Module 3

TREATMENT OF CHILDHOOD TB
Burden of TB in children

- Tuberculosis (TB) in children is common wherever TB is common in adults i.e. TB endemic settings
- TB is an important cause of illness and death in children in many TB endemic countries
- Over half a million (550 000) children become ill with tuberculosis (TB) each year.
- Up to 80 000 HIV-uninfected children die of TB every year*.
- 70–80% of children with TB, have the disease in their lungs (pulmonary TB). The rest are affected by TB disease in other parts of the body (extrapulmonary TB).
- There were over ten million orphans due to parental TB deaths in 2010.
- An understanding of the risks for infection and disease due to TB in children is critical for improved diagnosis and preventive management
- The HIV epidemic has increased the burden of childhood TB and the clinical challenges
- The main benefit of neonatal BCG is protection against severe disseminated TB in children
Treatment of TB in children

• Principles of treatment of TB in children are same as for adults – with similar regimens

• Most children have paucibacillary disease
Treatment response in children

- Children with TB usually respond well with symptomatic improvement during intensive phase and good outcome.

- HIV-infected children with TB show poorer response to TB treatment – and require ART and CPT as well as TB treatment.
### Short-course chemotherapy in children

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Site</th>
<th>% EPTB</th>
<th>F/up period</th>
<th>Relapse</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biddulph J. PIDJ 1990</td>
<td>639</td>
<td>PNG</td>
<td>35%</td>
<td>24 mths</td>
<td>7 of 373</td>
<td>2 %</td>
</tr>
<tr>
<td>Reis FJ et al. Am Rev Resp Dis 1990</td>
<td>117</td>
<td>Brazil</td>
<td>0%</td>
<td>21 mths</td>
<td>0</td>
<td>0 %</td>
</tr>
<tr>
<td>Te Water Naude et al. PIDJ 2000</td>
<td>206</td>
<td>South Africa</td>
<td>0%</td>
<td>18-36 mths</td>
<td>1</td>
<td>0 %</td>
</tr>
<tr>
<td>Al Dossary et al. PIDJ 2002</td>
<td>175</td>
<td>USA</td>
<td>9%</td>
<td>4 years</td>
<td>1</td>
<td>0 %</td>
</tr>
</tbody>
</table>
HIV infection was associated with a very poor outcome from TB in children in the pre-HAART era.

<table>
<thead>
<tr>
<th>Country</th>
<th>Complete recovery HIV+</th>
<th>Complete recovery HIV-</th>
<th>Mortality HIV+</th>
<th>Mortality HIV-</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Africa</td>
<td>65%</td>
<td>95%</td>
<td>0.002</td>
<td>15%</td>
<td>0%</td>
</tr>
<tr>
<td>Jeena et al 1994</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cote d’Ivoire</td>
<td>23%</td>
<td>3%</td>
<td>0.01</td>
<td>16%</td>
<td>0%</td>
</tr>
<tr>
<td>Mukadi et al 1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>63%</td>
<td>97%</td>
<td>&lt;0.001</td>
<td>16%</td>
<td>0%</td>
</tr>
<tr>
<td>Espinal et al 1994</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethiopia</td>
<td>55%</td>
<td>73%</td>
<td>0.01</td>
<td>38%</td>
<td>6%</td>
</tr>
<tr>
<td>Palme et al 2002</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Dosages are calculated according to weight (not age)

Weight gain is an important indicator of improvement

Record weight at each follow-up visit and dosages may need to be adjusted accordingly
Recommended dosages in WHO 2006 guidance have since been updated

The dosages were revised and changed in 2010 (Rapid Advice) but this has caused problems for implementation when using currently available FDCs – especially the ratio of R:H and the range for isoniazid.

The revised WHO Guidance 2014 has revised dose range for isoniazid and provided weight band tables to facilitate implementation using FDCs.

Important to be consistent with national guidelines and develop weight band tables depending on available drug preparations.
Revised dosages

These are the revised dosages (WHO 2014) for children up to 25 kgs:

- **Rifampicin**: 15 (10-20) mg/kg/day
- **Isoniazid**: 10 (7-15) mg/kg/day
- **Pyrazinamide**: 35 (30-40) mg/kg/day
- **Ethambutol**: 20 (15-25) mg/kg/day

From 25 kgs, can change to adult dosages and preparations

Note also other revisions to recommendations:

1. Four drugs (RHZE) in intensive phase for all new cases in HIV endemic setting
2. No intermittent regimens in HIV-endemic setting
3. Streptomycin no longer recommended for first-line therapy
4. 12-month regimens for TBM and osteo-articular TB
Pharmacokinetics of Isoniazid, Rifampin, and Pyrazinamide in Children Younger than Two Years of Age with Tuberculosis: Evidence for Implementation of Revised World Health Organization Recommendations\textsuperscript{7}

Thee S et al, AAC 2011
TB treatment and toxicity in children

- TB drugs are very well tolerated in almost all children.
- Adverse events are unusual and the most important is hepatotoxicity.
- Ethambutol can be safely used at recommended dosages in all ages.
## Adverse events are uncommon in children

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Regimen</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biddulph J. PIDJ 1990</td>
<td>639</td>
<td>2 RHZS 4 R₂H₂</td>
<td>2%</td>
</tr>
<tr>
<td>Te Water Naude et al. Pediatr Infect Dis J 2000</td>
<td>117</td>
<td>6 RHZ</td>
<td>Nil</td>
</tr>
<tr>
<td>Te Water Naude et al. Pediatr Infect Dis J 2000</td>
<td>89</td>
<td>2 R₂H₂Z₂ 4 R₂H₂</td>
<td>Nil</td>
</tr>
<tr>
<td>Al Dossary et al. Pediatr Infect Dis J 2002</td>
<td>175</td>
<td>2 RHZ 4 R₂H₂</td>
<td>1.2%</td>
</tr>
</tbody>
</table>
Use of ethambutol in children

- Ethambutol is recommended as fourth drug in intensive phase of first-line regimens
- Risk of toxicity is dose-related and related to duration of therapy
- The risk of toxicity is negligible for children of any age when ethambutol is used at recommended dosages – especially as duration is usually limited to 2 months
- Ethambutol can be safely used at recommended dosages in all ages
Ethambutol efficacy and toxicity: literature review and recommendations for daily and intermittent dosage in children
Drug dosages in children are determined by weight

- Useful to have a table showing numbers or portion of tablets required for weight bands up to 25 kg

- This will depend upon what is available and used for each single drug or as fixed-dose combination

- Important to achieve consistency of usage nationally and to ensure availability

- Weight often changes (increases) with treatment so that dosages may need to be adjusted accordingly
Survey of NTPs and current recommendations

34 countries from 5 regions
Dec 2011-Feb 2012
10 TB high-burden countries

12 use 2006 dosage guidelines and
19 use 2010 dosage guidelines

Majority recommend RHZ (some add E in older children > 10 years)

Obstacles to implementation relate to awaiting update of guidelines, need for training, that available FDCs do not match dosage guidelines, the need for change not accepted by local experts, and quantity of pills required is increased

Preventive therapy not implemented and shortages and stock outs of H100

Recommended drug dosages should be consistent with national guidelines
Example of a weight band table when using the most widely available FDC

<table>
<thead>
<tr>
<th>Weight bands</th>
<th>Intensive Phase</th>
<th>Continuation Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RHZ</td>
<td>E</td>
</tr>
<tr>
<td>60/30/150</td>
<td>100</td>
<td>60/30</td>
</tr>
<tr>
<td>4-6kg</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>7-10kg</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>11-14kg</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>15-19 kg</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>20-24kg</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>25 kg+</td>
<td>Go to adult dosages and preparations</td>
<td></td>
</tr>
</tbody>
</table>
Example of a weight band table when using the “new” FDC being developed

<table>
<thead>
<tr>
<th>Weight bands</th>
<th>Numbers of tablets</th>
<th>Intensive Phase</th>
<th>Continuation Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RHZ</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75/50/150</td>
<td>100</td>
</tr>
<tr>
<td>4-7kg</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>8-11kg</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>12-15kg</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>16-24 kg</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>25 kg+</td>
<td></td>
<td>Go to adult dosages and preparations</td>
<td></td>
</tr>
</tbody>
</table>
Treatment of TB and NTP in children

• Register all children receiving anti-TB treatment in the NTP register

• Report treatment outcomes for children
Treatment failure in children

- Treatment response is commonly noted by the end of the intensive phase and is indicated by resolution of symptoms and weight gain.
- Smear-positive cases should follow the standard NTP follow-up microscopy.
- HIV status should be determined in all children treated for TB as important confounder for outcome and other HIV-related treatment required (see TB/HIV section).
- A poor response to TB treatment may indicate:
  - Poor adherence
  - Incorrect diagnosis
  - TB due to drug-resistant organism (see MDR-TB section)
  - Incorrect dosages
  - Co-morbidities not managed e.g. HIV
Treatment outcomes in children with TB

• Treatment outcomes should be routinely recorded and reported for child TB cases

• Outcome categories are the same as for adult cases (although few child TB cases would meet the criteria for “cured”)

• Treatment outcomes are important data for monitoring & evaluation

• There are few NTP data of treatment completion – but may be poor in children
Treatment adherence in children

Adherence for the full course of TB treatment is a challenge in children

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>No.</th>
<th>Poor adherence or defaulted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al Dossary et al. PIDJ 2002</td>
<td>USA</td>
<td>175</td>
<td>9% poor adherence</td>
</tr>
<tr>
<td>Biddulph J. PIDJ 1990</td>
<td>PNG</td>
<td>639</td>
<td>28% defaulted</td>
</tr>
<tr>
<td>Te Water Naude et al. PIDJ 2000</td>
<td>South Africa</td>
<td>206</td>
<td>22% poor adherence</td>
</tr>
<tr>
<td>Meissner PE et al. Int J TB Lung Dis 2002</td>
<td>Uganda</td>
<td>236</td>
<td>28% poor adherence</td>
</tr>
<tr>
<td>Harries AD et al. Int J TB Lung Dis 2002</td>
<td>Malawi</td>
<td>2,739</td>
<td>13% defaulted</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21% unknown</td>
</tr>
</tbody>
</table>
WHO also now recommends that all cases of child TB should be registered and reported within age bands: 0-4 years and 5-14 years

### Quarterly Report on TB Case Registration in Basic Management Unit

<table>
<thead>
<tr>
<th>Programme</th>
<th>Form 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients registered</td>
<td>Patients registered during</td>
</tr>
<tr>
<td>coordinator:</td>
<td>quarter of year</td>
</tr>
<tr>
<td>Signature:</td>
<td></td>
</tr>
<tr>
<td>Date of completion</td>
<td></td>
</tr>
<tr>
<td>of this form:</td>
<td></td>
</tr>
</tbody>
</table>

#### Block 1: All TB cases registered

<table>
<thead>
<tr>
<th>Pulmonary sputum smear microscopy positive</th>
<th>New pulmonary sputum smear microscopy negative</th>
<th>Pulmonary sputum smear microscopy not done / not available</th>
<th>New extrapulmonary</th>
<th>Other previously treated</th>
<th>TOTAL</th>
<th>All cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>New cases</td>
<td>New cases</td>
<td>New cases</td>
<td>New cases</td>
<td>New cases</td>
<td>New cases</td>
<td>New cases</td>
</tr>
<tr>
<td>Previous treated</td>
<td>Previous treated</td>
<td>Previous treated</td>
<td>Previous treated</td>
<td>Previous treated</td>
<td>Previous treated</td>
<td>Previous treated</td>
</tr>
<tr>
<td>Relapses</td>
<td>Relapses</td>
<td>Relapses</td>
<td>Relapses</td>
<td>Relapses</td>
<td>Relapses</td>
<td>Relapses</td>
</tr>
<tr>
<td>After failure</td>
<td>After failure</td>
<td>After failure</td>
<td>After failure</td>
<td>After failure</td>
<td>After failure</td>
<td>After failure</td>
</tr>
<tr>
<td>0-4 yrs</td>
<td>0-4 yrs</td>
<td>0-4 yrs</td>
<td>0-4 yrs</td>
<td>0-4 yrs</td>
<td>0-4 yrs</td>
<td>0-4 yrs</td>
</tr>
<tr>
<td>5-14 yrs</td>
<td>5-14 yrs</td>
<td>5-14 yrs</td>
<td>5-14 yrs</td>
<td>5-14 yrs</td>
<td>5-14 yrs</td>
<td>5-14 yrs</td>
</tr>
<tr>
<td>≥ 15 yrs</td>
<td>≥ 15 yrs</td>
<td>≥ 15 yrs</td>
<td>≥ 15 yrs</td>
<td>≥ 15 yrs</td>
<td>≥ 15 yrs</td>
<td>≥ 15 yrs</td>
</tr>
<tr>
<td>Total</td>
<td>Total</td>
<td>Total</td>
<td>Total</td>
<td>Total</td>
<td>Total</td>
<td>Total</td>
</tr>
</tbody>
</table>

#### Block 2: New pulmonary sputum smear microscopy positive cases – Age group

<table>
<thead>
<tr>
<th>Sex</th>
<th>0-4</th>
<th>5-14</th>
<th>15-24</th>
<th>25-34</th>
<th>35-44</th>
<th>45-64</th>
<th>55-64</th>
<th>≥ 65</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Block 3: Laboratory activity – sputum smear microscopy

<table>
<thead>
<tr>
<th>No. of TB suspects examined for diagnosis by sputum smear microscopy</th>
<th>No. of TB suspects with positive sputum smear microscopy result</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of TB suspects with positive sputum smear microscopy result</td>
<td></td>
</tr>
</tbody>
</table>

#### Block 4: TB/HIV activities

<table>
<thead>
<tr>
<th>No. patients tested for HIV before or during TB treatment</th>
<th>No. patients HIV positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>New sputum smear microscopy positive TB cases</td>
<td></td>
</tr>
<tr>
<td>All TB cases</td>
<td></td>
</tr>
</tbody>
</table>

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1. Registration period is based on date of registration of cases in the TB Register, following the start of treatment. Q1: 1 January–31 March; Q2: 1 April–30 June; Q3: 1 July–30 September; Q4: 1 October–31 December.

2. All previously treated cases and those not treated in areas routinely using culture, a separate form for using culture should be used.

3. Other previously treated cases include pulmonary cases with unknown history of previous treatment, previously treated sputum smear microscopy negative pulmonary cases and previously treated extrapulmonary cases. Transferred in and chest cases are excluded.

4. Data entered from the TB Laboratory Register based on "Date specimen received" in the laboratory during the quarter, without including patients with examination because of follow-up.

5. Documented evidence of HIV tests (and results) performed in any recognized facility before TB diagnosis or during TB treatment (ill and of the quarter) should be reported here.
Importance of data of TB in children by NTP

- Value of audit to identify challenges/barriers
  - Situational analysis
  - Case management and outcome
  - Background data and potential focus for operational research

- Improved child-related NTP data and activities
  - Allocation of resources for child TB activities
  - Drug procurement
  - Focus for training
  - Advocacy

- Monitoring & evaluation
TB and HIV in children

- A comprehensive approach to management is critical

- HIV test is indicated in all children with suspected and confirmed TB

- Approach to diagnosis of TB is similar as for HIV-uninfected children

- Treatment for TB is same as for HIV-uninfected children

- All children with TB/HIV should receive CPT and ART – and nutritional support often needed

- All HIV-infected children need to be screened for TB disease.

- The management of children with TB/HIV should be integrated and all family members are counseled and tested for HIV and screened for TB

Possible reasons why outcome is poorer on TB treatment in HIV-infected children

- Immunosuppression
  - emphasises the importance of early ART in reducing mortality

- High risk of co-morbidities
  - invasive bacterial disease: emphasises the importance of concurrent cotrimoxazole preventive therapy
  - severe malnutrition: emphasises the importance of nutritional support

- Poorer adherence due to pill burden and risk of illness/death of primary caregiver

- Risk of DR TB in HIV-infected populations

- Diagnosis is incorrect and child has other HIV-related lung disease, e.g. lymphocytic interstitial pneumonitis (LIP)
Child TB management and HIV

Principles of treatment of TB in HIV-infected children is similar to HIV-uninfected children

ART improves outcome for HIV-infected children treated for TB

It is recommended that HIV-infected children receive
1. Four first-line drugs (RHZE) in intensive phase for suspected or confirmed drug-sensitive TB irrespective of severity of disease
2. Similar duration of regimens as for HIV-uninfected
3. ART as recommended within 2-8 weeks of starting TB treatment or continue ART
4. Cotrimoxazole preventive therapy
5. Pyridoxine supplement
6. Nutritional support

HIV-infected children are at increased risk of relapse and drug resistant TB
## Child TB management and ART

<table>
<thead>
<tr>
<th>Age / weight</th>
<th>Antiretroviral therapy (ART)*</th>
</tr>
</thead>
</table>
| <3yrs or <10kg | *Retain or start on the following regimens*  
| | Nucleoside Reverse Transcriptase Inhibitor (NRTI) backbone – use 2 NRTI’s  
| | Third drug  
| | If on nevirapine  
| | • switch to lopinavir/ritonavir (Kaletra®)  
| | with additional ritonavir to achieve mg for mg parity with lopinavir  
| | • continue for 1-2 weeks after TB treatment has been stopped  
| | • If not possible, – continue NVP dose at the upper end of the dosage scale  
| | If on lopinavir/ritonavir (Kaletra®)  
| | • use additional ritonavir as above  
| | • triple NRTI therapy is an option, if baseline viral load <100 000 copies/ml |
| ≥3yrs and ≥10kg | *Retain or start on the following regimens*  
| | 2 NRTI’s as backbone  
| | Third drug  
| | If on nevirapine  
| | • switch to efavirenz  
| | • if not available continue on nevirapine dose at the upper end of the dosage scale  
| | If on lopinavir/ritonavir (Kaletra®)  
| | • consider switch to efavirenz, only if undetectable viral load*  
| | • alternatively use additional ritonavir as above  
| | • triple NRTI therapy is an option, if baseline viral load <100 000 copies/ml |

TB treatment is not adjusted - should be initiated as soon as the diagnosis is made  
No ART adjustment is necessary with INH preventive therapy

### Monitoring
If previously on ART - monitor clinically for signs of drug toxicity.  
If ART newly initiated - monitor ALT after 2 & 4 weeks, then clinically for signs of drug toxicity.

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All newly diagnosed TB cases with HIV infection should be started on TB treatment as soon as possible after completing the first 2 weeks of anti-TB treatment.

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from Marais BJ et al. Paediatr Resp Rev 2011
Child TB/HIV and IRIS

HIV-infected children should be regularly screened for symptoms of possible TB including on commencement of ART

TB Immune Reconstitution Inflammatory Syndrome (IRIS) can occur as:
“unmasking” IRIS – subclinical TB disease becomes evident with immune reconstitution → TB treatment should be commenced

“paradoxical” IRIS – symptomatic deterioration despite adequate TB treatment → continue TB treatment – consider steroids

TB IRIS usually occurs within 1-2 months after starting treatment and does NOT indicate failure of TB treatment

BCG (M.bovis) IRIS is common in young infants initiated on ART

TB IRIS or BCG IRIS can be associated with significant morbidity but not with a high mortality
Treatment of TB in children - summary

- Principles of treatment of TB in children are same as for adults
- Children with TB usually respond well with symptomatic improvement during intensive phase and good outcome
- Dosages are calculated according to weight (not age)
- Weight is important for monitoring treatment response
- TB drugs are very well tolerated in almost all children
- The most important adverse event is hepatotoxicity
- Register all children receiving anti-TB treatment
- Report treatment outcomes for children
Checklist: the child treated for TB

1. **Dosages and regimens** for anti-TB treatment in children should follow NTP guidelines.

2. **Weight** is important for calculating dosages and for monitoring treatment response.

3. All children treated for TB should be **registered with NTP** and reported by disease type within age bands (0-4 years and 5-14 years)

4. Follow-up is critical and **treatment outcomes** should be recorded as per NTP guidelines.

5. **Adherence** is a challenge especially during the continuation phase and counseling of child and family about importance of completion of full course of anti-TB treatment is important.