Basic principles of MDR-TB treatment and prevention in children

H Simon Schaaf

Desmond Tutu TB Centre
Department of Paediatrics and Child Health, Stellenbosch University, and Tygerberg Children’s Hospital
Case

• 8-yr-old girl from Khayelitsha. Went to visit family in Eastern Cape – noticed **severe cough** and **LOW**. Took child to clinic.

• Xpert MTB/RIF done on sputum: Pos M.tb and RIF-resistant

• No known source case

• HIV: Exposed but HIV-negarive

• No extrapulmonary TB noted

• Was sent back home for evaluation and treatment (by taxi)
  
  CXR (see slide) and culture for *M.tb* and DST done

• To treat with WHO MDR-TB short-regimen? **Y** or **N**
Case

- Sputum 3+ smear-positive for AFB
- After 25 days final result of culture and LPA (GenoType MTBDRplus & sl):
  INH & RIF-resistant - (inhA mut)
  No FQN or SLID mutations

- She has two siblings – one is only 2-years-old and HIV exposed but PCR negative. Clinically well and CXR normal

- To give preventive treatment for MDR-TB? **Y or N**
MDR/XDR-TB in children

- Is mainly new (transmitted) drug resistance – this has been confirmed with DST and DNA-fingerprinting
- Is more difficult to acquire because of the paucibacillary nature of primary disease, but it is possible with cavitary pulmonary disease in mainly older children/adolescents
- In our experience DR-TB is not less infectious and may cause almost as much disease than DS-TB
- Disease (>90%) in children usually develops within 12 months after infection
Not all resistance is MDR/XDR

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

- **INH mono-resistance**
- RIF and PZA still susceptible, but need at least one more (bactericidal) drug if diagnosed early
- Ethionamide resistance if *inhA* promoter region mutation
- 6-9HRZE or 6-9RZE possible, but many would prefer also to add a fluoroquinolone
- Consider drug-penetration in CSF if TBM/miliary TB – in this case FQN plus cycloserine/terizidone or linezolid
Not all resistance is MDR/XDR

- INH polydrug resistance (usually also EMB or SM)
  - need two effective drugs in addition to rifampicin

- RIF resistance/INH susceptible:
  - Becoming more prevalent; majority of these not resistant to other drugs.
  - Beware interpretation of Xpert MTB/RIF as RMR!!!
  - Need BOTH LPA as well as phenotypic INH DST to confirm RMR-TB
  - Build regimen FOUR effective drugs including INH, add EMB, PZA, FQN and consider other drugs depending on extent of disease
  - If INH DST unknown/uncertain – 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 2\textsuperscript{nd}-line drugs
• Management – at a specialized MDR-TB clinic
• Use the adult index case’s isolate DST pattern if no isolate from the child is available.
• If empirical treatment for first-line treatment failure, use standardised MDR-TB treatment
• 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. Number of effective drugs depends on extent of disease and availability of drugs.
- Drugs in previously failed regimen likely not effective.
- 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 need to assess regularly.
- Of course: NEVER add one drug to a failing regimen!!!
REVIEW

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

James A. Seddon a,b,*, Anneke C. Hesseling a, Ben J. Marais c, Helen McIlron d, Charles A. Peloquin c, Peter R. Donald f, H. Simon Schaaf a,f

Tuberculosis 2012;92:9-17


DOI 10.1007/s40124-016-0100-9

INFECTIOUS DISEASES (B MARAIS, SECTION EDITOR)

Multidrug-Resistant Tuberculosis in Children: Recent Developments in Diagnosis, Treatment and Prevention

H. Simon Schaaf1 · Anthony J. Garcia-Prats1
INH and Ethionamide co- and cross resistance

Activation of INH
KatG
*katG gene*
INH resistance

Activation of ETH
EthA
*ethA gene*
ETH resistance

InhA
*inhA promoter region*
Low-level INH resistance & ETH resistance

Mycolic acid synthesis
Challenges with DR-TB treatment

• “Rapidly” changing scene! Both exciting and confusing to clinicians
• Getting the dose right. Very limited PK data on second-line anti-TB drugs in children
• New and repurposed drugs: how should we use these in children
• Absence of child-friendly formulations: creates problems with DOSING and ADHERENCE
• Duration of treatment: Do children need the same treatment duration as adults with MDR-TB if they have non-severe disease with fewer organisms?
New WHO Drug Groups 2016

- **Group A**: A Fluoroquinolone – levofloxacin or moxifloxacin
- **Group B**: A 2\textsuperscript{nd}-line injectable drug – kanamycin, amikacin or capreomycins (high rates of cross-resistance)
- **Group C**: Other core drugs in combination:
  - Ethionamide/Prothionamide (resistance if \textit{inhA} mutation)
  - Cycloserine/Terizidone
  - Clofazimine
  - Linezolid
- **Group D1**: Add-on drugs (not counted as effective drugs)
  - high-dose INH (low-level INH resistance / \textit{inhA} mutation)
  - pyrazinamide; ethambutol (high rates of resistance in MDR)
- **Group D2**: New drugs: Delamanid; Bedaquiline
- **Group D3**: Para-aminosalicylic acid (PAS); Amoxicillin/clavulanate plus a Carbapenem
Building a MDR/XDR-TB Regimen

MDR/XDR-TB diagnosed

Use a drug from Group A

Add a drug from Group B

Add drugs from Group C until four active drugs are prescribed

Consider adding drugs from Group D1 to strengthen the regimen

Consider adding drugs from Group D2 to strengthen regimen

If regimen not sufficient consider adding drugs from Group D3

Levofloxacin
Moxifloxacin

Amikacin
Kanamycin
Capreomycin

Ethionamide (or prothionamide)
Cycloserine (or terizidone)
Clofazimine
Linezolid

Pyrazinamide
Ethambutol
High-dose isoniazid

Bedaquiline
Delamanid

PAS
Imipenem
Amoxicillin-clavulanate
Meropenem
Amoxicillin-clavulanate
<table>
<thead>
<tr>
<th>WHO MDR-TB drug grs</th>
<th>Recommended doses</th>
<th>CSF penetration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr. A Fluoroquinolones</td>
<td>(PK studies ongoing!)</td>
<td></td>
</tr>
<tr>
<td>Levofloxacain</td>
<td>15-20 mg/kg</td>
<td>Moderate to good (60-80%)</td>
</tr>
<tr>
<td>Moxifloxacain</td>
<td>10-15 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Gr. B 2^{nd}-line Inject</td>
<td>18-20 mg/kg (TDM if higher doses used)</td>
<td>Poor (&lt;20%)</td>
</tr>
<tr>
<td>Km/Am/Cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr. C: Other core 2^{nd}-line drugs</td>
<td>(PK studies ongoing)</td>
<td></td>
</tr>
<tr>
<td>Ethionamide /Pto</td>
<td>15-20 mg/kg</td>
<td>Good</td>
</tr>
<tr>
<td>Cycloserine / Tzd</td>
<td>15-20 mg/kg</td>
<td>Good</td>
</tr>
<tr>
<td>Linezolid</td>
<td>&lt;10 yrs: 10mg/kg bd</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td>&gt;10 yrs: 300-600mg/day</td>
<td></td>
</tr>
<tr>
<td>Clofazimine</td>
<td>2-5 mg/kg; max 100mg (alternate day dosing?)</td>
<td>Poor</td>
</tr>
<tr>
<td>WHO MDR-TB drug groups</td>
<td>Recommended dose</td>
<td>CSF penetration</td>
</tr>
<tr>
<td>------------------------</td>
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<tr>
<td>Group D: Add-ons D1:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>30-40 mg/kg</td>
<td>Good</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>20-25 mg/kg</td>
<td>Poor (&lt;20%)</td>
</tr>
<tr>
<td>High-dose INH</td>
<td>15-20 mg/kg (max 400mg)</td>
<td>Good</td>
</tr>
<tr>
<td>D2: Bedaquiline</td>
<td>&gt;12 yrs &gt;33kg as in adults</td>
<td>Unknown but protein-bound</td>
</tr>
<tr>
<td></td>
<td>400mg/dx2w-200 3x/w</td>
<td>Yes? (evidence from rat study)</td>
</tr>
<tr>
<td></td>
<td>&gt;6yrs/&gt;20kg - 50mg bd</td>
<td>Poor – single dose for ↑C&lt;sub&gt;max&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td>&gt;12yrs/&gt;35kg - 100mg bd</td>
<td>Clav - Poor</td>
</tr>
<tr>
<td>D3: PAS</td>
<td>150-200 mg/kg/day</td>
<td>Meropenem - good</td>
</tr>
<tr>
<td>Amox/Clav with</td>
<td>25-30mg/kg tds</td>
<td></td>
</tr>
<tr>
<td>imipenem/meropenem</td>
<td>IV as per bacterial infection</td>
<td></td>
</tr>
</tbody>
</table>
WHO new shorter regimen for RMR/MDR-TB

• **ONLY for RMR-TB and strictly MDR-TB** (INH+RIF resistance, no FQN/SLID resistance). Only PTB (not yet tested in EPTB)

• **9-12 month** regimen (response to treatment)

• **4-6 Km Mfx Cfz H-hd E Pto Z / 5-6 Mfx Cfz E Z**

• **Approved for children** – Some practical problems
  - Need for rapid DST of second-line drugs
  - Levofloxacin instead of moxifloxacin (formulations)?
  - Clofazimine dose (only 50 or 100 mg gel-caps)
  - Still receiving an injectable agent – Am better (MIC lower)
  - Few long-term follow-up observational studies of regimen
Child-friendly formulations

- The lack of child-friendly formulations of anti-TB drugs makes manipulation of adult formulations necessary
  - poor medication palatability (e.g. Eto, FQNs)
  - makes accurate dosing in children challenging.

- Progress is being made, although slow
  - Dispersible delamanid and bedaquiline being tested
  - Levofloxacin dispersible 100mg tablet for TB CHAMP
  - Granular dosing spoon for PAS
What about the new drugs?

Bedaquiline (TMC207):

- 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 $t_{1/2e}$ of >5 months
- No dosage established for younger children yet, but studies starting. Already used children >12 years/>33kg at same dose as in adults (400mg daily x 2 weeks and then 3 x/week for 22 weeks (6 months total)
What about the new drugs?

**Delamanid (OPC-67683):**
A new Nitro-dihydroimidazo-oxazole derivative

- Inhibits mycolic acid synthesis
- No cross-resistance with current used anti-TB drugs
- Provisionally approved by EMEA (Europe) for use in MDR-TB – in addition to current MDR-TB regimen – in adults >18 yrs
- PK and safety studies for children ongoing (completed to from age 6 years)
- Available through compassionate use from Otsuka via ERS TB Consilium: [https://www.tbconsilium.org/](https://www.tbconsilium.org/)
Duration of treatment/injectable agents

- Optimal duration of Rx in children not known
- Severe/disseminated M/XDR-TB still 18-24 months
- Do children with non-severe or paucibacillary MDR-TB need 18-24 months treatment or even a second-line injectable agent – probably NOT!
- WHO: New shorter 9-12 month regimen approved
- Prospective study in Cape Town on 149 children treated for MDR-TB: (Table)

**High treatment success in children treated for multidrug-resistant tuberculosis: an observational cohort study**

James A Seddon, Anneke C Hesseling, Peter Godfrey-Faussett, H Simon Schaaf

Comparison of characteristics for children with severe and non-severe MDR-TB disease (n=149 unless otherwise stated)

<table>
<thead>
<tr>
<th>Severity of TB disease (Wiseman et al. PIDJ 2012)</th>
<th>Severe disease (n=45)</th>
<th>Non-severe disease (n=104)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR) months</td>
<td>54 (18-142)</td>
<td>31.5 (17.5-53.5)</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Median delay (IQR) days</td>
<td>39 (9-89)</td>
<td>2 (0-41.5)</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MDR-TB source case</td>
<td>23 (51.1)</td>
<td>88 (84.6)</td>
<td>0.19 (0.08-0.44)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>EPTB involvement</td>
<td>18 (40.0)</td>
<td>93 (10.6)</td>
<td>5.64 (2.24-14.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Confirmed diagnosis</td>
<td>33 (73.3)</td>
<td>26 (25.0)</td>
<td>8.25 (3.37-20.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Severe CR (n=148)</td>
<td>35/45 (77.8)</td>
<td>41/103 (39.8)</td>
<td>5.29 (2.23-12.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HIV infection (n=146)</td>
<td>20/44 (45.5)</td>
<td>12/102 (11.8)</td>
<td>6.25 (2.50-15.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hospital admission</td>
<td>42 (93.3)</td>
<td>61 (58.7)</td>
<td>9.87 (2.64-36.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Injectable drug use (n=142)²</td>
<td>39/41 (95.1)</td>
<td>55/101 (54.5)</td>
<td>16.3 (3.27-81.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median duration of injectable drug (n=94)²</td>
<td>6 (4-6)</td>
<td>4 (3-5)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median total duration of therapy (IQR; n=137)³</td>
<td>18 (18-20)</td>
<td>12 (10-16)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mortality</td>
<td>3 (6.7)</td>
<td>0</td>
<td></td>
<td>0.008</td>
</tr>
</tbody>
</table>
Adherence (and support)

- Treatment in hospital and in community needs to be observed – children are ingenious when it comes to making plans how NOT to take their treatment!
- Poor palatability of meds may contribute to adherence problems in some
- 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
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
Pharmaplan (Pty) Ltd

Reg.No./Nr.45/20.2.3.0037
Adherence (and support)

- 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
- 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 within two weeks of starting MDR-TB treatment** (watch out for IRIS especially TBM)

- **Nutritional rehabilitation**
Outcome of MDR-TB in children

- Cure/treatment completion rates in children with MDR-TB vary between 77-91% in different studies.
- However – this is in children DIAGNOSED and TREATED for MDR-TB – Many are missed and die! Furthermore, treatment outcome can still be improved.

Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis

Dena Etehad, H Simon Schaaf, James A Seddon, Graham S Cooke*, Nathan Ford*

Meta-analysis: 81% Cure/Treatment completion
Introduction to Prevention

• Prevention of tuberculosis (TB), including MDR-TB and XDR-TB is a top priority for global TB control

• Among infected contacts, preventive therapy promises to reduce the risk of disease progression. In MDR-TB this is only supported by observational cohort studies

• BCG does NOT provide good protection against infection and disease in children, although it does reduce the risk of severe TB such as TBM and miliary TB

Desired decline in global TB incidence rates to reach the 2035 targets

Current global trend: -1.5%/year

-10%/year by 2025

-5%/year

-17%/year

Optimize use of current & new tools emerging from pipeline, pursue universal health coverage and social protection

Introduce new tools: a vaccine, new drugs & treatment regimens for treatment of active TB disease and latent TB infection, and a point-of-care test

New diagnostics and healthcare for all

Including: Vaccine, treatment of TB infection and disease
THE END TB STRATEGY: PILLARS AND PRINCIPLES

PILLAR 1
Integrated, patient-centered TB care and prevention

PILLAR 2
Bold policies and supportive systems

PILLAR 3
Intensified research and innovation

Government stewardship and accountability, with monitoring and evaluation

Building a strong coalition with civil society and communities

Protecting and promoting human rights, ethics and equity

Adaptation of the strategy and targets at country level, with global collaboration
How pillar 1 works: Key components

A. Early diagnosis of TB including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups.

B. Treatment of all people with TB including drug-resistant TB, and patient support.

C. Collaborative TB/HIV activities; and management of co-morbidities.

D. Preventive treatment of persons at high risk; and vaccination against TB.
Five (or 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
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

High risk MDR-TB
Preventive Rx & follow-up

---

**EXPOSED TO MDR-TB?**

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

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

- **No**
  - **EXCLUDE TB DISEASE**

---

**RISK OF INFECTION?**

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

- **RISK OF DISEASE PROGRESSION?**

---

**MDR-TB STRAIN OR OTHER?**

- **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

---

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

- **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?**
IPT
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
Documented TB exposure, age and HIV status of child

Any current symptoms suggestive of TB?
cough, wheeze, fever, lethargy, fatigue, weight loss, neck swelling

NO

> 5 yrs AND HIV-uninfected
   **No Preventive therapy**
   Regular follow-up
   If typical symptoms develop
   Remains well
   **Complete Preventive therapy**

< 5 yrs OR HIV-infected
   **Preventive therapy**
   Regular follow-up
   If typical symptoms develop
   Remains well
   **Complete Preventive therapy**

YES

Does it meet strict symptom criteria?*
Note: If indicated – then hospitalize/refer#

NO

YES

Follow up after 2-4 weeks
Persistent non-remitting symptoms?

NO

YES

Regular follow-up
Refer if poor response to therapy after 2 months of taking TB treatment

**Treat for TB**

Regular follow-up
Mono-drug resistance prevention

• True rifampicin (RIF) mono-resistant contacts (confirmed by culture-based drug susceptibility test result to be susceptible to INH and not only Xpert MTB/RIF + with RIF resistance)
  Preventive Rx: INH 10 mg/kg daily for 6 months

• INH mono-resistant (RIF-susceptible) contacts:
  RIF 15 mg/kg (10-20mg/kg) for 4 months as single drug (or in RIF/isoniazid if single drug RIF not available at the same RIF dose)
Child contacts of MDR-TB

• In children, use “TB infection” rather than LTBI
• 90% of infected children who will progress to disease will do so within 12 months
• Biomarkers to determine which individuals have the highest risk of progression to TB disease are lacking
• TB disease risk among contacts exposed to MDR-TB is considerable. In a meta-analysis (25 studies), 7.8% of household contacts of MDR-TB patients developed TB
• Strain concordance of household members with DR-TB is high in child contacts <5 years with 75-88% concordance
• No RCTs on MDR prevention have been done. Prospective observational studies have shown the potential benefit

  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
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. 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 Eth (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)
Challenge: To prevent MDR/XDR-TB

- This policy brief (2015) followed a meeting of >50 TB practitioners from 19 countries on MDR-TB prevention
- The current evidence base includes at least ten observational studies (published and unpublished – all were presented), including >600 contacts treated for presumed MDR-TB infection – high rate of success
- The group felt strongly that the time for MDR-TB preventive treatment has come
- Fluoroquinolone-based preventive regimen preferred
- However – RCTs to confirm efficacy should go ahead
- Prevention of XDR-TB remains a problem – new drugs?
RCTs for MDR Preventive Therapy

- Three randomised controlled trials are planned to evaluate the effectiveness of preventive therapy for infected MDR-TB contacts:

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>MDR-TB contacts/ sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>V-QUIN</td>
<td>Levofloxacin vs Placebo</td>
<td>Adults &amp; children – Viet Nam</td>
</tr>
<tr>
<td>TB-CHAMP</td>
<td>Levofloxacin vs Placebo</td>
<td>Children &lt;5 years – South Africa</td>
</tr>
<tr>
<td>PHOENIx</td>
<td>Delamanid vs isoniazid</td>
<td>Adults and children – International (multi)</td>
</tr>
</tbody>
</table>
Conclusions

• MDR preventive Rx could be effective in preventing MDR-TB in children
• Current practice in some settings: 2-3 drug regimens e.g. hdINH/EMB/LFX – safe but complicated
• There is an urgent need RCTs on MDR-TB prevention
• Single drug preventive Rx with a FQN (e.g. levofloxacin) is considered (RCTs starting/ongoing)
• What about XDR-TB contact? Careful follow-up and possibly high-dose INH (no evidence). Considering new drug delamanid as option – to be studied
• In both MDR and XDR-TB regular clinical follow-up is indicated, but pendulum swinging towards preventive treatment.
• Financial Support: NIH, SA National Research Foundation, SA MRC