Implementation of TB disease severity assessment & new TB short course treatment regimens in children in Kenya

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University of Nairobi

Annual meeting of the Child and Adolescent TB working group
Tuesday 29 November 2022
Updated Guidelines on Management of TB in Children & Adolescents. W.H.O. *Launched in March 2022*

https://www.who.int/health-topics/tuberculosis
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 2RHZ (E) /2RH should be used [rather than the standard 6-month regimen (2RHZ(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.

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
• Current recommendation: 2 months HRZE followed by 10 months HR
  • (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 (6HRZEt, with slightly higher H and R dosing) vs WHO recommended regimen
  • Shorter intensive regimen: lower death rates, and higher successful treatment rates.... 
    \(\text{......but a high proportion of survivors with neurological sequelae}\)

• 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 (6RHZ + Ethionamide) may be used
  • [as an alternative option to the 12-month regimen (2HRZE/10HR).]
Kenya - process to review and implement new shorter course TB treatment for children & adolescents
Steps taken in adoption of the new guidelines in Kenya

- Paediatric TB Committee of Experts (COE) series of meetings.
  - Examined each new recommendation
  - July 2022

- Data synthesis and review of WHO 2022 recommendations workshop.
  - Drafted new guideline
    - Min of Health (NTLP, child health division) Academia, Implementors, funding & implementing partners
  - September 2022

- Presented revised guideline to all stakeholders
  - [Technical experts Professional associations
    Patient communities, CSOs]
  - Piloted in selected counties
  - October 2022
Data synthesis and review of WHO 2022 child & adolescent TB recommendations workshop

- Detailed review of the WHO guidelines
- Review of the evidence
- Review of the current and past Kenya guidelines - TB, Basic paediatric protocols
- Lecture on childhood TB
- Heated plenary discussions in country context, low access to CXR for children, bacteriologic test low yield and contribution to delay in child TB Rx decisions

Criteria for 4-month TB regimen

WHO 2022

Box 5.3 Eligibility criteria for the 4-month regimen (2HRZ(E)/2HR) in children and adolescents aged between 3 months and 16 years with non-severe pulmonary or peripheral lymph node TB in various settings

In children and adolescents who have undergone bacteriological testing and CXR, a 4-month treatment regimen should be started in children and adolescents meeting all of the following three criteria:

- CXR findings consistent with non-severe TB (can be performed at any point during the course of the disease):
  - intrathoracic lymph node TB without significant bronchial involvement
  - PTB confined to one lobe with no cavities
  - uncomplicated pleural effusion (without pleuro-pulmonary disease)

- TB that is negative, trace, very low or low using negative amplification test (if Xpert MTB/RIF or Ultra not available)

- the child or adolescent has mild TB symptoms that do not require hospitalization; a

In the absence of bacteriological testing and CXR, a 4-month treatment regimen may also be started in children and adolescents meeting any of the following two criteria:

- isolated extrathoracic (peripheral) lymph node TB, without involvement of other extrapulmonary sites of disease;

- the child or adolescent has mild TB symptoms that do not require hospitalization. a

In settings without access to CXR, a 4-month treatment regimen should be started in children and adolescents meeting all of the following four criteria:

- TB that is negative, trace, very low or low using negative amplification test (if Xpert MTB/RIF or Ultra not available)

- the child or adolescent has mild TB symptoms that do not require hospitalization; a

- TB symptoms resolved completely within 1 month of treatment initiation and the child is completely well, including a normal nutritional status, at 4 months of treatment.

- none of the danger or high-priority signs listed in Table 4.5;

- no asymmetrical and persistent wheezing;

- no signs of EPTB other than peripheral lymph node TB;

- none of the following: SAM, respiratory distress, high fever (over 39 °C), severe pallor, restlessness, irritability or lethargy.

a Mild symptoms that do not require hospitalization means:
To define severe versus non-severe TB Disease
WHO 2022 - with chest x-ray and/or bacteriologic tests

<table>
<thead>
<tr>
<th>Pulmonary TB</th>
<th>Detail</th>
<th>Severe</th>
<th>Non-severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest x-ray</td>
<td>Hilar LN</td>
<td>Compressing bronchi</td>
<td>No compression</td>
</tr>
<tr>
<td></td>
<td>Parenchyma</td>
<td>Lesions in &gt;1 lobe</td>
<td>&lt;= 1 lobe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Miliary</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cavitation</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Pleura</td>
<td>Complicated effusion</td>
<td>Uncomplicated effusion</td>
</tr>
<tr>
<td>Microbiologic tests</td>
<td>Bacillary load</td>
<td>High bacillary load</td>
<td>Paucibacillary, trace or negative</td>
</tr>
<tr>
<td>Extrapulmonary TB</td>
<td>Location EPTB</td>
<td>TB meningitis, bone-joint</td>
<td>Cervical LN TB</td>
</tr>
<tr>
<td></td>
<td>Dissemination</td>
<td>Any miliary</td>
<td>Other peripheral LN TB</td>
</tr>
</tbody>
</table>

TB in children & adolescents in Kenya 2019 - 2021

In Kenya, highest burden is in children <5yr and rises after age 10yr
55% of children <15y with TB are missed

Percent of all cases diagnosed:
0-4y: 52.2%
  (incidence 2020: 8,900)
5-14y: 36.9%
  (incidence 2020: 7,700)

All children <15y:
• Only 45% of children with TB are diagnosed.
  (incidence 2020: 16,600)
What is the access to CXR for TB diagnosis in Children & Adolescents?
Kenya 2019 CXR Data

<table>
<thead>
<tr>
<th>Age group</th>
<th>Total Patients 2019</th>
<th>X-rays Done 2019</th>
<th>X-ray Uptake (%)</th>
<th>Positivity rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>5118</td>
<td>3380</td>
<td>66%</td>
<td>96%</td>
</tr>
<tr>
<td>5-9</td>
<td>1141</td>
<td>589</td>
<td>52%</td>
<td>94%</td>
</tr>
<tr>
<td>10-14</td>
<td>2057</td>
<td>851</td>
<td>41%</td>
<td>92%</td>
</tr>
<tr>
<td>15-24</td>
<td>15056</td>
<td>4039</td>
<td>27%</td>
<td>94%</td>
</tr>
<tr>
<td>25-34</td>
<td>21945</td>
<td>6329</td>
<td>29%</td>
<td>95%</td>
</tr>
<tr>
<td>35-44</td>
<td>18479</td>
<td>6058</td>
<td>33%</td>
<td>95%</td>
</tr>
<tr>
<td>45-54</td>
<td>10842</td>
<td>3953</td>
<td>36%</td>
<td>95%</td>
</tr>
<tr>
<td>55-64</td>
<td>5645</td>
<td>2309</td>
<td>41%</td>
<td>96%</td>
</tr>
<tr>
<td>65+</td>
<td>5537</td>
<td>2735</td>
<td>49%</td>
<td>97%</td>
</tr>
<tr>
<td>Overall</td>
<td>85820</td>
<td>30243</td>
<td>35%</td>
<td>95%</td>
</tr>
</tbody>
</table>

What % of presumed TB cases got CXR?
<5 yrs: 66%  5 – 9 yrs: 52%  10 – 14 yrs: 41%  15 – 24 yrs: 27%

For all that got CXR >90% of the CXRs were suggestive of TB

Maleche-Obimbo, Child TB new guideline, Kenya 2022
What is the access to Xpert for TB diagnosis in Children & Adolescents? 
Kenya 2019 Data

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<thead>
<tr>
<th>Age group</th>
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<th>Xpers Done 2019</th>
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<th>Positivity rate (%)</th>
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<tbody>
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<td>5118</td>
<td>1103</td>
<td>22%</td>
<td>22%</td>
</tr>
<tr>
<td>5-9</td>
<td>1141</td>
<td>481</td>
<td>42%</td>
<td>34%</td>
</tr>
<tr>
<td>10-14</td>
<td>2057</td>
<td>1126</td>
<td>55%</td>
<td>54%</td>
</tr>
<tr>
<td>15-24</td>
<td>15056</td>
<td>9770</td>
<td>65%</td>
<td>81%</td>
</tr>
<tr>
<td>25-34</td>
<td>21945</td>
<td>14658</td>
<td>67%</td>
<td>78%</td>
</tr>
<tr>
<td>35-44</td>
<td>18479</td>
<td>12380</td>
<td>67%</td>
<td>74%</td>
</tr>
<tr>
<td>45-54</td>
<td>10842</td>
<td>7007</td>
<td>65%</td>
<td>66%</td>
</tr>
<tr>
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<td>5645</td>
<td>3529</td>
<td>63%</td>
<td>56%</td>
</tr>
<tr>
<td>65+</td>
<td>5537</td>
<td>3389</td>
<td>61%</td>
<td>47%</td>
</tr>
<tr>
<td>Total</td>
<td>85820</td>
<td>53443</td>
<td>62%</td>
<td>71%</td>
</tr>
</tbody>
</table>

What % of presumed TB cases got Xpert tests?
<5 yrs: 22%  
5 – 9 yrs: 42%  
10 – 14 yrs: 55%  
15 – 24 yrs: 65%

*TB was detectable in Xpert for only 22% of U5s, and 34% of 5-9yr olds*  
*Even in younger adolescents 10-14yr Xpert is + in only half* (NTLP 2019)
Kenya Paediatric Protocols – Approach to define severity of disease (evolved from IMCI / ETAT)
Kenya Paediatric Protocols – Approach to define severity of disease (*evolved from IMCI / ETAT*)

<table>
<thead>
<tr>
<th>Category</th>
<th>Detail</th>
<th>Severe</th>
<th>Non-severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>Distress SPO2, Work of breathing</td>
<td>Resp distress, Cyanosis, SPO2 &lt;90%, Increased work of breathing (alar flaring, chest indrawing, grunting)</td>
<td>Not in distress, SPO2 NORMAL</td>
</tr>
<tr>
<td>Circulatory</td>
<td>Dehydration, Shock</td>
<td>Capillary refill 2 sec+, weak pulse, Cold extremities, temp gradient</td>
<td>No dehydration</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Level of consciousness</td>
<td>Drowsy, Reduced level consciousness (AVPU &lt;A), (Alert-Verbal-Pain-Unresponsive &lt;A)</td>
<td>Alert</td>
</tr>
</tbody>
</table>

Widely used across paediatric services nationally
Enables clinical decisions at first assessment
Kenya Paediatric Protocols – Approach to define children at high risk of poor outcome or death

<table>
<thead>
<tr>
<th>Category</th>
<th>High risk of poor outcome</th>
<th>Low risk of poor outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Below age one year</td>
<td>Above age one year</td>
</tr>
<tr>
<td>HIV Status</td>
<td>HIV Infected</td>
<td>HIV uninfected</td>
</tr>
<tr>
<td>Nutritional Status</td>
<td>Severe malnutrition Age &lt;5yr: WHZ or WAZ &lt; -3 Age &gt;5yr: BMI &lt; -3</td>
<td>Well nourished</td>
</tr>
<tr>
<td>Other immune-suppressive conditions</td>
<td>Renal disease On steroid therapy Diabetes, Cancer</td>
<td>No major co-morbidity</td>
</tr>
</tbody>
</table>

Widely used across paediatric services nationally
Enables clinical decisions by health practitioners at first assessment
SHORTER 6 MONTH REGIMENS FOR TB MENINGITIS (WHO 2022 update)

• Current recommendation: 2 months HRZE followed by 10 months HR
  • (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 (6HRZEt, 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 (6RHZ + Ethionamide) may be used
  • [as an alternative option to the 12-month regimen (2HRZE/10HR).]

Kenya retained 12 month regimen for TB meningitis & bone-joint TB.
Rationale: ethionamide expensive & high toxicity seen in MDR Rx program
### Proposed treatment regimens for Kenya for children 10 years and below

*All children 11 years and above will require the 6 month regimen*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Eligibility for 4 month regimen</th>
<th>Eligibility for 6 month regimen</th>
<th>Eligibility for 12 month regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of TB</strong></td>
<td>Non-severe Pulmonary TB</td>
<td>Severe Pulmonary TB</td>
<td>TB Meningitis</td>
</tr>
<tr>
<td></td>
<td>Cervical LN TB</td>
<td>Extra Pulmonary TB <em>(excluding TB meningitis, Osteoarticular and peripheral LN TB)</em></td>
<td>Osteo-articular TB</td>
</tr>
<tr>
<td><strong>Indicators of severity</strong></td>
<td>Stable enough to be managed as an outpatient</td>
<td>All hospitalised patients</td>
<td>Any setting</td>
</tr>
<tr>
<td></td>
<td>No danger signs</td>
<td>A sick child at diagnosis with any danger sign</td>
<td>All</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Respiratory danger signs: In respiratory distress (oxygen saturation &lt;90%, cyanosis, grunting, chest in-drawing)</td>
<td></td>
</tr>
<tr>
<td><strong>Immune status</strong></td>
<td>Is HIV negative, not severely malnourished, not immune suppressed</td>
<td>Infants &lt; 1yr <em>(immature immune system)</em>, HIV positive, severe malnutrition, any immunosuppressed child</td>
<td>All</td>
</tr>
<tr>
<td><strong>Bacteriologic status (where available)</strong></td>
<td>Bacteriologically negative / Clinically diagnosed TB</td>
<td>Bacteriologically confirmed drug-susceptible TB</td>
<td>All</td>
</tr>
<tr>
<td><strong>Treatment regimen</strong></td>
<td>4 month regimen: 2HRZE/2HR</td>
<td>6 month regimen: 2HRZE/4HR</td>
<td>12 month regimen 2HRZE/10HR</td>
</tr>
</tbody>
</table>

*If the child has known contact with a person with drug-resistant TB, this table does not apply...*

*Start the child on treatment as per the DR TB guidelines*
Steps taken in adoption & implementation of the new child & adolescent TB guidelines in Kenya

Presentation at the TB Interagency Coordinating Committee
Endorsement & adoption

October 2022

Dissemination at Kenya Lung Conference
~250 participants from all over Kenya
Adopted in new updated Kenya Paediatric Protocols

November 2022

Roll out the algorithm in December 2022

Roll out of the shorter regimen 2023
(training, jobaids, commodity planning, transition period)

December 2022

Thank you! Asante! Merci!

Gracias! Orio! Obrigado!