WHO updates: latest epi data & development of new guidelines and operational handbook on the management of TB in children and adolescents

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Annual meeting of the Child and Adolescent TB Working Group, 30 November 2021
Outline

• Update on data included and reported for the 2021 Global TB Report
• Guideline development
  – Key updates based on the rapid communication on the updated guidance on the management of TB in children and adolescents
  – Consolidation of recommendations
  – Consultations on classification of TB disease and dosing of bedaquiline, delamanid and the new TBM regimen
• Other updates
• Next steps
Global burden estimates (2021 Global TB report)

- TB patients in 2020: 9.9 million
- TB deaths in 2020: 1.5 million
- Children (0-14 years) developed TB in 2020: 1.09 million
- Child (0-14) TB deaths in 2020: 226,000

- 7.5 million children (0-14) infected with TB each year
- 47.5% <5 years olds
- 727,000 adolescents (10-19 year-olds) developed TB in 2012

- 80% in children <5 years
- 96% of deaths in children who did not access TB treatment
- 21,000 (9%) deaths among children living with HIV

(Dodd et al, 2014, 2017a)

(2021 Global TB report)

Roadmap towards ending TB in children and adolescents
Second edition
Detailed age-disaggregated reporting

- 13 TB HBCs reported fully age disaggregated notifications: Brazil, China, India, Indonesia, Kenya, Lesotho, Myanmar, Namibia, Philippines, South Africa, Thailand, Uganda, Tanzania
- These 13 countries represent almost 54% of all notifications in the 0-14y age group
- Data on adolescents aged 10-19 years reported since 2020
  - Relatively high notification rates in older adolescents

New and relapse TB case notification rates by age group for children and adolescents in 10 TB HBCs, 2020
Treatment initiation in children with MDR/RR-TB

- Countries requested to report on the number of children/young ado’s (0-14y) initiated on second-line treatment for MDR/RR-TB since 2020
- **79 countries** reported **at least 1 child** started on second-line treatment in 2020
- **6 countries** (India, Russian Federation, South Africa, Ukraine, Pakistan and Kazakhstan) reported **≥100 children** started on second-line treatment (81% of all cases) in 2019, but only 3 of these reported over 100 children in 2020
- Drop in number starting treatment in 2020
  - Impact of COVID-19 pandemic: 43% drop between 2019 and 2020
  - % of children among all patients: 2.5%

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>India</td>
<td>3360 (60%)</td>
<td>1844 (57%)</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>476</td>
<td>54</td>
</tr>
<tr>
<td>South Africa</td>
<td>332</td>
<td>162</td>
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<td>Ukraine</td>
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<tr>
<td>Pakistan</td>
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<td>76</td>
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<tr>
<td>Kazakhstan</td>
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<tr>
<td><strong>Global total</strong></td>
<td><strong>5588</strong></td>
<td><strong>3235</strong></td>
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<table>
<thead>
<tr>
<th>Year</th>
<th>MDR/RR-TB (all ages)</th>
<th>MDR/RR-TB (0-14y)</th>
<th>% children among all MDR/RR-TB</th>
</tr>
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<tbody>
<tr>
<td>2018</td>
<td>156 205</td>
<td>3 398</td>
<td>2.2%</td>
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<tr>
<td>2019</td>
<td>177 099</td>
<td>5 588</td>
<td>3.2%</td>
</tr>
<tr>
<td>2020</td>
<td>128 338</td>
<td>3 235</td>
<td>2.5%</td>
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130 (of 215) countries reported treatment success rate in children and young adolescents (0-14y) for the 2019 cohort

22 (of the 30) TB HBCs reported (N=387,360 or 74% of total notifications in 0-14y in 2019)

Overall: 87.6% treatment success (range 69-100%)
Trends in provision of TPT to eligible <5 contacts

- Drop in # eligible due to drop in notifications among patients with bacteriologically confirmed TB
- Drop in number of TPT initiations from 433k to 386k
Impact of COVID on TB notifications in 2020

Trends in case detection in children (<15y)

Notified 0-14y

Impact of COVID on TB notifications in 2020

Drop in notifications: 2020 compared to 2019

Notifications 2019: Total: 7 120 320; 15+: 6 596 500; 0-14y: 523 820

Notifications 2020: Total: 5 834 188; 15+: 5 434 671; 0-14y: 399 517

Ages 15 +

Ages 0-14y

17.6%

23.7%

7.35%

6.85%
The case detection and prevention gaps remain... 

The case detection gap

% of missing TB patients in different age groups

- 0-4 years: 72.5%
- 5-14 years: 44.6%
- All <15 years: 63.5%
- All >15 years: 38.2%

The prevention gap

In 2020, almost two thirds of 1.1 million eligible contacts <5 years* did NOT access TB preventive treatment (TPT)

* Estimated number of eligible children was reduced due to lower notifications of bacteriologically confirmed patients in 2020.
No data collected on TPT for DR-TB.
Progress against UNGA HLM targets

Case detection and treatment

- 1,433,000 children notified with TB 2018 - 2020
  - 41% of the 2022 target (3.5m)
- 12,220 children started on second-line treatment for MDR/RR-TB 2018 - 2020
  - 10.6% of the 2022 target (115,000)

Provision of TB preventive treatment

- 1.2 million contacts < 5y initiated on TPT 2018 - 2020
  - 29% of the 2022 target (4m)
- 320,000 contacts ≥5y initiated on TPT 2018 - 2020
  - 1.6% of the 2022 target (20m)
- 7.2 million PLHIV initiated on TPT 2018 - 2020
  - >100% of the 2022 target (6m)
TB/HIV co-infection

- WHO requested data on TB/HIV in children/young adolescents for the 1st time for the 2021 Global TB Report, in line with the commitments of the Rome Action Plan on Paediatric HIV & TB
- 38 countries reported TB/HIV data in 0-14 years, including 16 TB/HIV HBCs, in 2020
  - 16 TB/HIV HBCs covered 98% of all testing
- Data reported:
  - # TB patients notified who have an HIV test result recorded
  - # TB patients tested for HIV who tested HIV-positive
  - # TB/HIV co-infected patients on ART

1 Paediatric HIV & TB: Rome Action Plan (website): 2020
Development of updated guidelines on the management of TB in children and adolescents

- GDG meeting held in May/June 2021
- Evidence reviewed on the following PICO questions, using GRADE* methodology:
  - Use of Xpert Ultra in gastric aspirate and stool specimens
  - Integrated treatment decision algorithms
  - Treatment shortening in children with non-severe TB
  - In children with MDR/RR-TB: Use of bedaquiline in children under 6 and delamanid in children under 3 years
  - Short intensive treatment regimen for TBM
  - Models of care for case detection and provision of TPT (decentralized and family-centred, integrated approaches)
- **Rapid communication** published in August 2021
- Internal/external review, submission to WHO GRC on 19 November
- **Consolidated guidelines** with **operational handbook** expected in the next months

[https://apps.who.int/iris/bitstream/handle/10665/344382/9789240033450-eng.pdf](https://apps.who.int/iris/bitstream/handle/10665/344382/9789240033450-eng.pdf)
TB diagnostic approaches in children – key updates

• In children with signs and symptoms of pulmonary TB, **Xpert MTB/ RIF Ultra in gastric aspirate or stool specimens** should be used as the initial diagnostic test for TB and the detection of rifampicin resistance, rather than smear microscopy/culture and phenotypic drug susceptibility testing (DST)
  • In addition to sputum or NPA specimens, already recommended for Xpert Ultra testing, in the same population
  • Both Xpert MTB/RIF and Ultra now recommended on all paediatric specimens

• In children with presumptive pulmonary TB, **treatment decision algorithms** may be used to diagnose pulmonary TB
  • Bacteriological confirmation needs to be sought whenever possible, using available and recommended diagnostic tests and appropriate paediatric specimens – especially in children with a high likelihood of DR-TB
  • Newly developed treatment decision algorithms for different settings with detailed practical guidance on their use will be included in the operational handbook to be published alongside the guidelines.

• Consolidation of existing recommendations on rapid diagnostics for TB detection, including for EPTB, detection of resistance to first- and second-line drugs (e.g. Xpert MTB/Rif, Ultra, LAMP, LF-LAM, FL/SL LPA, low/moderate/high complexity NAAT)

[https://apps.who.int/iris/bitstream/handle/10665/344382/9789240033450-eng.pdf](https://apps.who.int/iris/bitstream/handle/10665/344382/9789240033450-eng.pdf)
Treatment for drug-susceptible TB – key updates

- Evidence from the SHINE trial reviewed by the GDG:
  - Main finding: 4-month treatment non-inferior to the 6-month regimen (consistent across all key analyses - including age groups, HIV status, type of TB and adherence)
  - In children and adolescents (3 months to 16 years) with non-severe, presumed drug-susceptible TB, a 4-month regimen (2HRZ(E)/2HR) should be used rather than the standard 6-month regimen (2HRZ(E)/4HR).
    - Important implementation considerations were noted to determine eligibility for the shorter treatment regimen and will be described in the consolidated guidelines and in the operational handbook.

- Consolidation of new recommendation based on review of data from TBTC study 31/ACTG A5349 (to be included in updated guidelines on DS-TB treatment): Patients aged 12 years and older with drug-susceptible pulmonary TB, may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide.

Rapid communications:
Child and adolescent TB: https://apps.who.int/iris/bitstream/handle/10665/344382/9789240033450-eng.pdf
Drug-susceptible TB: https://apps.who.int/iris/rest/bitstreams/1350979/retrieve
Treatment of TB meningitis in children and adolescents

- TBM: most serious, second most common form of EPTB; poor outcomes, even with treatment
- Current recommendation: 2HRZE/10HR (Based on 2009 literature review, non-randomized, non-comparative studies, not entered into GRADE)

- Systematic review and meta-analysis to compare the effectiveness of a shorter intensive regimen (6HRZEto, with slightly higher H and R dosing) vs WHO recommended regimen
  - Shorter intensive regimen: lower death rates, and higher successful treatment rates, but a high proportion of survivors with neurological sequelae

- Key update: In children and adolescents with bacteriologically confirmed or clinically diagnosed TB meningitis (without suspicion or evidence of MDR/RR-TB), a **6-month intensive regimen (6HRZEto)** may be used as an alternative option to the **12-month regimen (2HRZE/10HR)**.
Treatment of DR-TB in children – key updates

- Children usually tolerate second-line treatment well, with favourable treatment outcomes.
- Data reviewed:
  - BDQ: Data from TMC207-C211 (children aged 5-18) and IMPAACT P1108 (children aged 0-18).
  - DLM: Phase I PK/safety/tolerability study and corresponding extension study (protocols 242-12-232 and 233); cohorts 1 (12-17 years), 2 (6-11 years), 3 (3-5 years) and 4 (0-2 years) for both protocols.
  - Both: Paediatric DR-TB IPD (24,231 records, majority from India and South Africa; just under 20,000 used for matched analysis of treatment outcomes).
- **UPDATE:** In children of all ages with MDR/RR-TB, an all-oral treatment regimen containing bedaquiline may be used.
  - as part of the shorter, all oral BDQ regimen (conditionally recommended by WHO in 2020) or as part of longer treatment regimens.
- **UPDATE:** In children of all ages with MDR/RR-TB, delamanid may be used as part of longer treatment regimens.

WHO consolidated guidelines on tuberculosis. Module 4: Treatment. Drug resistant tuberculosis treatment. Available at: https://www.who.int/publications/i/item/9789240007048
Models of care for case detection and provision of TB preventive treatment in children and adolescents

- Paediatric TB services often highly centralized, with limited capacity at PHC level, leading to missed opportunities for contact tracing, TB prevention, TB detection, care and management

- Decentralization and family-centred, integrated care: one of 10 key actions in 2018 Roadmap Towards Ending TB in Children and Adolescents.

- Systematic review:
  - Impact of combined health facility and community approaches on the number of children and adolescents diagnosed with TB; of decentralized services on levels of TPT initiation.
  - Impact of different types of service integration on TB case notifications in children and adolescents; of socio-economic support for families affected by TB on TPT coverage/completion among children and adolescents.

- Key update: In high TB burden settings, decentralized and family-centred, integrated services may be implemented to improve TB case detection and the uptake of TB preventive treatment.
  - In this context, decentralized services do not replace centralized or specialized child and adolescent TB services, rather, they complement them.
Consolidation of recommendations from other guidelines

WHO TB Module 1: Prevention - Tuberculosis preventive treatment (2020)
WHO TB Module 2: Screening - Systematic screening for tuberculosis detection (2021)
BCG position paper (2018)
WHO TB Module 3: Diagnosis – Rapid diagnostics for tuberculosis detection (2021)
WHO TB Module 4: Treatment - Drug-resistant tuberculosis treatment (2020)
Treatment – Drug-susceptible tuberculosis treatment (in progress)
WHO guidance for national TB programmes on the management of TB in children (2014)
WHO nutritional care and support for patients with TB (2013)
Updates on the management of SAM in infants and children (2013)
Follow-up consultations (Sept/Oct. 2021)

- **Expert Consultation on classification of intrathoracic TB disease in children under 10 years**
  - Intrathoracic lymph node TB disease currently classified as extra-pulmonary TB
  - Ben Marais prepared background documentation including the historical perspective and rationale, and a motivation to update the classification from a pathophysiological, clinical, and surveillance perspective
  - Conclusions and updates be provided in the guidelines and operational handbook, as well as upcoming Global guidance on TB surveillance

- **Expert consultation on dosing of bedaquiline and delamanid and the short intensive treatment regimen for TB meningitis**
  - Background documentation prepared by Elin Svensson (bdq and dlm) and Kelly Dooley, Roeland Wasmann, Paolo Denti (TBM)
  - Review of latest evidence from PK studies, relevant pharmacometric simulations and implementation considerations on dosing for BDQ and DLM and for the TBM regimen to ensure that the new WHO recommendations can be implemented
  - Interim dosing strategies to be included in the operational handbook
Other updates

• Publication of the PADO-TB virtual review report
• Update of the WHO Prequalification Expression of Interest (EOI)
  – Included 150 mg scored dispersible tablet for rifapentine (to ensure flexible dosing across indications and age groups for current and future needs) – 3HP, 1HP, DS-TB treatment
• Update of the Global Fund Expert Review Panel EOI
  – Inclusion of rifapentine 150mg dispersible tablet (scored)
• Essential medicines list for children (EMLc) updates (October 2021)
  – Inclusion of bedaquiline 20mg tablet and delamanid 25mg dispersible tablet

Next steps at global level

- Release of **operational handbook** with practical operational guidance
e.g. on treatment decision algorithms; eligibility criteria for shorter treatment regimens for children with non-severe TB; building treatment regimens for children with MDR/RR-TB not eligible for shorter all-oral bdq regimens; updated dosing tables for second-line drugs, dosing strategy for short TBM regimen; examples of models of care from various settings; post-TB health; palliative care; TB and pneumonia; TB and malnutrition
- **Launch event** around World TB Day (to be confirmed)
- Dissemination of guidelines and handbook, through WHO webinars, WHO Knowledge Sharing Platform, global, regional and country meetings
- Development of **training materials** (2022)
- Second meeting of the Paediatric Anti-TB Drug Optimization group (**PADO-TB 2**, end 2022)
- Update of the 2018 **Roadmap** (2023)
Acknowledgements

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