MDR-TB preventive treatment considerations

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I have no Conflict of Interest to report.
Background

• 460,000 new cases of MDR-TB in 2017
• 25-32,000 MDR-TB paediatric cases estimated (2010)
• 2 million children infected with MDR-TB
• Current MDR-TB treatment long, toxic, expensive
• MDR-TB prevention is important but no evidence from randomised controlled trials

Five (Six?) priority actions to address the global MDR-TB crisis

1. Prevent the development of drug resistance through high quality treatment of drug-susceptible TB
2. Expand rapid testing and detection of drug-resistant TB cases
3. Provide immediate access to effective treatment and proper care
4. Prevent transmission through infection control
5. Increase political commitment with financing
6. Contact tracing and preventive therapy?

WHO: Multidrug-resistant Tuberculosis 2014 Update
WHO Global TB Report 2018 refers to “universal access to TB prevention” but WHO guidelines on LTBI not strong support for MDR-TB preventive therapy
25. Commit to prevent tuberculosis for those most at risk of falling ill through the rapid scale-up of access to testing for tuberculosis infection, according to the domestic situation, and provision of preventive treatment, with a focus on high burden countries, so that at least 30 million people, including 4 million children under five years of age, 20

26. Commit to overcome the global public health crisis of multidrug-resistant tuberculosis through actions for prevention, diagnosis, treatment and care, including: compliance with stewardship programmes to address the development of drug
Introduction: Infection/prevention

- MDR-TB in children is mainly through infection with MDR *M. tuberculosis* strains from infectious (adult) PTB cases
- Although AFB sputum smear-positive cases are more infectious than smear-negative/culture-positive cases, the latter is also infectious
- BCG does NOT provide good protection against infection and disease in children
- Starting adult source cases on TB Rx or separating the child from the source case could prevent ongoing transmission BUT does not mean the child does not need preventive Rx (may already be infected)

Rieder H. (The Union) Epidemiologic Basis of Tuberculosis Control - 1999
Child contacts of MDR-TB (1)

• The majority (90%) of infected children who will develop disease will progress to disease within 12 months – almost all in 2 years

• Biomarkers to determine which individuals have the highest risk of progression to TB disease are lacking

• The risk of TB disease among contacts exposed to MDR-TB is considerable. In a meta-analysis of 25 studies, 7.8% of household contacts of MDR-TB patients developed TB, most within three years.

Shah NS et al. Yield of contact investigations in households of patients with drug-resistant tuberculosis: systematic review and meta-analysis. CID 2014;58:381-91
Results: Of 538 children included, 312 had DS-TB and 226 had MDR-TB exposure. 107 children with DS-TB exposure had TB infection (34.3%) vs. 101 (44.7%) of children with MDR-TB exposure (adjusted Odds Ratio [aOR]: 2.05; 95% confidence interval [CI]: 1.34–3.12). A total of 15 (6.6%) MDR-TB vs. 27 (8.7%) DS-TB child contacts had TB disease at enrolment (aOR: 0.43; 95% CI: 0.19–0.97).

Conclusions: Our results suggest a higher risk of TB infection in child contacts with household MDR-TB vs. DS-TB exposure, but a lower risk of TB disease. Although potentially affected by residual confounding or selection bias, our results are consistent with the hypothesis of impaired virulence in MDR-TB strains in this setting.

However, there remains a significant risk for development of disease in child contacts of infectious MDR-TB cases.
Child contacts of MDR-TB (2)

• Strain concordance of household members with DR-TB is high in child contacts <5 years with 75-88% concordance
• No RCTs have been completed evaluating preventive therapy for MDR-TB contacts
• However, a number of prospective observational studies (some unpublished) have shown the potential of preventive treatment in preventing MDR-TB
• Despite this, the debate on the management of MDR-TB contacts is ongoing
Rationale for preventive treatment

• Prophylactic treatment is given after exposure to prevent TB infection, and treatment given after TB infection is intended to prevent progression to TB disease.

• Preventive treatment includes both these situations

• To provide preventive treatment
  - contact with a source case and risk of infection needs to be established and
  - TB disease should have been excluded
The individual risk assessment should take into consideration the following:

• TB contact’s (child’s) risk for progression to TB disease (age, immune status)

• Infectiousness of the source case AND the closeness and duration of contact with the source case

• Whether there is one or more source cases

• The DST pattern(s) of the source case(s)

• The risk for adverse events upon initiating preventive therapy
Decision algorithm for assessing child contacts of MDR-TB

Management of children exposed to multidrug-resistant *Mycobacterium tuberculosis*.
Seddon JA et al.
*Lancet Infect Dis* 2012

**EXPOSED TO MDR-TB?**
- Start treatment
- Obtain microbiological samples
- Start treatment for MDR tuberculosis disease

**Disease - Rx**

**RISK OF INFECTION?**

**RISK OF DISEASE PROGRESSION?**

**MDR-TB STRAIN OR OTHER?**

**High risk MDR-TB**
- Preventive Rx & follow-up

**Low risk**

**Excluded TB disease**

**Assess risk of infection**
- TST/IGRA
- Severity of disease in source case
- Proximity and intensity of contact
- Duration of contact

**Assess 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

**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

**DS-TB risk?**
- PT for DS-TB
How to investigate contacts

Clinical assessment:

• History (Symptoms – not only chronic symptoms; closeness and duration of contact; DST of source case’s isolate)

• Clinical examination (PTB/EPTB)

Clinical assessment alone is sufficient to decide whether contact is well or symptomatic (developing countries)

If available:

• TST (IGRA) – but even if TST/IGRA is negative and exposure has been confirmed, preventive Rx is indicated – reassess after 2-3 months?

• CXR (for diagnosis of disease) – or other imaging/tests

• If DR-TB suspected and contact is symptomatic or has abnormal CXR – specimens culture/DST before starting Rx
HIV: Impact of ART on child TB

- Retrospective study at Tygerberg Hospital (2003-2005)
- 136 episodes TB in 290 children
- Pre-ART - 9m period before ART initiation
- ART is essential in prevention of TB in HIV-infected children

Walters et.al. BMC Pediatrics 2008
Observational studies that started to change opinions

CDC - Chuuk study, Micronesia

- Contacts of 2 source cases: strain (A) resistant to HRZES; strain (B) resistant to HREto
- 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. 15 of the 119 cases refused, preventive Rx was initiated in 104 contacts
- A FQN-based regimen was used: FQN alone or in combination with Eto (strain A) or E (strain B) with DOT for 12 months
- Of the 104 who started on MDR preventive Rx (93 completed) – none developed TB disease
- 3 of 15 who refused preventive therapy developed MDR-TB disease (P = 0.002)
Preventive Therapy for Child Contacts of Multidrug-Resistant Tuberculosis: A Prospective Cohort Study. Seddon/Schaaf et al. CID 2013

Table 6. Assessment of Risk Factors for Poor Outcome (Death or Incident Tuberculosis Disease) in Children Exposed to Multidrug-Resistant Tuberculosis and Treated With a Preventive Therapy Regimen (N = 186)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>No. of Events</th>
<th>Years of Observation</th>
<th>Incidence Rate With 95% CI (Events per 1000 py)</th>
<th>Rate Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;12 mo</td>
<td>2</td>
<td>175.5</td>
<td>11.4 (1.4–41.1)</td>
<td>1.0</td>
<td>.009</td>
</tr>
<tr>
<td>0–12 mo</td>
<td>5</td>
<td>43.5</td>
<td>114.9 (37.3–266.2)</td>
<td>10.1 (1.65–105.8)</td>
<td>.009</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
<td>95.6</td>
<td>31.4 (6.5–91.7)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4</td>
<td>123.4</td>
<td>32.4 (8.8–83.0)</td>
<td>1.03 (1.17–7.05)</td>
<td>1.00</td>
</tr>
<tr>
<td>TST</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>4</td>
<td>132.1</td>
<td>30.3 (8.3–77.5)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>2</td>
<td>84.8</td>
<td>23.6 (2.9–85.2)</td>
<td>0.78 (0.07–5.43)</td>
<td>1.00</td>
</tr>
<tr>
<td>Source cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>2</td>
<td>152.4</td>
<td>13.1 (3.28–52.5)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Multiple</td>
<td>5</td>
<td>56.4</td>
<td>88.6 (36.9–213.0)</td>
<td>6.75 (1.11–70.9)</td>
<td>.036</td>
</tr>
<tr>
<td>HIV status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>5</td>
<td>201.5</td>
<td>24.8 (8.1–579.1)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>2</td>
<td>7.6</td>
<td>263.8 (31.9–950.6)</td>
<td>10.6 (1.01–64.9)</td>
<td>.049</td>
</tr>
<tr>
<td>Adherence</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Good</td>
<td>2</td>
<td>164.3</td>
<td>12.2 (1.5–44.0)</td>
<td>1.0</td>
<td>. .</td>
</tr>
<tr>
<td>Poor</td>
<td>5</td>
<td>54.8</td>
<td>91.3 (29.6–212.9)</td>
<td>7.50 (1.23–78.7)</td>
<td>.026</td>
</tr>
<tr>
<td>Type of delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOT</td>
<td>0</td>
<td>31.5</td>
<td>0 (0–117.1)</td>
<td>. .</td>
<td>. .</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td>187.6</td>
<td>37.3 (15.0–76.8)</td>
<td>. .</td>
<td>.68</td>
</tr>
</tbody>
</table>

Risk factors:
- Young age
- Multiple source cases
- HIV-positive status
- Poor adherence to prevention

Abbreviations: CI, confidence interval; DOT, daily observed therapy; HIV, human immunodeficiency virus; py, person-years; TST, tuberculin skin test.
Many opinions published on preventive therapy in MDR-TB contacts

Post-exposure management of multidrug-resistant tuberculosis contacts: evidence-based recommendations.
Policy Brief No. 1. Dubai, United Arab Emirates: Harvard Medical School
Center for Global Health Delivery–Dubai.
Results: .... The estimated MDR-TB incidence reduction was 90% (9%-99%) using data from 5 comparison studies. We found...high treatment discontinuation rates due to adverse effects in persons taking pyrazinamide-containing regimens. Cost-effectiveness was greatest using a fluoroquinolone/ethambutol combination regimen.

Conclusions—Few studies met inclusion criteria, therefore results should be cautiously interpreted.
WHO 2018 Consolidated Guidelines for Programmatic Management of LTBI

• In high-risk HHCs of MDR TB patients, preventive treatment may be based on individualised risk assessment and sound clinical justification. *(New, Conditional recommendation, low quality of evidence)*

• Confirmation of infection with LTBI tests is required

• Recommendation must not affect RCTs of PT for MDR-TB HHCs on ethical grounds since these trials are critical given current limited evidence
What do guidelines agree on regarding management of MDR-TB contacts?

• Screening for excluding active disease is important (if disease, treat according to likely source case’s DST pattern)
• Follow-up of exposed/infected individuals (especially people with high risk, such as children and immunocompromised patients) is essential (1-2 years)
• Although some older guidelines still do not recommend preventive therapy with second-line drugs, this opinion is definitely changing with more guideline agreeing on preventive therapy in at least high risk contacts
• Choice of regimens vary, but most guidelines agree that a fluoroquinolone should be included, with or without a second drug
• RCTs are needed to prove effectiveness of preventive regimens – preferably a single drug
<table>
<thead>
<tr>
<th><strong>SUMMARY OF ONGOING AND PLANNED MDR-TB PREVENTION TRIALS</strong></th>
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<tr>
<td><strong>TB-CHAMP</strong></td>
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<tr>
<td><strong>Intervention</strong></td>
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</table>
| **Target Population** | <5 years regardless of IGRA or HIV status  
*Only study powered for efficacy in children* | • All ages  
• TST +  
• Children not yet treated | • HIV +  
• Children <5 years  
• TST/IGRA + >5 years |
| **Sample size** | 778 Households  
1556 contacts < 5 y | 1326 Households  
2785 contacts | 1726 Households  
3452 contacts |
| **Sites** | South Africa  
DTTC, Shandukani,  
PHRU Matlosana | Viet Nam  
NTP | ACTG & IMPAACT sites |
| **Timelines** | Open; n=230 enrolled | Open; 70% enrolled | Q1 2019 |
| **Funder, PI** | BMRC/Wellcome Trust/DFID, SA MRC  
SHIP; Hesseling  
MRC CTU at UCL | Australian MRC  
Fox, Nguyen  
SA NTP | DAIDS, ACTH/IMPAACT  
Churchyard, Gupta,  
Hesseling, Swindells |
TB-CHAMP study

• Realized need for child-friendly levofloxacin formulation and with pharmaceutical company developed 100mg dispersible tablet (now WHO approved)

• Palatability and acceptability study was done in 27 children

• The dispersible tablet was found to be highly palatable and acceptable by children and their caregivers

(S. Purchase et al, submitted)

• A lead-in pharmacokinetic study of this formulation was done in 24 children (median age 2.1 years, IQR 1.2, 2.7)
Levofloxacin 100 mg DT (TB-CHAMP lead-in PK)

N=109 children MDR treatment/prevention

N=24 children <5y with HH MDR-TB exposure

Using the same model, bioavailability is estimated to be 70% higher with the 100mg dispersible tablet compared to the Lfx 250mg adult formulation tablet

P. Denti, Antimicrobials and Therapy, 2018
A.J. Garcia-Prats, submitted
Conclusions

• MDR preventive therapy likely effective in preventing MDR-TB in children
• Randomised controlled trial(s) are ongoing – for choice of regimen, efficacy and safety
• Currently, single drug preventive therapy regimens with a fluoroquinolone (e.g. levofloxacin) or a novel drug is considered
• Child-friendly levofloxacin formulation for preventive therapy looks promising (acceptability, pharmacokinetics and safety)
• What about XDR-TB contacts? Careful follow-up and possibly a novel drug (delamanid) – treat as XDR-TB if TB develops
• In both MDR and XDR-TB regular clinical follow-up is indicated, but pendulum swinging towards preventive treatment.
• **Financial Support:** SA National Research Foundation, SA MRC, BMRC

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