Module 2

DIAGNOSIS OF CHILDHOOD TB
TB disease in children: clinical epidemiology

• Most cases occur in young children ( <5 years)

• 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

## Childhood TB caseload: Malawi 1998


<table>
<thead>
<tr>
<th>Malawi NTP, 1998</th>
<th>numbers (proportion of childhood caseload)</th>
<th>proportion of child TB caseload</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total caseload</td>
<td>22,982</td>
<td></td>
</tr>
<tr>
<td>Total childhood</td>
<td>2,739</td>
<td></td>
</tr>
<tr>
<td>0-4 years</td>
<td>1,615</td>
<td>59 %</td>
</tr>
<tr>
<td>5-14 years</td>
<td>1,124</td>
<td>41 %</td>
</tr>
<tr>
<td>Smear-positive PTB</td>
<td>127</td>
<td>5 %</td>
</tr>
<tr>
<td>Smear-negative PTB</td>
<td>1,804</td>
<td>65 %</td>
</tr>
<tr>
<td>EPTB</td>
<td>808</td>
<td>30 %</td>
</tr>
</tbody>
</table>
# Types of childhood EPTB disease

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

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 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%
  - < 3 years: specificity: 82.6%; PPV: 88.6%
- Less useful in young
- Performed poorly in HIV-infected

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
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

Robert Gie, IUATLD

Freely available on-line

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

# 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

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

<table>
<thead>
<tr>
<th>Feature</th>
<th>PTB</th>
<th>Bronchiectasis</th>
<th>LIP</th>
<th>Miliary TB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Persistent fever</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Wasting</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Generalised lymphadenopathy</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Parotid enlargement</td>
<td>Rare</td>
<td>Rare</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Clubbing</td>
<td>Uncommon</td>
<td>Common</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Chest X-ray</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal parenchymal</td>
<td>Common</td>
<td>Common</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Diffuse micronodular</td>
<td>Negative</td>
<td>Negative</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Diffuse reticular</td>
<td>Negative</td>
<td>Negative</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

Note that co-morbidities are common in HIV-infected children.
Miliary TB
Approach to TB diagnosis in HIV-uninfected child

TB suspected on basis of typical and persistent symptoms

- Sputum smear-negative or not done
- Sputum smear-positive

Clinical diagnosis:
- Positive contact history
- Physical signs suggestive of PTB
- CXR suggestive of PTB

If only one or none of the features are present

- Make a diagnosis of TB if two or more of these features are present

If child sick, admit to hospital for further investigation

If child well, review after 2-4 weeks

TREAT FOR TB

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

- TB suspected on basis of typical and persistent symptoms
  - Sputum smear-negative or not done
    - Consider contact history
      - Contact smear-negative or not known
        - Physical signs and CXR suggest other diagnosis#
      - Contact smear-positive
        - Physical signs or CXR suggestive of PTB#
    - Sputum smear-positive
      - TREAT FOR TB

# 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

Symptoms suggestive of TB?

Sputum smear-negative or not done

Typical and persistent symptoms?

Follow-up in 1-2 weeks

Persistent non-remitting symptoms?

Documented TB contact in the preceding year?

Physical signs or CXR supportive of TB diagnosis?

Consider other diagnosis

Follow-up after 2 weeks until symptom resolution or refer if symptoms persist

Sputum smear-positive

Check:
Is hospitalisation/referral indicated?
Is HIV test indicated/done?

NO

YES

TREAT FOR TB

Regular follow-up
Refer if poor response to therapy after 2 months
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.

<table>
<thead>
<tr>
<th>Test</th>
<th>Publications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adults</td>
</tr>
<tr>
<td>Fine needle aspiration</td>
<td>&gt; 6000</td>
</tr>
<tr>
<td>Fluorescence Microscopy (FM)</td>
<td>299</td>
</tr>
<tr>
<td>LED-FM</td>
<td>33</td>
</tr>
<tr>
<td>MODS</td>
<td>31</td>
</tr>
<tr>
<td>BACTEC 960</td>
<td>49</td>
</tr>
<tr>
<td>Fully automated BACTEC</td>
<td>13</td>
</tr>
<tr>
<td>Line Probe assays</td>
<td>113</td>
</tr>
<tr>
<td>LAMP</td>
<td>13</td>
</tr>
<tr>
<td>Automated NAAT (Xpert)</td>
<td>32</td>
</tr>
</tbody>
</table>
### Xpert MTB/RIF studies in African children

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