Accelerating the Roll-Out of TB Innovations through the Stop TB/GDF Launchpad: The Stop TB /GDF Paedaitric Drug-Resistant TB Initiative

Progress Report as of 30 November 2019

Executive Summary

The Stop TB Partnership's Global Drug Facility is using its Launchpad approach to accelerate the uptake of new, child-friendly medicines and regimens for the treatment of drug-resistant tuberculosis (DR-TB) in children. This report documents the progress of implementation since the Initiative started through 30 November 2019. This Initiative is funded by the Government of Japan and the United States Agency for International Development (USAID).

It is estimated that between 25,000-30,000 children develop drug-resistant TB each year while only 1,000 children are reported to have been treated. There remain significant difficulties in identifying and diagnosing children with TB. However, new, quality-assured, child-friendly formulations of medicines are now available that can make treatment easier for clinicians and caregivers. Additionally, recommendations from the World Health Organization reiterate the need to use only all-oral regimens, removing the risk of permanent adverse events from the use of injectable agents. Making these formulations and regimens widely available should alleviate at least one barrier to treating children and may help spur additional investment into reaching the United Nations High-Level Meeting targets of treating 115,000 children for drug-resistant TB by 2022.

StopTB/GDF has taken a multiprong approach to implementing this Initiative, working to address implementation barriers at both the global level and those that are country-specific. Globally, STBP/GDF has supported the Sentinel Project on Drug-Resistant TB in Children to develop implementation guidance documents and quantification and forecasting approaches to assist countries when implementing these new formulations. They are currently available in English and Russian and are being translated into French. STBP/GDF's annual competitive tender has resulted in an increased number of quality-assured suppliers of these formulations and significant price reductions, up to an 80% decrease. The price reductions resulted in cost savings for procurement and allowed STBP/GDF expand the scope of countries eligible for support. A total of 56 countries are now eligible for support under this Initiative.

The Stop TB GDF Launchpad: What is it?

Introduction of newly WHO-recommended innovations in countries is often delayed, even for products like new formulations or next-generation tests that require relatively limited clinical and technical assistance. The GDF Launchpad serves as a mechanism to overcome the existing barriers for these products and catalyse their introduction for later wide roll-out. Under the Launchpad, GDF engages with countries and partners to identify early adopter programmes that would be able to implement select new tools. This gives visibility on initial demand, enabling GDF to negotiate supply side terms with manufacturers, including launch prices, volume-based price reductions, minimum order quantities and production planning, among other aspects. The initial demand consolidation and coordination with partners and programmes also helps GDF to develop the procurement and supply planning tools and approaches needed to successfully implement the new tools. With available funds, GDF provides targeted procurement support (e.g., grants) to programmes to fund the initial orders. Monitoring implementation then enables GDF to refine and improve quantification approaches and assist the programmes with budget planning for wider roll-out under other funding sources.

At the country level, STBP/GDF has contracted the Sentinel Project to provide in-country clinical assistance to implement these formulations. Sentinel has assessed the country readiness to implement the new formulation and regimens in 56 countries and is or has provided clinical support to nearly all the countries. STBP/GDF has completed quantification and forecasting exercises in most of the countries. STBP/GDF expects more than 1,100 children will be treated with new formulations and regimens.

Procurement is ongoing and deliveries are expected to begin in quarter 1, 2020 and to continue through quarter 2. STBP/GDF will be monitoring the consumption of these formulations closely to refine the quantification and forecasting approach and will work closely with programmes to identify sustainable funding for procurements beginning in 2021.

STBP/GDF is planning to launch its mass communications strategy in December 2019. This launch is intended to increase awareness of these formulations and help to build demand. It is also intended to help build general awareness of the burden of drug-resistant TB in children and difficulties in identifying and diagnosing children.

Introduction

In 2018, the World Health Organization (WHO) estimated that 484,000 people developed tuberculosis (TB) that was resistant to rifampicin (RR-TB), a key medicine used in the treatment of TB or that was resistant to rifampicin and at least one other medicine used to treat TB, (e.g. Multidrug-resistant TB [MDR-TB])[1].

Estimates of the TB burden (including both drug-susceptible and drug-resistant) are available from the WHO disaggregated by age <15 years old and ≥ 15 years old. It is estimated 168,000 children died from TB in 2018 (about 14% of all TB deaths). However, there are no reported estimates of the DR-TB burden

[1] Global Tuberculosis report 2019. Geneva: World Health Organization; 2019. License: CC BY-NC-SA 3.0 IGO.

and DR-TB related deaths in children, nor are the estimates of disease burden further stratified by age, making it difficult to determine how many children are less than 5 years of age (or less than 25 kg) and who may benefit most from child-friendly formulations. However, it is estimated that between 25,000-30,000 children develop DR-TB annually[2,3,4].

The proportion of children diagnosed with TB and the proportion of those started on treatment are also unknown, which can at least partly be explained by a lack of appropriate paediatric-friendly TB diagnostics and, until recently, by medicines that were suboptimal for children. Indeed, according to the Treatment Action Group, the microbiological confirmation of the disease is missed in more than 80% of the paediatric cases with clinically diagnosed TB[5]. Other challenges in the management of DR-TB treatment in children include: regimens are long, often composed of medicines that are not in paediatric formulations, the monitoring of side effects is complex, the adherence to treatment is poor, and children with TB may need additional family and social support. This is likely further exacerbated in children with MDR-TB and results in sub-optimal DR-TB treatment for children[6,7].

In 2019, WHO released the Consolidated Guidelines on DR-TB Treatment that includes using delamanid in children as young as 3 years of age and reinforced the concept of using all-oral regimens, particularly in children, to avoid the toxic and in many cases permanent side effects from using injectable agents[8]. Additionally, 2019 saw a second supplier begin producing many of the paediatric formulations, which resulted in both increased supply security and price reductions from competition between suppliers. A tablet formulation of clofazimine which can be dispersed in water also became available, a vast improvement from the previous clofazimine gel cap formulations that required extracting the liquid from the capsule using a syringe. Now, nearly all the formulations needed to complete an all-oral regimen for children are quality-assured and available (with the notable exception of linezolid 150mg dispersible tablets which are still in development). Table 2 shows the number of quality-assured suppliers and price range for the available formulations classified by the 2019 WHO Guidance groups.

[2] Jenkins HE et al. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. Lancet 2014; 383:1572-9.
[3] Dodd et al. Global burden of drug-resistant tuberculosis in children: a mathematical modelling study. Lancet Infect Dis 2016; 16:1193-201.
[4] Jenkins HE. The global burden of childhood tuberculosis. Pneumonia 2016.
[5] Pipeline report 2019, Pediatric Tuberculosis Diagnosis, Treatment, and Prevention. New York: Treatment Action Group; 2019. Available from: http://www.treatmentactiongroup.org/sites/default/files/pipeline_tb_pediatrics_2019.pdf.
[6] Dheda K et al. Clinical management of adults and children with multidrug-resistant and extensively drug-resistant tuberculosis. Clinical Microbiology and Infection 2017; 23(3):131-140.
[7] McAnaw S.E. et al. Pediatric multidrug-resistant tuberculosis clinical trials: challenges and opportunities. International Journal of Infectious Diseases 2017; 56: 194–199.
[8] WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019. Available from: https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/.

Table 1. Number of quality-assured suppliers and price range per medicine

2019 WHO Guidance Medicines classification	Formulation	# of Quality Assured Suppliers	GDF Price range
Group A	Levofloxacin 100mg dispersible tablet	2	$12.91 - $85
	Moxifloxacin 100mg dispersible tablet	2	$19.90-$85
Group B	Clofazimine 50mg tablet	1	$49.12
	Cycloserine 125mg mini capsule	1	$45
Group C	Ethambutol 100mg dispersible tablet	1	$22.5
	Delamanid 50mg tablet	1	$1700
	Pyrazinamide 150mg dispersible tablet	2	$9.40 -$25
	Ethionamide 125mg dispersible tablet	2	$13-$21.25

The Sentinel Project on Pediatric Drug-Resistant Tuberculosis completed its 2019 "Management of Multidrug-Resistant Tuberculosis in children: A Field Guide" based on the new WHO recommendations[9]. A Russian version of the guide has been developed and is available on the Sentinel Project website.

Activity Report

The activity report section is structured around key categories. Within each category, activities that were completed at the global level are presented first, followed by country-specific work. For each country, there is a list of key milestones that need to be completed. Those milestone and definitions are:

- **Assessment of current approaches to treatment of children with DR-TB**: Each country is assessed to determine if they are following the current WHO 2019 Guidance and Sentinel Project 2019 Field Guide. Countries requiring support will receive clinical technical assistance;
- **Clinical technical assistance provided**: Clinical support through the provision of technical guidance material, training, missions, and direct communications to support the uptake of the new formulations has been provided to the country;
- **Quantification and forecasting**: The country-specific quantification and forecasting exercise has been completed to determine the required number of tablets needed for each medicine to treat the estimated number of children for one year;

[9] Management of Drug-Resistant Tuberculosis in Children: A Field Guide. Boston, USA: The Sentinel Project for Pediatric Drug-Resistant Tuberculosis; November 2018, Fourth edition. Available from: http://sentinel-project.org/wp-content/uploads/2019/02/Updated_DRTB-Field-Guide-2019-V3.pdf.

- **Order prepared**: A Procurement Request Form (PRF) has been developed based on the results of the country quantification and forecasting exercise, the country has reviewed and confirmed the quantities and the formal grant agreement between the programme and Stop TB/GDF has been signed;
- **Order placed with suppliers**: The orders have been pooled together and sent to the suppliers of the product and the suppliers have acknowledged receipt and given an estimated goods readiness date (e.g., when the products will be ready for shipment);
- **Order delivered**: All of the medicines for each order have been sent by the suppliers to the warehouse in the Netherlands, the orders have been consolidated (to ensure that each shipment to the programme includes all of the ordered medicines) and the shipments have been delivered to the country;
- **Consumption monitoring**: Monitoring of the use of each medicine is captured in programmes every quarter and compared to assumptions used in the quantification and forecasting exercise, adjustments to the assumptions are made as needed;
- **Sustainable funding is secured**: Funding to continue the use of these formulations after 2020 is identified and secured in advance, this may include other donors (e.g., the Global Fund) or national resources.

The status of the key milestones under each category in the Activity Report is reported in a table format by country.

Country Support

Global

Stop TB/GDF has contracted the Sentinel Project on Pediatric Drug-Resistant Tuberculosis to provide clinical support to country programmes to align their treatment guidelines with the most current WHO treatment recommendations, including the use of new tools in paediatric populations, and to support the introduction of the dispersible formulations. In these efforts, the Sentinel Project developed a set of tools that are designed to support all aspects of the implementation, from procurement and supply specialists to clinicians, pharmacists, and nurses, to patients and families. The tools are:

- *Summary points on paediatric formulations of second-line drugs for TB*;
- *Drugs sheets for dispersible formulations*;
- *Standard Operating Procedures (SOPs) for administration of dispersible formulations of second-line drugs*;
- *SOPs for storage and administration of dispersible formulations of second-line drugs*;
- *Drug-Resistant TB & Me: Caring for a child with drug-resistant TB*.

All are available in English and Russian and are posted on the Sentinel Project's website (http://sentinel-project.org/). They are also annexed to this report.

Country-Specific

All 56 countries wanting to move forward with grants have been assessed and offered technical assistance – through missions, workshops, and direct communications - to help ensure that the medicines will be used to improve treatment for children with DR-TB as per the most recent WHO DR-TB recommendations.

Countries received targeted emails including technical guidance material (SOPs and clinical input tools) developed by Sentinel and in many cases with direct discussions on how to introduce the new medicines effectively.

Central African Republic, Congo, and Mali do not expect to have any DR-TB paediatric cases next year. The Philippines have indicated they have enough stocks of paediatric DR-TB products to cover their needs through 2020.

The consumption of the medicines in the country will be conducted by the GDF's Regional Technical Advisors (RTAs) every quarter upon delivery of the medicines. It has already started for the countries that received a first order earlier in 2019.

Table 2. Status of the Country Support's milestones, per country

Country	Assessment of current approaches to the treatment of children with DR-TB	Clinical technical assistance provided
Afghanistan	Completed	Ongoing
Angola	Ongoing	Ongoing
Armenia	Completed	Ongoing
Azerbaijan	Completed	Ongoing
Bangladesh	Completed	Completed
Belarus	Completed	Completed
Benin	Ongoing	Ongoing
Botswana	Completed	Ongoing
Burkina Faso	Completed	Ongoing
Cambodia	Ongoing	Ongoing
Cameroon	Ongoing	Ongoing
CAR*	N/A	N/A
Chad	Completed	Ongoing
Congo*	N/A	N/A
DRC	Completed	Ongoing
Eswatini	Completed	Completed
Ethiopia	Completed	Completed
Georgia	Completed	Ongoing
Ghana	Completed	Ongoing
Guinea	Ongoing	Ongoing
Haiti	Completed	Completed
India**	Completed	Completed
Indonesia	Completed	Completed
Ivory coast	Completed	Ongoing
Kazakhstan	Completed	Ongoing
Kenya	Completed	Ongoing
Kyrgyzstan	Completed	Ongoing

Country	Assessment of current approaches to the treatment of children with DR-TB	Clinical technical assistance provided
Laos	Ongoing	Ongoing
Lesotho	Completed	Completed
Liberia	Completed	Completed
Malawi	Completed	Ongoing
Mali*	N/A	N/A
Moldova	Ongoing	Ongoing
Mongolia	Ongoing	Ongoing
Morocco	Completed	Ongoing
Mozambique	Completed	Completed
Myanmar	Completed	Ongoing
Namibia	Completed	Completed
Niger	Completed	Ongoing
Nigeria	Completed	Completed
Pakistan	Completed	Completed
Papua New Guinea	Completed	Completed
Philippines***	N/A	N/A
Rwanda	Completed	Ongoing
Senegal	Ongoing	Ongoing
Sierra Leone	Completed	Ongoing
Somalia	Completed	Ongoing
South Africa	Completed	Ongoing
Sri Lanka	Ongoing	Ongoing
Tajikistan	Completed	Ongoing
Tanzania	Completed	Completed
Thailand	Ongoing	Ongoing
Timor-Leste	Ongoing	Ongoing
Turkmenistan	Completed	Ongoing
Uganda	Completed	Ongoing
Ukraine	Ongoing	Ongoing
Uzbekistan	Completed	Ongoing
Viet Nam	Completed	Completed
Zambia	Completed	Ongoing
Zimbabwe	Completed	Ongoing

** Countries with no expected DR-TB paediatric cases in 2020*

*** Supporting the B.J. Wadia Hospital for Children in Mumbai, one of the largest paediatric DR-TB sites in India. Support does not cover all of India*

**** Country with enough stock of paediatric DR-T products to cover 2020 estimated needs*

Supply and Demand Alignment

Global

On the demand side, the Sentinel Project was able to capture paediatric enrolment data from the initial countries over the last three years and to use this information to develop a model of how children have been treated over time. With this model, RTAs were able to develop a quantification model for QuanTB. Together, the RTAs and the Sentinel Project quantified the needs for the upcoming year.

On the supply side, a second supplier entered the market for these new paediatric formulations and due to GDF's tender approach, there were significant decreases in the prices for many of these formulations, including a more than 80% price decrease in one of the key fluoroquinolones.

Following the release of the new WHO Consolidated Guidelines on DR-TB Treatment and the new, more child-friendly formulation of clofazimine, the GDF's RTAs and partners from the Sentinel Project and programmes reworked their quantification approaches to take into account the updated approaches to treatment and to then translate this into new demand estimates and programme orders.

Country-Specific

STBP/GDF has worked with the National TB Control Programmes (NTPs) to determine the estimated number of DR-TB paediatric patients they plan to enrol in 2020, the treatment regimen they will be in, and the dosages required per medicine in order to appropriately quantify and forecast the needs for 2020. The quantification and forecasting exercise have been completed in 43 countries and is ongoing in the remaining 13 countries.

Based on the quantification and forecasting exercise, it is estimated that more than 1,100 DR-TB treatments will be provided to children in 2020 in 56 countries. The country-specific estimates are shown in Table 3.

Table 3. Target number of children on DR-TB treatment per country

Country	Estimated Number of children on DR-TB treatment in 2020
Afghanistan	15
Angola	27
Armenia	6
Azerbaijan	6
Bangladesh	21
Belarus	10
Benin	1
Botswana	12
Burkina Faso	6
Cambodia	3
Cameroon	5
CAR*	N/A
Chad	2

Country	Estimated Number of children on DR-TB treatment in 2020
Congo*	N/A
DRC	20
Eswatini	3
Ethiopia	60
Georgia	3
Ghana	7
Guinea	10
Haiti	5
India	50
Indonesia	50
Ivory coast	12
Kazakhstan	50
Kenya	16
Kyrgyzstan	30
Laos	2
Lesotho	10
Liberia	6
Malawi	8
Mali*	N/A
Moldova	14
Mongolia	15
Morocco	8
Mozambique	114
Myanmar	30
Namibia	35
Niger	2
Nigeria	66
Pakistan	60
Papua New Guinea	50
Philippines*	N/A
Rwanda	1
Senegal	2
Sierra Leone	7
Somalia	15
South Africa	100
Sri Lanka	2
Tajikistan	40
Tanzania	21

Country	Estimated Number of children on DR-TB treatment in 2020
Thailand	43
Timor-Leste	1
Turkmenistan	20
Uganda	16
Ukraine	50
Uzbekistan	60
Viet Nam	5
Zambia	19
Zimbabwe	12

** Countries with no expected DR-TB paediatric cases in 2020*

*** Country with enough stock of paediatric DR-T products to cover 2020 estimated needs*

Procurement

As each country's quantification and forecasting exercise for 2020 is completed, STBP/GDF works with the NTP to finalize the documents needed to order the products. It takes multiple formulations to create a full regimen, so each programme is placing orders for many different products. And, each of these formulations has a minimum order quantity that must be reached before the manufacturer will product the batch. GDF is pooling all of these different orders together to make sure that minimums are reached and that all programmes can access these formulations, even if there are only a few children that need them each year. GDF plans to have all of the orders finalized by the end of 2019.

Table 4. Status of the Procurement's milestones, per country

Country	Order prepared*	Order placed with suppliers*
Afghanistan	Ongoing	Planned Q4 2019
Angola	Not started	Planned Q4 2019
Armenia	Ongoing	Planned Q4 2019
Azerbaijan	Ongoing	Planned Q4 2019
Bangladesh	Ongoing	Planned Q4 2019
Belarus*	Completed	Completed
Benin	Not started	Planned Q4 2019
Botswana	Ongoing	Planned Q4 2019
Burkina Faso	Ongoing	Planned Q4 2019
Cambodia	Not started	Planned Q4 2019
Cameroon	Not started	Planned Q4 2019
CAR**	N/A	N/A
Chad	Ongoing	Planned Q4 2019
Congo**	N/A	N/A
DRC	Ongoing	Planned Q4 2019

Country	Order prepared*	Order placed with suppliers*
Eswatini*	Ongoing	Planned Q4 2019
Ethiopia*	Ongoing	Planned Q4 2019
Georgia*	Ongoing	Planned Q4 2019
Ghana	Ongoing	Planned Q4 2019
Guinea	Not started	Planned Q4 2019
Haiti*	Ongoing	Planned Q4 2019
India	Ongoing	Planned Q4 2019
Indonesia	Completed	Completed
Ivory coast	Ongoing	Planned Q4 2019
Kazakhstan*	Ongoing	Planned Q4 2019
Kenya	Ongoing	Planned Q4 2019
Kyrgyzstan*	Ongoing	Planned Q4 2019
Laos	Not started	Planned Q4 2019
Lesotho*	Completed	Completed
Liberia*	Ongoing	Planned Q4 2019
Malawi	Ongoing	Planned Q4 2019
Mali**	N/A	N/A
Moldova	Ongoing	Planned Q4 2019
Mongolia	Not started	Planned Q4 2019
Morocco	Ongoing	Planned Q4 2019
Mozambique*	Completed	Completed
Myanmar	Ongoing	Planned Q4 2019
Namibia*	Ongoing	Planned Q4 2019
Niger	Ongoing	Planned Q4 2019
Nigeria*	Completed	Completed
Pakistan*	Completed	Completed
Papua New Guinea	Ongoing	Planned Q4 2019
Philippines***	N/A	N/A
Rwanda	Ongoing	Planned Q4 2019
Senegal	Not started	Planned Q4 2019
Sierra Leone	Ongoing	Planned Q4 2019
Somalia	Ongoing	Planned Q4 2019
South Africa*	Ongoing	N/A
Sri Lanka	Not started	Planned Q4 2019
Tajikistan*	Ongoing	Planned Q4 2019
Tanzania*	Completed	Completed
Thailand	Not started	Planned Q4 2019
Timor-Leste	Not started	Planned Q4 2019

Country	Order prepared*	Order placed with suppliers*
Turkmenistan	Ongoing	Planned Q4 2019
Uganda	Ongoing	Planned Q4 2019
Ukraine	Ongoing	Planned Q4 2019
Uzbekistan*	Ongoing	Planned Q4 2019
Viet Nam	Ongoing	Planned Q4 2019
Zambia	Ongoing	Planned Q4 2019

** 2nd order for the initial countries and 1st order for the expanded countries*

*** Countries with no expected DR-TB paediatric cases in 2020*

**** Country with enough stock of paediatric DR-T products to cover 2020 estimated needs*

Demand Generation

Under this project GDF aims to raise awareness on the challenges faced by children affected with TB to get diagnosed and treated, especially in the case of DR-TB, and it should also aim to trigger and support the discussion around the need to have more investment and support to foster innovation in developing new tools to diagnose and treat all types of TB. Additionally, GDF aims to:

- Highlight how the quality of life improves for children and their families when using child-friendly formulations;
- Promote the new formulations and new tools;
- Communicate on successes and lessons learned as the project is implemented that could help support other countries and programmes when introducing these products.

Initial Feedback from Nigeria

"*The children are the future of the country and we need to do all that is within our reach to ensure that they get prompt diagnosis and treatment for Drug-Resistant TB*" explains Dr Urioke Ochukwu, Assistant Director and Head Childhood Tuberculosis Unit. He says that over time there has been an increasing trend of childhood DR-TB in Nigeria. From 9 cases in 2015 to 52 in 2018. In 2019 they already have 34 cases up to August.

"*It has to do with ensuring that there's an uninterrupted drug supply and that's when GDF comes in. GDF has been very supportive to Nigeria in ensuring that we get drugs for Drug Susceptible TB and also get drugs for DR-TB. And when you come to DR-TB on the children. The new drugs for children paediatric formulations, Global Drug Facility has been very supportive. Without the GDF, I think we would have run into a lot of problems*" states Dr Babawale Victor, TB specialist at the

Nigerian National TB and Leprosy Control Program, colleague and friend of Dr Urhioke.

Planned activities

The focus of the next six months of the Initiative's implementation will be to finalize all orders, to track the delivery of the products, to analyse the consumption of the medicines in countries, and to continue offering clinical support if needed.

One additional key activity for all countries will be to ensure that the NTPs who benefited from the grant secure funding for the procurement of the 2021 DR-TB paediatric treatments needs. GDF has worked with the Global Fund to ensure that these formulations are eligible to be included in the upcoming grant period (2020-2022). GDF's Regional Technical Advisors and StopTB's teams that work with programmes to develop their Global Fund Concept Notes will be working to actively incorporate a focus on paediatric DR-TB.

Annexes

Annex 1. Acronyms

DLM	Delamanid
DR-TB	Drug-resistant tuberculosis
GDF	Global Drug Facility
MDR-TB	Multidrug-resistant tuberculosis
NTP	National Tuberculosis Programme
PRF	Procurement Request Form
RR-TB	Rifampicin-resistant tuberculosis
RTA	Regional Technical Advisor
SLD	Second-line drug
SOPs	Standard operating procedures
TB	Tuberculosis
WHO	World Health Organization

Annex 2. Technical Support Documents from Sentinel Project

1. Summary points on paediatric formulations of second-line drugs for TB

1.Summary points on paediatric formu

2. Drugs sheets for dispersible formulations

2. Drugs sheets for dispersible formulat

3. SOPs for administration of dispersible formulations of second-line drugs

3. SOPs for administration of di

4. SOPs for storage and administration of dispersible formulations of second-line drugs

4. SOPs for storage and administration

5. Drug-Resistant TB & Me: Caring for a child with drug-resistant TB

5. Drug-Resistant TB & Me Caring for