Management of drug-resistant TB in children and adolescents

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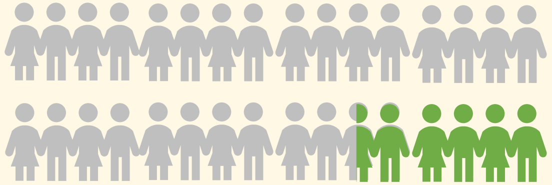
Drug-resistant TB in children and adolescents



The **case detection gap** for children & young adolescents with MDR/RR-TB is bigger than for DS-TB

1000 children with MDR/RR-TB detected and treated

1000 children with MDR/RR-TB not detected nor treated

- Modelling estimates: **32,000 children develop MDR/RR-TB every year** (0-14 years)
- Number started on treatment: **4,000 – 6,000 per year** (majority from India, Russian Federation, South Africa)

Benefit Kids 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**

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Case finding of children with MDR/RR-TB

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

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

- High **index of suspicion** needed
- **Bacteriological testing** critical
- If bacteriological testing negative or cannot be done, a **clinical diagnosis** can be made
- The **resistance pattern** of the child/adolescent or the **most likely source case** informs treatment

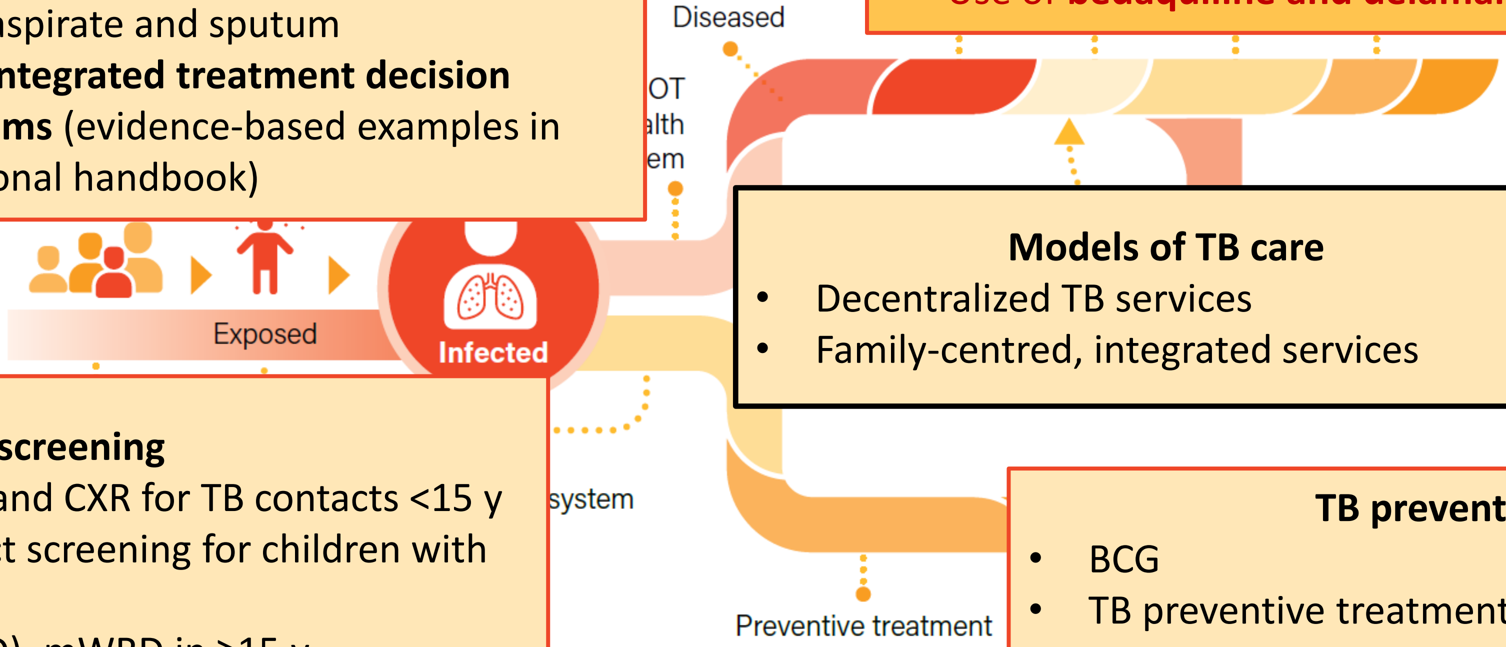
WHO policy guidance

TB treatment

- 4-month regimen (2HRZ(E)/2HR) for **non-severe TB** (3 months – 16 years) – eligibility criteria detailed in operational handbook
- Alternative regimens for **TB meningitis**: 6HRZEto and 2HRZ(E)/10HR
- Use of **bedaquiline and delamanid** for all ages (MDR/RR-TB)

TB diagnostic approaches

- Use of rapid diagnostic tests
- Xpert Ultra and MTB/RIF on **stool**, NPA, gastric aspirate and sputum
- Use of **integrated treatment decision algorithms** (evidence-based examples in operational handbook)



Models of TB care

- Decentralized TB services
- Family-centred, integrated services

TB screening

- Symptom screening and CXR for TB contacts <15 y
- Symptom and contact screening for children with HIV < 10 y
- Use of CXR (with CAD), mWRD in ≥15 y
- Use of CXR, CRP, mWRD in PLHIV ≥15 y

TB prevention

- BCG
- TB preventive treatment:
  - Target groups: TB contacts, CALHIV
  - Regimens: 3HR, 3HP, 1HP, 6-9H
- TB infection prevention and control

Guidelines: https://www.who.int/publications/i/item/9789240046764
Handbook: https://www.who.int/publications/i/item/9789240046832
WHO TB Knowledge Sharing Platform: https://extranet.who.int/tbknowledge

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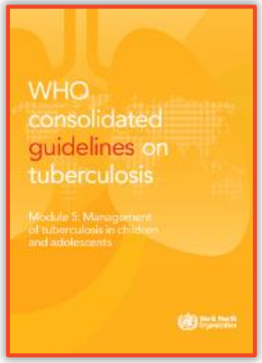
Treatment of DR-TB in children – use of bdq & dlm in children



- **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

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

Delamanid: https://apps.who.int/iris/rest/bitstreams/1514046/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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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 – use of bdq & dlm in children

	9 month all-oral*	BPaLM / BPaL	Individualized
Age	All ages	Preferred in ≥14 years	All ages
MDR/RR-TB (FQ susceptible)	Yes	Yes (BPaLM)	Yes
Pre-XDR-TB	No	Yes (BPaL)	Yes
XDR-TB	No	No	Yes
Extensive PTB	No	Yes	Yes
EPTB	Yes (except TBM, miliary, osteo-articular, pericardial TB)	Yes (except CNS, miliary, osteo-articular TB)	Yes
Clinical diagnosis	Yes	No	Yes
Duration	9 (–11) months	6 months	12–18 months

Additional factors:

- Drug intolerance or adverse events
- Treatment history, previous exposure to regimen drugs, likelihood of drug effectiveness
- Patient or family preference
- Access to child-friendly formulations, cost

* **Ethionamide variation:** *Initial phase*: 4–6 Bdq(6m)-Lfx/Mfx-Cfz-Z-E-Hh-**Eto;** *Continuation phase*: 5 Lfx/Mfx-Cfz-Z-E

Linezolid variation: *Initial phase*: 4–6 Bdq(6m)-**Lzd(2m)**-Lfx/Mfx-Cfz-Z-E-Hh; *Continuation phase*: 5 Lfx/Mfx-Cfz-Z-E

Mapping: current situation (since 2022)

How long is longer?
Duration can be "much shorter" in non-severe TB

BPaLM/BPaL

Use over

Use over

9-11-month regimen (either with Eto or Lzd)

Use over

Longer individualized regimens

Not recomended in ages < 14 years, pregnancy, breastfeeding

Acceptability?
7 medicines, high pill burden, even with dispersible formulations

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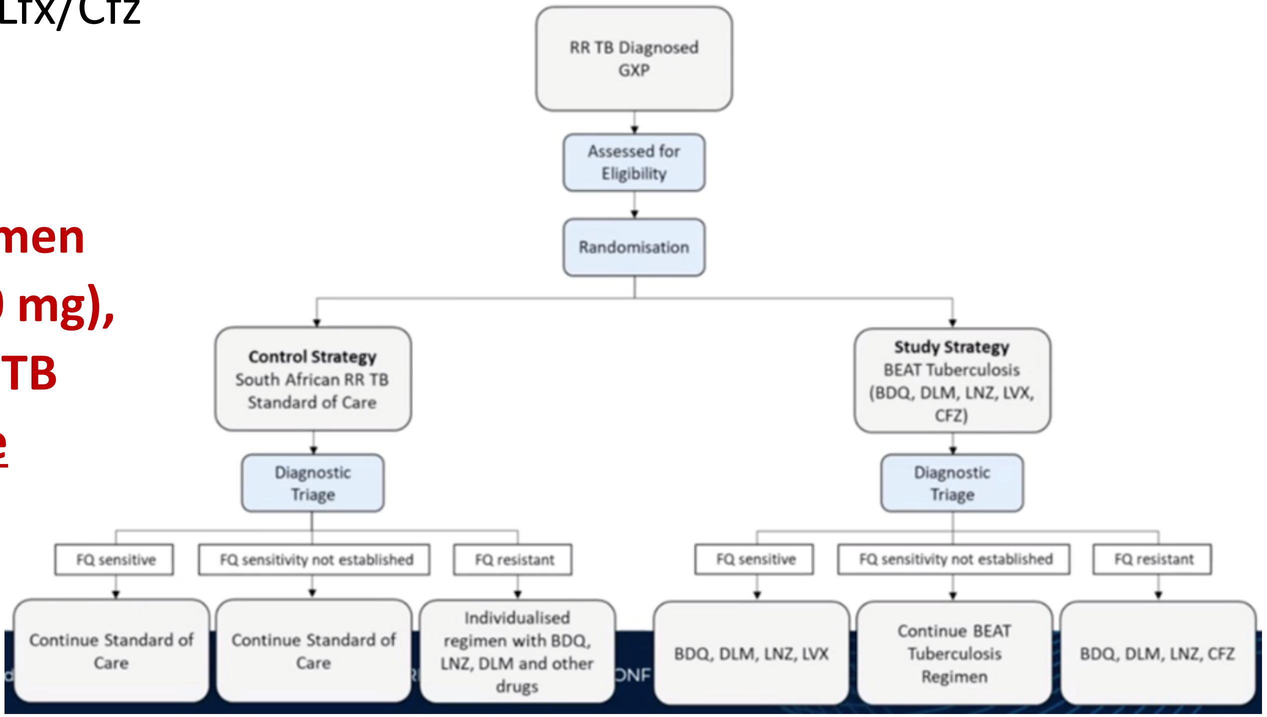
Treatment of DR-TB in children – forthcoming updates

- **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 <u>with or without fluoroquinolone resistance</u>

  (Conditional recommendation, very low certainty of evidence)



☑ **FQ S**
☑ **FQ R**

- 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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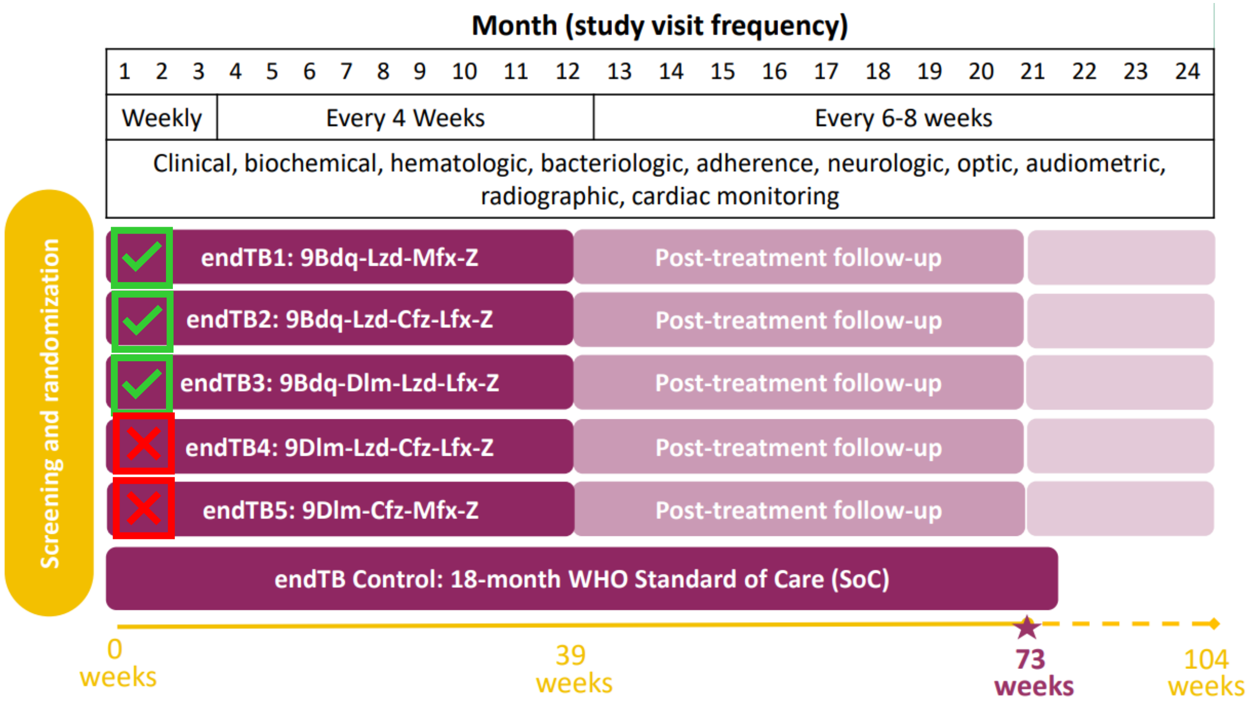
Treatment of DR-TB in children – forthcoming updates

- **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)

☑ **FQ S**
☒ **FQ R**

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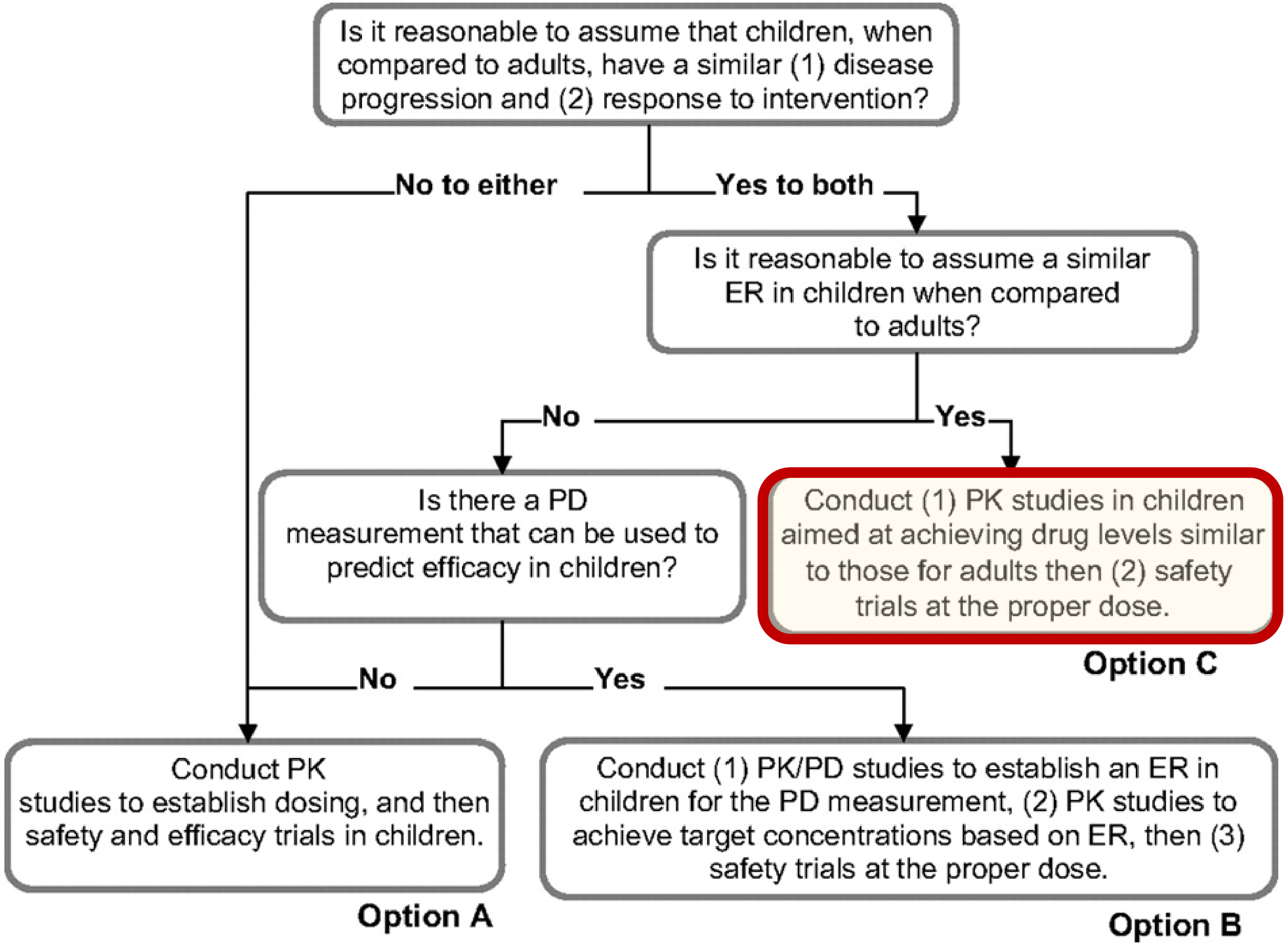
Paediatric extrapolation framework



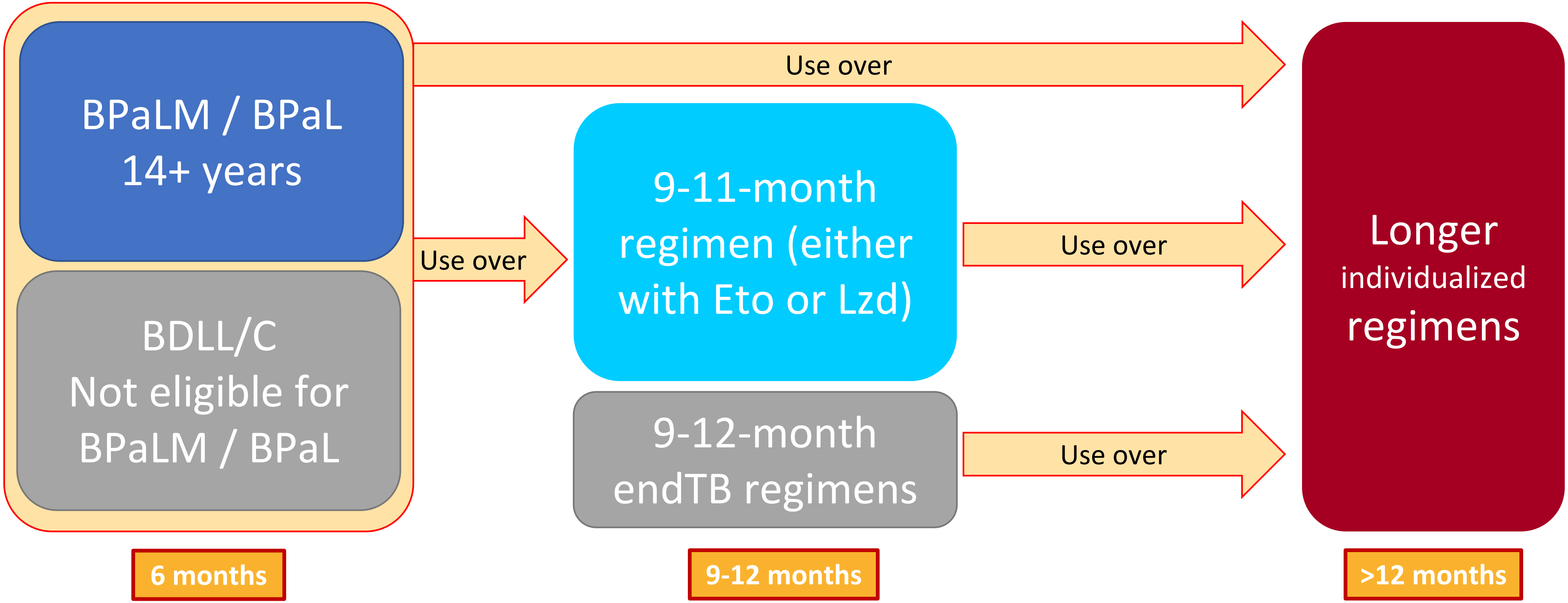
PAEDIATRIC EXTRAPOLATION

"An approach to providing evidence in support of effective and safe use of drugs in the pediatric population ***when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the pediatric [target] and reference (adult or other pediatric) population.****"*

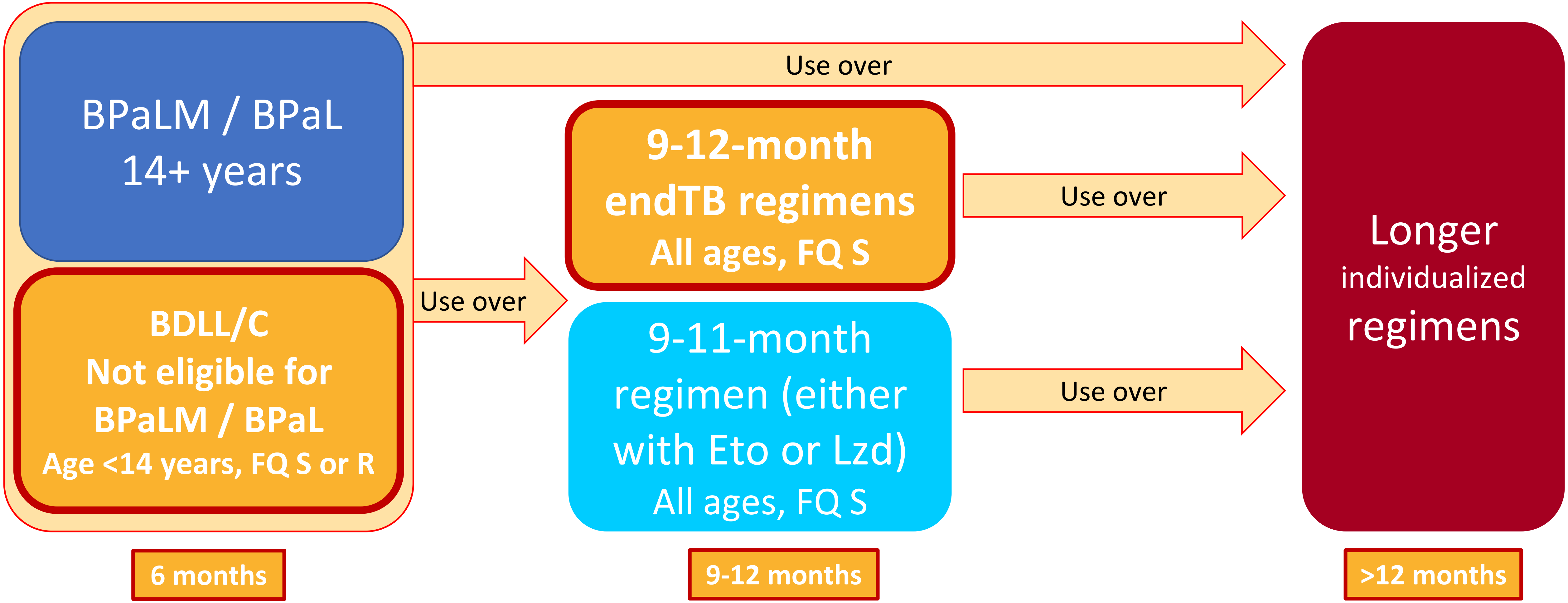
(ICH E1 1(R1) guideline)

https://www.fda.gov/media/161190/download

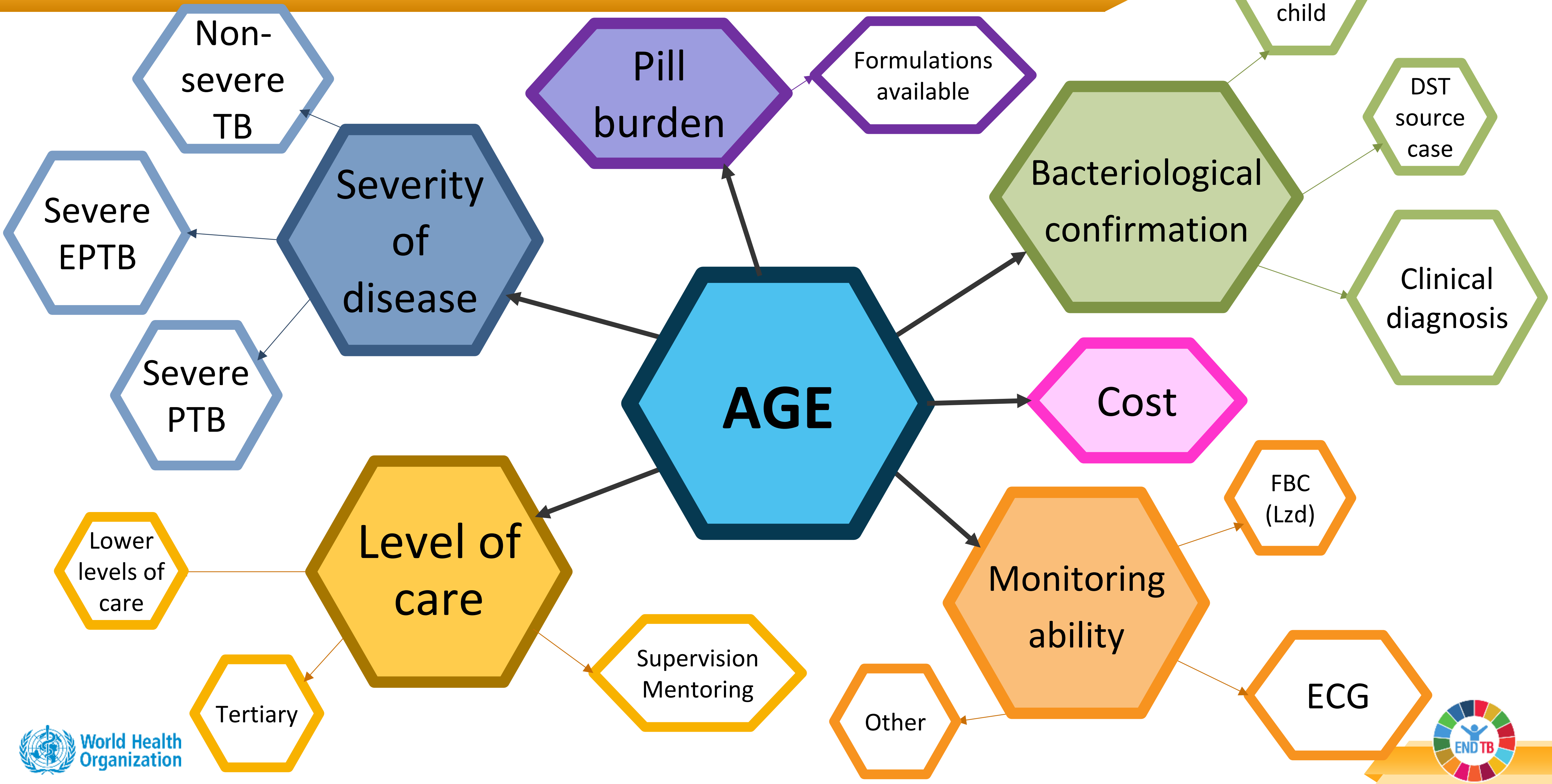
Updated mapping of DR-TB regimens



Updated mapping of DR-TB regimens – children & adolescents



Considerations for choosing paediatric DR-TB regimens



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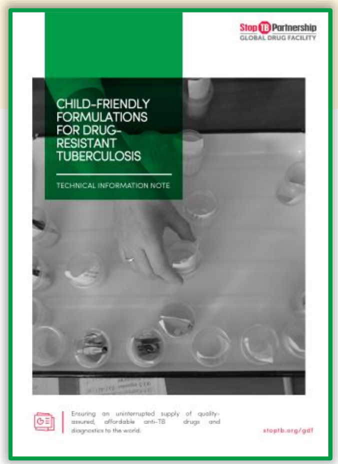
Child-friendly formulations: second-line medicines

- 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]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	

- 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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