PADO TB 1: Process and main outcomes

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PADO-TB 1 report back webinar, 27/2/2019
Outline

- Some data: TB in children
- WHO policies
- PADO TB objectives
- PADO meeting: participants, agenda, process
- Main outcomes: priorities and remaining research questions
Burden and mortality of TB in children and adolescents: Huge and unrecognized

- 7.5 million children (0-14) infected with TB each year
  (Dodd et al. 2014 [12])

- 10 million TB patients in 2017

- 1.6 million TB deaths in 2017

- 1 million children (0-14) years developed TB in 2017
  - 52% <5 year olds

- 727,000 adolescents (10-19 year-olds) developed TB in 2012
  (Snow et al., 2018 [13])

- 233,000 children (0-14) TB deaths in 2017
  - 80% in children <5 years
  - 96% of deaths in children who did not access TB treatment
  - 39,000 (17%) deaths among children living with HIV

World Health Organization
GLOBAL TB PROGRAMME
END TB
The case detection gap

Notifications 2017:
- 0-4 years: 161,000
- 5-14 years: 289,000
**Total 0-14 years: 450,000**

Overall 55% of estimated children with TB (0-14 years) are not reported to national TB programmes

% of TB patients that are missed in different age groups

- TB reporting gap is biggest among younger children
- 69% missed (under-diagnosis and under-reporting)
- 31% reported
- 40% missed (under-diagnosis and under-reporting)
- 60% reported
- 35% missed (under-diagnosis and under-reporting)
- 65% reported

All other ages combined
The prevention gap

Globally in 2017, less than 300,000 children under 5 (23%) (out of 1.3 million eligible household contacts under 5 years of age) received TB preventive treatment.
Drug-resistant TB in children

An estimated 25,000 children <15 years fell ill with MDR-TB in 2014

Less than 10% of them were diagnosed and had access to treatment

(Dodd et al, 2016
Jenkins et al, 2014)

Drug-resistant TB is a major contributor to antimicrobial resistance
Treatment of DS-TB with child-friendly fixed dose combinations (FDCs)

- **2 RHZ(E) / 4 HR**
- FDCs launched in December 2015 (WHO and TB Alliance, funded by Unitaid and USAID)
- In line with revised dosing to achieve appropriate therapeutic levels (WHO 2014)
- Formulations (water-dispersible, fruit-flavoured tablets) available:
  - For the intensive phase: 3 FDC (rifampicin 75 mg + isoniazid 50 mg + pyrazinamide 150 mg).

<table>
<thead>
<tr>
<th>Weight band</th>
<th>Numbers of tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intensive phase: RHZ 75/50/150*</td>
</tr>
<tr>
<td>4-7 kg</td>
<td>1</td>
</tr>
<tr>
<td>8-11 kg</td>
<td>2</td>
</tr>
<tr>
<td>12-15 kg</td>
<td>3</td>
</tr>
<tr>
<td>16-24 kg</td>
<td>4</td>
</tr>
<tr>
<td>25+ kg</td>
<td>Adult dosages recommended</td>
</tr>
</tbody>
</table>

*Ethambutol should be added in the intensive phase for children with extensive disease or living in high HIV and/or INH resistance prevalence settings.

Treatment options for LTBI:

- **Isoniazid monotherapy for 6 months** for adults and children in countries with high and low TB incidence
- **Rifampicin plus isoniazid daily for 3 months** for children and adolescents aged < 15 years in countries with a high TB incidence
- **Rifapentine and isoniazid weekly for 3 months** for both adults and children in countries with a high TB incidence
- In **low incidence** countries: **9 months isoniazid**, **3 months weekly rifapentine plus isoniazid**, **3-4 months rifampicin plus isoniazid**, **3-4 months rifampicin** alone
TB prevention: MDR-TB contacts

• In selected high-risk household contacts of patients with MDR-TB, preventive treatment may be considered based on individualised risk assessment and a sound clinical justification.

• Awaiting results of ongoing studies to better inform further recommendations
  – TB-CHAMP: Lfx versus placebo daily for 6 months (< 5 years)
  – PHOENIx: Dlm versus standard dose INH daily for 26 weeks (Children <5 years, TST/IGRA + >5 years)

• Drug choice: later generation fluoroquinolones (e.g. Lfx, Mfx) unless source case resistant. Concern regarding retardation of cartilage development in children – not demonstrated in humans.
## Updated WHO MDR- and RR-TB guidelines (2018)

<table>
<thead>
<tr>
<th>GROUP</th>
<th>MEDICINE</th>
</tr>
</thead>
</table>
| **Group A:** Include all three medicines (unless they cannot be used) | Levofloxacin (Lfx) or Moxifloxacin (Mfx)  
Bedaquiline (Bdq)\(^1,4\)  
Linezolid (Lzd)\(^2\) |
| **Group B:** Include one or both medicines (unless they cannot be used) | Clofazimine (Cfz)  
Cycloserine (Cs) OR Terizidone (Trd) |
| **Group C:** Add to complete the regimen and when medicines from Groups A and B cannot be used | Ethambutol (E)  
Delamanid (Dlm)\(^3,4\)  
Pyrazinamide (Z)\(^5\)  
Imipenem-cilastatin (Ipm-Cln) OR Meropenem (Mpm)\(^6\)  
Amikacin (Am) (OR Streptomycin S)\(^7\)  
Etionamide (Eto) OR Prothionamide (Pto)  
p-aminosalicylic acid (PAS) |
Targets of UNGA HLM on TB - political declaration

(i) 40 million people with TB to be reached with care during the period 2018 and 2023, **including 3.5 million children** and 1.5 million people with drug-resistant TB, **including 115,000 children**; and,

(ii) At least 30 million people to be reached with TB prevention services during the period 2018-2023 **including 4 million children under 5 years of age**, 20 million other household contacts and 6 million people living with HIV (including children).
Roadmap: Key actions

1. Strengthen advocacy at all levels
2. Foster national leadership and accountability
3. Foster functional partnerships for change
4. Increase funding for child and adolescent TB programmes
5. Bridge the policy-practice gap
6. Implement and expand interventions for prevention
7. **Scale up child and adolescent TB case-finding and treatment**
8. Implement integrated family- and community-centred strategies
9. Improve data collection, reporting and use
10. **Encourage child and adolescent TB research**

End the tuberculosis epidemic by 2030

World Health Organization
PADO for TB: Background

• Despite recent advances, major barriers to timely access for children to improved treatments remain, related to:
  – Lack of or delayed clinical trials and rigorous pharmacokinetic and safety studies in children
  – Lack of investments into appropriate paediatric formulation development
  – Regulatory barriers
  – A small, fragmented market with limited uptake

• No formal transparent process exists for establishing evidence-based consensus, or for discussing barriers and solutions to their development and uptake

• Limited commercial incentives exist to develop and supply paediatric products

• Complimentary to ongoing/planned work, e.g. TPMAT, GAP-f
The first PADO for TB meeting: Objectives

1. Discuss the PADO for TB platform and modus operandi

2. Develop a list of short/medium- and long-term priorities for paediatric TB drug optimization

3. Agree on a way forward to accelerate development and uptake of the priority medicine formulations
# The first PADO for TB meeting: Participants and structure

- NTPs from TB high burden and priority countries
- Clinicians
- Scientists
- Funders
- International organizations/technical partners

| 1: Introduction to size and specifics of paediatric anti-TB drug market |
| 2: Experiences with anti-TB drug development and market shaping |
| 3: Current adult and paediatric TB research landscape |
| 4: PADO for TB |
| 5: Group work to define priorities |
| 6: Where do we go from here? |
# PADO for TB 1: Summary of short-term priorities

<table>
<thead>
<tr>
<th>Short-term list</th>
<th>DS-TB</th>
<th>DR-TB</th>
<th>LTBI</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin (RIF)</td>
<td>√</td>
<td></td>
<td></td>
<td>NOT for 4R LTBI regimen</td>
</tr>
<tr>
<td>Rifapentine (RPT)</td>
<td>√</td>
<td></td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Bedaquiline (BDQ)</td>
<td>√</td>
<td>(✓)</td>
<td></td>
<td>On watch-list DR-TB LTBI</td>
</tr>
<tr>
<td>Clofazimine (CFZ)</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delamanid (DLM)</td>
<td>√</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linezolid (LZD)</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretomanid (Pa-824)</td>
<td>√</td>
<td>(✓)</td>
<td></td>
<td>On watch-list DR-TB LTBI</td>
</tr>
</tbody>
</table>

Formulations: All dispersible scored
## Short-term priorities – implementation considerations

<table>
<thead>
<tr>
<th>DR</th>
<th>Notes</th>
</tr>
</thead>
</table>
| **RIF** | • Data available: can increase efficacy and lead to regimen shortening,  
  • Single rather than FDC as ratios will change across weight bands (for “top up”)  
  • Ideal dose of a dispersible tab to be determined |
| **RPT** | • Same rationale as for RIF for single need  
  • Formulation dispersible (potentially scored) – dose TBD on PK study |
| **BDQ** | • Group A WHO DR-TB guidelines, recommended from age 6* |
| **CFZ** | • Group B WHO DR-TB guidelines |
| **DLM** | • Group C WHO DR-TB guidelines, recommended from age 3** |
| **LZD** | • Group A WHO DR-TB guidelines  
  • Syrup (very expensive); 150mg dispersible tablet in development |
| **Pa** | • PK and safety studies underway |

* and ** - no data for younger age groups at the moment
## PADO for TB 1: Summary of watch list

<table>
<thead>
<tr>
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<th>DS-TB</th>
<th>DR-TB</th>
<th>LTBI</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>RHZLfx FDC</td>
<td>✓</td>
<td></td>
<td></td>
<td>If SHINE not successful and TBTC study 31 LFX arm successful</td>
</tr>
<tr>
<td>RHZE FDC</td>
<td></td>
<td>✓</td>
<td></td>
<td>To address barriers to the use of ethambutol</td>
</tr>
<tr>
<td>Telacebec (Q203)</td>
<td></td>
<td></td>
<td>✓</td>
<td>Currently phase IIa</td>
</tr>
<tr>
<td>Sutezolid (PNU-100480)</td>
<td></td>
<td></td>
<td>✓</td>
<td>Currently phase IIa</td>
</tr>
<tr>
<td>Delpazolid (LCB01-0371)</td>
<td></td>
<td></td>
<td>✓</td>
<td>Currently phase IIa</td>
</tr>
<tr>
<td>OPC-167832</td>
<td></td>
<td></td>
<td>✓</td>
<td>Currently phase IIb/IIa</td>
</tr>
<tr>
<td>Moxifloxacin (MFX)</td>
<td></td>
<td></td>
<td>✓</td>
<td>Taste-masked</td>
</tr>
</tbody>
</table>
Venn-diagram: short-term priorities

**DS-TB**

**DR-TB**
- CFZ
- LZD

**LTBI**
- DLM (BDQ)*
- (Pa)*

* BDQ and Pa: Short-term priorities for DR-TB treatment, on watch list for LTBI
Examples of remaining research priorities

DS-TB:
• PK of high-dose daily RPT (not yet started)
• PK/safety in malnourished kids
• PK of high-dose RIF and DTG (maybe DRV/r)

DR-TB:
• New delivery and administration ways (including with food)
• Understanding acceptability, adherence
• Optimal dosing strategies for children under 5 kg (young infants)
• Market size:
  – possible use of drugs for other indications;
  – number of children per weight and age groups
• Costing the research agenda to inform donors and manufacturers
• Explore potential candidates for long acting formulations
Examples of remaining research priorities (2)

LTBI:

• Shorter preventive regimens for children:
  – for DS TB (1HP, 3HP) – for children younger than 2 years of age
  – for DR TB (FQs, Dlm, possibly Bdq)

• Lfx: establish PK, safety and optimal dosing for children (emerging evidence – bioavailability appears higher than expected in initial reports with 15-20mg/kg)

• Mfx: formulation: taste masking

• Optimal ratio of isoniazid:rifapentine (HP) FDC

• Long-acting novel formulations for children

• Operations research to understand barriers and facilitators to uptake of treatment of LTBI in children, including acceptability and palatability assessed earlier for all paediatric formulations
Next steps

- Meeting report with wide dissemination
- Suggest establishment of STAG sub-group of PADO TB and report to STAG TB
  - Show need for prioritization
  - Learn more from PADO HIV experiences
  - Make use of advantage of having GDF and UNITAID funding
  - Work closely with WHO HIV and WHO MVP, in particular PQ
- In future, involve more representatives from TB high burden countries as well as communities affected by TB in PADO TB
- Share outcome of PADO TB with the Working Group on Child and Adolescent TB
Thank you for your attention!
The time for action is NOW
Together we will END TB in children and adolescents