Module 2

DIAGNOSIS OF CHILDHOOD TB

International Union Against Tuberculosis and Lung Disease

World Health Organization

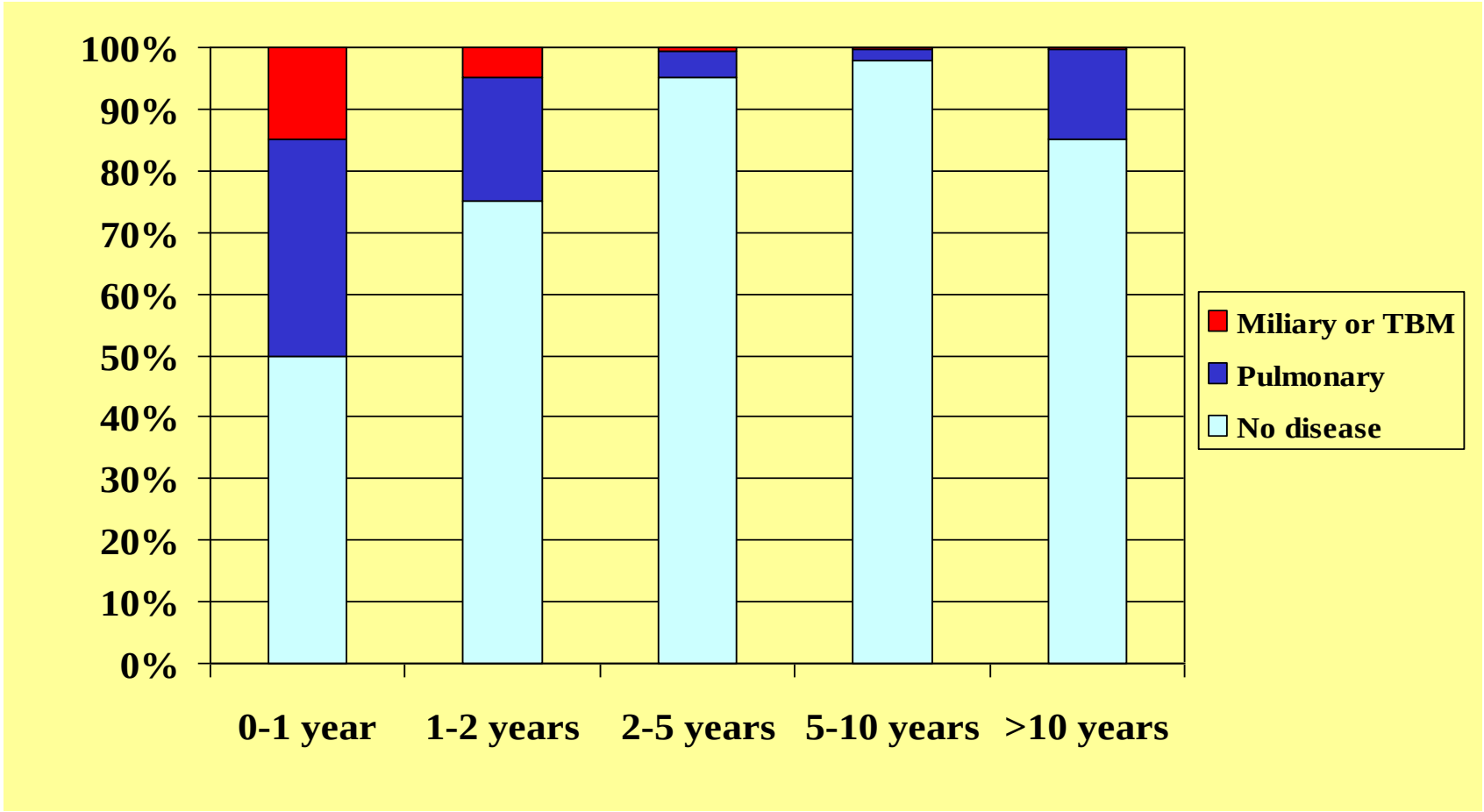
TB disease in children: clinical epidemiology

- **Most cases occur in young children (<5years)**

- **Most disease occurs within 2 years after exposure/infection**
  - The majority within 1 year

- **Most cases in children are pulmonary TB**
  - Smear negative or smear not done are the majority
  - Extrapulmonary TB is also common and the type depends on age
  - Smear positive disease is usually in older children

Age specific risk for disease in children after infection with TB in the pre-BCG era



Adapted from Marais B, et al. Int J Tuberc Lung Dis 2004

Childhood TB caseload: Malawi 1998

Harries AD, et al. Int J Tuberc Lung Dis 2002

Malawi NTP, 1998	numbers (proportion of childhood caseload)	proportion of child TB caseload
Total caseload	22,982	
Total childhood	2,739	
0-4 years	1,615	59 %
5-14 years	1,124	41 %
Smear-positive PTB	127	5 %
Smear-negative PTB	1,804	65 %
EPTB	808	30 %

Types of childhood EPTB disease

	Malawi NTP, 1998	PNG, 2005-6
EPTB cases	808	1097
Lymphadenitis	331 (41%)	342 (31%)
Pleural effusion	101 (12%)	94 (9%)
Spinal	83 (10%)	41 (4%)
Pericarditis	60 (7%)	12 (1%)
Abdominal	39 (5%)	173 (16%)
Miliary	34 (4%)	64 (6%)
Meningitis	30 (4%)	257 (23%)
Bone disease	12 (1%)	15 (1%)
Not indicated/others	118 (14.6%)	99 (9%)

The diagnosis of TB can be made with confidence in the majority of children using careful clinical assessment

It is difficult to *confirm* diagnosis of TB in many children but it is usually not so difficult to *make a clinical diagnosis* of TB in a child

Recommended approach to diagnose TB in children

WHO Guidance for NTP on management of TB in children

1. **Careful history**
   - includes history of TB contact
   - symptoms suggestive of TB
2. **Clinical examination**
   - includes growth assessment
3. **Tuberculin skin test**
4. **Bacteriological confirmation whenever possible**
5. **Investigations relevant for suspected PTB or suspected EPTB**
6. **HIV testing**

Recommended approach to diagnose TB in children

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6. **HIV testing routine**

Note that TST and culture are often unavailable. Neither is required for a decision to treat for TB in most cases.

CXR is an important tool for diagnosis of TB in children

Sputum should be collected for smear microscopy if available as in older children

Diagnosis of PTB

Typical symptoms

- ❖Cough especially if persistent and not improving
- ❖Weight loss or failure to gain weight
- ❖Fever and/or night sweats
- ❖Fatigue, reduced playfulness, less active

Especially if symptoms persist (>2 weeks) without improvement following other appropriate therapies (e.g. broad-spectrum antibiotics for cough; anti-malarial treatment for fever; or nutritional rehabilitation for malnutrition)

Diagnosis – well-defined symptoms

- Characteristics of cough: persistent (>2 weeks), unremitting and unresponsive to antibiotics
- Fatigue, reduced playfulness
- Documented weight loss, failure to thrive (in preceding 3 months)
- Well characterized symptoms improve diagnostic accuracy
  ≥ 3 years: specificity: 98.9%; PPV: 85.1%
- Less useful in young
  < 3 years: specificity: 82.6%; PPV: 88.6%
- Performed poorly in HIV-infected

Marais BJ, et al. Pediatrics 2006; Marais BJ, et al. Arch Dis Child 2005

History of contact

note the following…….

- ❖ Closeness of contact
- ❖ Sputum smear result of index case (if known)
- ❖ Timing of contact
  children usually develop TB within 2 years after exposure and most (90%) within the first year
- ❖ If no source case is identified, always ask about anyone in household with cough – if so, request assessment of that person for possible TB

Maternal/infant TB

- TB in pregnancy or post-partum is common especially in HIV-infected women
- Maternal TB is associated with maternal mortality, low birth weight and infant mortality
- The risk of TB infection and disease to the infant of a mother with TB is extremely high

Clinical examination for suspected TB

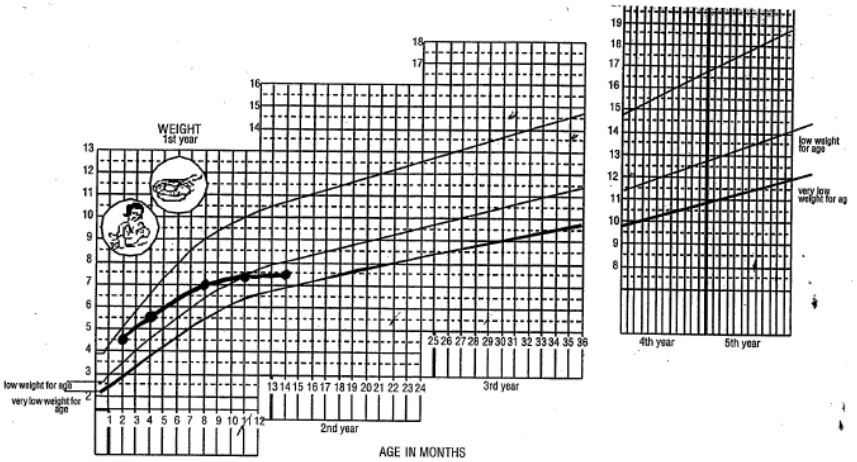
Check weight, record weight and compare to previous weights

Vital signs: temperature and respiratory rate

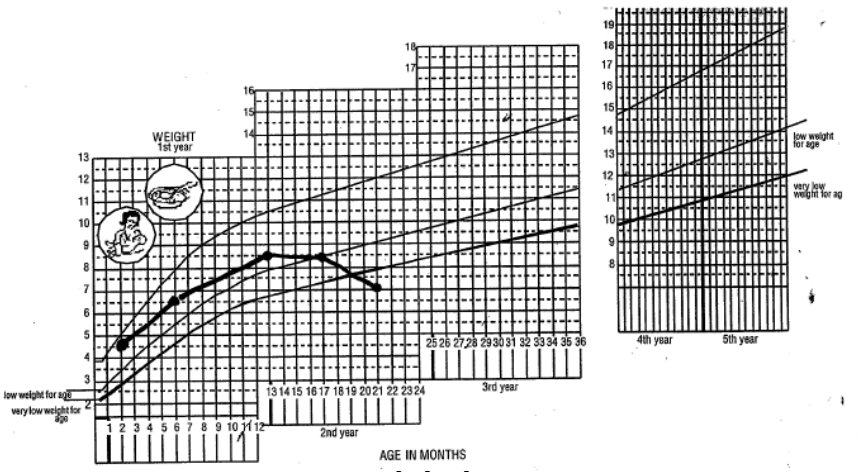
Respiratory system: signs of respiratory distress

Auscultation and percussion: usually normal but may reveal lung disease or pleural effusion

Clinical features that might suggest other causes of chronic lung disease
e.g. recurrent cough and/or wheeze responsive to bronchodilators suggests asthma;
finger clubbing suggests bronchiectasis



Growth faltering or failure to thrive



Weight loss

Atypical clinical presentations of PTB

Acute severe pneumonia

Presents with fast breathing and chest indrawing

- Especially in **infants and HIV-infected** children
- Suspect PTB if poor response to antibiotic therapy AND especially if a positive contact history as there will be in most cases
- If HIV-infected also suspect other HIV-related lung disease e.g. PcP

Wheeze

- Asymmetrical and persistent wheeze can be caused by airway compression due to enlarged tuberculous hilar lymph nodes
- Suspect PTB when wheeze is asymmetrical, persistent, not responsive to bronchodilator therapy and associated with other typical features of TB such as malnutrition (asthma is very rare in malnourished children)

Scoring systems for child TB diagnosis

- Many systems developed – all related and rely on the usual clinical approach:
  - clinical features, contact history, CXR and TST (often unavailable)
- Likely to identify the most obvious cases but should not be used to exclude TB as diagnostic possibility
- Wide variation in performance and perform worse in the most clinically challenging groups e.g. TB/HIV

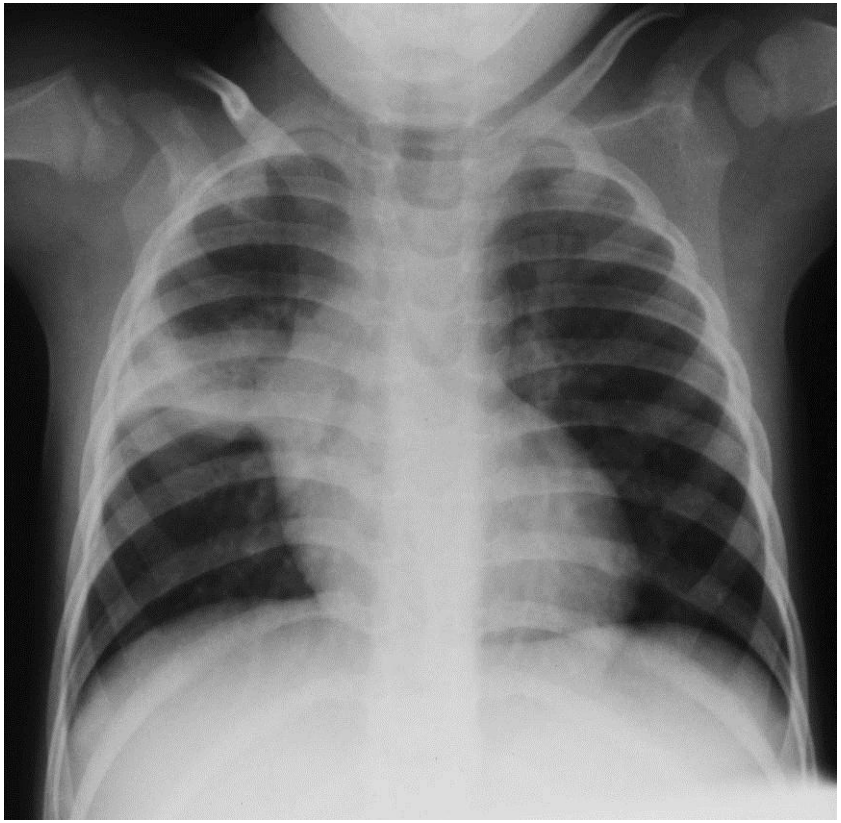
CXR remains an important tool for diagnosis of PTB in children

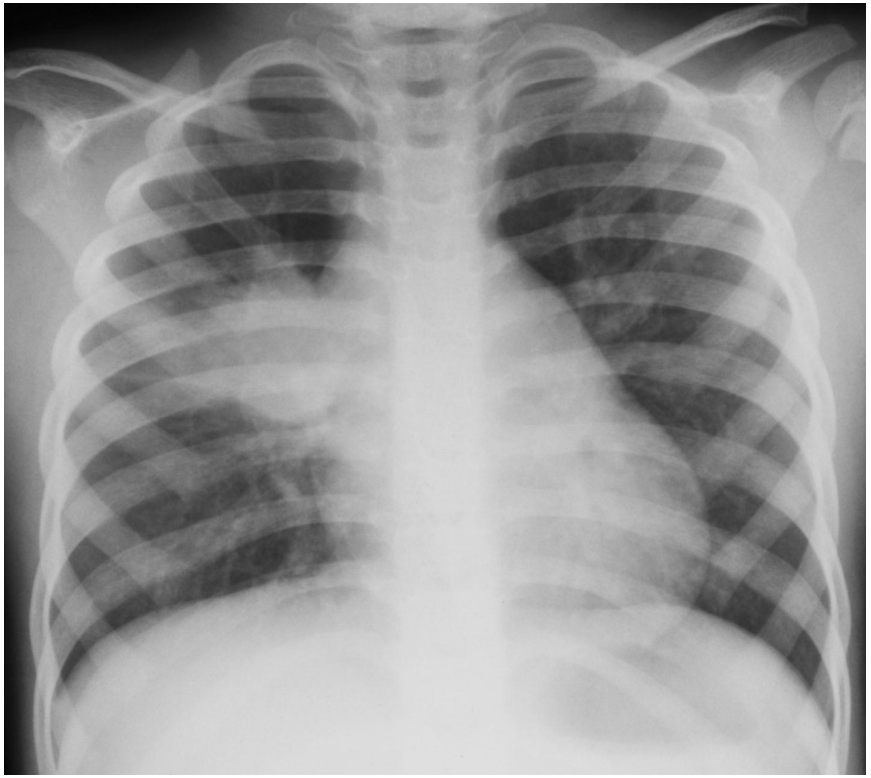
Commonest abnormality is due to lymphadenopathy and tends to be asymmetrical

CXR does have limitations especially as quality of CXR is often poor and no lateral view available

Diagnostic atlas of intrathoracic tuberculosis in children: a guide for low-income countries 2003.

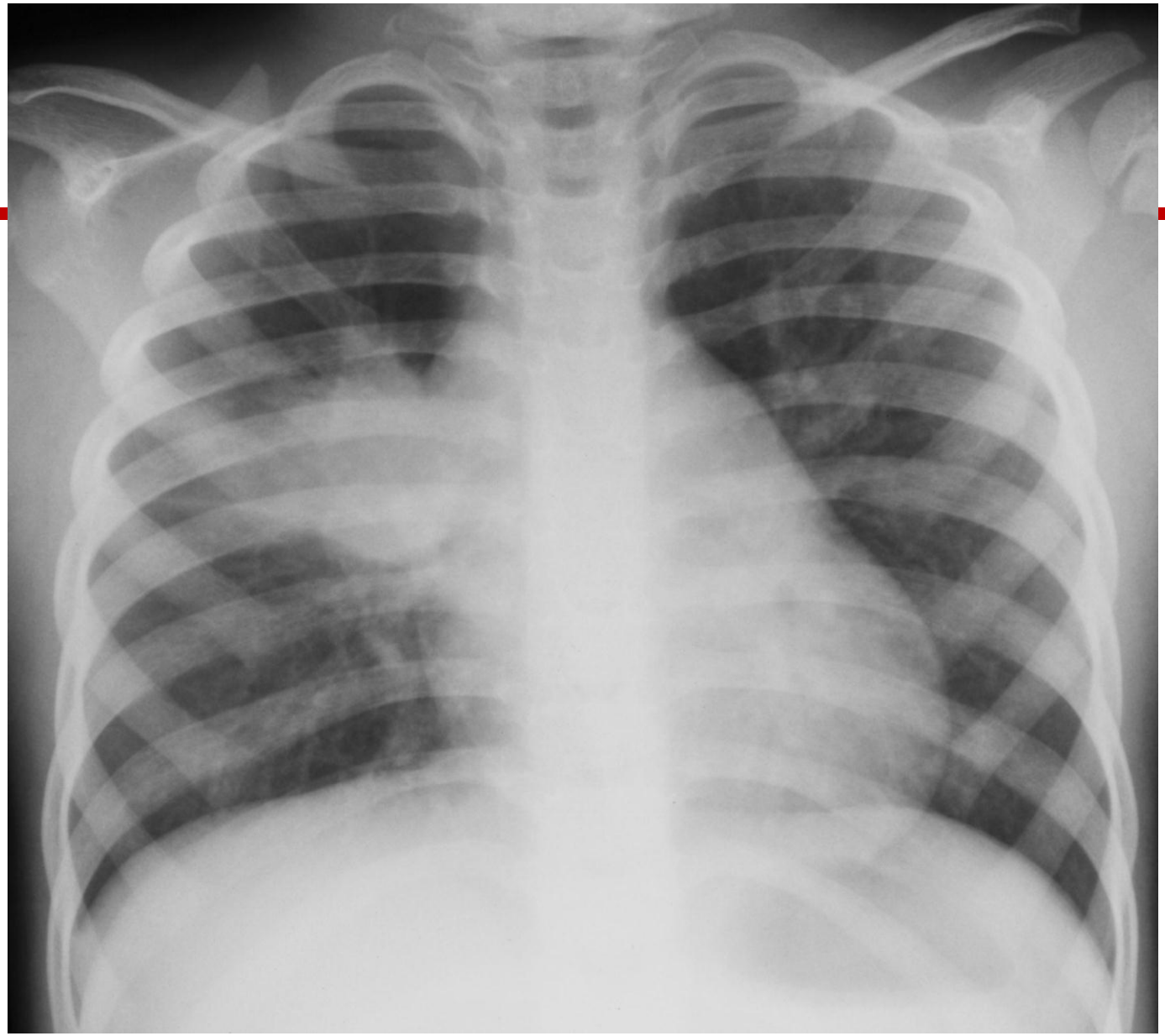
Robert Gie, IUATLD





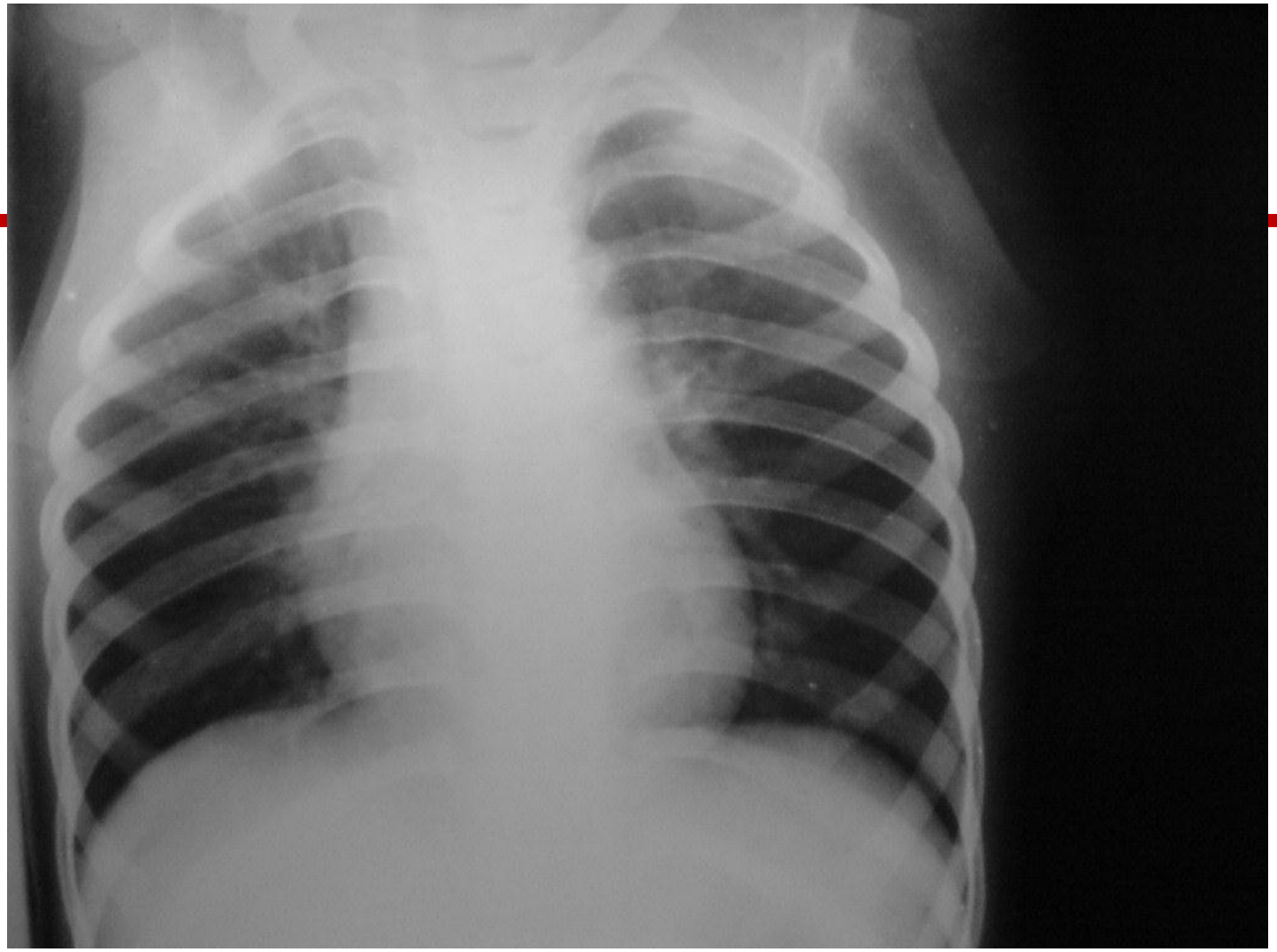
Freely available on-line

http://www.theunion.org/index.php/en/component/flexicontent/items/item/110-diagnostic-atlas-of-intrathoracic-tuberculosis-in-children



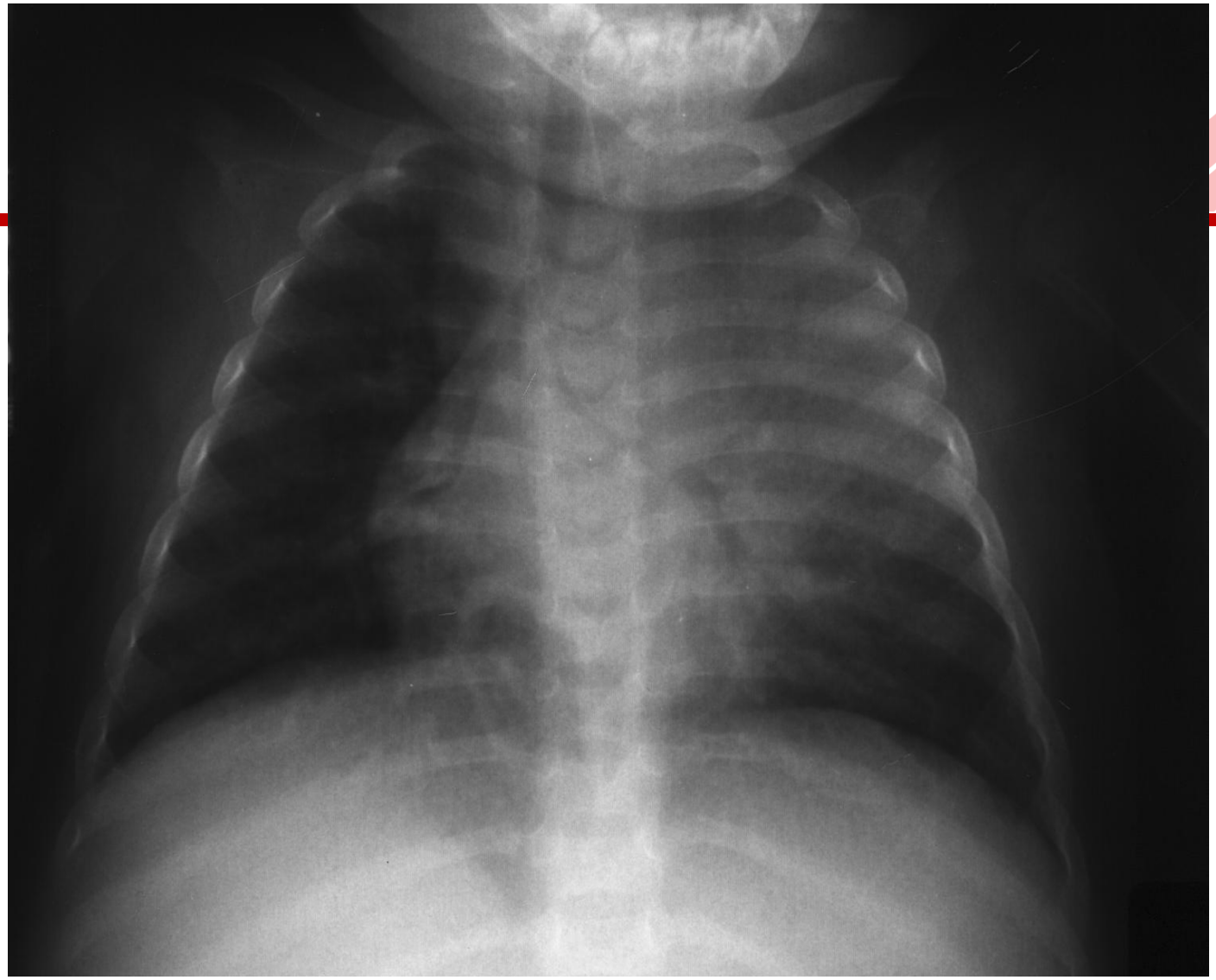
Obvious right perihilar adenopathy with surrounding inflammatory changes

Perihilar lymphadenopathy is a common radiological finding in children with PTB

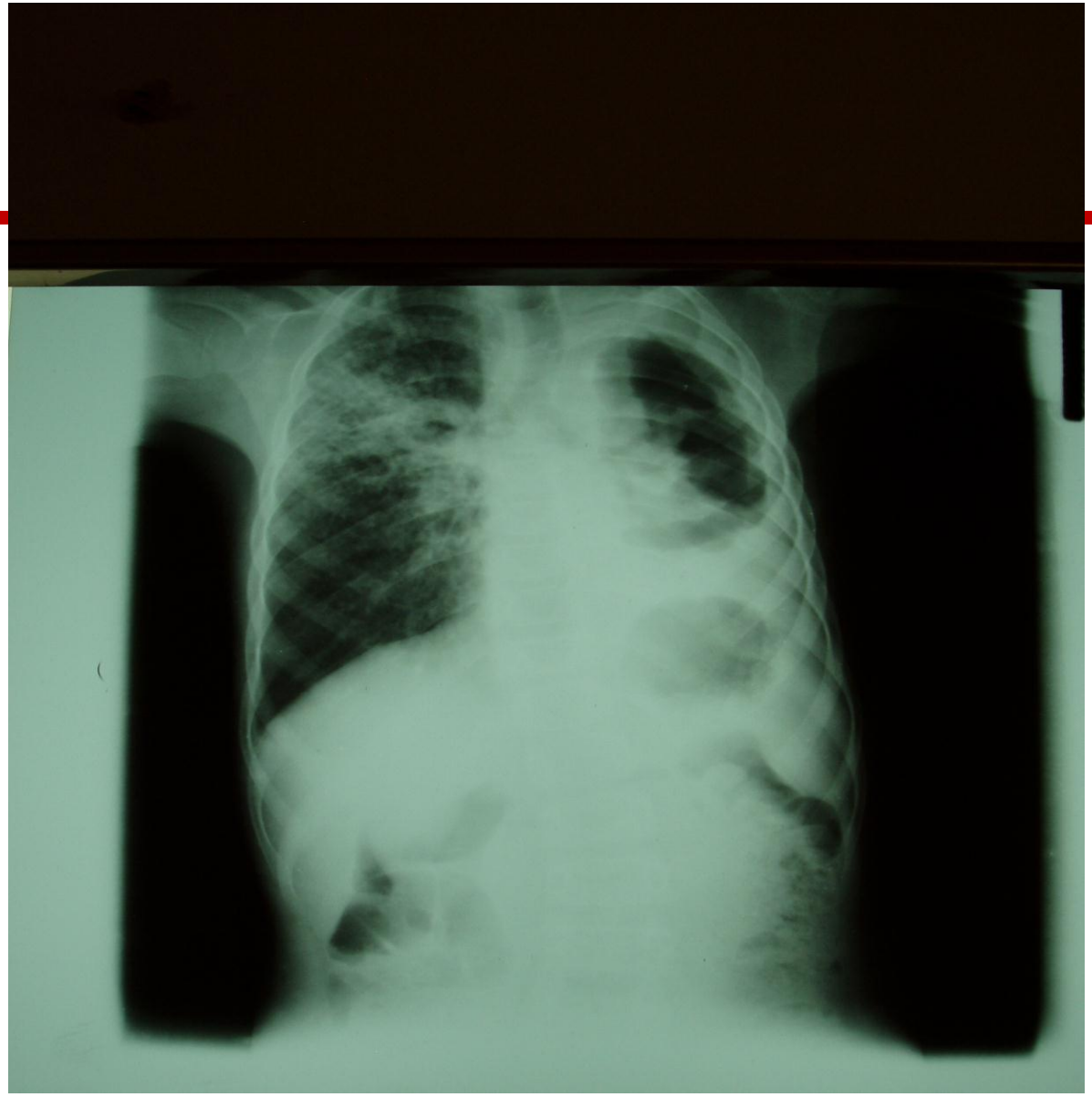


Perihilar lymphadenopathy is not always so obvious as previous CXR and may appear as widened mediastinum.

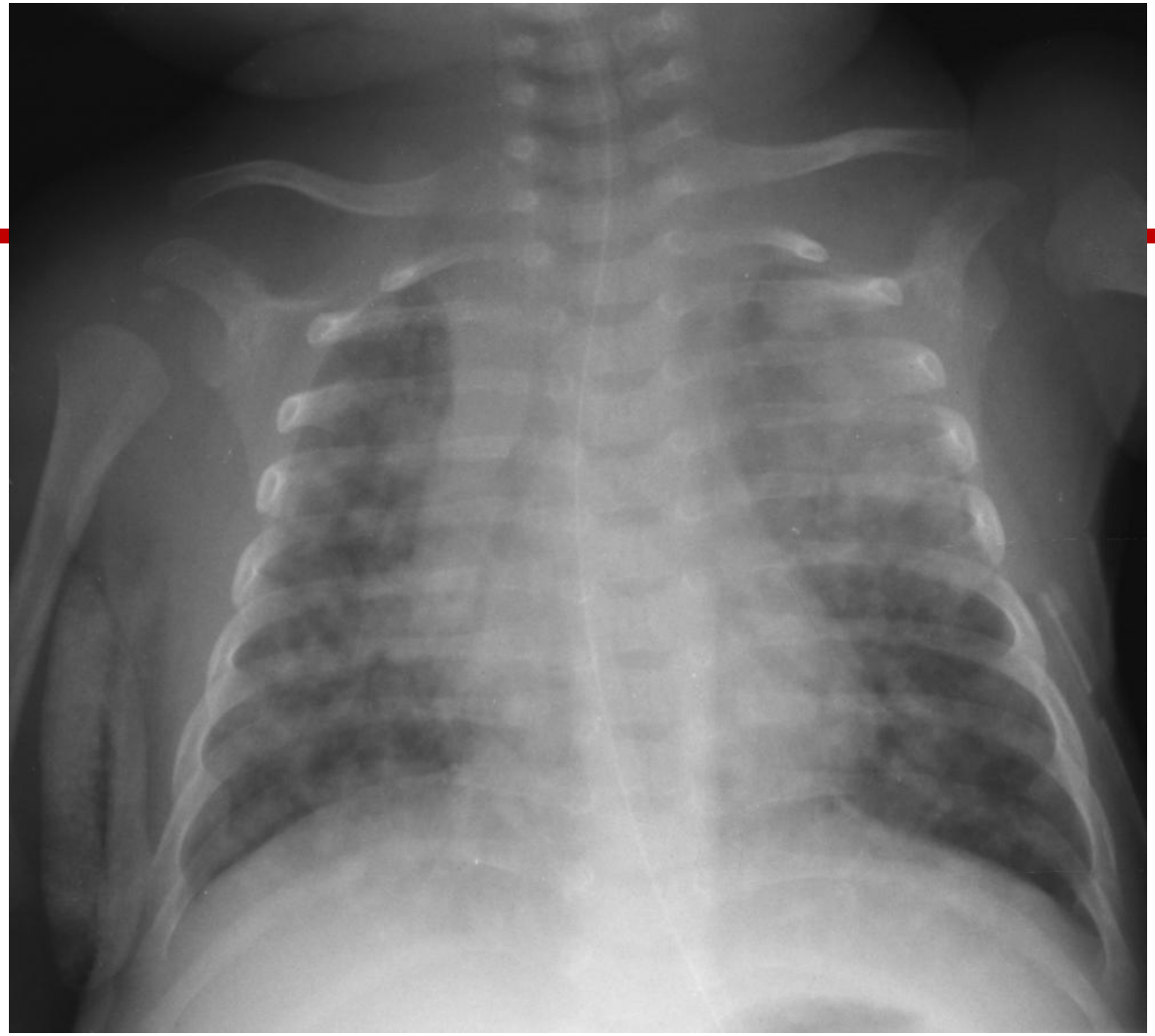
Lateral X-ray helpful. Normal thymic shadow in infants may appear as widened mediastinum on AP film (typical sail sign).



The consequences of intrathoracic lymphadenopathy is responsible for much of the parenchymal disease by airway compression (as seen here) and/or rupture of nodal TB abscess into airways.



Adolescents with PTB present with similar picture to adults with cavities and often sputum smear-positive disease.



Infants can present as severe pneumonia with extensive parenchymal disease and respiratory distress that is challenging to differentiate from the many other possible cause of pneumonia in infants.

Note that a contact history is very important and often positive in infants with TB disease.

Clinical approach to diagnosis of EPTB

- Extrapulmonary TB is common in children and presentation varies with age.
- The table on next slide lists typical clinical features of forms of EPTB and suggested investigations for each category.
- Symptoms vary depending on site of disease and characteristically are persistent, progressive and may be associated with weight loss or poor weight gain.
- *Clinical assessment in all cases should consider:*

  History of contact
  Sputum for smear microscopy
  HIV test

Site of EPTB	Typical clinical presentation	Investigation	Comment
TB adenitis	Asymmetrical, painless, non-tender lymph node enlargement for more than one month +/- discharging sinus Most commonly in neck area	Fine needle aspiration when possible for culture and histology TST usually positive - not necessary for diagnosis	Treat If axillary node enlarged on same side as BCG, consider BCG disease
Pleural TB	Dullness on percussion and reduced breath sounds +/-chest pain	CXR Pleural tap#	Treat If pus in pleural tap, consider empyema
Usually young (< 5 years) with disseminated disease and severely ill			
TB meningitis	Headache, irritability/abnormal behaviour, vomiting (without diarrhoea), lethargic/reduced level of consciousness, convulsions, neck stiffness, bulging fontanelle, cranial nerve palsies	Lumbar puncture obtain CSF# CXR	Hospitalise for TB treatment §
Miliary TB	Non-specific, lethargic, fever, wasted	CXR	Treat and refer §
Usually 5 years and older			
Abdominal TB	Abdominal swelling with ascites or abdo masses	Ascitic tap#	Refer §
Spinal TB	Deformity of spine May have lower limb weakness/paralysis	X-ray spine	Refer §
Pericardial TB	Cardiac failure Distant heart sounds Apex beat difficult to palpate	CXR Cardiac ultrasound Pericardial tap#	Refer §
TB bone and joint	Swelling end of long bones with limited movement Unilateral effusion of usually knee or hip	X-ray bone/joint Joint tap#	Refer §

typical findings of straw coloured exudate with high protein and predominately lymphocytes
§ referral may be for investigation as well as clinical care. If referral not possible, start anti-TB treatment.

Diagnosis of TB adenitis

TB adenitis is most common in cervical region. Lymph node enlargement is painless and asymmetrical, often multiple, discreet or matted.

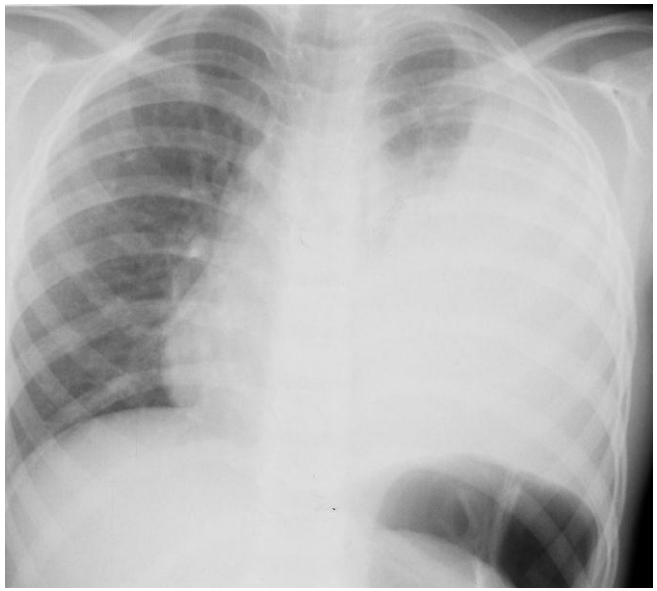
Nodes are typically large (>2 x 2 cm) i.e. visibly enlarged not just palpable.

Lymph node enlargement is persistent (>1 month) and not responsive to other treatment such as antibiotics.

Sinus and discharge may develop.
Usual age is 2-10 years.

May or may not be associated with other symptoms of TB.

TST (if available) usually strongly reactive.



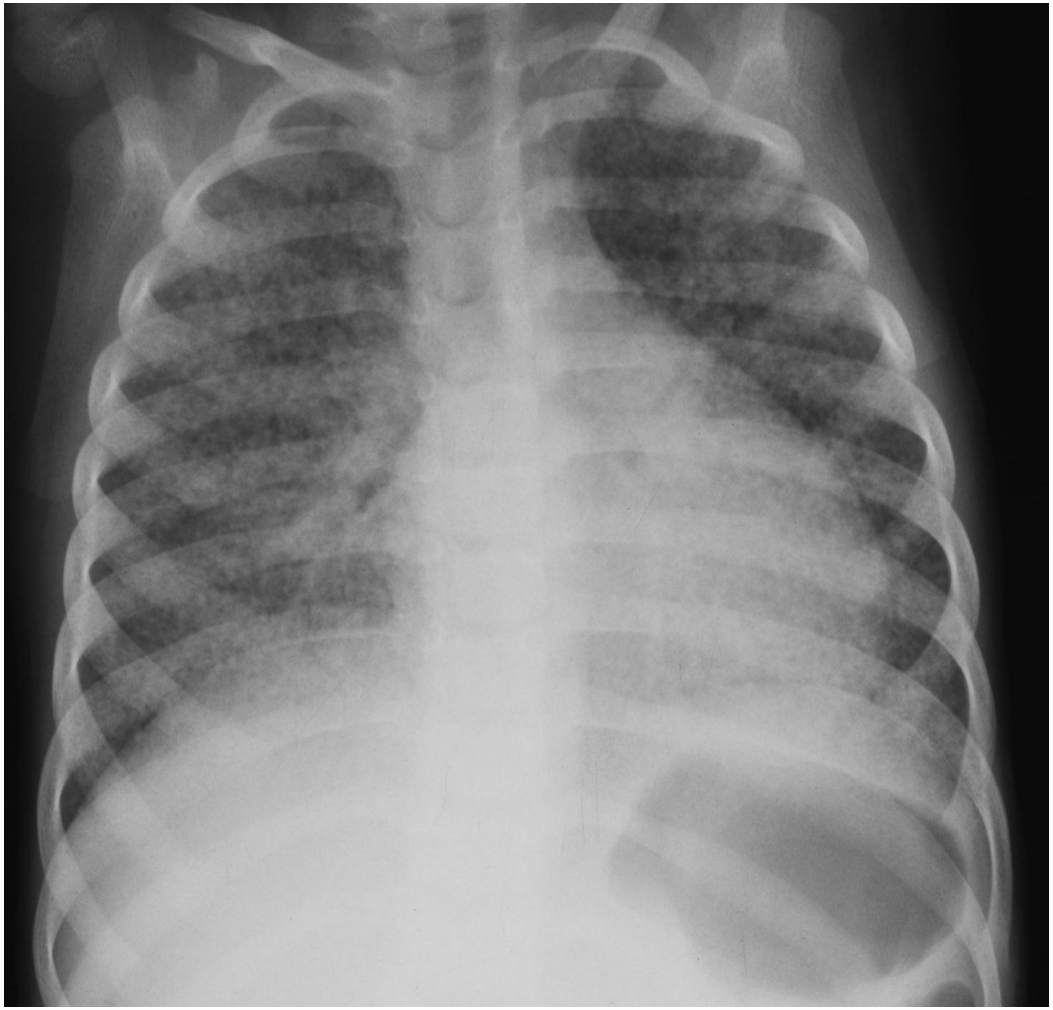
TB pleural effusion is common and tends to occur in school-aged children.

Pleural tap safe and very useful as may need to differentiate TB from suppurative empyema

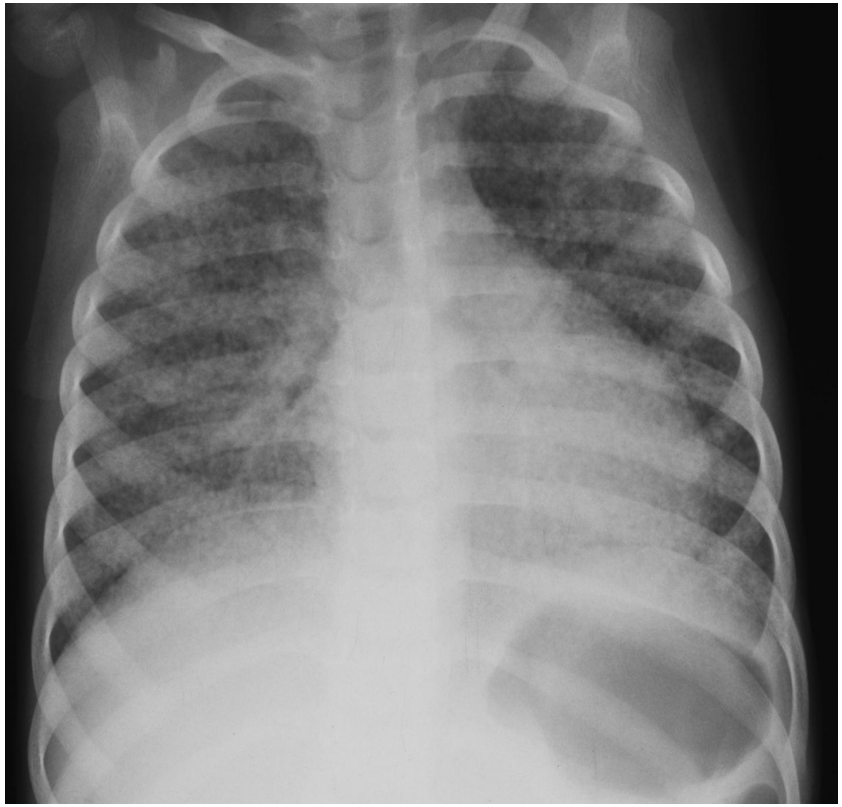
Other less common sites for effusion, usually painless, include peritoneal and pericardial spaces, also usually in school-aged children.

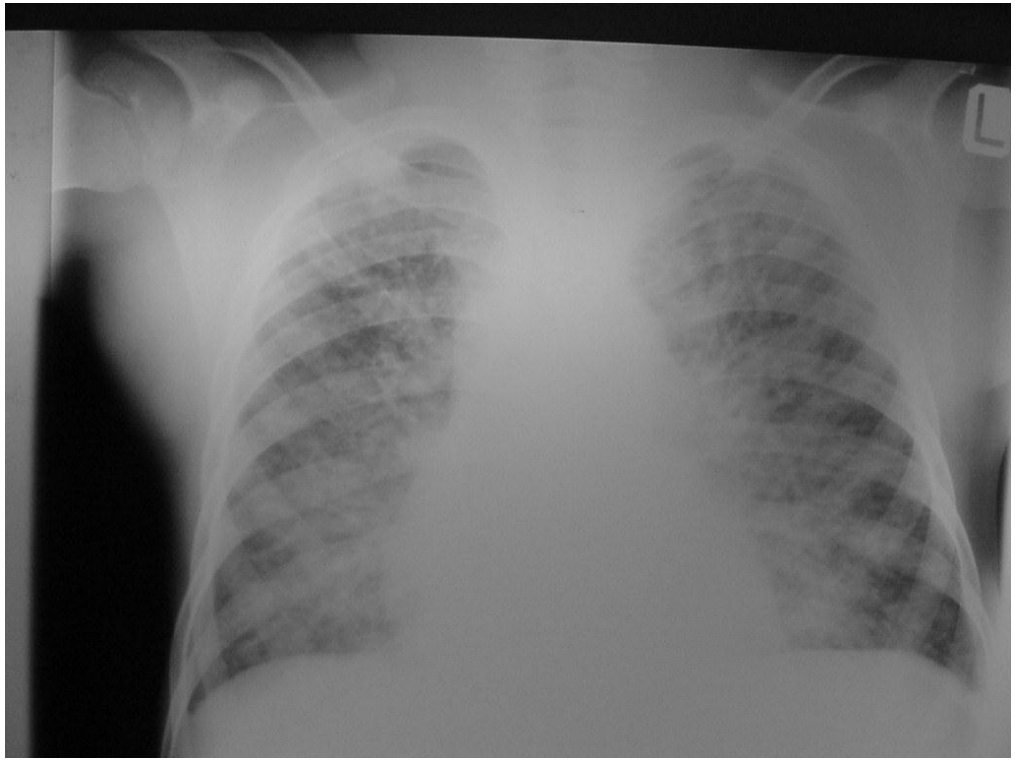
Ultrasound and tap of effusion for microscopy and protein is very useful.

This CXR shows the classical bilateral diffuse micronodular pattern consistent with miliary TB.



Miliary TB can be difficult to differentiate in HIV-infected children from the diffuse reticulonodular pattern of LIP.





Osteoarticular TB is not uncommon in children, again in school-aged group.

Spinal TB causes destruction of vertebral bodies leading to typical spinal deformity and possibly paralysis.

Hips and knees are the other typical site, usually mono-articular with painless effusion. Joint tap helpful to distinguish from septic arthritis.

HIV and TB in children

- HIV infected children at increased risk of exposure to TB and therefore TB infection
- HIV-infected children at high risk of TB disease in TB endemic setting
- Clinical approach to TB diagnosis in HIV-infected children is similar as for HIV-uninfected children
- Management of TB more complicated in HIV-infected children with significantly poorer outcomes
- Clinical diagnosis is more difficult especially for PTB as other HIV-related lung disease is common
- CPT and ART have a role in reducing TB-related death which is especially common within the first months following TB treatment

HIV and TB in children

- HIV infection status should be established in all children with suspected TB

- HIV test is extremely useful and important because:
  1. Exclusion of HIV reduces the diagnostic possibilities
  2. Need for HIV-related care in addition to management of TB

The diagnosis of PTB can be particularly challenging in HIV-infected child because clinical overlap with other HIV-related lung disease is common

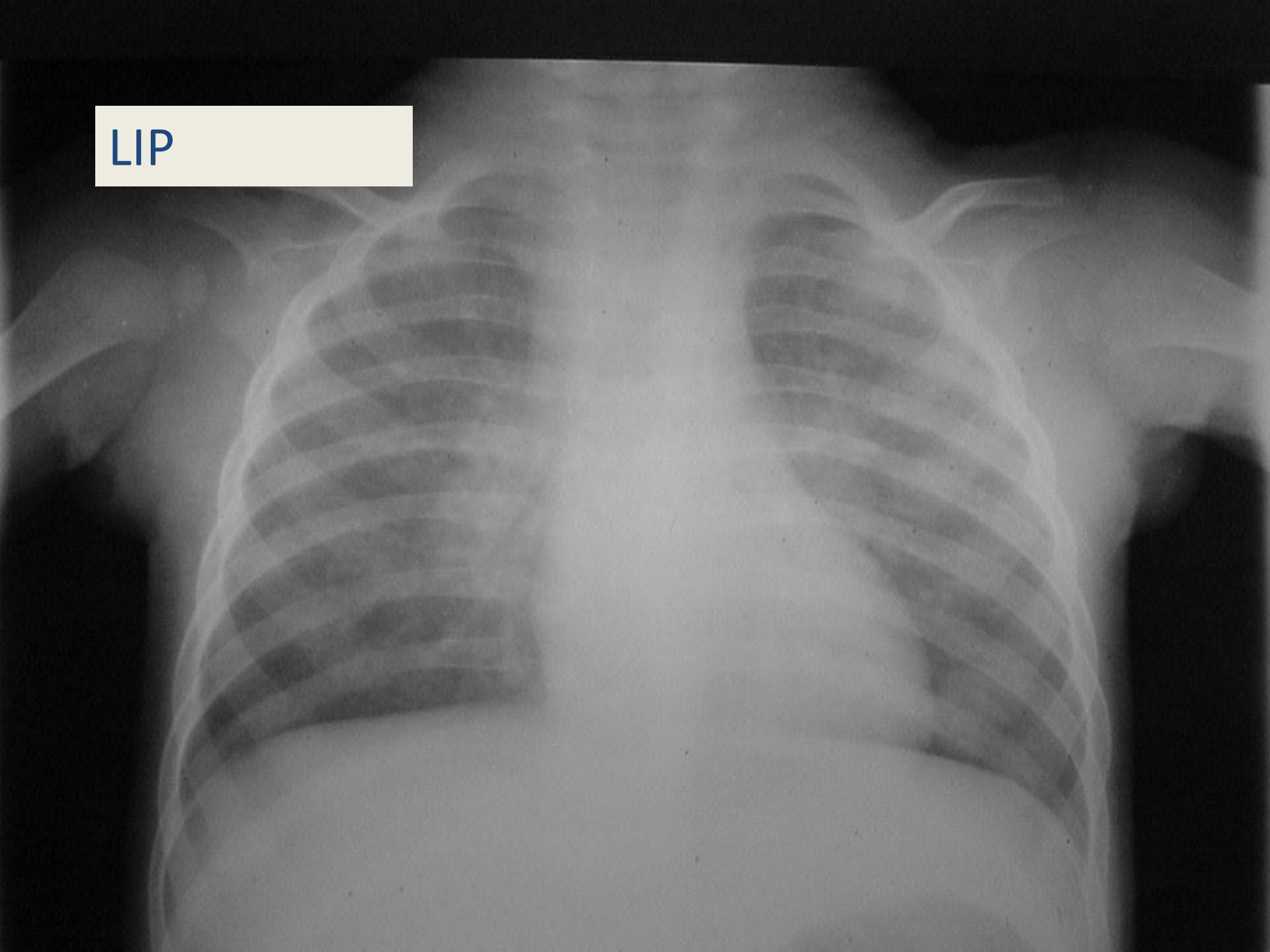
Cause	Clinical features
Recurrent pneumonia	Recurrent episodes of cough, fever and fast breathing that usually respond to antibiotics
LIP	Unusual before 1 year of age Associated with generalised symmetrical lymphadenopathy, clubbing, parotid enlargement. Nutritional status variable. CXR: diffuse reticulonodular pattern and bilateral perihilar adenopathy. No compression of airways
Tuberculosis	Persistent respiratory symptoms not responding to antibiotics. Often poor nutritional status; positive TB contact especially in younger children CXR: focal abnormalities and perihilar adenopathy
Bronchiectasis	Cough productive or purulent sputum; clubbing CXR: honeycombing usually of lower lobes Complicates recurrent bacterial pneumonia, LIP or TB
PcP	Common cause of severe, fatal pneumonia especially in infants. Persistent hypoxia is common Unusual after 1 year of age CXR: diffuse interstitial infiltration or hyperinflation
Mixed infection	Common problem: LIP, bacterial pneumonia, TB Consider when poor response to first-line empiric management
Kaposi sarcoma	Uncommon Characteristic lesions on skin or palate

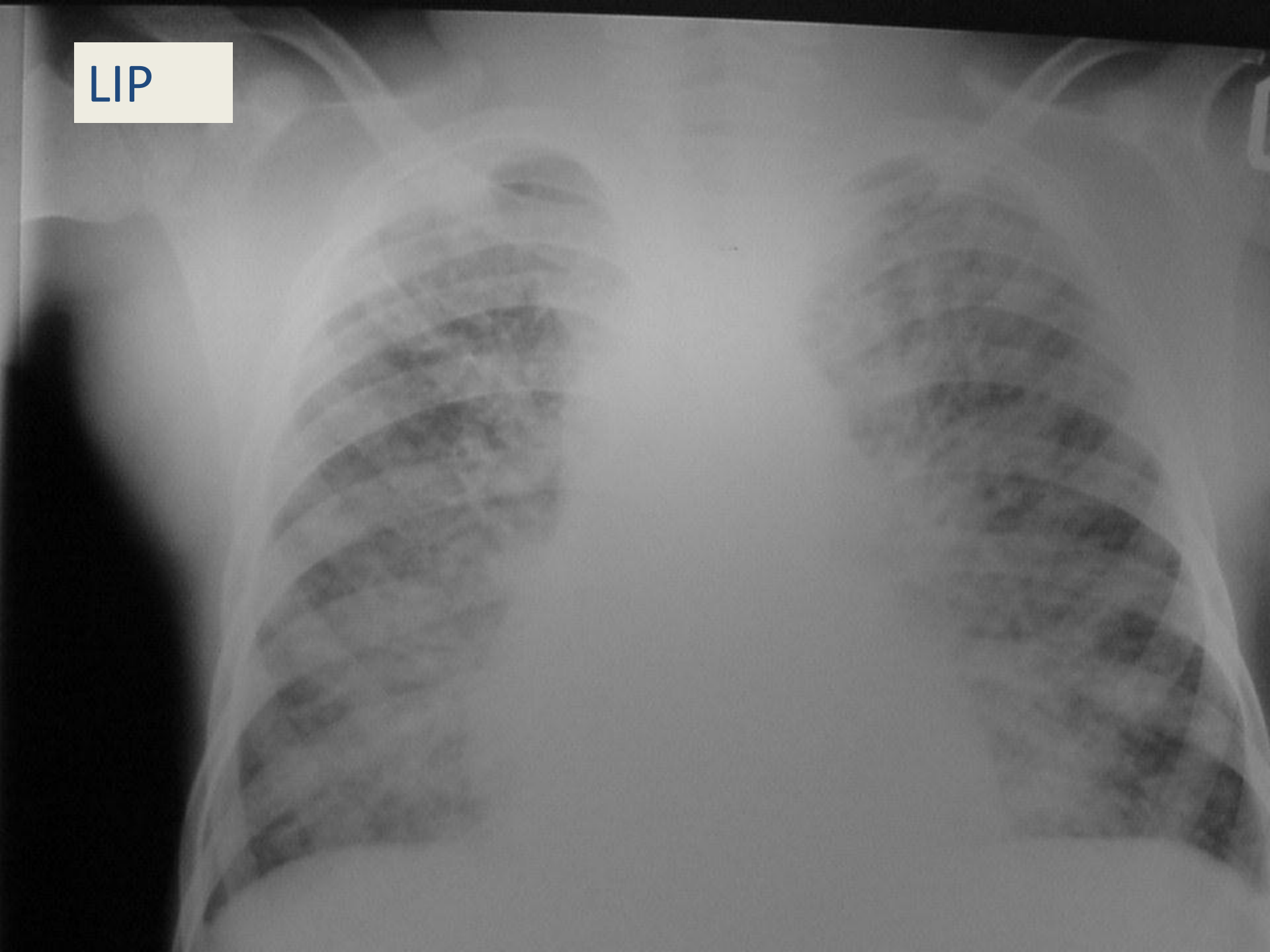
Clinical and radiological features that differentiate causes of chronic lung disease in HIV-infected children

Feature	PTB	Bronchiectasis	LIP	Miliary TB
Clinical				
Respiratory symptoms	Common	Common	Common	Uncommon
Persistent fever	Common	Common	Common	Common
Wasting	Common	Common	Variable	Common
Generalised lymphadenopathy	Uncommon	Uncommon	Common	Uncommon
Parotid enlargement	Rare	Rare	Common	Rare
Clubbing	Uncommon	Common	Common	Rare
Chest X-ray				
Focal parenchymal	Common	Common	Uncommon	Uncommon
Diffuse micronodular	Negative	Negative	Uncommon	Common
Diffuse reticular	Negative	Negative	Common	Negative
Lymphadenopathy	Common	Variable	Common	Uncommon

Note that co-morbidities are common in HIV-infected children

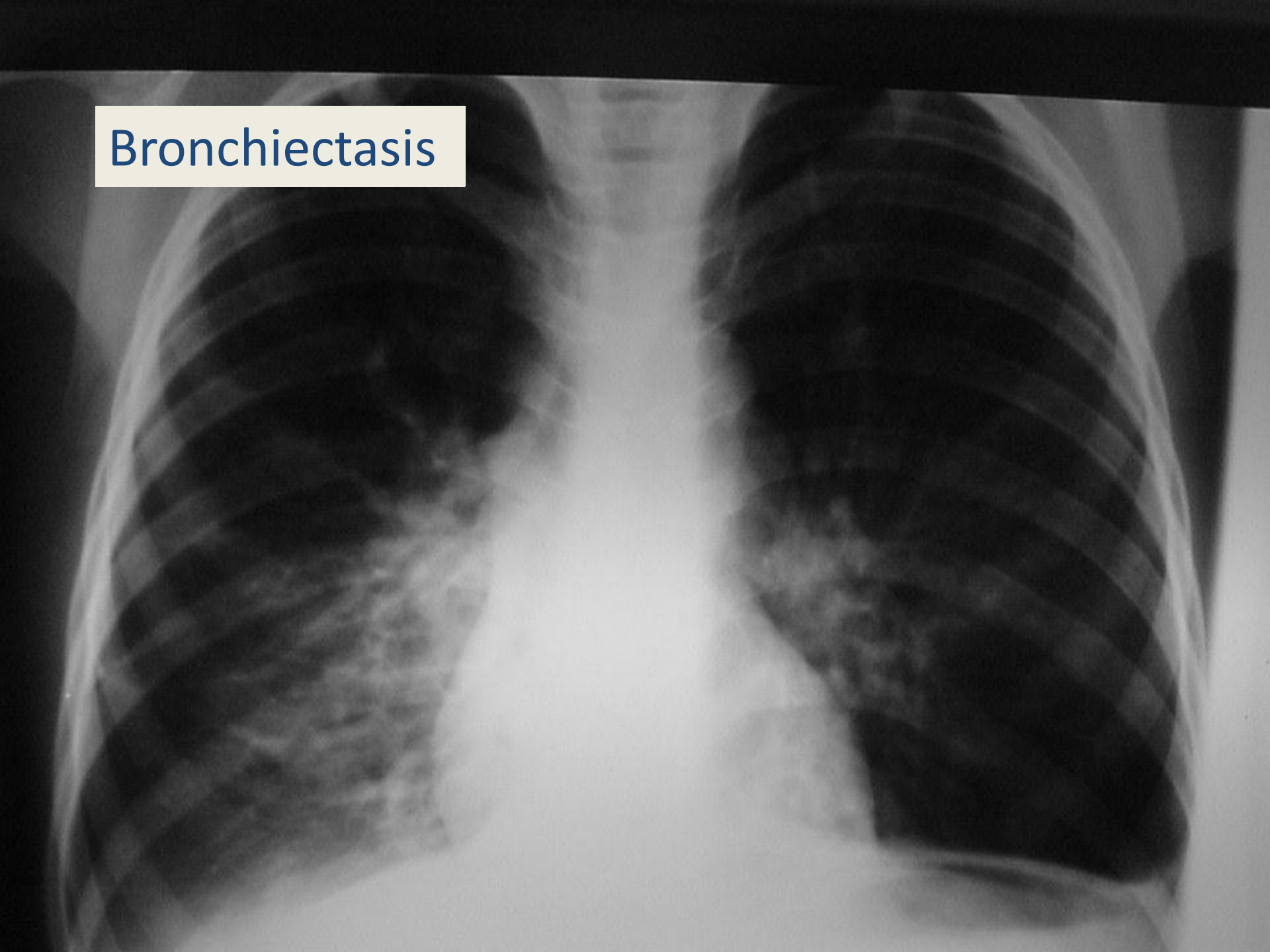
LIP



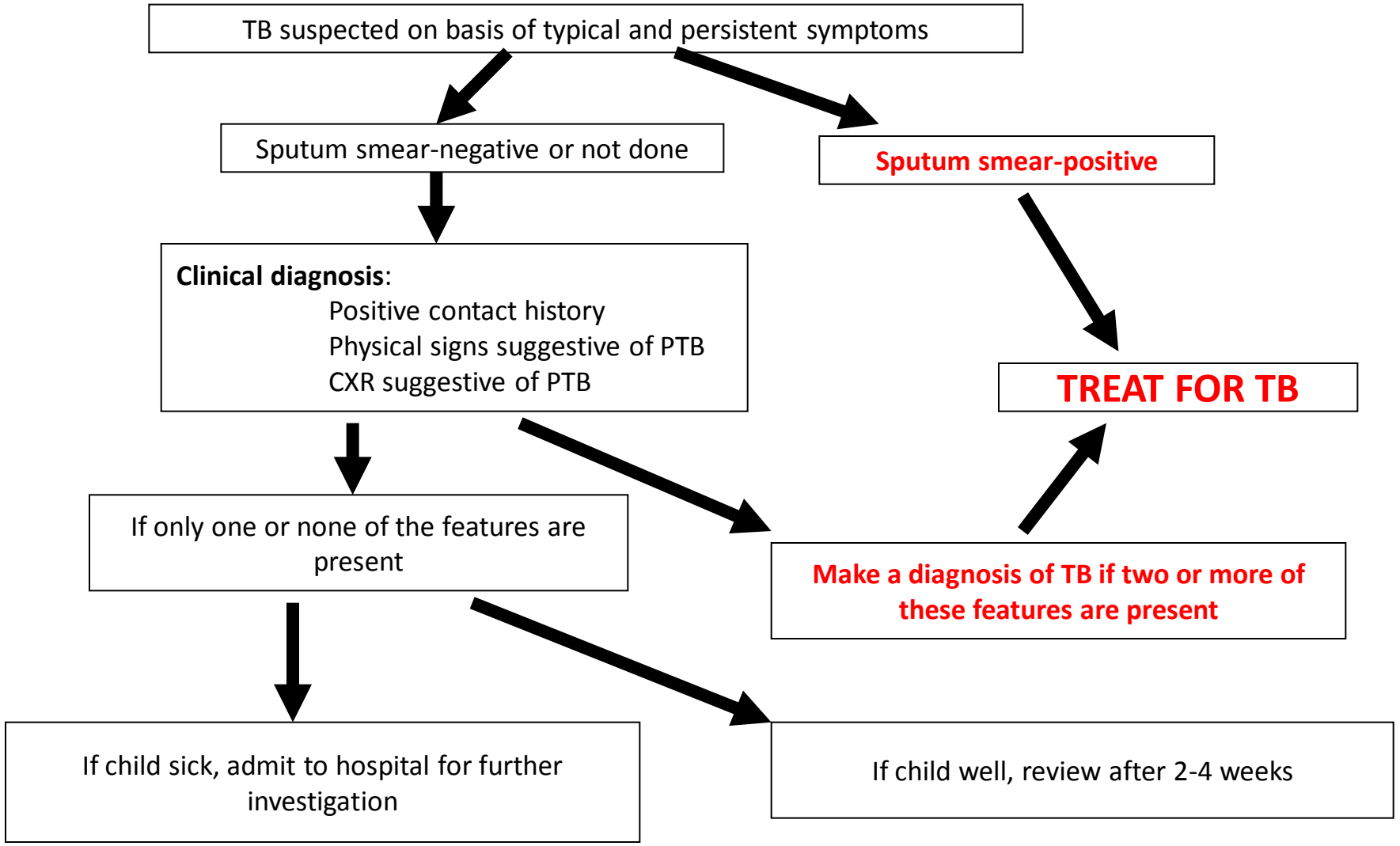

LIP

Miliary TB

Bronchiectasis

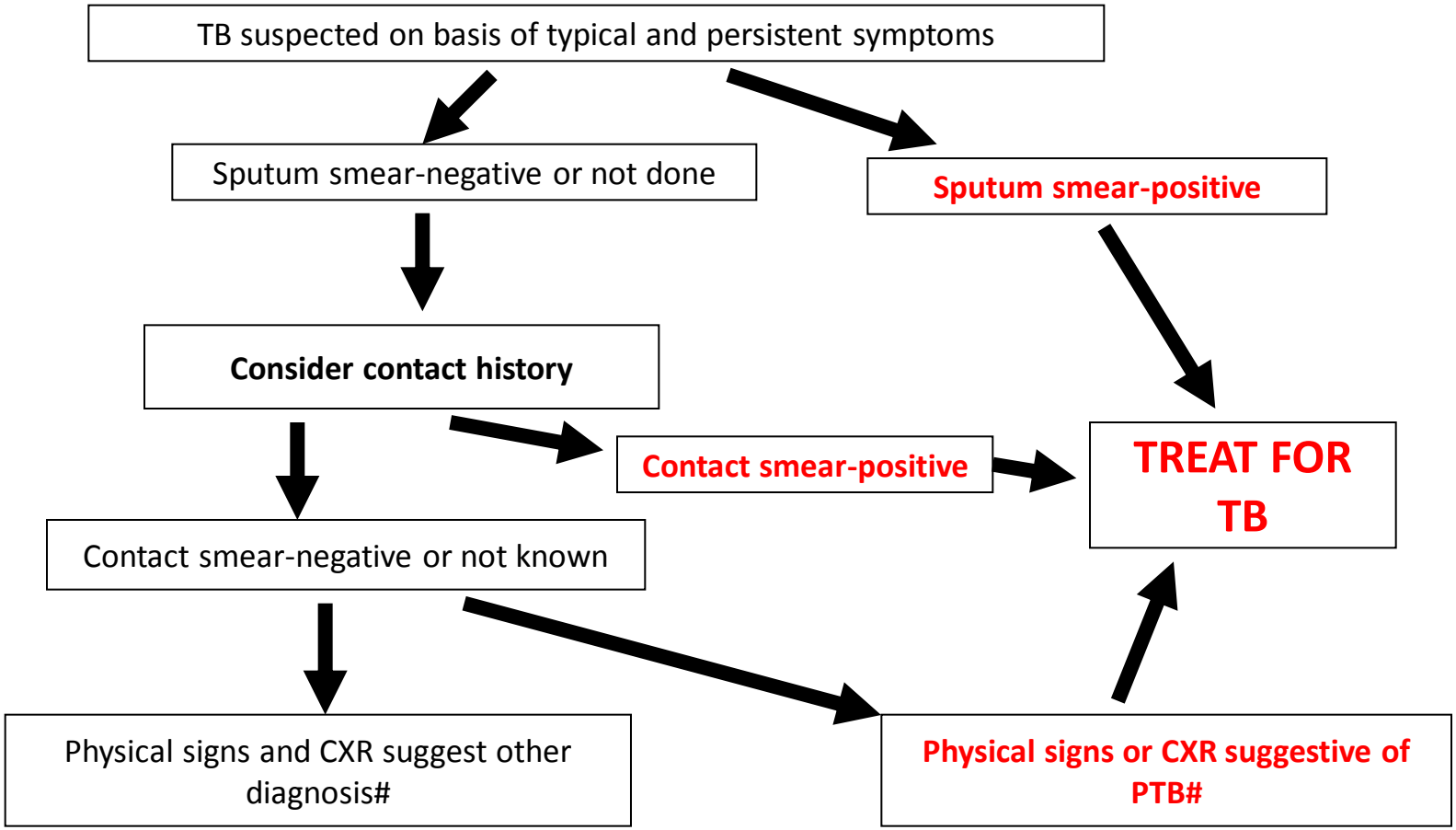


Approach to TB diagnosis in HIV-uninfected child



Decision for further outpatient review or inpatient management or referral will clearly depend on clinical state and available levels of care.

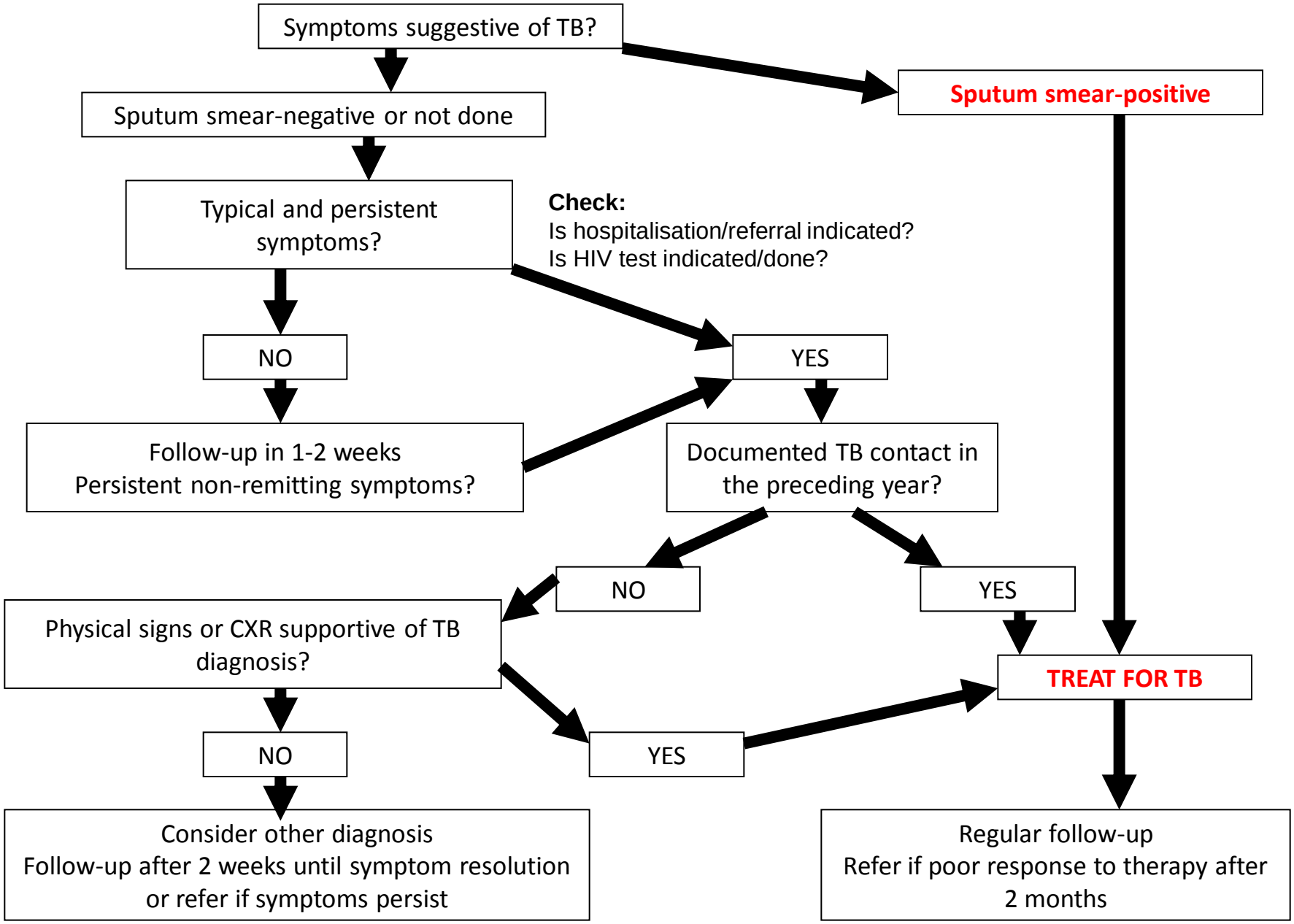
Approach to TB diagnosis in HIV-infected child



It can be difficult to clearly define what is “suggestive of PTB” on clinical or radiological findings in HIV-infected children because of clinical overlap between PTB and other forms of HIV-related lung disease: note further slides with Table and CXRs.

CXR abnormalities of PTB in HIV-infected children are mainly similar to those in HIV-uninfected children.

Guidance for the diagnosis of children who present with symptoms



Clinical approach to TB diagnosis

Note that clinical assessment should include decision for hospitalisation or referral depending on severity of clinical signs or need for other appropriate management

INDICATIONS REQUIRING HOSPITALIZATION/REFERRAL

- Severe forms of PTB and EPTB for further investigation and initial management
- Severe malnutrition for nutritional rehabilitation
- Signs of severe pneumonia (i.e. chest in-drawing) or respiratory distress
- Other co-morbidities e.g. severe anaemia

Referral should also be considered if

- Diagnostic uncertainty requiring further investigation at referral level
- Necessary for HIV-related care e.g. to commence ART

Checklist:
the symptomatic child with suspected TB

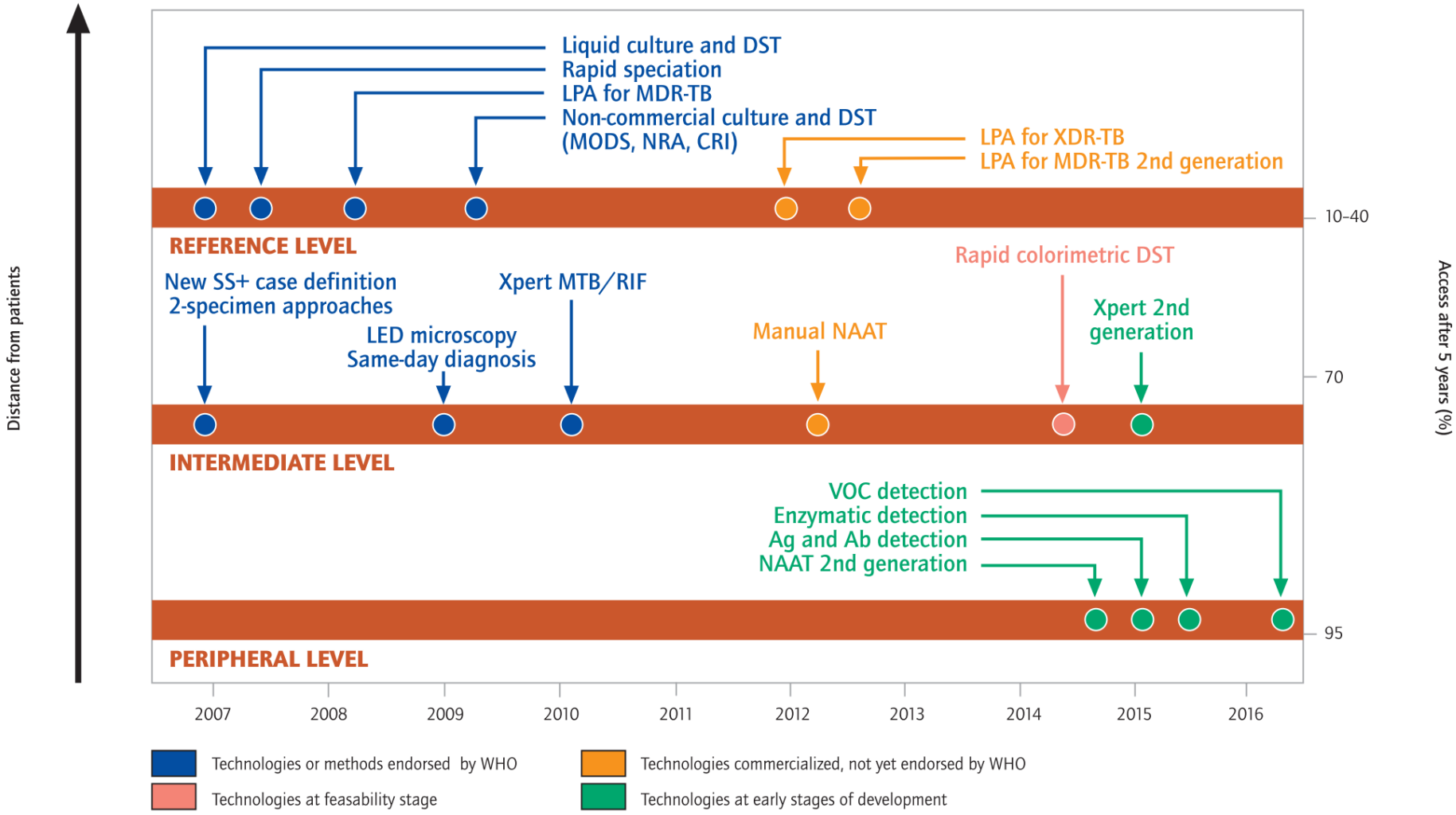
1. **Are the symptoms persistent and typical of TB?**
2. **Is there a positive contact history?**
3. **Check growth chart and record weight**
4. **Is the child HIV infected?**
5. **Is hospitalization or referral indicated?**

If the child is not so sick that hospitalization or immediate referral is required, then follow-up is an important tool to determine persistence of symptoms or poor weight gain.

Improving diagnosis of TB in children

- Improving collection of samples
  - Sputum induction yield usually higher than gastric aspirate
  - Two specimens better than one
  - Sputum induction can be done as outpatient
- Improving diagnosis of TB infection
  - IGRAs not recommended (not better than TST)
- Improving laboratory diagnosis
  - Improving culture methods
  - Xpert
- Improving quality of research of new diagnostics
  - Standardizing research approaches and reporting
  - Multi-centre collaborations improve sample size and standards

Diagnostics pipeline aims for an accurate point of care test for use at all levels of care – close to patient



Children are rarely involved in novel diagnostic studies of TB especially those that continue to use sputum

Test	Publications	
	Adults	Children
Fine needle aspiration	> 6000	140
Fluorescence Microscopy (FM)	299	1
LED-FM	33	0
MODS	31	2
BACTEC 960	49	0
Fully automated BACTEC	13	0
Line Probe assays	113	1
LAMP	13	0
Automated NAAT (Xpert)	32	4

Xpert MTB/RIF studies in African children

	South Africa Nicol M et al Lancet Infect Dis 2011	Tanzania Rachow A et al Clin Infect Dis 2012	Zambia Bates M et al Lancet Infect Dis 2012
Numbers	452	164	930
Median age	19.4 months	5.8 years	2 years
HIV prevalence	24 %	51 %	31 %
Smear positive	27 (6%)	7 (4%)	15 (1.6%)
Culture positive	70 (15%)	28 (17%)	58 (6.2%)
Xpert sensitivity	74 %	75 %	72 %
Xpert specificity	98 %	100 %	99 %
Median time to result	1 day	2 days	

Child TB data and NTP

- All children diagnosed with TB should be registered with NTP
- Important information includes age, TB type, HIV status and treatment outcome – as for all cases with TB
- These data are important for M&E as well as informing training activities, drug procurement, strategic plans etc

Revision and self-assessment

List three common clinical symptoms in a child presenting with TB

List three reasons why age is important in assessment of a child with suspected TB disease

List three aspects of contact history that are relevant

Discuss sputum for examination: indications and limitations

List clinical presentation of three common forms of EPTB in children

Discuss HIV testing: indications and implications for management