Childhood TB and new TB drugs in the WHO European Region

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<table>
<thead>
<tr>
<th>Key indicators</th>
<th>2011</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approach to drug resistant TB</td>
<td>Small scale pilot projects</td>
<td>Nation-wide integrated programmes</td>
</tr>
<tr>
<td>TB notification rate / 100 000</td>
<td>40</td>
<td>36</td>
</tr>
<tr>
<td>Drug-susceptible success rate (%)</td>
<td>72</td>
<td>76</td>
</tr>
<tr>
<td>MDR-TB detection rate (%)</td>
<td>30</td>
<td>63</td>
</tr>
<tr>
<td>MDR-TB treatment coverage (%)</td>
<td>63</td>
<td><strong>Universal access</strong></td>
</tr>
<tr>
<td>MDR-TB success rate (%)</td>
<td>48</td>
<td>51</td>
</tr>
</tbody>
</table>

- Full scale programmes
- Less new TB cases per year
- More people successfully treated
- More drug-resistant patients diagnosed
- Universal access to treatment
- Increase in MDR-treatment success rate
- Loss to follow-up among new lab-confirmed TB
- Decrease in drug stock-outs
- Increase in coverage for drug-susceptibility testing
- Improved electronic and individual data surveillance
- Ameliorated awareness and political commitment
Key programmatic achievements in the WHO European Region in at country level

- Number of up-to-date childhood TB national clinical and programmatic guidelines
- Number of Member States with childhood TB in their Global Fund TB concept notes/Global Fund grants
- Number of Member States with childhood TB reflected in their national strategic plans
Key strategic directions

1. Full scale-up of rapid diagnosis
2. Rapid uptake of new medicines
3. Expanding people-centred models of care
4. Shorter and more effective treatment regimens
5. Research for new tools
6. Intersectoral approach to address inequities
Main impact indicators

**TB and TB/HIV mortality, EUR, 2000-2015**

-8.5% annual decline between 2010-2015

3.6% annual increase between 2010-2015

Impressive decline in TB mortality combined with growing burden of TB/HIV mortality

**TB and TB/HIV incidence, EUR, 2000-2015**

-4.3% annual decline between 2010-2015

6.2% annual increase between 2010-2015

WHO European Region has fastest decline in TB incidence, however ... still growing TB/HIV co-infection
Drug-resistant TB is in every country

Globally: 480,000 new cases of MDR-TB in 2015
+ 100,000 new cases of rifampicin-resistant TB (RR-TB) needing MDR-TB treatment
Multidrug resistant TB, WHO/Europe, 2015

In 2015 about one in four MDR-TB patients have XDR-TB.

Percentage of XDR-TB among detected MDR-TB cases, WHO European Region, 2015

<table>
<thead>
<tr>
<th>Year</th>
<th>XDR-TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>12%</td>
</tr>
<tr>
<td>2012</td>
<td>9%</td>
</tr>
<tr>
<td>2013</td>
<td>13%</td>
</tr>
<tr>
<td>2014</td>
<td>18%</td>
</tr>
<tr>
<td>2015</td>
<td>23%</td>
</tr>
</tbody>
</table>

On in five TB had MDR-TB.

One in four MDR-TB patients had XDR-TB.

XDR-TB is more difficult to treat than MDR-TB.

Source: WHO Europe / ECDC. Tuberculosis surveillance and monitoring in Europe 2017
MDR-TB in children: incidence (size) and proportion (colour)

*P Dodd et al. Lancet ID 2016*
Comparison of TB case detection rate in adults and children by WHO Regions, 2014

Of estimated ~30,000 child TB cases only ~10,000 are detected by health systems in WHO European Region, TX success >85%
## Shift TB care to more people-centredness

| Governance                          | - Large variation in public spending on health  
|                                    | - Serious inefficiencies in health systems     
|                                    | - Weak coordination across sectors             |
| Service delivery                   | - Overinvestment in secondary and tertiary (hospital-based) care  
|                                    | - Underinvestment in outpatient and primary health care |
| Health financing                   | - Payment mechanisms that do not facilitate reconfiguration of existing services or collaboration across the health system |
| Pharmaceuticals & Human resources  | - Insufficient access to M/XDR–TB drugs         
|                                    | - Primary health care workers not sufficiently trained |
Methodology

22 regional GLC mission reports from 15 sites were analyzed against elements needed to be addressed for introduction of new TB drugs \((Bdq \text{ and } Dlm)\), as per the Policy Implementation Package.

<table>
<thead>
<tr>
<th>Year of the assessment</th>
<th>Armenia</th>
<th>Azerbaijan</th>
<th>Belarus</th>
<th>Georgia</th>
<th>Kazakhstan</th>
<th>Serbia (UN AT Kosovo)</th>
<th>Kyrgyzstan</th>
<th>FYR Macedonia</th>
<th>Moldova</th>
<th>Romania</th>
<th>Republic of Moldova (Transnistria)</th>
<th>Tajikistan</th>
<th>Turkmenistan</th>
<th>Ukraine</th>
<th>Uzbekistan</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>2017</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
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<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
</tbody>
</table>
Out of 15 countries assessed, 13 introduced Bdq and/or Dlm

Number of countries that introduced new TB drugs

- 2013: 2
- 2014: 2
- 2015: 8
- 2016: 10
- 2017: 13
National implementation plan for introduction of new TB drugs

Availability of the National Implementation Plan

- Available in Armenia, Azerbaijan, Belarus, Georgia, Kyrgyzstan, Moldova, Tajikistan, Uzbekistan
- No information on Kazakhstan, Turkmenistan, Ukraine
- Not available in Serbia (UN AT Kosovo), FYR Macedonia, Romania, Moldova (Transnistria)
Minimum requirements for country preparedness and planning: National health context

Availability of the National Strategy to fight TB up to 2020

- Available in Azerbaijan, Armenia, Belarus, Georgia, Kazakhstan, Serbia (UN AT Kosovo), Kyrgyzstan, FYR Macedonia, Moldova, Romania, Tajikistan, Turkmenistan, Ukraine, Uzbekistan

- No information on Moldova (Transnistria)
Minimum requirements for country preparedness and planning: Laboratory

Drug susceptibility testing (DST) to first-line drugs (FLD)

- Available in Azerbaijan, Armenia, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Serbia (UN AT Kosovo), FYR Macedonia, Moldova, Romania, Moldova (Transnistria), Tajikistan, Turkmenistan, Ukraine, Uzbekistan

- Passed in Azerbaijan, Armenia, Belarus, Georgia, Kazakhstan, Kyrgyzstan, FYR Macedonia, Romania, Tajikistan, Ukraine, Uzbekistan

- No information on Moldova, Moldova (Transnistria), Turkmenistan

- Not passed in Serbia (UN AT Kosovo)

Quality assurance for DST to FLD

- Available in 15 countries
- Passed in 11 countries
- No information in 3 countries
- Not passed in 1 country
Minimum requirements for country preparedness and planning: Laboratory

Drug susceptibility testing (DST) to second-line drugs (SLD)

- Available in Azerbaijan, Armenia, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Romania, Moldova (Transnistria), Tajikistan, Turkmenistan, Ukraine, Uzbekistan
- Not available in Serbia (UN AT Kosovo), FYR Macedonia

Quality assurance for DST to SLD

- Passed in Azerbaijan, Armenia, Belarus, Georgia, Moldova, Kazakhstan, Kyrgyzstan, Romania, Tajikistan, Moldova (Transnistria), Turkmenistan, Uzbekistan, Ukraine
- Not passed in Serbia (UN AT Kosovo), FYR Macedonia
Minimum requirements for country preparedness and planning: Drug supply and management

Shortage of TB drugs reported during the last 2 years

- No shortage reported in Armenia, Georgia, Kazakhstan, Serbia (UN AT Kosovo), FYR Macedonia, Moldova, Tajikistan, Turkmenistan, Uzbekistan

- Shortage reported by Azerbaijan, Belarus, Kyrgyzstan, Romania, Moldova (Transnistria), Ukraine
Minimum requirements for country preparedness and planning: Drug supply and management

- Registration of Clofazimin (Cfz), Bdq, Dlm is problematic at all countries. Pharmacological companies are not interested to apply for registration, hence, alternative mechanisms should be thought out.
- Bdq and Dlm are imported based on one-time license, mainly because these drugs are still on a clinical trial.
- TB drugs procured with the support from the Global Fund are quality assured. However, drugs procured through local budget, mainly do not hold WHO-prequalification.
Country preparedness and planning: Monitoring and evaluation

- All countries use updated WHO definitions for TB (2013 update)
- Some countries still do not have functional electronic TB database and execute paper-based reporting (Azerbaijan, Tajikistan, Turkmenistan, Uzbekistan, Kyrgyzstan)
- Supportive supervisions in majority countries are performed by the National TB Programs, but are heavily relying on the Global Fund support
Children and adolescents – Dlm (XDR or “MDR+”)

### Pediatric Cohort Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dlm (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at admission, years</td>
<td>16 (13-17,3)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>10 (59%)</td>
</tr>
</tbody>
</table>

### Treatment Outcome

<table>
<thead>
<tr>
<th>Treatment Outcome</th>
<th>Total (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cured</td>
<td>3</td>
</tr>
<tr>
<td>Treatment completed</td>
<td>1</td>
</tr>
<tr>
<td>Ongoing treatment</td>
<td>13</td>
</tr>
<tr>
<td>Died / LTFU / Failure</td>
<td>0</td>
</tr>
<tr>
<td>Sputum Culture Conversion at 6 m.</td>
<td>4 / 4</td>
</tr>
</tbody>
</table>

### Pediatric Patients on Dlm Reported for

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious AE: All resolved w/o dose change</td>
<td>3</td>
</tr>
<tr>
<td>Grade 3 QTcF prolongation (&gt; 60 msec or QTcF &gt; 500ms)</td>
<td>0</td>
</tr>
<tr>
<td>Non Serious AE</td>
<td>7</td>
</tr>
<tr>
<td>Grade 1-2 QTcF prolongation</td>
<td>4</td>
</tr>
</tbody>
</table>

September 2016
Children and adolescents - Bdq

Experience from MSF and Belarus NTP

• 27 children/adolescents – median age 16 (10-17)
• 65% culture positive at baseline
• 67% presumed or confirmed XDR-TB
• Companion drugs:
  – Mfx (22%), Cfz (96%), Lzd (96%), Imp (15%)
• 100% culture negative after 24w Bdq
• 5 patients had prolonged QTcF – none ceased Bdq
Early diagnosis of all forms of tuberculosis and universal access to drug-susceptibility testing, including the use of rapid tests

The Regional Office, in collaboration with partners, will prepare a guide and *diagnostic algorithms* for expanded and accelerated quality-assured new diagnostic technologies (taking into account pediatric tuberculosis and extrapulmonary tuberculosis diagnostics).

Management of latent tuberculosis infection and preventive treatment of persons at high risk, and vaccination against tuberculosis

Member States will ensure that WHO policy *recommendations* on bacillus Calmette-Guérin (BCG) *vaccination* for infants are implemented and BCG revaccination is discontinued.
C. Equitable access to quality treatment and continuum of care for all people with tuberculosis, including drug-resistant tuberculosis, and patient support to facilitate treatment adherence

• Member States will ensure that their tuberculosis and drug-resistant tuberculosis treatment guidelines, including childhood tuberculosis guidelines, are regularly updated and implemented according to the latest available evidence and WHO recommendations (ongoing activity).

• Member States will develop a plan for achieving universal access to treatment, including the treatment of vulnerable populations and children, and uninterrupted drug supply (ongoing activity).

• Member States will ensure the rational, safe and effective introduction of new tuberculosis medicines, including for children, according to the most recent WHO policy guidance (as soon as possible and not later than 2016)

• Member States will sustain countrywide use of first-line fixed-dose combination drugs (for adults and children) and paediatric drug formulations in the treatment of drug-susceptible tuberculosis, where possible.
C. Regulatory frameworks for case-based surveillance, strengthening vital registration, quality and rational use of medicines, and pharmacovigilance

The Regional Office will assist Member States in the development of procedures for the procurement of medical supplies with an emphasis on quality assurance through strengthened regulatory authorities and particular emphasis including, but not limited to, paediatric tuberculosis diagnostics and treatment (drug formulations), and limiting the availability of new drugs on the free market (over the counter) without a tuberculosis indicated prescription sale.
Investing in TB prevention and care: Value for money, the most cost-effective single disease approach investment, 1 USD invested, yields 40 USD return

Political commitment is key
Conclusions

• More (high level) advocacy needed
• Childhood TB to be integrated further within overall TB and beyond, i.e. PHC, pediatrics
• More rapid mechanisms for new drug introductions needed at country levels
• Need for more evidence, partnerships are key
• Capacity building
Acknowledgements

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http://www.euro.who.int/en/health-topics/communicable-diseases/tuberculosis

eurotb@who.int
Thank you very much for your consideration.