

Management of DR-TB in children and adolescents – implementation considerations

Sabine Verkuijl, WHO GTB

Joint SEAR-WPR workshop to plan the accelerated implementation of new TB WHO policies, Hanoi, VietNam, 1-4 April 2025

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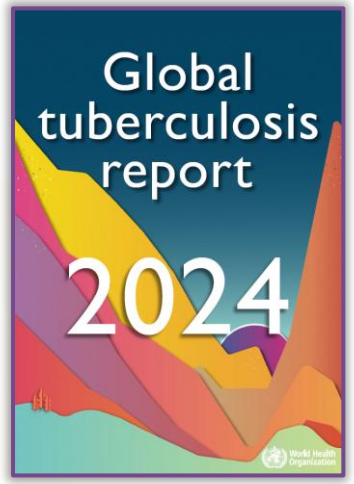
TB incidence and mortality in children and adolescents, 2023



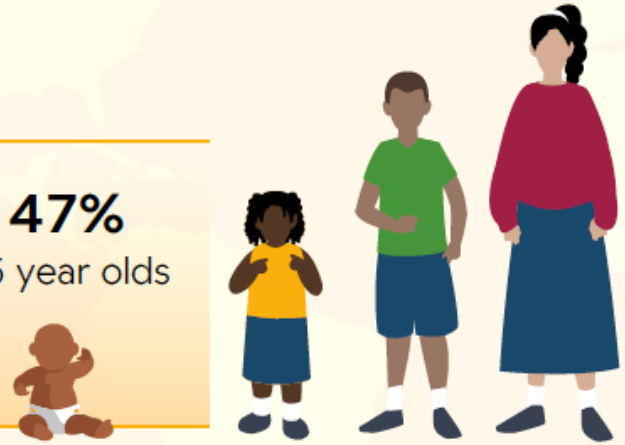
10.8 million
TB among all ages in 2023

1.25 million
TB deaths in 2023

1.25 million
children (0–14 years) developed TB in 2023 (12% of all TB)

191 000
TB deaths in 2023 (15% of all TB deaths)

47%
<5 year olds



727 000 adolescents
(10–19 year-olds) developed TB in 2012 (Snow et al, 2018)

Among deaths in HIV-negative children and young adolescents 0–14

73% were in children <5 years

96%
of deaths occurred in children who did not access TB treatment

(Dodd et al, 2017)

25 000
(14%) TB deaths in the 0–14 year age group were among children living with HIV

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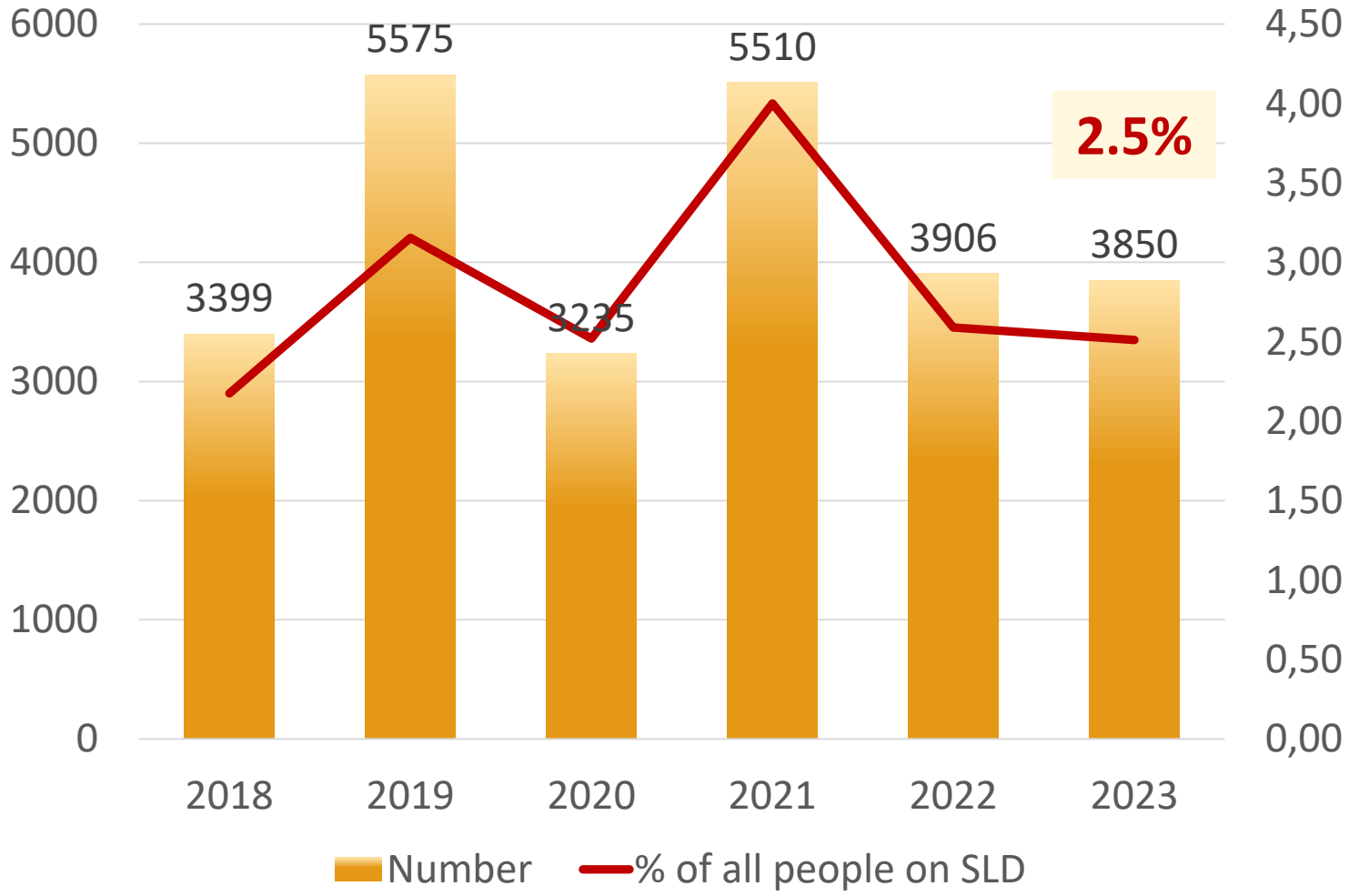
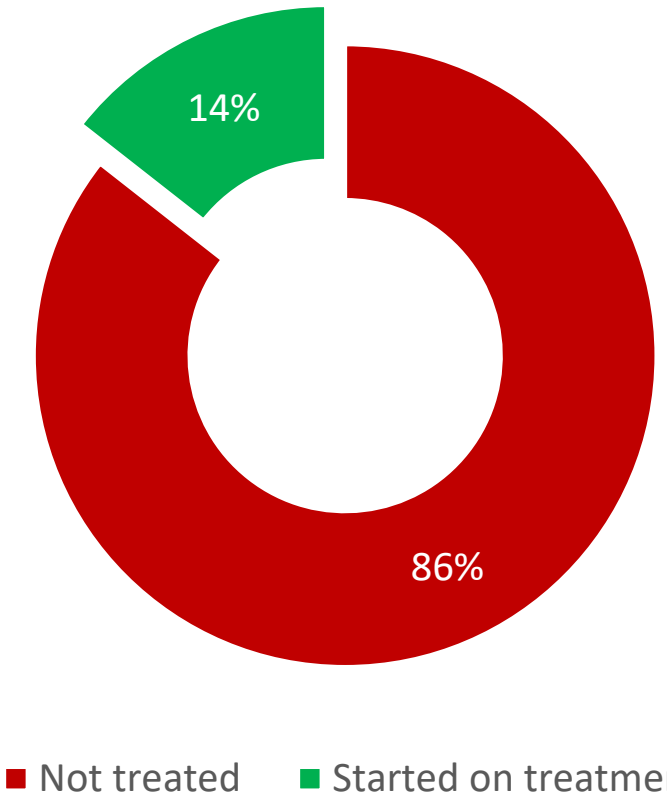
Treatment initiation in children with MDR/RR-TB (global)

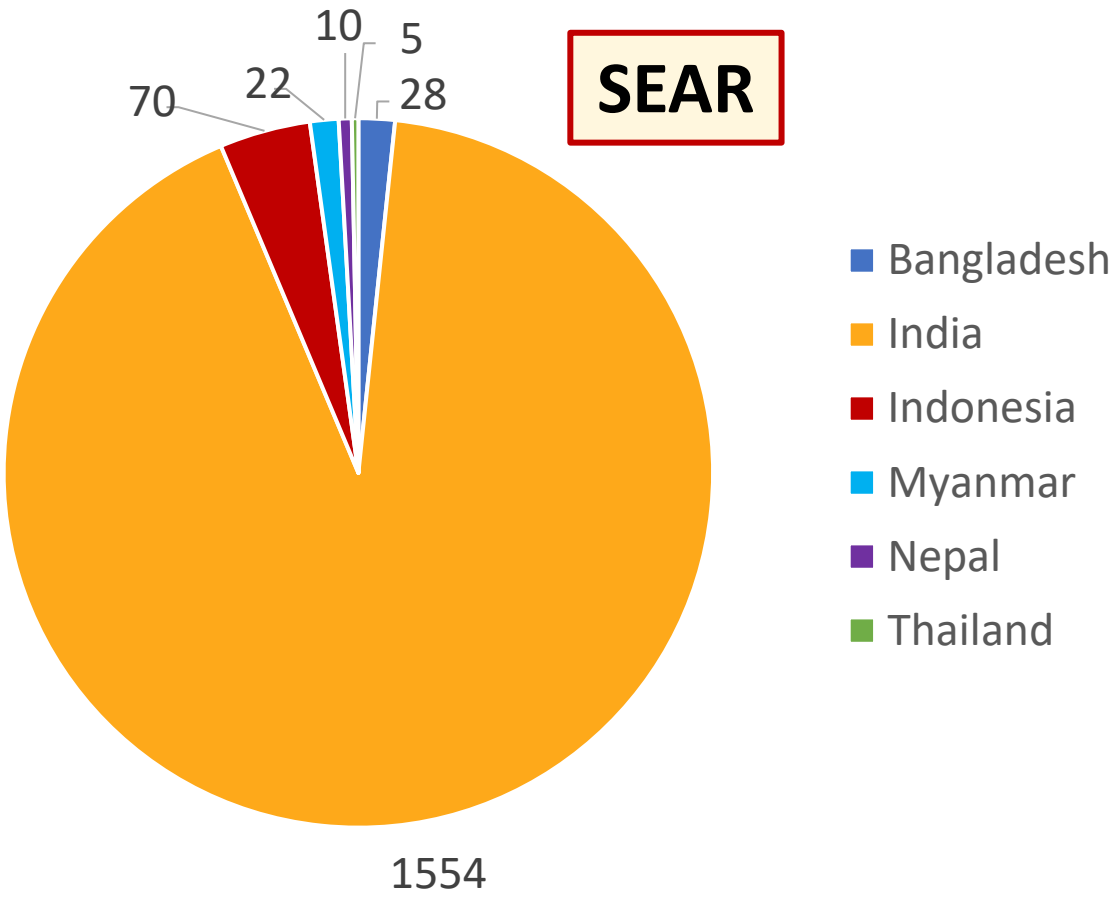
Second-line treatment initiation in 0-14y, 2018-2023

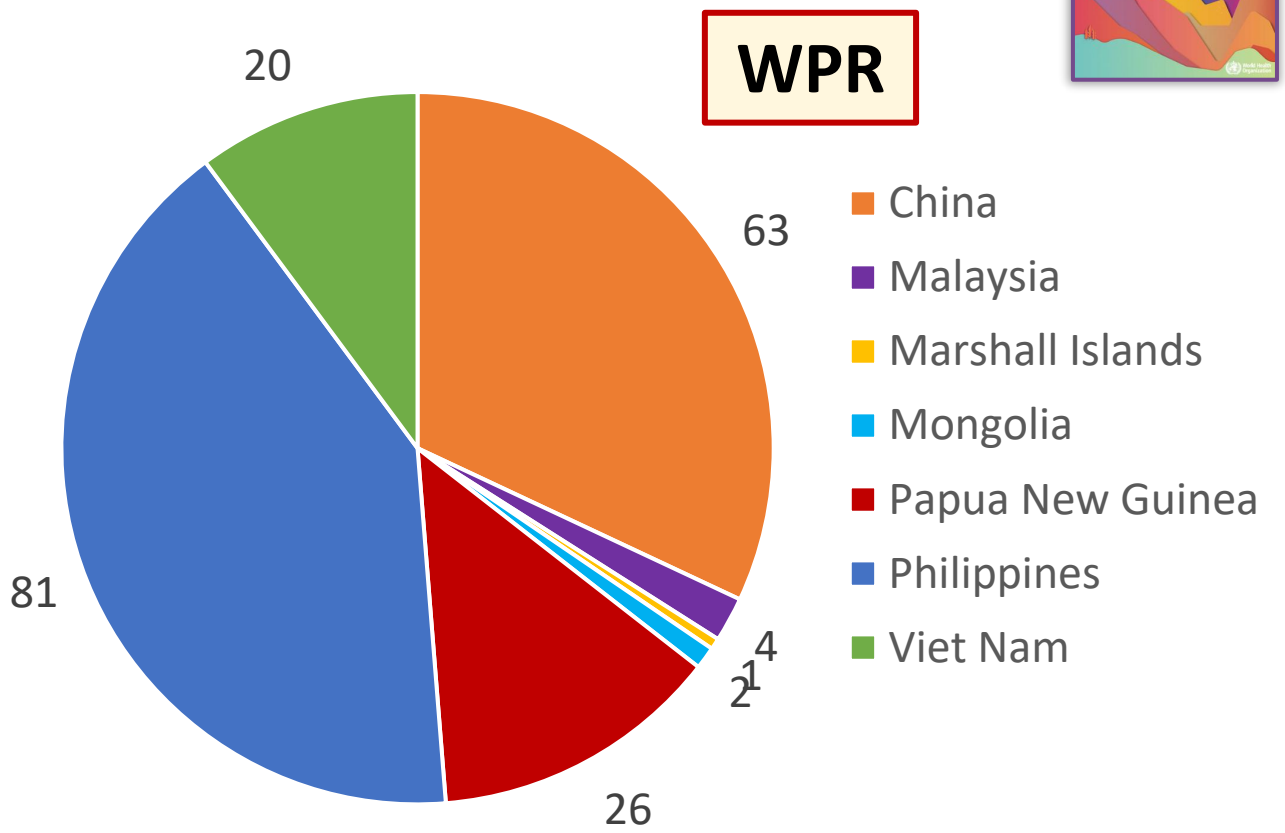


MDR/RR-TB treatment coverage in children and young adolescents, average for 2018-2023 (out of an estimated 30 000 per year)



Second-line treatment initiation for DR-TB in <15 years in the SEAR and WPR, 2023





SEAR:
0-14 years = 2.7% of all MDR/RR-TB initiated on second-line treatment (1689 out of 62 850)

WPR:
0-14 years = 0.7% of all MDR/RR-TB initiated on second-line treatment (197 out of 27 313)

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Reasons for the treatment coverage gap

Characteristics of children and adolescents with multidrug-resistant and rifampicin-resistant tuberculosis and their association with treatment outcomes: a systematic review and individual participant data meta-analysis

Anthony J Garcia-Prats, Maria Garcia-Cremades*, Vivian Cox, Tamara Kredo, Rory Dunbar, H Simon Schaaf, James A Seddon, Jennifer Furin, Jay Achar, Kendra Radke, Tina Sachs, Amanzhan Abubakirov, Saman Ahmed, Onno W Akkerman, Nadia Abdulkareem Al Ani, Farhana Amanullah, Nafees Ahmad, Laura F Anderson, Meseret Asfaw, Funeka Bango, Torsten Bauer, Mercedes Becerra, Martin Boeree, Folke Brinkmann, Rosemary Brown, James Brust, Jonathon R Campbell, Anna Cristina Carvalho, Isabel Carvalho, J Peter Cegielski, Rosella Centis, Edward D Chan, Sandeep Chauhan, Silvia S Chiang, Pei-Chun Chan, Lia D'Ambrosio, Margareth Dalcolmo, Narine Daneilyan, Gerard de Vries, Heather R Draper, the endTB Study Group, Lee Fairlie, Joshua R Francis, Molly Franke, Medea Gegia, Camilo Gomez Restrepo, Annette Guenther, Tatyana Gureva, Brit Haecker, Elizabeth Harausz, Catherine Hewison, Robert M Hicks, Helena Huerga, Jennifer Hughes, Petros Isaakidis, Syed M Kadri, Mazhar Ali Khan, Tinatin Kotrikadze, Liga Kuksa, Nathalie Lachenal, Christoph Lange, Leonid Lecca, Elisa Lopez-Varela, Sheila Lucena, Andrei Mariandyshev, Sanjay Mattoo, Ana Mendez-Echevarria, Giovanni Battista Migliori, Carole Mitnick, Erika Mohr-Holland, Winston Mulanda, Totugul Murzabakova, Bakyt Myrzalieve, Norbert Ndjeka, Stefan Niemann, Iveta Ozere, Nesri Padayatchi, Malik Parmar, Nargiza Parpieva, Mohammad Manzur-Ul-Alam, Natasha Rybak, Kuldeep Singh Sachdeva, Kelly Salmon, Begoña Santiago-Garcia, Dagmar Schaub, Ira Shah, Sarita Shah, Vaibhav Shah, Sangeeta Sharma, Tae Shun Shim, Sonya Shin, Animesh Sinha, Alena Skrahina, Hardik Solanki, Belen P Solans, Antoni Soriano-Arandes, Atyrkul Toktogonova, Tjip van der Werf, Gustavo E Velásquez, Bhanu Williams, Jae-Joon Yim, Rada Savic†, Anneke Hesseling†*

Lancet Child Adolesc Health 2025; 9: 100–11

See Comment page 78

*Contributed equally

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Summary

Background There are few data on the treatment of children and adolescents with multidrug-resistant (MDR) or rifampicin-resistant (RR) tuberculosis, especially with more recently available drugs and regimens. We aimed to describe the clinical and treatment characteristics and their associations with treatment outcomes in this susceptible population.

Paediatric drug-resistant TB individual patient database:

- High % of **adolescents**
- High % of **bacteriological confirmation**

Suggesting:

- **Young children** with DR-TB not detected
- Treatment seldomly started in **absence of bacteriological confirmation**

https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(24)00330-4/abstract

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Risk factors for MDR/RR-TB in children

Risk factors for MDR/RR-TB in children and adolescents

- **Exposure** to person with **confirmed** DR-TB
- **Exposure** to person who **failed** TB treatment or who died from TB
- **Non-response** to first-line TB treatment
- **Previous** TB treatment

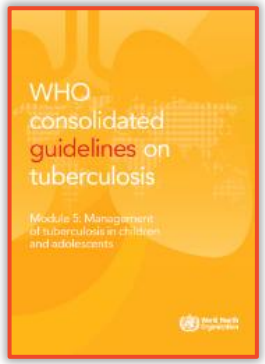
Children with a decision to start treatment based on the treatment decision algorithms need to be assessed for risk of DR-TB

Contact investigation: a critical intervention to identify children and adolescents exposed to DR-TB

Evaluation and diagnosis

- High **index of suspicion** needed
- **Bacteriological testing** critical
  - Concurrent testing with different samples (respiratory and stool) increases sensitivity (fewer false negative results)
- If bacteriological testing negative or cannot be done, a **clinical diagnosis** can be made (include detailed guidance in national guidelines)
- The **DST pattern** of the child/adolescent or the most likely source case informs treatment

Treatment of DR-TB in children – use of bdq & dlm in children



- **In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used**
- **In children with MDR/RR-TB aged below 3 years, delamanid may be used as part of longer regimens**

*(**NEW:** both conditional recommendations, very low certainty of the evidence)*

Remarks:

- *Applies to and complements current WHO recommendations on shorter and longer regimens that contain bedaquiline*
- *Complements the current WHO recommendation on longer regimens that contain delamanid*

These recommendations make it possible to build all oral regimens for children of all ages

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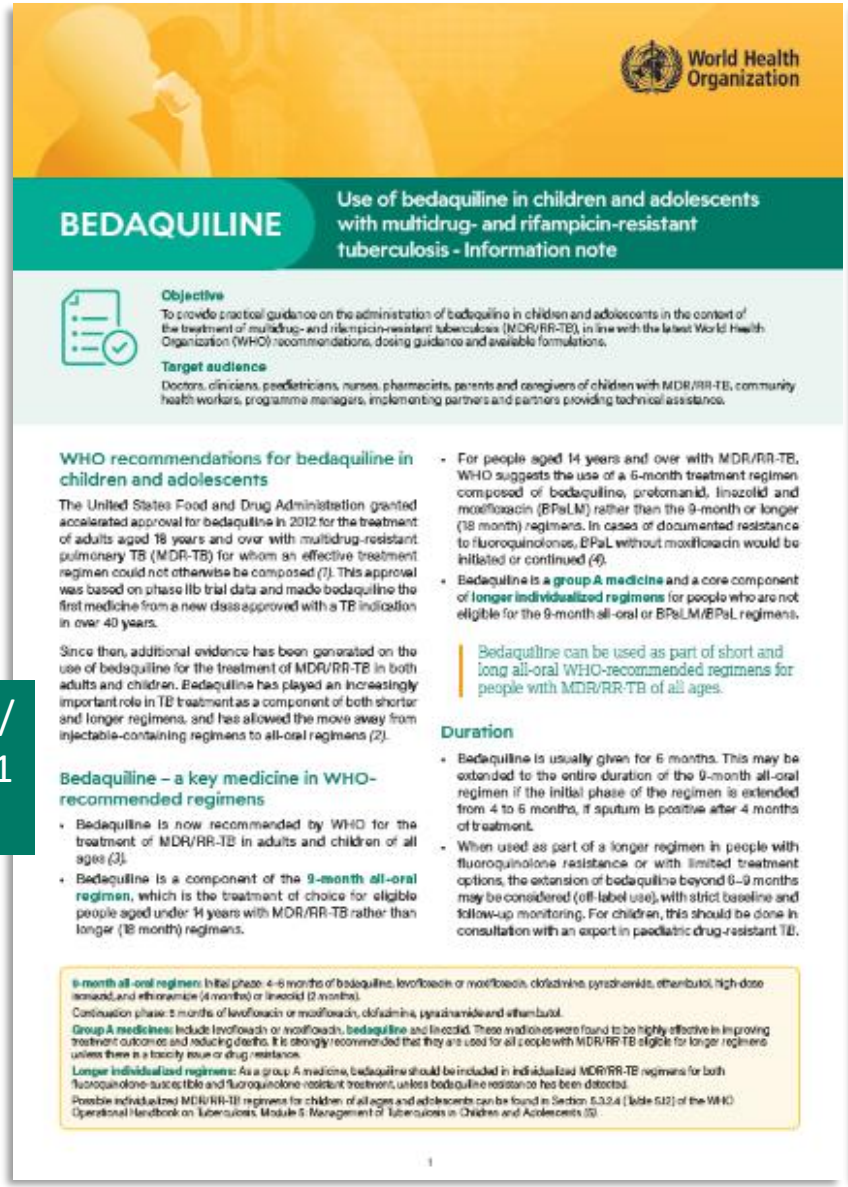
Information notes on bedaquiline and delamanid

https://apps.who.int/iris/rest/bitstreams/1514053/retrieve



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BEDAQUILINE

Use of bedaquiline in children and adolescents with multidrug- and rifampicin-resistant tuberculosis - Information note

Objective

To provide practical guidance on the administration of bedaquiline in children and adolescents in the context of the treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB), in line with the latest World Health Organization (WHO) recommendations, dosing guidance and available formulations.

Target audience

Doctors, clinicians, paediatricians, nurses, pharmacists, parents and caregivers of children with MDR/RR-TB, community health workers, programme managers, implementing partners and partners providing technical assistance.

WHO recommendations for bedaquiline in children and adolescents

The United States Food and Drug Administration granted accelerated approval for bedaquiline in 2012 for the treatment of adults aged 18 years and over with multidrug-resistant pulmonary TB (MDR-TB) for whom an effective treatment regimen could not otherwise be composed (1). This approval was based on phase IIb trial data and made bedaquiline the first medicine from a new class approved with a TB indication in over 40 years.

Since then, additional evidence has been generated on the use of bedaquiline for the treatment of MDR/RR-TB in both adults and children. Bedaquiline has played an increasingly important role in TB treatment as a component of both shorter and longer regimens, and has allowed the move away from injectable-containing regimens to all-oral regimens (2).

Bedaquiline – a key medicine in WHO-recommended regimens

- Bedaquiline is now recommended by WHO for the treatment of MDR/RR-TB in adults and children of all ages (3).
- Bedaquiline is a component of the **9-month all-oral regimen**, which is the treatment of choice for eligible people aged under 14 years with MDR/RR-TB rather than longer (18 month) regimens.
- For people aged 14 years and over with MDR/RR-TB, WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) rather than the 9-month or longer (18 month) regimens. In cases of documented resistance to fluoroquinolones, BPaL without moxifloxacin would be initiated or continued (4).
- Bedaquiline is a **group A medicine** and a core component of **longer individualized regimens** for people who are not eligible for the 9-month all-oral or BPaLM/BPaL regimens.

> Bedaquiline can be used as part of short and long all-oral WHO-recommended regimens for people with MDR/RR-TB of all ages.

Duration

- Bedaquiline is usually given for 6 months. This may be extended to the entire duration of the 9-month all-oral regimen if the initial phase of the regimen is extended from 4 to 6 months, if sputum is positive after 4 months of treatment.
- When used as part of a longer regimen in people with fluoroquinolone resistance or with limited treatment options, the extension of bedaquiline beyond 6–9 months may be considered (off-label use), with strict baseline and follow-up monitoring. For children, this should be done in consultation with an expert in paediatric drug-resistant TB.

9-month all-oral regimen: Initial phase: 4–6 months of bedaquiline, levofloxacin or moxifloxacin, clofazimine, pyrazinamide, ethambutol, high-dose isoniazid, and ethionamide (4 months) or linezolid (2 months).
Continuation phase: 5 months of levofloxacin or moxifloxacin, clofazimine, pyrazinamide and ethambutol.
Group A medicines: Include levofloxacin or moxifloxacin, **bedaquiline** and linezolid. These medicines were found to be highly effective in improving treatment outcomes and reducing deaths. It is strongly recommended that they are used for all people with MDR/RR-TB eligible for longer regimens unless there is a toxicity issue or drug resistance.
Longer individualized regimens: As a group A medicine, bedaquiline should be included in individualized MDR/RR-TB regimens for both fluoroquinolone-susceptible and fluoroquinolone-resistant treatment, unless bedaquiline resistance has been detected.
Possible individualized MDR/RR-TB regimens for children of all ages and adolescents can be found in Section 5.3.2.4 (Table 5.12) of the WHO Operational Handbook on Tuberculosis. Module 5: Management of Tuberculosis in Children and Adolescents (5).

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https://apps.who.int/iris/rest/bitstreams/1514046/retrieve

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DELAMANID

Use of delamanid in children and adolescents with multidrug- and rifampicin-resistant tuberculosis - Information note

Objective

To provide practical guidance on the administration of delamanid in children and adolescents in the context of the treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB), in line with the latest World Health Organization (WHO) recommendations, dosing guidance and available formulations.

Target audience

Doctors, clinicians, paediatricians, nurses, pharmacists, parents and caregivers of children with MDR/RR-TB, community health workers, programme managers, implementing partners and partners providing technical assistance.

WHO recommendations for delamanid in children and adolescents

The European Medicines Agency granted conditional approval to delamanid in 2014 "as part of an appropriate combination regimen for pulmonary multidrug-resistant tuberculosis in adult patients (≥18 years of age) when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability" (1). This made delamanid the second new medicine from a new class approved with a TB indication, following on from bedaquiline.

Since then, additional evidence has been generated on the use of delamanid for the treatment of MDR/RR-TB in both adults and children. Its use has expanded the list of medicines available to design all-oral longer individualized regimens for people with MDR/RR-TB, moving away from toxic injectable agents. The availability of delamanid is particularly important for people, including children, with limited options due to a more extensive resistance profile.

> Delamanid can be used as part of individualized longer regimens for people of all ages with MDR/RR-TB.

Delamanid – a medicine for people of all ages with limited treatment options

- Delamanid is now recommended by WHO for the treatment of MDR/RR-TB in adults and children of all ages (2, 3).
- Delamanid is a **group C medicine** and can be used as part of **longer individualized regimens** for people with MDR/RR-TB, including children and adolescents, who are not eligible for the 9-month all-oral regimen or the 6-month regimen composed of bedaquiline, pretomanid and linezolid, with or without moxifloxacin (BPaLM/BPaL).
- As a group C medicine, delamanid can be included in MDR/RR-TB regimens when a treatment regimen cannot be composed of **group A or B** agents alone, due to resistance or intolerance.

Duration

- Delamanid is usually given for 6 months. The duration may be extended beyond 6 months (off-label use) in people, including children, with fluoroquinolone resistance or with limited treatment options. Studies undertaken between 2020 and 2022 showed that the use of delamanid beyond 6 months (when given alongside other medicines, including bedaquiline) is safe (4, 5).

Group A medicines: Include levofloxacin or moxifloxacin, bedaquiline and linezolid.
Group B medicines: Include clofazimine and cycloserine or terizidone.
Group C medicines: Include ethambutol, **delamanid**, pyrazinamide, imipenem–cilastatin or meropenem in combination with clavulanic acid, amikacin or streptomycin (only used as salvage therapy in children and adolescents aged under 18 years), ethionamide or prothionamide and *P*-aminosalicylic acid. Group C medicines are included in longer regimens if the regimen cannot be composed of Group A and B medicines alone.
Longer individualized regimens: Examples of individualized MDR/RR-TB regimens for children of all ages and adolescents can be found in Section 5.3.2.4 (Table 5.12) of the WHO Operational Handbook on Tuberculosis. Module 5: Management of Tuberculosis in Children and Adolescents (6).

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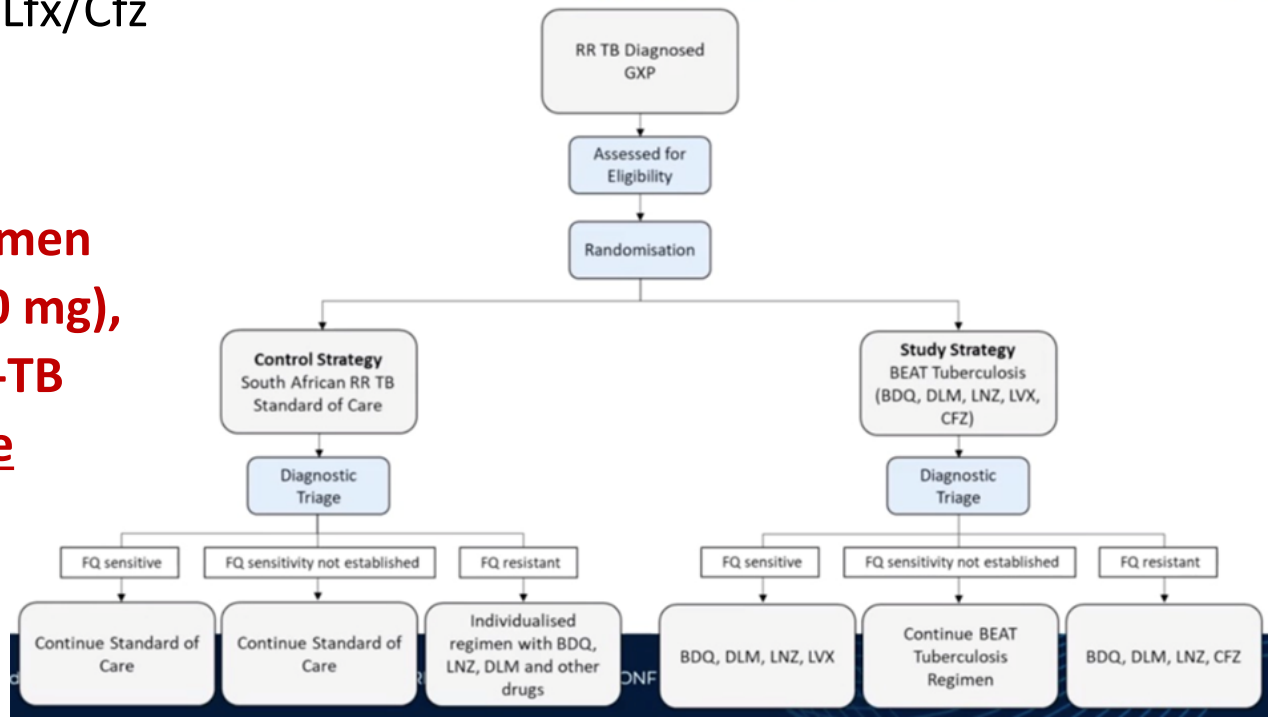
Treatment of DR-TB in children – updates

- **BEAT-TB trial** in South Africa – 6-month Bdq-Lzd-Dlm-Lfx/Cfz (or both) vs Standard of Care

- New recommendation:

  WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, delamanid, linezolid (600 mg), levofloxacin, and clofazimine (BDLLfxC) in MDR/RR-TB patients with or without fluoroquinolone resistance

  (Conditional recommendation, very low certainty of evidence)



- Applies to (among others):

  ☑ FQ S
  ☑ FQ R

  a. PTB TB, including **children, adolescents, PLHIV, pregnant and breastfeeding women**
  b. EPTB except CNS, osteoarticular, or disseminated forms of TB with multi-organ involvement
  c. **Children and adolescents without bacteriological confirmation of TB or DST but with a high likelihood of MDR/RR-TB** (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB)

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Rapid communication: https://www.who.int/publications/i/item/B09123

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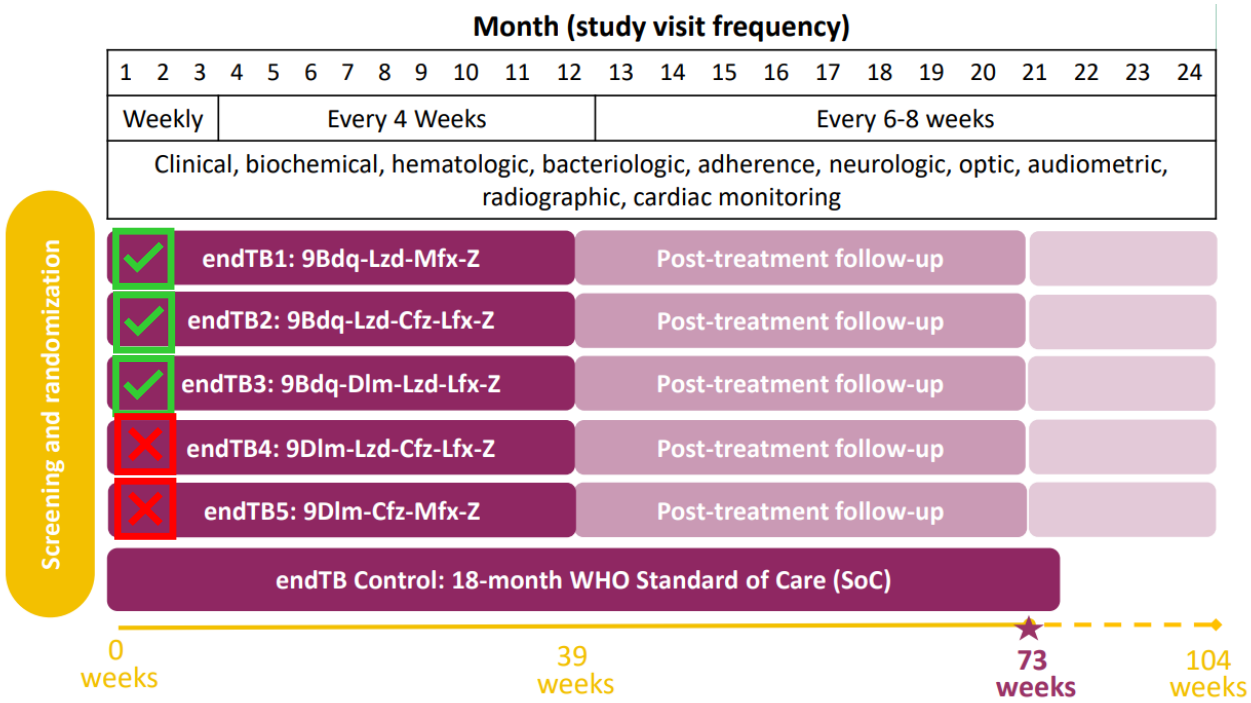
Treatment of DR-TB in children – updates

- **endTB trial** – 9-month regimens vs Standard of Care
- New recommendation:

  WHO suggests using the 9-month all-oral regimens (BLMZ, BLLfxCZ and BDLLfxZ) over currently recommended longer (>18 months) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. Amongst these regimens, using BLMZ is suggested over BLLfxCZ, and BLLfxCZ is suggested over BDLLfxZ

  (Conditional recommendation, very low certainty of evidence)



- Applies to (among others):
  a. PTB TB, including **children, adolescents, PLHIV, pregnant and breastfeeding women**
  b. EPTB except CNS, osteoarticular, or disseminated forms of TB with multi-organ involvement
  c. **Children and adolescents without bacteriological confirmation of TB or DST but with a high likelihood of MDR/RR-TB** (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB)

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Rapid communication: https://www.who.int/publications/i/item/B09123

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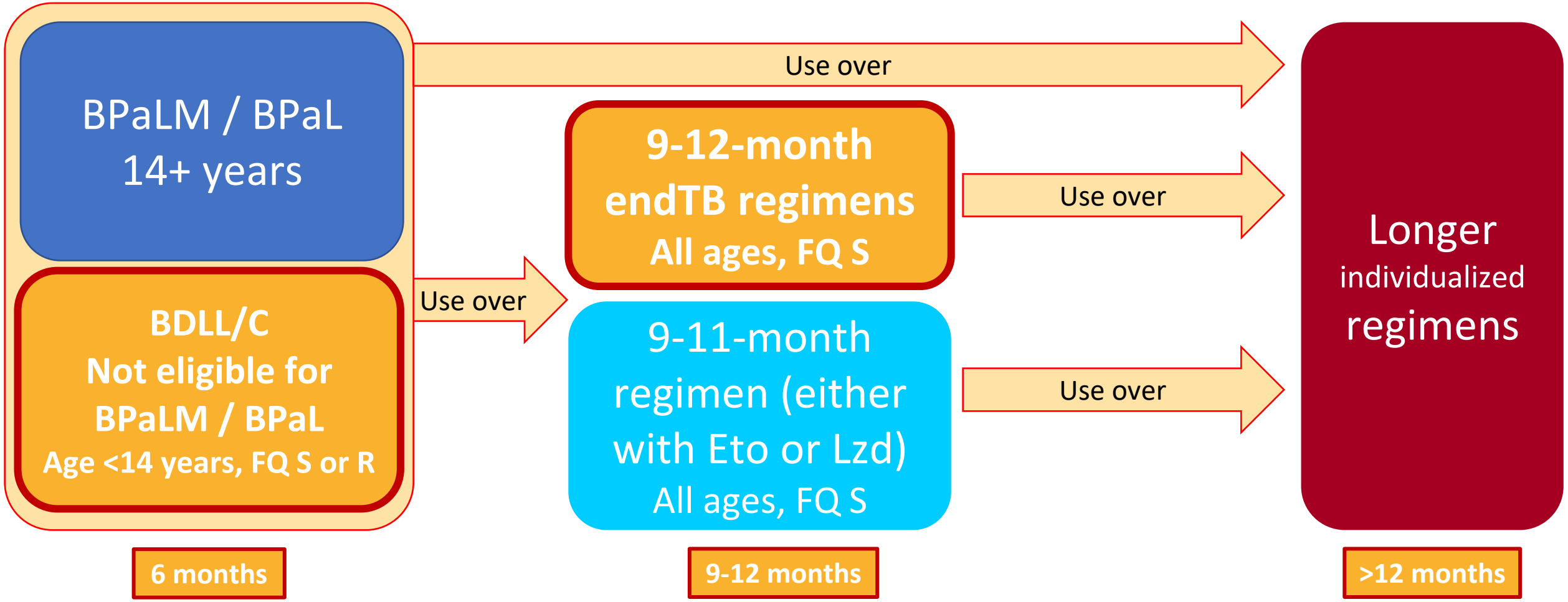
Updated mapping of DR-TB regimens – children & adolescents



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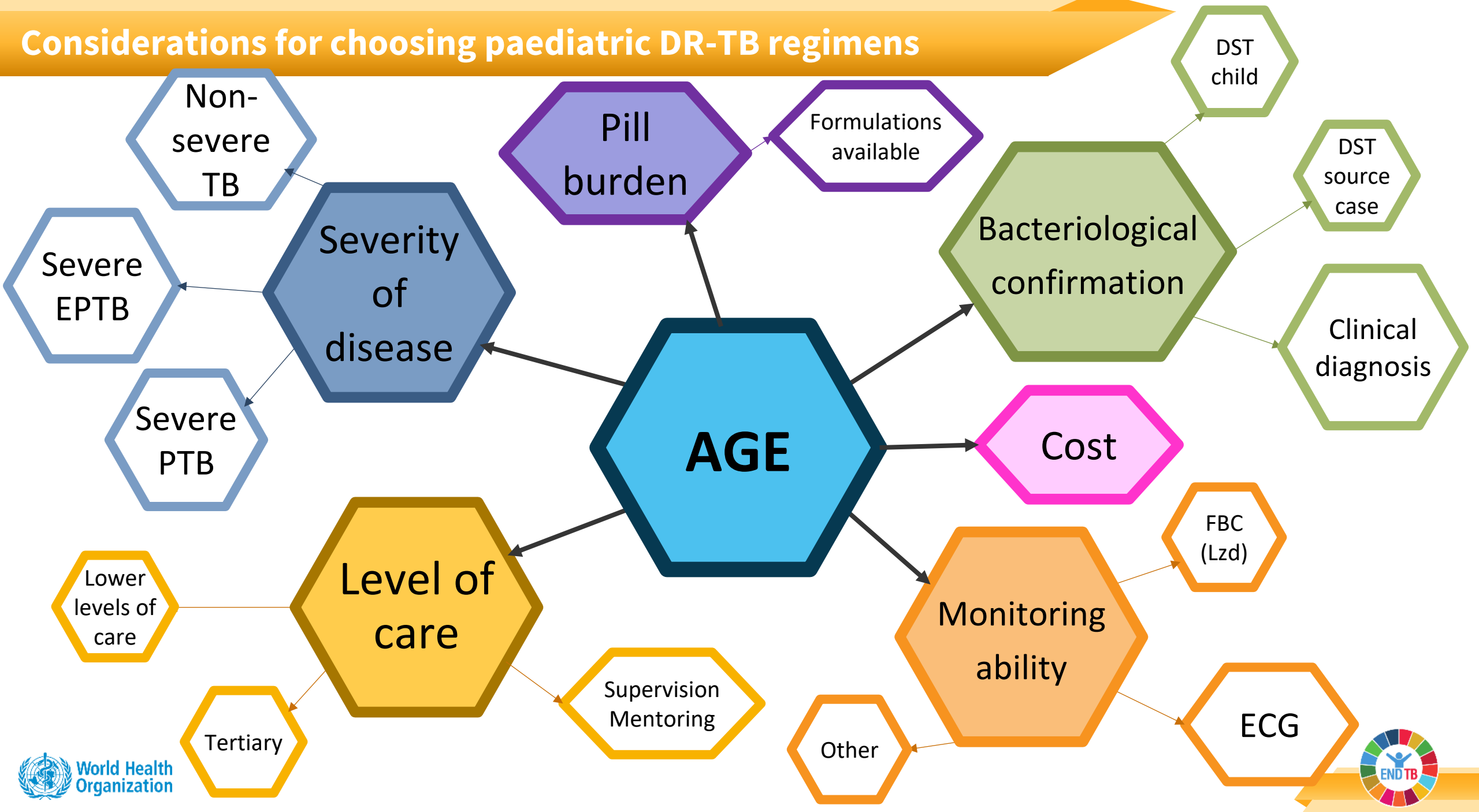
Considerations for choosing paediatric DR-TB regimens



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Child-friendly formulations: second-line medicines

- Child-friendly formulations of second-line medicines should be used whenever possible and included in funding requests

- New formulations available through GDF:
  - Bedaquiline 20 mg tab
  - Delamanid 25 mg disp tab
  - Linezolid 150 mg disp tab

WHO-RECOMMENDED GROUPING	MEDICINE	FORMULATION	PACK SIZE	SHELF-LIFE	STORE BELOW
A	Levofloxacin 100mg	Dispersible tablet	100 in blister	36 months	30°C
	Moxifloxacin 100mg	Dispersible tablet	100 in blister	24 or 36 months	30°C
	Bedaquiline 20mg	Tablet	60 in jar	36 months	30°C
	Linezolid 150mg	Dispersible tablet	100 in blister	24 months	30°C
B	Clofazimine 50mg	Tablet	100 in blister	36 months	30°C
	Cycloserine 125mg	Mini-Capsule	100 in blister	24 months	25°C
C	Ethambutol 100mg	Dispersible tablet	100 in blister	24 months	30°C
	Delamanid 25mg	Dispersible tablet	48 in blister	36 months	25°C
	Pyrazinamide 150mg	Dispersible tablet	100 in blister	36 months	30°C
	Ethionamide 125mg	Dispersible tablet	100 in blister	36 or 48 months	30°C
None	Isoniazid 100mg	Dispersible tablet	100 in blister	36 months	30°C

https://www.stoptb.org/sites/default/files/gdfmedicinescatalog_1.pdf
https://www.stoptb.org/sites/default/files/gdf_tin_drtb_pediatric.pdf

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Dosing guidance for second-line treatment

Dosing calculator in KSP app

Annex to the Module 4 operational handbook: weight-based dosing of medicines used in MDR-TB regimens, adults and children

Group A medicines	Formulation (tablets, diluted in 10 mL of water, as applicable)	3–<5 kg	5–<7 kg	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
Levofloxacin (Lfx)	100 mg dt (10 mg/mL)	5 mL (0.5 dt)	1	1.5	2	3	–	–					
	250 mg tab (25 mg/mL)	2 mL[b]	5 mL (0.5 tab)[b]		1	1.5	2	3		4			
	500 mg tab	–					1	1.5		2			
	750 mg tab	–						1		1.5			
Moxifloxacin (Mfx)	100 mg dt (10 mg/mL)	4 mL	8 mL	1.5	2	3	4	4		–			
	400 mg tab (40 mg/mL) Standard dose	1 mL[b]	2 mL[b]	3 mL[b]	5 mL (0.5 tab)[b]	7.5 mL (0.75 tab)[b]	1	1					
	400 mg tab high dose[c]												

- Dosing guidance available for children, adolescents and adults
- 3 kg to >70 kg
- Age and weight-based approach for bedaquiline and delamanid
- Dosing provided using child-friendly formulations (preferred) but can also be given using adult formulations
- Final approach to dosing depending on formulations available in country

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Acknowledgements

Tereza Kasaeva, Director WHO GTB

Annemieke Brands, Kerri Viney, Tiziana Masini, Farai Mavhunga, PCD unit, WHO GTB

Thank you for your attention!

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