kg)	Intensive Phase (2 months) Treatment given 7 days a week			Continuation Phase (4 months) Treatment given 7 days a week	
	RHZ (60, 30, 150)	RH (150,75)	Z (400mg)	RH (60, 30)	RH (150, 75)
5 – 7.9	1			1	
8 – 14.9	2			2	
15 – 19.9	3			3	
20 – 29.9		2	2		2

Regimen	Definition	Initial phase Daily treatment	Continuation phase Daily treatment
Regimen 3B	New smear positive PTB, smear negative with extensive parenchymal involvement, severe forms of extra pulmonary TB	HRZE for 2 months	HR for 4 months
Regimen 3C	Previously treated smear positive PTB returning after default, failure or relapse	HRZE + Streptomycin for 2 months followed by HRZE for 1 month	HRE for 5 months
Regimen 3A	New smear negative PTB without parenchymal involvement, Less severe forms of extra pulmonary TB	HRZ for 2 months	HR for 4 months
Regimen 3D	TB Meningitis	HRZS for 2 months	HR for 4 months
		HRZ (S or Ethionamide) for 2 months	HR for 7-10 months
		HRZ + Ethionamide for 6 months only	

Indications for oral steroids in children with TB include:

- TB meningitis
- TB pericarditis
- Mediastinal lymph glands obstructing the airways.
- Severely ill children with disseminated TB (miliary)


1. INFECTION?
Recent exposure with a high likelihood of infection
or
Immunological proof of infection
NO
YES
2. DISEASE?
Symptom-based screening and/or diagnosis
and/or
Radiological signs indicative of disease
and/or
Bacteriological confirmation
NO
YES
3. RISK OF PROGRESSION TO DISEASE?
If infected and/or exposed
< 3 years of age
and/or
Immunocompromised
NO
YES
Low risk*
Monitor for future disease
High risk
Preventive chemotherapy
4. DISEASE GROUP?
Sputum smear-negative disease
Treatment – 3 drugs
Sputum smear-positive disease
Treatment – 4 drugs
Disseminated (miliary) disease
Treatment – 4 drugs
5. COMPLICATING FACTORS TO CONSIDER?

Use of steroids in children with TB

- TBM
- TB pericarditis
- Mediastinal LN obstructing airway
- Severely ill children with miliary TB
- Dosage 1-2mg/kg daily orally for 4-6wks added to TB drugs
- Taper dose to stop over 2wks

Definitions

- Poly-drug resistance: Resistance to 2 or more drugs, but not to both INH and RMP
- MDR TB: Resistance to INH & RMP +/- other
- XDR TB: MDR & 2nd-line injectable & quinolone

Counseling / Support

- Carefully explain to parents

  - Both treatments require good adherence

- Watch out for
  - Nausea/vomiting/ abd tenderness
  - Signs of peripheral neuropathy
  - Jaundice!
- DOTS is advised for TB Rx

  DOTS supporter can assist with ART adherence as well

Thank you!

Acknowledgements

- Dr Nicolette Du Plessis (use of some of her slides)

References

- National dept of Health TB guidelines 2009
- Guidelines for the management of HIV in children. National dept of Health 2nd edition 2010
- Coovardia and Wittenberg, 6th edition

SOUTH TO SOUTH