

DR-TB in children and adolescents – global guidance and the roadmap, 3rd ed.

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WHO GTB/PCD

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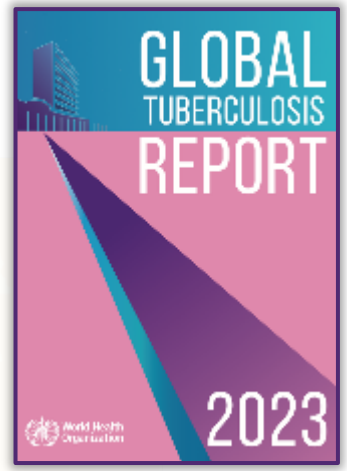
END TB

TB incidence and mortality in children and adolescents, 2022



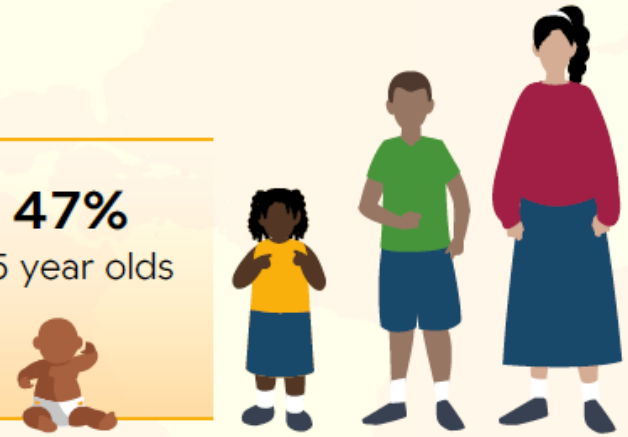
10.6 million
TB among all ages in 2022

1.3 million
TB deaths in 2022

1.25 million
children (0–14 years) developed TB in 2022 (12% of all TB)

214 000
TB deaths in 2022 (16% 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 years,
76% were in children <5 years

96%
of deaths occurred in children who did not access TB treatment
(Dodd et al, 2017)

31 000
(14%) TB deaths in the 0–14 year age group were among children living with HIV

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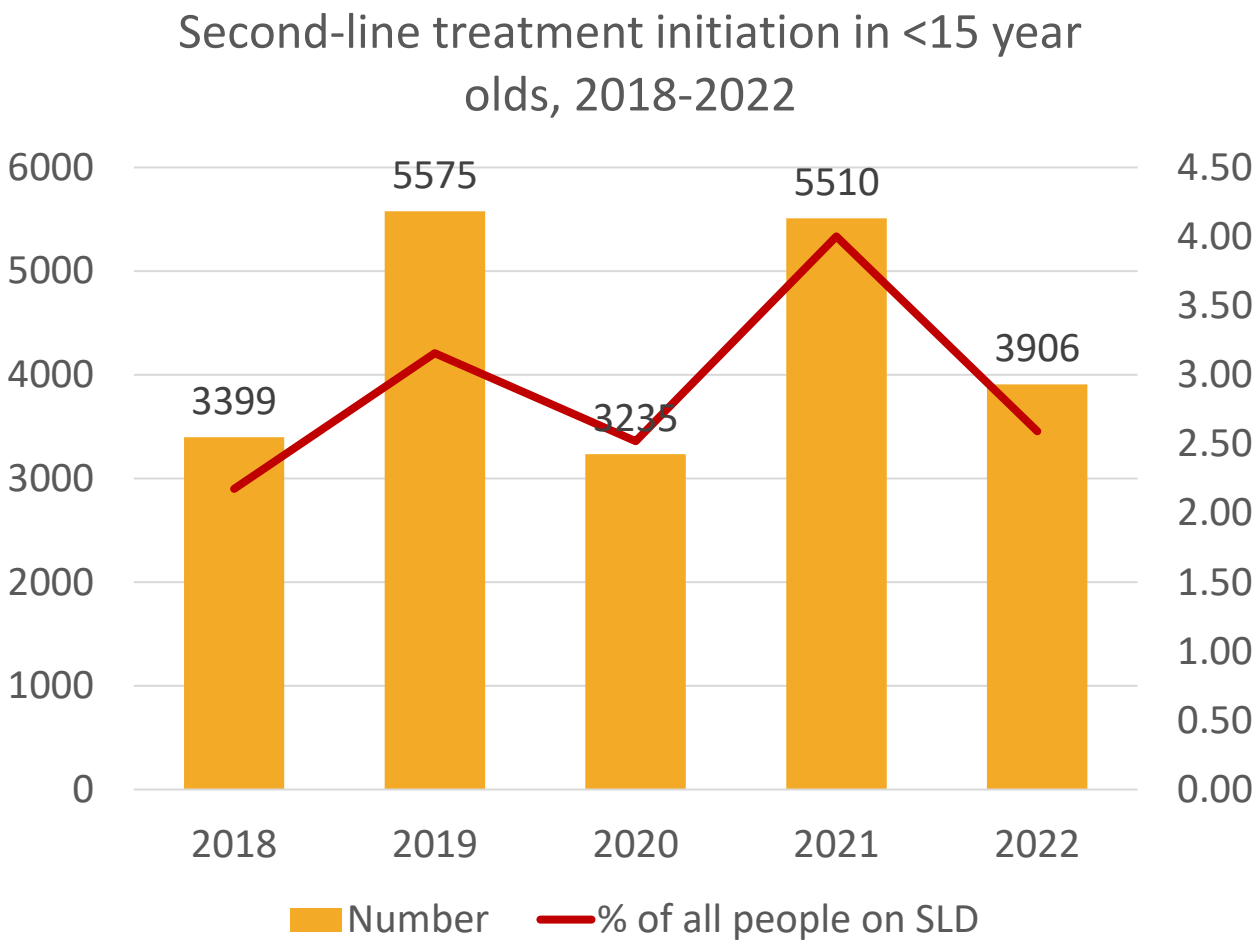
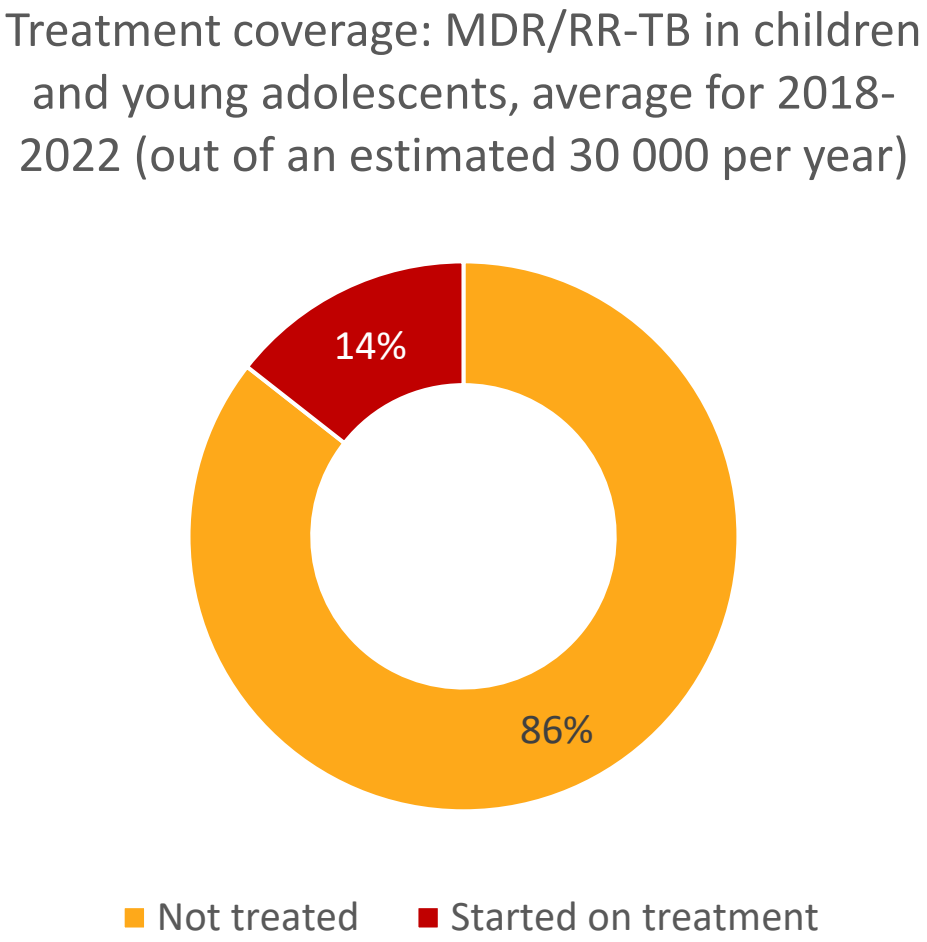
Treatment initiation in children with MDR/RR-TB





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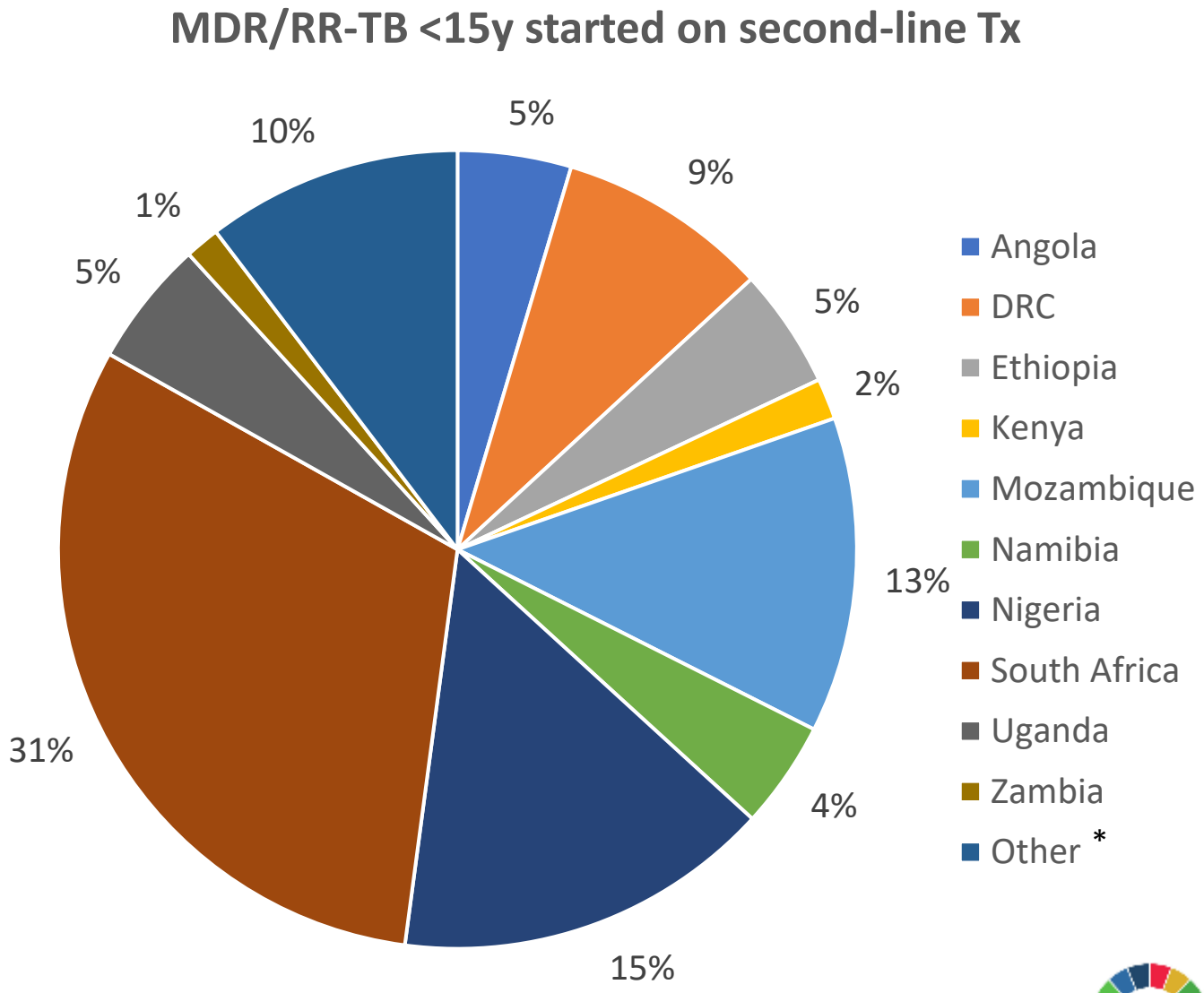
DR-TB in <15 years in the African region

	Global	AFR (% of global)
Total MDR/RR-TB	150 587	20 649 (13.7%)
MDR/RR-TB <15 years	3 906	783 (20.0%)
% MDR-TB <15 years	2.6%	3.8%

MDR-TB HBC in AFR:
Angola, DRC, Mozambique, Nigeria, South Africa, Zambia, Zimbabwe



*__Other__: countries with ≤10 children started on SLD (Cameroon, CAR, Chad, eSwatini, Gabon, Ghana, Guinea, Liberia, Madagascar, Malawi, Mali, Niger, Rwanda, Senegal, Sierra Leone, South Sudan, UR Tanzania, Zimbabwe)

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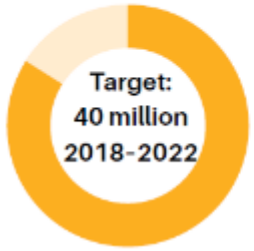
Progress against UNGA HLM targets, 2018-2022

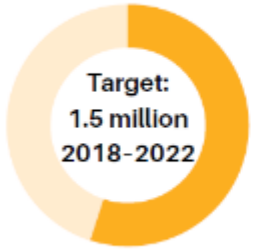
Treatment for DS- and DR-TB

TB treatment (all ages)



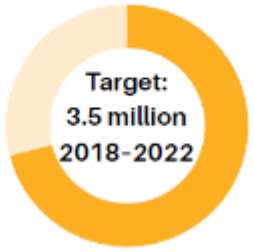
34 million (84%)
treated in 2018-2022

MDR/RR-TB treatment (all ages)



825 000 (55%)
treated in 2018-2022

TB treatment (children)



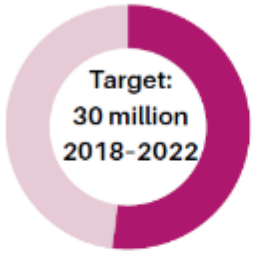
2.5 million (71%)
treated in 2018-2022

MDR/RR-TB treatment (children)

21 600 (19%)
treated in 2018-2022

TB Preventive Treatment

All ages

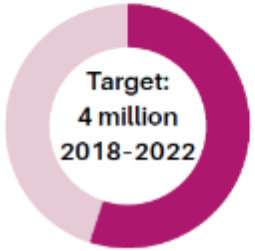


16 million (52%)
treated in 2018-2022

People living with HIV

11 million (>100%)
treated in 2018-2022

Household contacts aged <5 years



2.2 million (55%)
treated in 2018-2022

Household contacts aged ≥5 years

2 million (10%)
treated in 2018-2022

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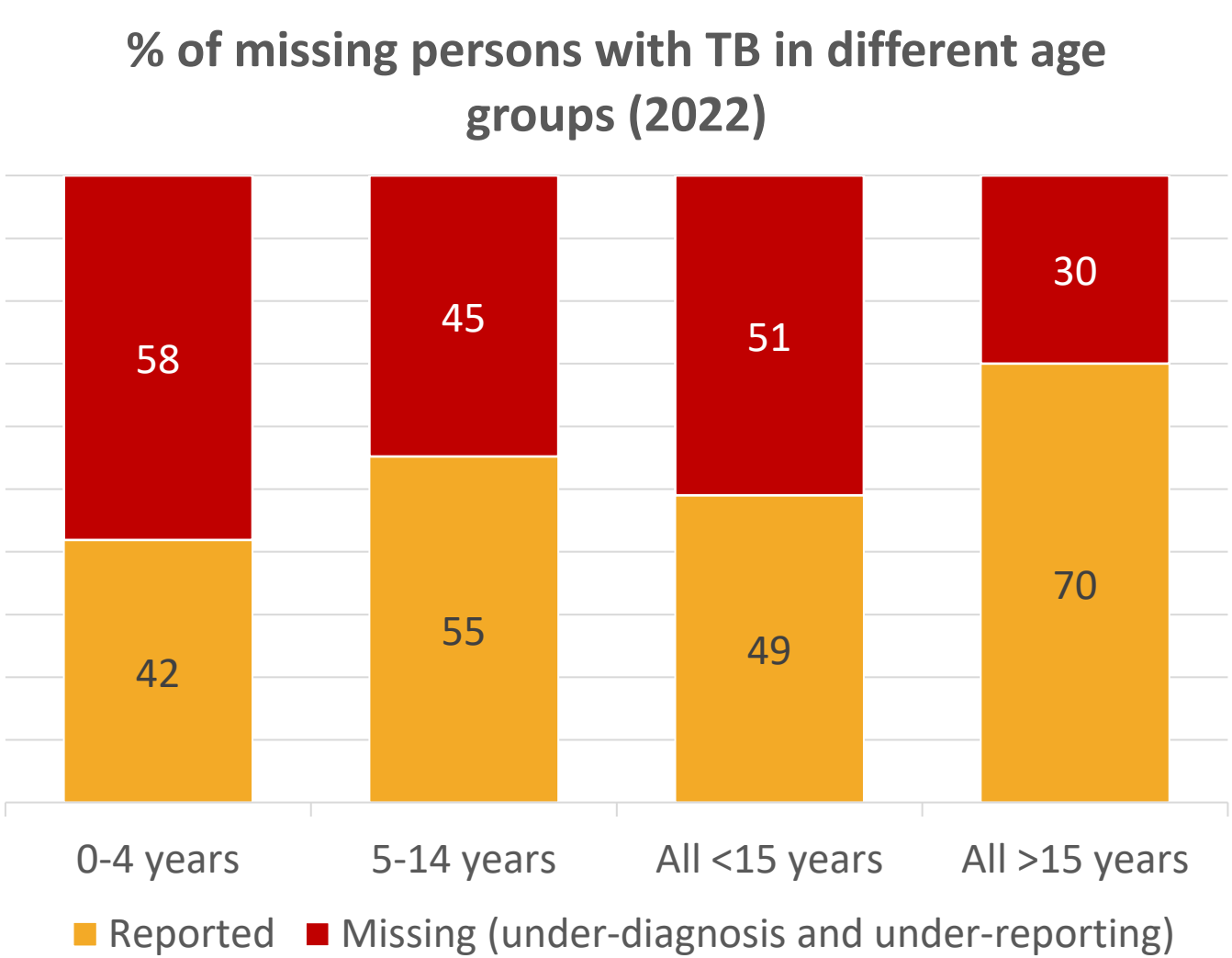
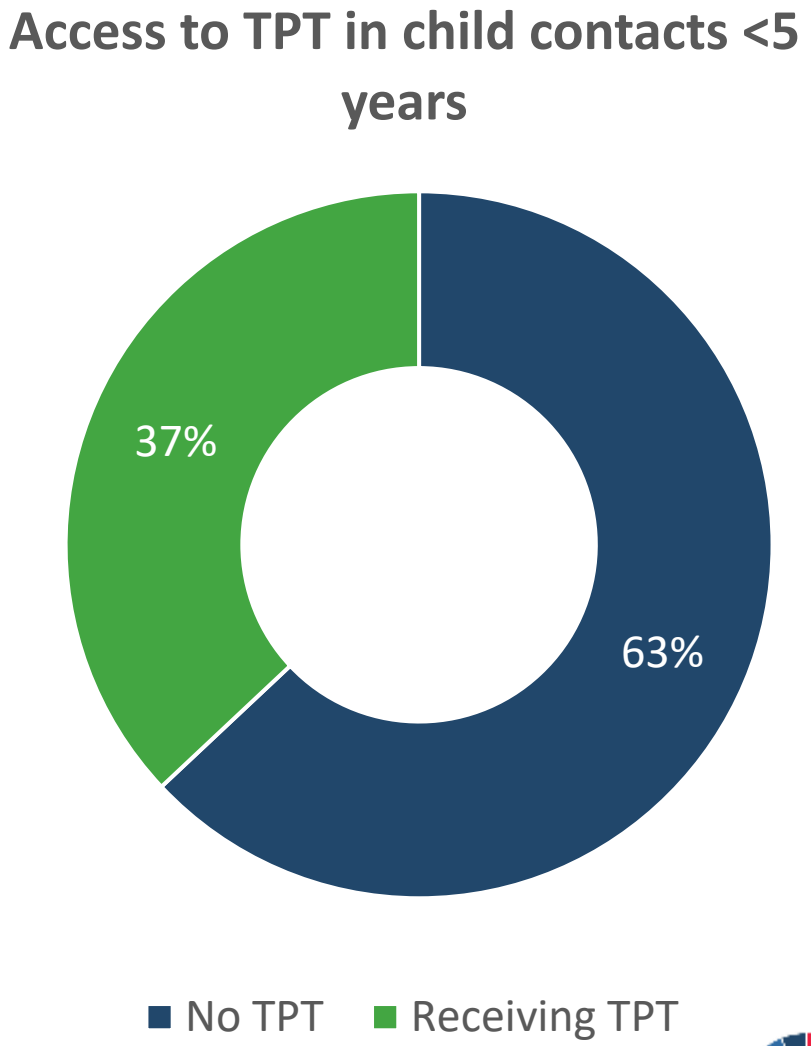
Remaining programmatic gaps





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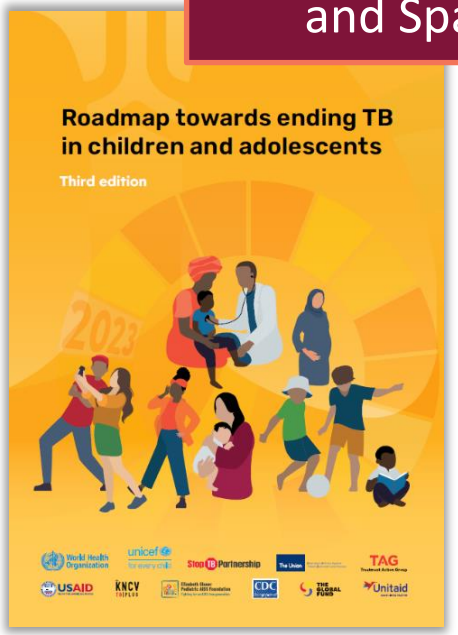
The third edition of the Roadmap (2023)

Available in French and Spanish!



- **Aim**: to define actions to be prioritized and implemented over the next 5 years to reduce TB-related morbidity and mortality in children and adolescents
- Aligned with the **UN HLM 2023** targets
- Highlight details on DR-TB?

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https://www.who.int/publications/i/item/9789240084254

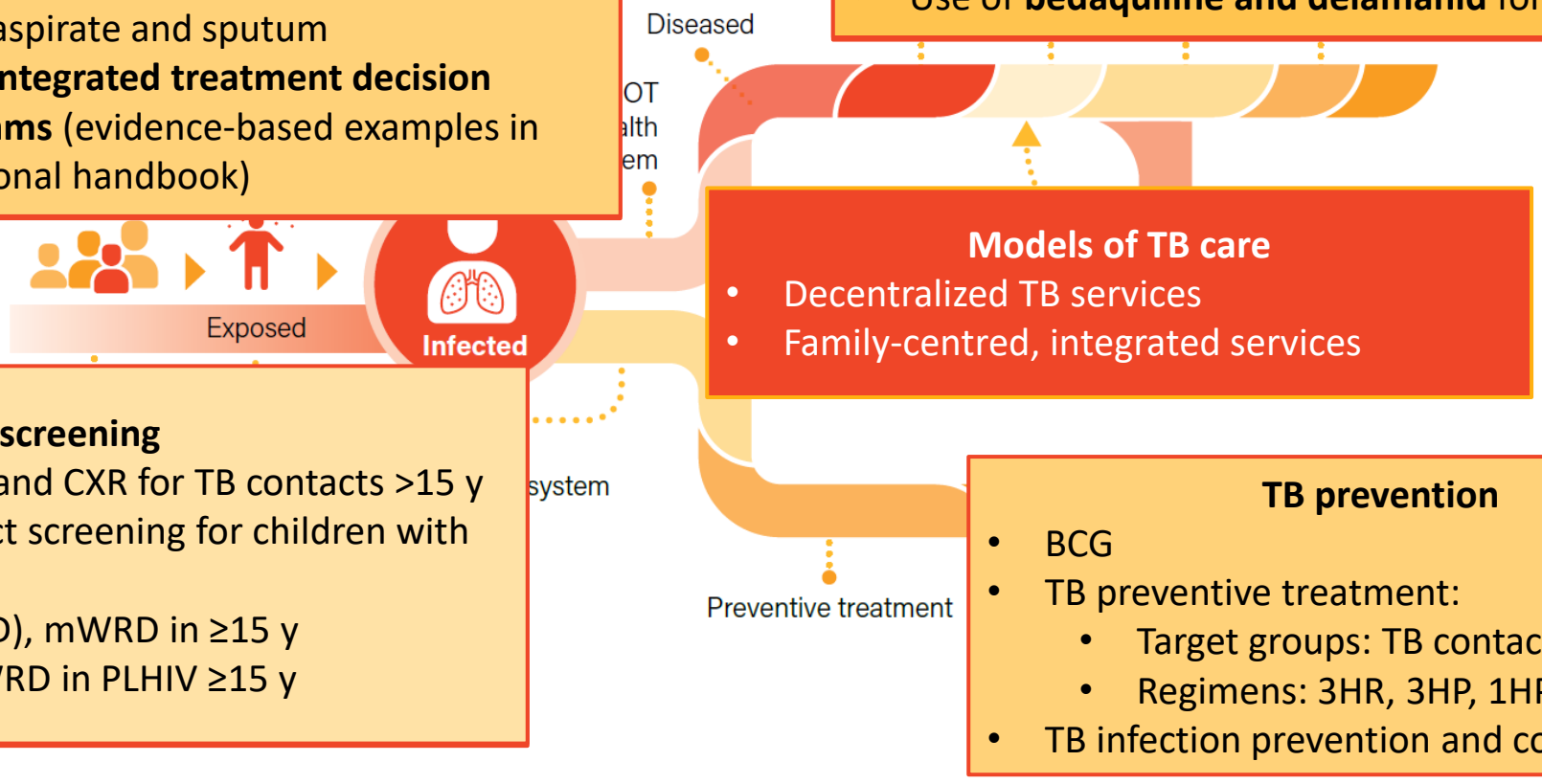
WHO policy guidance

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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Shorter treatment duration in children with non-severe TB

- **In children and adolescents between 3 months and 16 years of age with non-severe TB (without suspicion or evidence of MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used.**

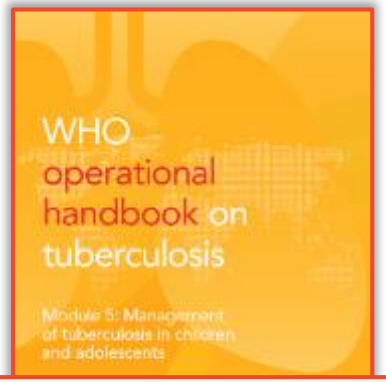
  *(**NEW:** Strong recommendation, moderate certainty of evidence)*

SHINE:
Shorter Treatment for Minimal Tuberculosis in Children

Remarks:

- *Non-severe TB is defined as: Peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary, non-cavitary disease, confined to one lobe of the lungs, and without a miliary pattern*
- *Children and adolescents who do not meet the criteria for non-severe TB should receive the standard 6-month treatment regimen (2HRZE/4HR), or recommended treatment regimens for severe forms of EPTB*
- *The use of ethambutol in the first 2 months of treatment is recommended in settings with a high prevalence of HIV, or of isoniazid resistance*

Assessing eligibility for the 4-month regimen

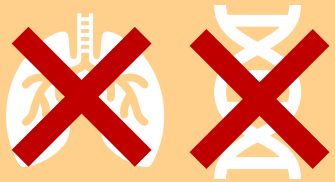


3m-16y

- Based on CXR features
- Xpert MTB/RIF or Ultra neg, trace or (very) low
- Mild symptoms not requiring hospitalization

3m-16y

- Xpert MTB/RIF or Ultra neg, trace or (very) low (PTB) or isolated peripheral LN TB
- Mild symptoms not requiring hospitalization



<10y

- Isolated peripheral LN TB
- Mild symptoms not requiring hospitalization

Mild symptoms:

- no danger or high-priority signs
- no asymmetrical and persistent wheezing
- no signs of EPTB other than peripheral LN TB
- none of the following: SAM, respiratory distress, high fever, severe pallor, restlessness, irritability or lethargy

Children/adolescents started on 4-month regimen without CXR:

- Follow-up monthly
- Symptoms expected to have resolved within 1 month
- At 4 months: completely well (including normal nutritional status)
- Lack of response after 4 months: continue treatment until 6 months; evaluate for DR-TB and non-TB related disease, poor adherence

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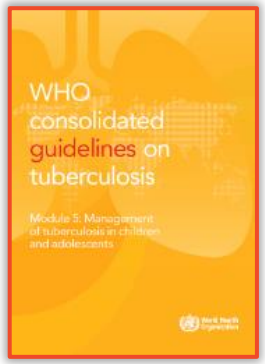
Treatment of DR-TB in children – use of bdq & dlm in children



- **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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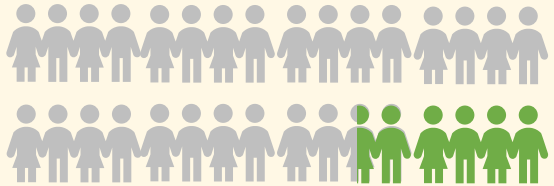
Drug-resistant TB in children and adolescents



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)

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

- 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

- 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

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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

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Individualized (longer) regimens - considerations

- At least 4 drugs likely susceptible; some drugs shorter period; 5th drug if extensive disease
- Prioritize group A and B drugs, add delamanid and other group C drugs
- Include bedaquiline for all ages; standard duration 6 months; extension beyond 6 months if no other options (consult paediatric DR-TB expert)
- Linezolid (Group A): frequent haematological toxicity – use often limited to 1st few months
- Delamanid: option to add if (suspected) FQ resistance or severe disease (5th drug) – standard duration 6 months
- Injectables should not be used in <18 years

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Designing individualized MDR/RR-TB regimens

Fluoroquinolone susceptibility	Regimen [a]	Additional medicines
Fluoroquinolone-susceptible	Bdq–Lfx–Lzd–Cfz–(Cs)	Cs, Dlm, PAS, Eto [b,c] (E, Z) [d]
Fluoroquinolone-resistant	Bdq–Lzd–Cfz–Cs–(Dlm) [e]	Dlm [e], PAS, Eto [b,c] (E, Z) [d]
Fluoroquinolone-resistant and bedaquiline (±clofazimine)-resistant	Lzd–Cs–Dlm [e]–E–Z [d]	Mpm/Clav, Eto [b,c], PAS [c]

Bdq: bedaquiline; Cfz: clofazimine; Cs: cycloserine; Dlm: delamanid; E:ethambutol; Eto: ethionamide; FQ: fluoroquinolone; Lfx: levofloxacin; Lzd: linezolid; Mpm/Clav: meropenem–clavulanate; PAS: P-aminosalicylic acid; Z: pyrazinamide.

[a] Medicines in parentheses in this column are suggestions for a fifth medicine when there is severe disease.

[b] Use ethionamide only if the child or source case does not have a known or suspected *inhA* mutation.

[c] P-aminosalicylic acid and ethionamide showed effectiveness only in regimens without bedaquiline, linezolid, clofazimine or delamanid, and are proposed only when other options to compose a regimen are not possible.

[d] Ethambutol and pyrazinamide should be considered if there is evidence of susceptibility and a regimen with sufficient medicines cannot be composed.

[e] When administering delamanid and cycloserine concurrently, monitoring for neuropsychiatric side-effects is important.

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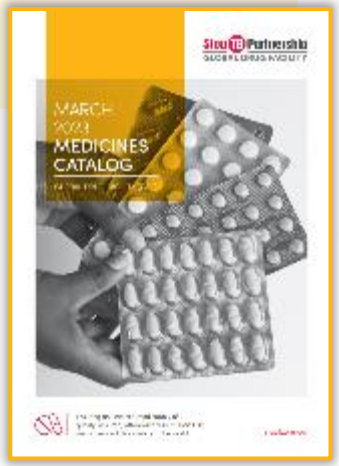
Child-friendly formulations: second-line medicines

- 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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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).

1

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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Dosing guidance

Dosing calculator in KSP app

Annex: 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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E-courses on TB in children and adolescents

https://openwho.org/courses/TB-child-adolescent-EN

https://openwho.org/courses/TB-child-adolescent-programmatic

Register first on **openwho.org** before enrolling in the courses

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