Updated WHO MDR-TB treatment guidelines and the use of new drugs in children

Annual meeting of the Childhood TB subgroup
Liverpool, UK, 26 October 2016

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WHO/HQ, Global TB Programme
Outline

• Latest epidemiological data
• Existing guidelines
• 2016 update of the DR-TB treatment guidelines
• New recommendations for treatment of RR-TB and MDR-TB in children
• Delamanid guideline for use in children and adolescents
• Research gaps
• Conclusions
## The Global Burden of TB - 2015

<table>
<thead>
<tr>
<th>Category</th>
<th>Estimated number of cases</th>
<th>Estimated number of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>All forms of TB</td>
<td>10.4 million</td>
<td>1.8 million*</td>
</tr>
<tr>
<td></td>
<td>• 1 million Children (10%)</td>
<td>• 210,000 children (170,000 HIV negative and 40,000 HIV-positive)</td>
</tr>
<tr>
<td>HIV-associated TB</td>
<td>1.2 million (11%)</td>
<td>390,000</td>
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<tr>
<td>Multidrug-resistant TB</td>
<td>480,000 +100,000 RR cases</td>
<td>190,000</td>
</tr>
</tbody>
</table>
Childhood TB: MDRTB estimates

Dodd P., Sismanidis B., Seddon J., Lancet Inf Dis, 21 June 2016:
Global burden of drug-resistant tuberculosis in children: a mathematical modelling study

• It is estimated that over 67 million children are infected with TB and therefore at risk of developing disease in the future;
  – 5 mln with INH resistance; 2 mln with MDR; 100,000 with XDR

• Every year 25,000 children develop MDRTB and 1200 XDR TB
MDR-TB in children

- MDR-TB in children is mainly the result of transmission of a strain of *M. tuberculosis* that is MDR from an adult source case, and therefore often not suspected unless a history of contact with an adult pulmonary MDR-TB case is known.

- Referral to a specialist is advised for treatment.
Annex 3 – Management of drug-resistant TB in children

- Do not add a drug to a failing regimen.
- Treat the child according to the drug susceptibility pattern (and using the treatment history) of the source case’s *M. tuberculosis* strain if an isolate from the child is not available.
- Use at least four drugs certain to be effective.
- Use **daily treatment only**; directly observed therapy is essential.

- **Counsel the child’s caregiver** at every visit, to provide support, advice about adverse events and the importance of compliance and completion of treatment.
- **Follow-up** is essential: clinical, radiological and bacteriological (mycobacterial culture for any child who had bacteriologically confirmed disease at diagnosis).
- With correct dosing, **few long-term adverse events** are seen with any of the more toxic second line drugs in children.
2016 WHO guidelines on the management of drug resistant TB
WHO guidelines for the treatment of drug-resistant tuberculosis. 2016 update

**Key changes**

- A shorter MDR-TB treatment regimen is recommended for RR-/MDR-TB patients (under several conditions)
- The design of conventional MDR-TB regimens uses a different regrouping of second-line medicines
- **Recommended treatment of children with RR-/MDR-TB** based on a first-ever meta-analysis of individual-level paediatric patient data for treatment outcomes
- Recommendation on partial lung resection surgery
Shorter MDR-TB regimen (1)

In patients (adults and children) with

- rifampicin-resistant TB or MDR-TB,
- who have not been previously treated with second-line drugs and
- in whom resistance to fluoroquinolones and second-line injectable agents has been excluded or is considered highly unlikely

a shorter MDR-TB regimen of 9–12 months may be used instead of a conventional regimen

- Conditional recommendation – very low quality of evidence
Main remarks

• Standardized regimen; limited modifications are possible
• 4-6 Km-Mfx-Pto-Cfz-Z-H\text{high-dose}-E / 5 Mfx-Cfz-Z-E
• Recommendation applies to adults, children, PLHIV
• Ideally, patients are tested for resistance to fluoroquinolones and second-line injectable drugs; not recommended in case of 2\textsuperscript{nd} line drug resistance, extrapulmonary disease and pregnancy
Shorter MDR-TB regimen (2)

Main remarks

- Lowered costs (<US$1,000 in drug costs/patient)
- Monitoring for effectiveness, relapse, and harms (active TB drug safety monitoring and management (aDSM)) applies
- Trials expected to provide high-certainty evidence
<table>
<thead>
<tr>
<th>GROUP A</th>
<th>Fluoroquinolones</th>
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<tbody>
<tr>
<td></td>
<td>Levofloxacin</td>
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<tr>
<td></td>
<td>Moxifloxacin</td>
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<td></td>
<td>Gatifloxacin</td>
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<thead>
<tr>
<th>GROUP B</th>
<th>Second-line injectable agents</th>
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<tbody>
<tr>
<td></td>
<td>Amikacin</td>
</tr>
<tr>
<td></td>
<td>Capreomycin</td>
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<td></td>
<td>Kanamycin (Streptomycin)</td>
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<tr>
<th>GROUP C</th>
<th>Other Core Second-line Agents</th>
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<tbody>
<tr>
<td></td>
<td>Ethionamide / Prothionamide</td>
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<tr>
<td></td>
<td>Cycloserine / Terizidone</td>
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<tr>
<td></td>
<td>Linezolid</td>
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<td></td>
<td>Clofazimine</td>
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<tr>
<th>GROUP D</th>
<th>Add-on agents</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>(not core MDR-TB regimen components)</td>
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<tr>
<td></td>
<td>D1</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
</tr>
<tr>
<td></td>
<td>Ethambutol</td>
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<td></td>
<td>High-dose isoniazid</td>
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<tr>
<td></td>
<td>D2</td>
</tr>
<tr>
<td></td>
<td>Bedaquiline</td>
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<tr>
<td></td>
<td>Delamanid</td>
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<tr>
<td></td>
<td>D3</td>
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<tr>
<td></td>
<td>p-aminosalicylic acid</td>
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<tr>
<td></td>
<td>Imipenem-Cilastatin</td>
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<td></td>
<td>Meropenem</td>
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<td></td>
<td>Amoxicillin-Clavulanate (Thioacetazone)</td>
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</table>
In patients with rifampicin-resistant TB or MDR-TB, a regimen with at least five effective TB medicines during the intensive phase is recommended, including pyrazinamide and four core second-line TB medicines – one chosen from Group A, one from Group B, and at least two from Group C.

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
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<tbody>
<tr>
<td>levofloxacin; moxifloxacin;</td>
<td>amikacin, capreomycin,</td>
<td>ethionamide/ prothionamide,</td>
</tr>
<tr>
<td>gatifloxacin</td>
<td>kanamycin, (streptomycin)</td>
<td>cycloserine/ terizidone,</td>
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<td></td>
<td></td>
<td>linezolid, clofazimine</td>
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Recommendation on longer MDR-TB regimen (1)

- If the minimum number of five effective TB medicines cannot be composed as given above, an agent from Group D2 and other agents from Group D3 may be added to bring the total to five.

- The regimen may be further strengthened with high-dose isoniazid and/or ethambutol.

Group D2
bedaquiline, delamanid

Group D3
\( p \)-aminosalicylic acid, imipenem–cilastatin, meropenem, amoxicillin–clavulanate, (thioacetazone)
Choosing the treatment regimen for RR-/MDR-TB

- Confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance)?
- Exposure to ≥1 second-line medicines in the shorter MDR-TB regimen for >1 month?
- Intolerance to ≥1 medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)?
- Pregnancy?
- Extrapulmonary disease?
- At least one medicine in the shorter MDR-TB regimen not available?

**NO**

[Box: Shorter MDR-TB regimen]

**YES**

[Box: Longer MDR-TB regimens]

Failing regimen, drug intolerance, return after interruption >2 months, emergence of any exclusion criterion
Delamanid

- Children (6 – 11 years) - 50 mg – 2x /day for 6 months and
- Adolescents (12-17 years) – 100mg 2x /day for 6 months in adolescents aged 12 to 17
- may be added to a WHO recommended longer MDR-TB treatment regimen

- (conditional recommendation, very low confidence in estimates of effects)
Delamanid (2)

- Patients with additional resistance or intolerance to fluoroquinolones or second line injectable drugs
- Patients with extended lesions, advanced disease and others deemed at higher baseline risk for poor outcomes
- Patients with XDR-TB
Delamanid (3)

- Excludes paediatric cases with reported QTc prolongation (greater than 500msec);

- Paediatric patients with HIV co-infection were excluded from the analysed studies; drug has not been tested in patients with extra-pulmonary MDR-TB

- Studies are underway, currently there are no data on the effect of delamanid in children younger than 6 years of age and weighting under 20 kg.
Bedaquiline

• No data available on the use of BDQ in children (patients younger than 18 years),

• Janssen BDQ compassionate use programme excluded paediatric patients
Research gaps

• Need for more randomised control studies, especially involving new drugs and regimens (adults and children)
• Inclusion of children and separate reporting of outcomes
• Identification of factors which determine the optimal duration of treatment for children
• PK studies to determine optimal drug dosing and safety
• Improved diagnostics and DST methods for children
• Studies on preventive chemotherapy for children in contact with MDR-TB
Conclusions

• MDR-TB in children recognized and guidelines available
• Finally evidence based recommendations for treatment of RR-TB and MDR-TB in children

BUT

• Need for more data, especially on the use of new drugs and new regimens

AND

• Evidence needed to promote preventive chemotherapy for children in contact with a confirmed MDR TB in the household
Acknowledgements

Annemiek Brands and Ernesto Jaramillo
Thank you for your attention to childhood TB!