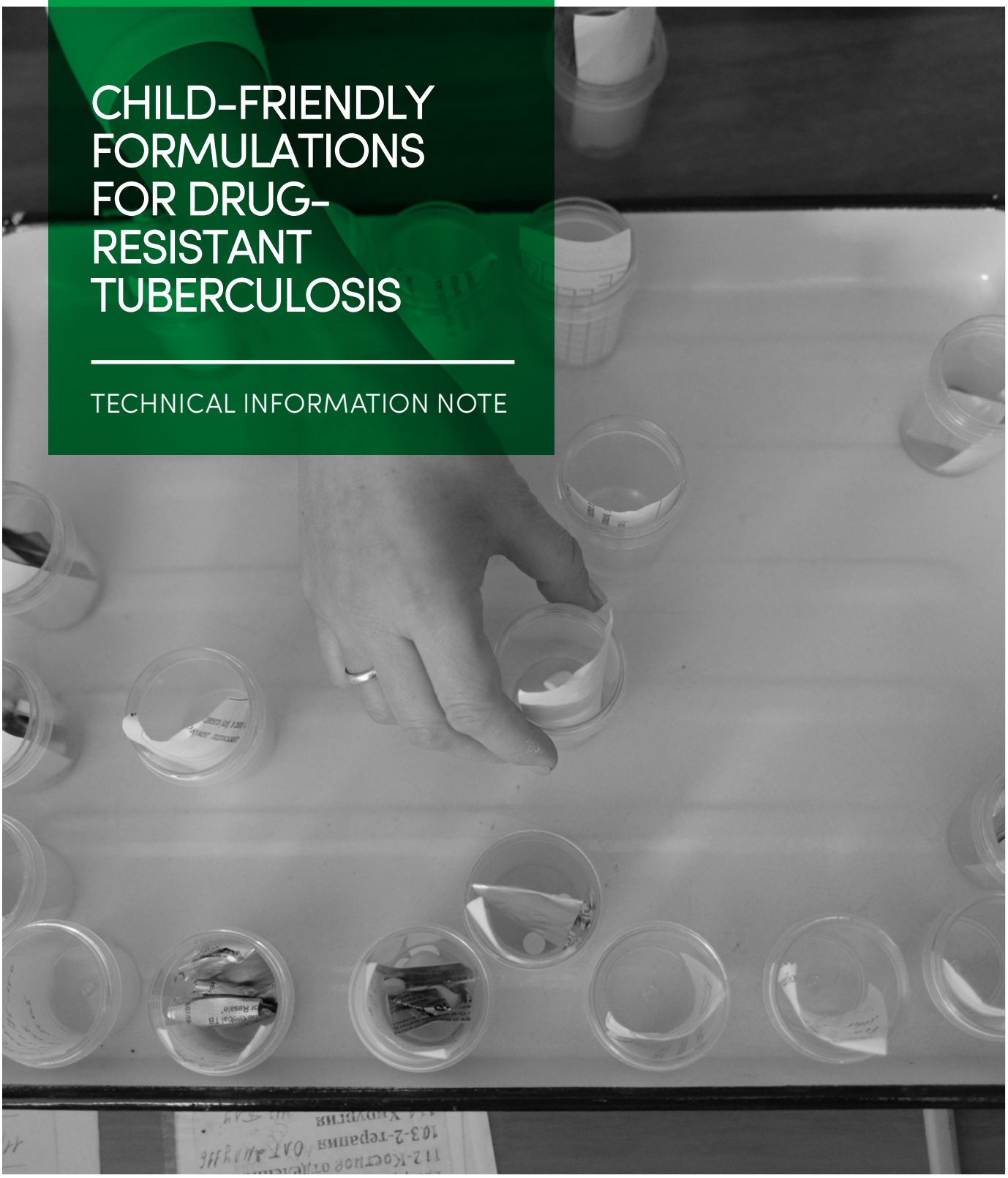
Stop TB Partnership
GLOBAL DRUG FACILITY

# CHILD-FRIENDLY FORMULATIONS FOR DRUG-RESISTANT TUBERCULOSIS

TECHNICAL INFORMATION NOTE



Ensuring an uninterrupted supply of quality-assured, affordable anti-TB drugs and diagnostics to the world.

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Stop TB Partnership
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# TECHNICAL INFORMATION NOTE
# Child-Friendly Formulations of Medicines for Drug-Resistant Tuberculosis

**Great strides have been made in availability of child-friendly formulations of medicines to treat drug-resistant tuberculosis (DR-TB) since the first formulations were quality-assured and made available by the Global Drug Facility (GDF) in 2018. By 2022, all World Health Organization (WHO)-recommended oral medicines for the treatment of DR-TB in children have a child-friendly formulation commercially available – despite only 30,000 children becoming ill with DR-TB each year and only a fraction of those treated. These formulations have a lower strength, making it easier to ensure children get the correct doses for each medicine. They are flavoured and can be dispersed in water or food, making them easier to administer for a caregiver and easier for a child to take.**

This technical information note has been developed to provide guidance to TB programme managers and quantification and procurement officers. The note provides information about the child-friendly DR-TB formulations and guidance on how to quantify and plan an order. This note provides supply management advice and is not intended to guide clinical management. Guidelines on the treatment of people with DR-TB are rapidly changing. The most current guidelines, recommendations and rapid communications can be found on the WHO website.

# SUPPLY INFORMATION

→ Available in the GDF medicines catalog
**Manufacturer:** Multiple, including Micro Labs, Macleods, Janssen and Otsuka

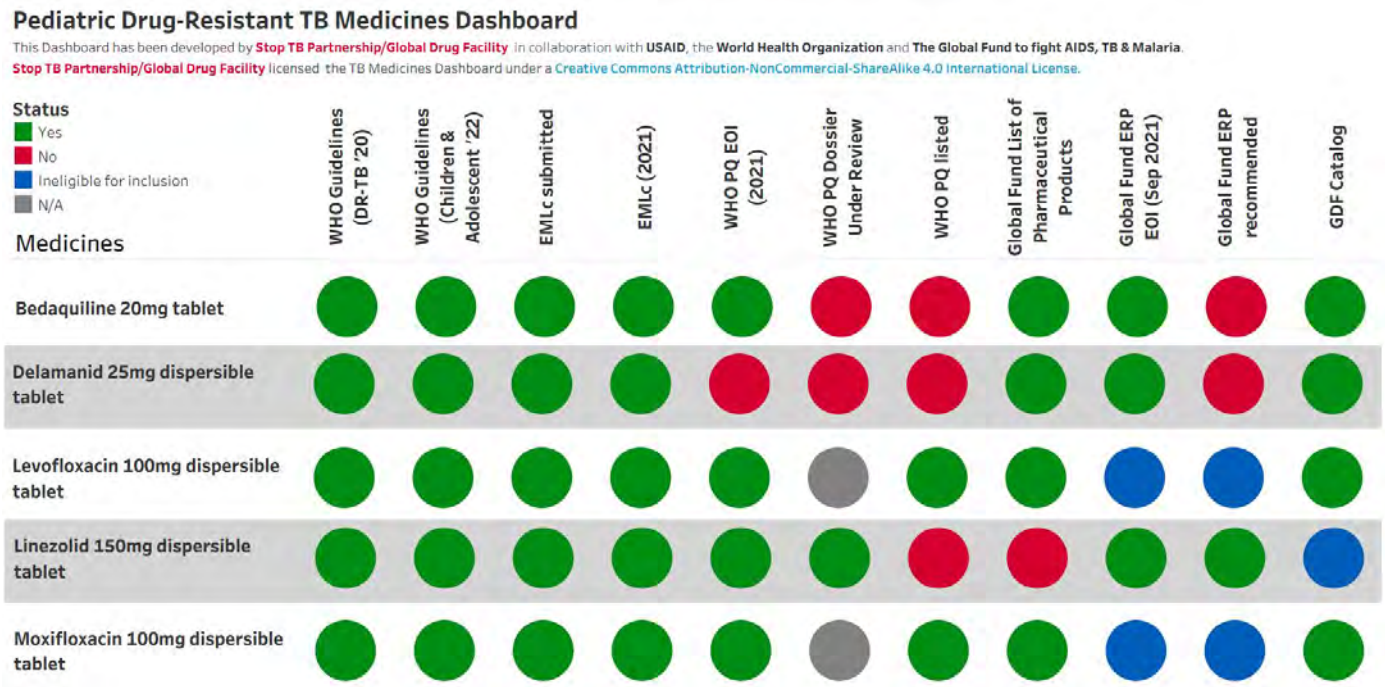
| WHO-RECOMMENDED GROUPING | MEDICINE | FORMULATION | PACK SIZE | SHELF-LIFE | STORE BELOW |
|---|---|---|---|---|---|
| A | Levofloxacin 100mg | Dispersible tablet | 100 in blister | 36 months | 30°C |
| | Moxifloxacin 100mg | Dispersible tablet | 100 in blister | 24 or 36 months | 30°C |
| | Bedaquiline 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 |

All child-friendly DR-TB formulations available from GDF have at least 24 months shelf-life from the date of manufacture. These formulations do not require cold storage, but should be stored in dry conditions, protected from light below 30ºC (below 25ºC for cycloserine and delamanid).

# FACILITATING GLOBAL POLICY

GDF, in collaboration with WHO and the Global Fund, developed the TB Medicines Dashboard to monitor ongoing developments in the TB medicines pipeline to identify and address any barriers to product introduction. The Dashboard has allowed GDF and partners to track the development of the child-friendly formulations and ensure an enabling global policy environment for their introduction. For example, all of these formulations are included on the WHO Model Essential Medicines List fo Children.

The TB Medicines Dashboard is publicly available and update regularly.



# FORECASTING & ORDER PLANNING

There are two approaches to quantifying and forecasting for the introduction of new child-friendly formulations depending on the data available and if treatment guidelines have or will change. If there is historical data on enrollment available and the treatment guidelines have not changed, this information should be used to develop the forecast. If the historical data is not available or the treatment regimens have or will change, forecasting should be based on assumptions on the number of children estimated to be enrolled and the expected regimen(s) and medicines to be used.

## Using historical data and unchanged treatment recommendations

In this scenario, the forecast was often based on available historical pediatric enrollment data (with possible consideration of expanded case finding activities). This data includes:

- The weight of children less than 25kg who started and completed treatment in a year. In case weight details are unavailable, age can be used as a substitute.[1]
- The regimens and medicines that have been used for treating these pediatric cases.

[1] Preference is given to weight groups, since the WHO recommendations on dosages of anti-TB medicines are given based on weight groups.

## Using assumptions and estimates

**Step 1: Estimate the number of pediatric DR-TB cases for the forecast period (e.g., one year).** *For example: 5% of all reported DR-TB cases in the country would be estimated to be in children.*[2]

**Step 2: Estimate the number of pediatric DR-TB cases with weight below 25kg and thus likely benefiting the most from child-friendly formulations.** *For example: 75% of all pediatric DR-TB cases (from step 1) would be estimated to be in children <25kg.*[3]

**Step 3: Estimate the number of pediatric DR-TB cases with fluoroquinolone (FQ) sensitivity or resistance, as this is the main parameter leading the choice of treatment regimen.** *For example: apply the proportions of FQ resistance and FQ sensitive among overall DR-TB cases derived from the national routine drug resistance survey to the estimate from step 2.*

**Step 4: Confirm within the TB programme on the regimens to be used for FQ sensitive and FQ resistant pediatric DR-TB cases.**

**Step 5: Calculate the required quantity of child-friendly DR-TB formulations.** *Based on GDF's technical experts' previous experiences with paediatric fixed-dose combination products, 20 kg can be used as an average weight for calculation of dosages for medicines in regimens.*

**Step 6: Adjust for any current or planned remaining stocks.**

[2] This is an estimated figure derived from WHO global TB report data 2019 where 206,030 people with DR/MDR-TB were detected and notified where 8,986 out of them were children. Ref. Global tuberculosis report 2020. Geneva: World Health Organization; 2020.

[3] This proportion is derived from GDF's experience with scaling-up pediatric fixed-dose combination tablets for drug-sensitive TB.

## Example of How to Forecast for Child-Friendly DR-TB Formulations

*This example presents the Scenario 2 calculation for a country with 800 DR-TB cases reported annually and 30% of FQ resistance among DR-TB cases.*

**Step 1: Estimate number of children with DR-TB.** *5% x 800 = 40*

**Step 2: Estimate number of children with weigh below 25kg**.*40 x 75% = 30*

**Step 3: Estimate number of children with DR-TB and FQ resistance.** *30 x 30% = 9*
**Estimate number of children with DR-TB and FQ sensitivity.** *30 – 9 = 21*

**Step 4: Agree on regimens to be provided.**
*In this example only, it is assumed that the programme has decided to use the following 3 regimens:*

- *FQ sensitive DR-TB cases will receive one of the following:*
  - *4-6 Bdq (6 months) – Lfx – Cfz – Z- E – Hh – Eto/ 5 Lfx – Cfz – Z – E*
  - *12 Bdq (6 months) – Lfx – Lzd - Cfz*
- *FQ resistant DR-TB cases will receive:*
  - *12 Bdq (6 months) - Lzd - Cfz – Cs – (Dlm 6 months)*

*Use Excel or a specialized quantification, forecasting, and early warning software (e.g., QuanTB) to calculate the needed quantities for the forecasting period.*[4]

*Calculations can be based on an average weight of a child (e.g., 16 < 24kg). The calculation starts with establishing the standard quantity of medicines needed to treat one case weighing 20kg with each of the 3 agreed regimens:*

| | | Bedaquiline 20mg | Linezolid 150mg | Levofloxacin 100mg | Clofazimine 50mg | Cycloserine 125mg | Ethambutol 100mg | Delamanid 25mg | Pyrazinamide 150 mg | Ethionamide 125mg | Isoniazid 100mg |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Average tablets per day for a 20kg case: | | 470* | 2 | 3 | 1 | 3 | 4 | 3 | 5 | 3 | 3 |
| FQ sensitive Bdq Lzd Cfz Cs Lfx 12 months. BDQ only 6 months | 1 | 470 | | 810 | 270 | | 1,080 | | 1,350 | 360 | 360 |
| FQ sensitive Bdq Lfx Cfz Z E Hh Eto 11 months. Bdq, Hh and Eto only 6 months | 1 | 470 | 720 | 1,080 | 360 | | | | | | |
| FQ resistant Bdq Lzd Cfz Dlm Cs 12 months | 1 | 470 | 720 | | 360 | 1,080 | | 1,080 | | | |

** Number of tablets per treatment regimen*

[4] QuanTB is an electronic quantification and early warning system designed to improve procurement processes, ordering, and supply planning for TB treatment, which is a free, downloadable desktop tool that transforms complicated calculations into user-friendly graphs displaying key information for managing medicines http://siapsprogram.org/tools-and-guidance/quantb/

*The forecasted 21 FQ sensitive and 9 FQ resistant cases are then distributed across the agreed regimens:*

| | | Bedaquiline 20mg | Linezolid 150mg | Levofloxacin 100mg | Clofazimine 50mg | Cycloserine 125mg | Ethambutol 100mg | Delamanid 25mg | Pyrazinamide 150 mg | Ethionamide 125mg | Isoniazid 100mg |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Average tablets per day for a 20kg case:** | | **470*** | **2** | **3** | **1** | **3** | **4** | **3** | **5** | **3** | **3** |
| FQ sensitive<br>4 Bdq Lfx Cfz Z E Hh Eto/ 5 Lfx Cfz Z E.<br>BDQ only 6 months | 10 | 4,700 | | 8,100 | 2,700 | | 10,800 | | 13,500 | 3,600 | 3,600 |
| FQ sensitive<br>12 Bdq Lfx Lzd Cfz.<br>Bdq only 6 months | 11 | 5,170 | 7,920 | 11,880 | 3,960 | | | | | | |
| FQ resistant<br>12 Bdq Lzd Cfz Cs Dlm<br>Bdq and Dlm only 6 months | 9 | 4,230 | 6,480 | | 3,240 | 9,720 | | 9,720 | | | |
| Total: 30 cases | | 14,100 | 14,400 | 19,980 | 9,900 | 9,720 | 10,800 | 9,720 | 13,500 | 3,600 | 3,600 |

** Number of tablets per treatment regimen*

*Countries are advised to use realistic pediatric DR-TB targets and minimize buffer stocks for these products in order to avoid overstock and wastage. Initially, the number of children enrolled will likely be small and orders should be planned for the full quantity needed without adjusting for possible attrition.*

**Step 6: Adjust for remaining stocks.**

*For the initial orders of these formulations, it is unlikely that there will be available stocks that need to be factored into the quantification; however, for subsequent orders, it is recommended that programmes check whether forecasted quantities need to be adjusted to account for quantities of each medicine in stock or on outstanding orders still to be received.*

# PROCURING CHILD-FRIENDLY DR-TB FORMULATIONS

Procurement of child-friendly DR-TB formulations is often more challenging than procurement of adult formulations. Presently, procuring a full range of pediatric DR-TB medicines requires programmes to contract at least four different manufacturers. This increases transaction costs and products may arrive in separate deliveries over time. Not having all of the child-friendly DR-TB formulations available at the same time may delay the start of treatment. Additionally, manufacturer batch sizes are typically far larger than what most country programmes will be able to use during the shelf-life period. Programmes directly contracting manufacturers often have to wait longer for these medicines as manufacturers wait for enough orders from multiple programmes to meet a batch size, pay higher prices to reduce the manufacturer's risk of wastage, and/or receive products from a previous batch with a lower remaining shelf-life.

By pooling together many countries' actual and anticipated demand for child-friendly DR-TB formulations, GDF is in a position to negotiate with suppliers and procure full batches from manufacturers, helping to keep prices low. GDF also keeps these medicines in its Strategic Rotating Stockpile (SRS), helping to ensure stocks are available for urgent orders. A programme's pediatric DR-TB requirements can be managed as a single contract, requiring just a single import permission and arriving as a consolidated consignment. This can help decrease programme time for import and ensure all child-friendly DR-TB formulations are available at the same time.

# Other Procurement Considerations

→ Country Level Registration: All child-friendly DR-TB formulations available from GDF have been reviewed and approved by the WHO Prequalification Scheme, a Stringent Regulatory Authority and/or recommended by the Global Fund Expert Review Panel. As there are a number of newly-developed child-friendly DR-TB formulations, country-level regulatory approval of these formulations may take time to complete. In many countries, an application for exceptional import permission can be made to the national drug regulatory authority. Exceptional permission may be granted as these medicines are of great importance and will be used exclusively within the national TB programme. Additional technical details about many of these formulations are available on the WHO Prequalification website.

→ Customs clearance: When ordering from GDF, the country programme team receiving the child-friendly DR-TB formulations should identify which documents are required to facilitate the customs clearance process (e.g., invoice, packing list, airway bill, Certificate of Analysis, etc.) as early as possible in the procurement process. Any specific documents required for programmes to apply for waivers of import duties, Value Added Tax, Goods and Services Tax, and any other types of taxes should also be identified as early as possible and communicated to the country's GDF focal point.

# TECHNICAL SUPPORT

- GDF has been supporting country programmes with technical assistance on procurement and supply chain planning, forecasting, quantification, and procurement-related aspects of introducing these child-friendly formulations. This technical assistance is available to additional country programmes that may want procurement-related support to introduce these formualtions. Please contact GDF at gdf@stoptb.org
- Programmatic technical assistance can also be requested through the Sentinel Project, a partnership of researchers, caregivers, and advocates that provides technical and clinical support for the introduction of new child-friendly DR-TB formulations. The Sentinel project can be contacted by email: tbsentinelproject@gmail.com

# RESOURCES AVAILABLE

- WHO consolidated guidelines on tuberculosis Module 5: Management of tuberculosis in children and adolescent 2022
- WHO operational handbook on tuberculosis Module 5: Management of tuberculosis in children and adolescent 2022
- Sentinel Project on paediatric drug-resistant tuberculosis Management of Multidrug-Resistant Tuberculosis in Children: A Field Guide. Fifth edition, March 2022
- GDF-WHO-GF TB Medicines Dashboard
- GDF Product Catalog
- GDF Category and Product-level Procurement and Delivery Planning Guide
- GDF Budgeting Prices for TB Medicines
- WHO Model Essential Medicines List and Model Essential Medicines List for Children
- WHO Prequalification of Medicines Programme

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