Treatment of DR-TB in children and preventive therapy for children exposed to DR-TB

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Diagnosis: M/XDR-TB in children

- **DR TB** is a *microbiological diagnosis*
- **In children often difficult (paucibacillary TB):**
  - **Confirmed** if DR *M. tuberculosis* strain is isolated from a child
  - **Probable** DR-TB if known contact with an adult DR PTB case (>78-90% concordance in several studies)
  - **Suspect** DR-TB if:
    - a child gets worse on Rx, failing *adherent* Rx
    - an adult source case with unknown DST result is a treatment failure, a retreatment case or died of TB during adherent Rx
Not all resistance is MDR/XDR

Focus today is on MDR-TB and more (e.g. XDR-TB)
However, consider the following:

• **INH monoresistance/polyresistance:**
  RIF and PZA most likely still susceptible, but need at least one more bactericidal drug if diagnosed early. Ethionamide resistance if *inhA* promoter region mutation. Consider drug-penetration in CSF if TBM/miliary TB

• **RIF monoresistance:**
  Becoming more prevalent; majority of these not resistant to other drugs.
  Beware interpretation of Xpert MTB/RIF as RMR!!! Keep INH, add FQN, EMB and other depending on extent of disease – many will treat as MDR-TB
Principles of childhood MDR-TB Rx

• Confirm the MDR-TB in the child if at all possible
• If MDR-TB is confirmed, also do DST for 2nd-line drugs
• Management – at a specialized MDR-TB clinic
• Use the adult index case’s isolate DST pattern if no isolate from child is available. (Standardised MDR-TB treatment if empirical treatment for treatment failure)
• DOT with daily treatment only in DR-TB
• Counsel patients/parents at every visit for support, about adverse events, and importance of adherence
• Follow-up is essential; clinical, radiological and cultures
Principles of childhood MDR-TB Rx

• Give 4 or more drugs to which the patient’s isolate is susceptible and/or naïve (depends on extent of disease and availability of drugs)
• Be aware of the different drug groups and cross-resistance (and co-resistance) amongst these drugs
• 2nd-line drugs are generally more toxic than 1st-line drugs
• Adverse effects more difficult to assess in children, but screen regularly
• Not complete if I don’t add: NEVER add one drug to a failing regimen
REVIEW

Paediatric use of second-line anti-tuberculosis agents: A review

James A. Seddon\textsuperscript{a,b,*}, Anneke C. Hesseling\textsuperscript{a}, Ben J. Marais\textsuperscript{c}, Helen McIlreron\textsuperscript{d}, Charles A. Peloquin\textsuperscript{e}, Peter R. Donald\textsuperscript{f}, H. Simon Schaar\textsuperscript{a,f}
Building a regimen: Drugs in M/XDR-TB Rx

- **Group 1**: 1\textsuperscript{st}-line drugs – susceptibility to EMB, PZA?
- **Group 2**: A 2-nd line injectable drug, kanamycin, amikacin or capreomycin: high rates of cross-resistance
- **Group 3**: A fluoroquinolone – OFX, LFX or MFX. Best of 2\textsuperscript{nd}-line drugs available
- **Group 4**: Other oral 2\textsuperscript{nd}-line drugs in combination:
  - Ethionamide/prothionamide (*inhA* mutation?)
  - Terizidone/cyclosorine
  - PAS
- **Group 5**:
  - high-dose INH – as added drug in low-level INH resistance (or *inhA* promoter region mutation)
  - reserve drugs for XDR-TB – especially linezolid, clofazimine
Absence of child-friendly drugs and dosages

11-month-old with morning tablets MDR-TB Rx

Difficult to accurately break tablets to correct dosage.

Also receives an injectable
Dosages for 2\textsuperscript{nd}-line drugs in children

- Only recently PK studies done in children – ongoing, therefore watch this space!
- 2\textsuperscript{nd}-line Injectable drugs: IM or IV – high concentrations achieved with amikacin at 20mg/kg in children compared to adults at 15mg/kg:
  Suggested dosage 15-20mg/kg/day

<table>
<thead>
<tr>
<th>Age group</th>
<th>N</th>
<th>Median (IQR)</th>
<th>p-value</th>
<th>N</th>
<th>Mean (SD)</th>
<th>p-value</th>
<th>N</th>
<th>Median (IQR)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 years</td>
<td>6</td>
<td>43.65 (42.20 - 49.20)</td>
<td>1.00</td>
<td>6</td>
<td>1.00 (0.00)</td>
<td>1.00</td>
<td>6</td>
<td>103.85 (96.80 - 119.10)</td>
<td>1.00</td>
</tr>
<tr>
<td>2-5 years</td>
<td>7</td>
<td>49.10 (40.70 - 59.20)</td>
<td>1.14</td>
<td>7</td>
<td>1.14 (0.38)</td>
<td>0.38</td>
<td>7</td>
<td>124.15 (97.75 - 162.05)</td>
<td>0.38</td>
</tr>
<tr>
<td>6-15 years</td>
<td>15</td>
<td>49.60 (40.30 - 56.40)</td>
<td>0.845</td>
<td>15</td>
<td>1.13 (0.35)</td>
<td>0.593</td>
<td>14</td>
<td>159.25 (124.20 - 179.48)</td>
<td>0.016</td>
</tr>
</tbody>
</table>
# Drugs for treatment of MDR-TB

## Group 3: Fluoroquinolones – PK data still needed in all

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dosage</th>
<th>Unit size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/kg</td>
<td>Maximum in mg</td>
</tr>
<tr>
<td>Fluoroquinolones:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ofloxacin</td>
<td>15-20</td>
<td>800mg</td>
</tr>
<tr>
<td>- Levofloxacin*</td>
<td>15-20</td>
<td>1000mg</td>
</tr>
<tr>
<td>- Moxifloxacin</td>
<td>7.5-10</td>
<td>400mg</td>
</tr>
<tr>
<td>- Ciprofloxacin</td>
<td>30-40</td>
<td>2.0g</td>
</tr>
<tr>
<td>(Ciprofloxacin</td>
<td></td>
<td>250/5ml</td>
</tr>
<tr>
<td>NOT recommended)</td>
<td></td>
<td>250/500</td>
</tr>
</tbody>
</table>
# 2nd-line anti-TB drugs

Group 4: Second-line oral bacteriostatic drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dosage</th>
<th>Unit size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethionamide/Prothionamide</td>
<td>15-20 mg/kg</td>
<td>1.0g in 250 mg</td>
</tr>
<tr>
<td>Cycloserine/Terizidone</td>
<td>15-20 mg/kg</td>
<td>750 mg in 250 mg</td>
</tr>
<tr>
<td>PAS (para-aminosalisylic acid)</td>
<td>150-200 mg/kg</td>
<td>8-12.0g in 4 g sachets</td>
</tr>
</tbody>
</table>
# 2nd-line or reserve anti-TB drugs

## Group 5: Drugs of **unclear role** in DR-TB treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dosage</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linezolid</td>
<td>10 mg/kg/dose 12 hrly</td>
<td>300-600/day</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>7.5 mg/kg/dose 12 hrly</td>
<td>1000/day</td>
</tr>
<tr>
<td>Amoxicillin/Clavulanic acid</td>
<td>25 (amox) mg/kg/dose 8 hrly</td>
<td></td>
</tr>
<tr>
<td>Clofazimine</td>
<td>3-5mg/kg daily</td>
<td>100/day</td>
</tr>
<tr>
<td>Thioacetazone</td>
<td>Not available – not in HIV-infected</td>
<td></td>
</tr>
<tr>
<td>Imipenem/cilastatin</td>
<td>20-40mg/kg IV every 8 hours</td>
<td>6000</td>
</tr>
</tbody>
</table>
 Delayed-Release Granules
4 g p-aminosalicylic acid

Store in a refrigerator (2 °C – 8 °C).
Avoid excessive heat.
PASER packets may be stored at or below 25°C for not longer than 7 days.

KEEP OUT OF REACH OF CHILDREN
Pharmplan (Pty) Ltd

Reg. No./Nr.45/20.2.3/0037: 49
# MDR-TB Weight-Based Dosing Chart for Children

**Group 1:** Oral first-line anti-TB drugs
- Ethambutol
  - 15-25 mg/kg (oral tablet)
- Pyrazinamide
  - 30-40 mg/kg (oral tablet)

**Group 2:** Injectable anti-TB drugs (injectable agents or injectable anti-TB agents)
- Injectables
  - Levofloxacin
    - 100 mg tablet
  - Moxifloxacin
    - 15 mg tablet
  - Ofloxacin
    - 20 mg tablet

**Group 3:** Fluoroquinolones
- Fluoroquinolones
  - 250 mg tablet
  - 25 mg/mL suspension

**Group 4:** Oral bacteriostasis agents
- Oral bacteriostasis agents
  - Cycloserine
    - 150-200 mg/day
  - Terizidone
    - 15-20 mg/kg
  - PAS
    - 500 mg tablet

**Group 5:** Anti-TB drugs with uncertain efficacy or unclear role in MDR-TB treatment
- Anti-TB drugs with uncertain efficacy or unclear role in MDR-TB treatment
  - 100 mg tablet

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Available Formulations</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3</td>
<td>100 mg tablet, 400 mg tab in 8 mL of water for a 50 mg/mL suspension, 200 mg tab in 32 mL of water for a 60 mg/mL suspension</td>
<td>3-3.9 mg/kg</td>
</tr>
<tr>
<td>3-3.9</td>
<td>50 mg tablet, 200 mg tab in 10 mL of water for a 20 mg/mL suspension</td>
<td>4-4.9 mg/kg</td>
</tr>
<tr>
<td>4-4.9</td>
<td>25 mg/mL suspension, 100 mg tablet in 10 mL of water for a 10 mg/mL suspension</td>
<td>5-5.9 mg/kg</td>
</tr>
<tr>
<td>5-5.9</td>
<td>5 mg/mL suspension, 25 mg/mL suspension</td>
<td>6-6.9 mg/kg</td>
</tr>
<tr>
<td>6-6.9</td>
<td>25 mg/mL suspension, 50 mg/mL suspension</td>
<td>7-7.9 mg/kg</td>
</tr>
<tr>
<td>7-7.9</td>
<td>50 mg/mL suspension, 100 mg/mL suspension</td>
<td>8-8.9 mg/kg</td>
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<tr>
<td>8-8.9</td>
<td>100 mg/mL suspension, 200 mg/mL suspension</td>
<td>9-9.9 mg/kg</td>
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<td>9-9.9</td>
<td>200 mg/mL suspension, 400 mg/mL suspension</td>
<td>10-10.9 mg/kg</td>
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<td>10-10.9</td>
<td>400 mg/mL suspension, 800 mg/mL suspension</td>
<td>11-11.9 mg/kg</td>
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<td>11-11.9</td>
<td>800 mg/mL suspension, 1600 mg/mL suspension</td>
<td>12-12.9 mg/kg</td>
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<tr>
<td>12-12.9</td>
<td>1600 mg/mL suspension, 3200 mg/mL suspension</td>
<td>13-13.9 mg/kg</td>
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<td>13-13.9</td>
<td>3200 mg/mL suspension, 6400 mg/mL suspension</td>
<td>14-14.9 mg/kg</td>
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<td>15-15.9</td>
<td>12800 mg/mL suspension, 25600 mg/mL suspension</td>
<td>16-16.9 mg/kg</td>
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<td>16-16.9</td>
<td>25600 mg/mL suspension, 51200 mg/mL suspension</td>
<td>17-17.9 mg/kg</td>
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<td>17-17.9</td>
<td>51200 mg/mL suspension, 102400 mg/mL suspension</td>
<td>18-18.9 mg/kg</td>
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<td>18-18.9</td>
<td>102400 mg/mL suspension, 204800 mg/mL suspension</td>
<td>19-19.9 mg/kg</td>
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<td>19-19.9</td>
<td>204800 mg/mL suspension, 409600 mg/mL suspension</td>
<td>20-20.9 mg/kg</td>
</tr>
<tr>
<td>20-20.9</td>
<td>409600 mg/mL suspension, 819200 mg/mL suspension</td>
<td>21-21.9 mg/kg</td>
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<tr>
<td>21-21.9</td>
<td>819200 mg/mL suspension, 1638400 mg/mL suspension</td>
<td>22-22.9 mg/kg</td>
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<td>23-23.9 mg/kg</td>
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<td>24-24.9 mg/kg</td>
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<tr>
<td>24-24.9</td>
<td>6553600 mg/mL suspension, 13107200 mg/mL suspension</td>
<td>25-25.9 mg/kg</td>
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<tr>
<td>25-25.9</td>
<td>13107200 mg/mL suspension, 26214400 mg/mL suspension</td>
<td>26-26.9 mg/kg</td>
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<tr>
<td>26-26.9</td>
<td>26214400 mg/mL suspension, 52428800 mg/mL suspension</td>
<td>27-27.9 mg/kg</td>
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<tr>
<td>27-27.9</td>
<td>52428800 mg/mL suspension, 104857600 mg/mL suspension</td>
<td>28-28.9 mg/kg</td>
</tr>
<tr>
<td>28-28.9</td>
<td>104857600 mg/mL suspension, 209715200 mg/mL suspension</td>
<td>29-29.9 mg/kg</td>
</tr>
<tr>
<td>29-29.9</td>
<td>209715200 mg/mL suspension, 419430400 mg/mL suspension</td>
<td>30-30.0 mg/kg</td>
</tr>
</tbody>
</table>

Consult with a clinician experienced in pediatric MDR-TB prescribing for neonates (<28 days of age) and infants weighing <3 kg.

For preventive regimens, consult with experts regarding optimal regimen construction.

The doses of isoniazid, ethambutol, and fluoroquinolones for preventive regimens are the same as in this dosing chart.
What about the new drugs?

Bedaquiline (TMC207): Janssen Pharmaceutical
• A diarylquinoline – unique mechanism of action – inhibits ATP synthesis - results in bactericidal activity
• Provisionally approved by FDA for use in MDR-TB – in addition to current MDR-TB regimen – in adults >18 yrs
• A strange drug with $t_{1/2}$ of >5 months
• No dosage established for children yet. Now phase 3 studies and planning child PK studies

Delamanid (OPC-67683): (Otsuka Pharmaceutical)
• A new Nitro-dihydroimidazo-oxazole derivative
• No cross-resistance with any current used anti-TB drugs
• Phase 2 b trials done
• No dosages or PK for children yet, but study ongoing
Adherence (and support)

- Treatment in hospital and in community needs to be observed – children are ingenuous when it comes to making plans how NOT to take their treatment!
- Ask children/caregivers to identify the tablets/capsules and how many of each are taken – can check on dosage
- Phone the clinics who dispense the treatment – do they collect the drugs regularly or is there DOT?
- Pill counts and other methods may be used
- Most important: identify a reliable caregiver to provide the drugs and observe the child taking it
- Monitor adverse effects and address these, as could lead to defaulting treatment
Adherence (and support)

- Teenagers – notoriously difficult group to adhere to treatment: Communication (clinic staff) and peer pressure (stigma/mocking) – both common problems
- Nutritional support and financial support often required by families – especially if caregivers/parents also ill
Additional treatment

• Pyridoxine (Vit B6)
  Levels of B6 remain low in HIV-infected children despite multivitamin supplementation
  With terizidone and high-dose INH supplementation with pyridoxine recommended

• Cotrimoxazole
  Outcome of TB/HIV co-infected adults improved if given CTX preventive therapy. Role in TB treatment?

• Start ART early iv HIV-infected – within 2 weeks of starting anti-TB treatment

• Nutritional rehabilitation
Drug-drug interactions

• Data on pharmacokinetic interactions between ART and the 2\textsuperscript{nd}-line anti-TB drugs are incomplete, therefore unanticipated interactions may occur.
• The potential for clinically important changes in ART or anti-TB drug concentrations is less for 2\textsuperscript{nd}-line anti-TB regimens compared to RIF-containing 1\textsuperscript{st}-line regimens.
• ART and 2\textsuperscript{nd}-line anti-TB drugs have many adverse effects in common.

Seddon et al. Tuberculosis 2012;92:7-12
Duration of treatment

- Optimal duration of treatment in children is not known
- Cavitary or extensive pulmonary TB: as for adults 18 months after first negative culture (XDR-TB possibly longer?)
- Primary, non-cavitary MDR-TB - Often culture-negative (paucibacillary): 12-15 months treatment probably sufficient in most cases (contacts of MDR-TB cases)
- Intensive phase including 2\textsuperscript{nd}-line injectable drug, continuation phase mainly stop injectable drug
- In carefully selected cases (paucibacillary, no 2\textsuperscript{nd}-line resistance) may elect not to use injectable drug
Table 2  Treatment and outcome in children treated for MDR-TB (n=149 unless otherwise stated)

<table>
<thead>
<tr>
<th>Feature/outcome</th>
<th>Variable</th>
<th>Number (%) unless otherwise indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admitted to hospital</td>
<td></td>
<td>103 (69.1)</td>
</tr>
<tr>
<td>Median duration of admission in months (n=103; IQR)</td>
<td></td>
<td>5 (3–7)</td>
</tr>
<tr>
<td>Treated with injectable drugs (n=142)*</td>
<td></td>
<td>94 (66.2)</td>
</tr>
<tr>
<td>Median duration of injectable drug use (n=94; IQR)</td>
<td></td>
<td>4 (4–6)</td>
</tr>
<tr>
<td>Median duration of total treatment (n=137; IQR)†</td>
<td></td>
<td>13 (11–18)</td>
</tr>
<tr>
<td>Median weight gain (IQR; kg)</td>
<td></td>
<td>3 months (n=115) 0.6 (0.2–1.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 months (n=102) 1.4 (0.7–2.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 months (n=84) 2.9 (1.0–4.0)</td>
</tr>
<tr>
<td>Median number of months to culture conversion (n=40)‡</td>
<td></td>
<td>1 (0.5–2)</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td>Cure 36 (24.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Probable cure§ 101 (67.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Transferred out 1 (0.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lost to follow up 8 (5.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Died¶ 3 (2.0)</td>
</tr>
</tbody>
</table>
Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis

Dena Ettechad, H Simon Schaaf, James A Seddon, Graham S Cooke*, Nathan Ford*
Management of DR-TB contacts

- Guidelines vary in opinion
  - NICE, WHO, RSA DOH – follow up and isoniazid
  - CDC, ATS, IDSA, AAP – regimen containing two drugs to which index case is susceptible
  - ECDC – Follow-up with or without preventive Rx
- Few studies have examined the treatment of contacts of cases with MDR-TB (or any other DR-TB) – no RCTs
- Early onset of ART in HIV-infected infants/children is important for both prevention of TB and improved outcome if they develop TB

Decision algorithm for assessing child contacts of MDR-TB

High risk MDR-TB Preventive Rx & follow-up

**EXPOSED?**

Does the child have tuberculosis disease?
- History
- Examination
- Chest radiography

**EXCLUDE TB DISEASE**

Risk of infection?
- TST/IGRA
- Severity of disease in source case
- Proximity and intensity of contact
- Duration of contact

Risk of disease progression?
- Age of child
- HIV status and degree of immunosuppression
- Nutritional status
- Other immunodeficiency

Assess likelihood of infection with MDR strain
- Local prevalence of tuberculosis
- Likelihood of other source case(s)
- Intensity of interaction with source case(s)
- Age of child

**MDR-TB STRAIN OR OTHER?**

Progression likely with MDR strain
- Consider MDR tuberculosis preventive treatment
- Follow up for ≥12 months, irrespective of treatment decision

Progression likely with susceptible strain
- Treat with isoniazid (10 mg/kg) daily for 6 months

Start treatment
- Obtain microbiological samples
- Start treatment for MDR tuberculosis disease

Disease - Rx
WHO 2008 Guidelines for Drug-Resistant TB Management - Update

Key recommendations:
• DR-TB contact investigation should be a high priority
• Consider contact investigation of XDR-TB as an emergency situation
• Close contacts of DR-TB patients should receive careful clinical follow-up

Definition of close contact:
• People living in the same household (adults & children)
• Spending many hours a day together with the patient in the same indoor living space
• Contacts of MDR-TB patients may not be infected with the same strain; some may be infected with isoniazid-susceptible strains, particularly in high-burden areas

• Strain concordance of HH members with TB is high: In adults (50-67%) and in child contacts <5 years (75-88%)

• Close contacts of MDR-TB patients should receive careful clinical follow-up for at least two years

• If active disease is present or develops, prompt initiation of MDR-TB treatment is recommended (empiric MDR-TB regimen, even in adults, if DST and culture not available)

• WHO does not recommend the universal use of second-line drugs for preventive therapy in MDR-TB contacts
ECDC guidance (2012): Summary

• Expresses support for two different options:
  - preventive therapy and/or
  - careful clinical observation

The central principle is that a comprehensive risk assessment should be part of the evaluation of any MDR-TB or XDR-TB contact.

• The individual risk assessment should consider:
  - the MDR-TB contact’s risk for progression to TB disease
  - the DST pattern of the source case
  - the risk for adverse events upon initiating preventive Rx

• In case of XDR-TB, available drug regimens are limited and without proven efficacy, thus close observation is likely the only option.
ECDC Guidance: Summary

- Urgent need for further research, specifically in two areas:
  - studies evaluating the benefit of preventive therapy in MDR-TB and XDR-TB contacts
  - cost-benefit analyses of implementing preventive Rx
- Acknowledge that there are on-going studies which appear to support the use of preventive therapy, but these results need to be confirmed in larger studies and other settings
- Additional drugs may become available for treatment of MDR-TB, which will necessitate an update of this guidance document
Problems faced with child MDR-TB contacts

- High risk of infection and disease in children <3 years of age, especially breastfeeding infants
- HIV-infected children similar or higher risk
- Extensively drug-resistant (XDR)-TB contacts increasing – which drugs for prevention?
- High TB burden areas:
  - clinical follow-up challenging over long periods
  - >1 source case not uncommon
- Failure of adherent low-dose (4-6mg/kg/d) INH and combination (INH/RMP) preventive Rx common in our experience
Studies supporting preventive therapy?
Preventive Rx in MDR-TB contacts - systematic review

• Two observational studies met inclusion criteria.
• A prospective cohort study found individualised tailored treatment to be effective for preventing MDR-TB disease in children (OR 0.20, 95%CI 0.04–0.94) (Schaaf et al. Pediatrics 2002)
• A retrospective cohort study found INH not to be effective (OR 0.46, 95%CI 0.07–2.32)

Fraser et al. IJTLID 2006
CDC - Chuuk study, Micronesia

• Contacts of 2 source cases: strain (A) resistant to HRZES; strain (B) resistant to HREth

• Evaluation of MDR-TB contacts: 15 had MDR-TB disease, 5 had DS-TB, and 119 had LTBI with positive TST.

• LTBI contacts were offered preventive Rx. 14 of the 119 cases refused, preventive Rx was initiated in 105 contacts.

• A FQN-based regimen was used: FQN alone or in combination with Eth (strain A) or E (strain B).

• All therapy was DOT x 12 months.

• 93 completed the MDR preventive Rx – no TB disease.

• 28 contacts (15 initial screen & 11 additionally linked MDR-TB cases in persons not previously identified as contacts, and 2 out of 14 who refused preventive therapy) developed MDR-TB disease.
Preventive therapy for child contacts of multidrug-resistant tuberculosis: a prospective cohort study

• **Aim:** To study the tolerability and toxicity of a standard preventive therapy regimen, given to children exposed to MDR-TB, and explore risk factors for poor outcome.

• **Method:** HEO x 6 months to contacts <5 years or HIV-infected <15 years as preventive therapy

RESULTS

- 186 children, median age 34 months (IQR: 14-47)
- Of 179 children tested for HIV, 9 (5.0%) were positive
- Adherence was good in 141 (75.8%) children
- Only 7 (3.7%) children developed Grade 3 adverse events
- One child (0.5%) died and 6 (3.2%) developed incident TB during 219 patient years of observation time
- Factors associated with poor outcome were:
  - age <1 year (RR: 10.1; 95%CI: 1.65-105.8; p=0.009)
  - HIV-pos status (RR: 10.6; 95%CI: 1.01-64.9; p=0.049)
  - exposure to multiple source cases (RR: 6.75; 95%CI: 1.11-70.9; p=0.036)
  - poor adherence (RR: 7.50; 95%CI: 1.23-78.7; p=0.026)
Conclusions

• This three-drug preventive therapy regimen was well tolerated and few children developed TB or died if adherent to therapy.

• The provision of preventive therapy to vulnerable children following exposure to MDR-TB should be considered.

Preventive Rx for DR-TB contacts

- No RCT available.
- Failure of INH or INH/RMP to prevent MDR-TB reported.
- INH mono-resistance: RMP x 4 mo
- RMP-monoresistance: INH x 6 mo (LPA and Xpert?)
- MDR-TB: FQN & EMB (or ETH) x 6-12 mo (hd INH?)
- Pre-XDR or XDR-TB – only hd INH (15-20mg/kg)?
- In both MDR and XDR-TB regular clinical follow-up is indicated: both ECDC and WHO recommends 2 years of follow-up (minimum is 1 year – 95% disease in 1 year). Pendulum swinging towards preventive treatment.
Conclusions

• Appropriate MDR preventive Rx – using 2 drugs with/without high-dose INH – could be effective in preventing MDR-TB in children

• There is an urgent need to address this issue in a randomised controlled trial(s)

• Single drug preventive therapy with a FQN (e.g. levofloxacin) or novel anti-TB agent considered?

• Until such a trial is conducted, routine clinical data collected as part of existing TB control programmes could be useful

• What about XDR-TB contact? Careful follow-up and possibly high-dose INH are probably the only options – treat as XDR-TB if TB develops
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Why consider high-dose INH?

- In one study, 38 of 45 INH resistant isolates were resistant at 0.1-0.2µg/ml but susceptible at 5.0µg/ml. Only 7 resistant at 5µg/ml or more

  *Schaaf et al. Eur J Clin Microbiol Infect Dis 2007*

- *inhA* promoter region mutations, which make up 60% of current MDR-TB cases and 80-90% of XDR-TB cases’ INH conferring mutations (WC & EC provinces) usually causes low-level INH resistance

- High-dose INH at 15-20mg/kg/day could still add value preventive therapy of child contacts of MDR/XDR-TB cases