PEDIATRIC FORMULATIONS OF SECOND-LINE DRUGS FOR THE TREATMENT OF DRUG-RESISTANT TUBERCULOSIS

A Step-by-Step Guide for Forecasting, Ordering and Implementing these Novel Tools

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The Sentinel Project on Pediatric Drug-Resistant Tuberculosis

INTRODUCTION

For the first time ever, there are pediatric formulations of many of the second-line drugs used in the treatment of drug-resistant tuberculosis (DR-TB). The availability of these products stands to revolutionize the treatment of children infected with and sick from DR-TB, as the current standard of care where adult tablets are cut, broken, crushed and mixed not only violates Good Clinical Practice but also results in inadequate treatment for children living with DR-TB. In fact, studies have shown that not only are dispersible formulations of second-line drugs preferred by children, caregivers and providers but also result in better and more stable drug levels in the blood.* Thus it is urgent that countries begin procuring the new pediatric formulations of the second-line drugs that are now available though the StopTB Partnership's Global Drug Facility (GDF).

Despite great need among the 32,000 children estimated to have DR-TB each year, very few children are diagnosed and started on treatment. As a result, few countries have experience forecasting pediatric DR-TB drug needs. The shelf-life of dispersible tablets is short so it is important that countries are accurate in forecasting their pediatric treatment needs. Furthermore, although the drugs are either pre-qualified or approved by the Global Fund Expert Review Panel, they will not be registered in any countries in the near future. Thus countries will need to utilize waivers or other available mechanisms to import these formulations. Many TB programs have used these mechanisms before to import bedaquiline and/or delamanid. This document is meant to serve as a "Step-by-Step" guide to help countries introduce the use of these new formulations to improve treatment for children. Technical support related to ordering and implementing these formulations, and other information and support is available from the Sentinel Project on Pediatric Drug-Resistant Tuberculosis and can be accessed by writing to tbsentinelproject@gmail.com.

* Purchase, S., Gracia-Prats, A., Wademan, D, et. al.

EARLY EXPERIENCES OF THE ACCEPTABILITY AND PALATABILITY OF A NOVEL CHILD-FRIENDLY LEVOFLOXACIN FORMULATION IN YOUNG CHILDREN

Presentation at the 48th Union World COnference on Lung Health, 2017, Guadalajara, Mexico.

Step 1: Know the products available and the products you need

Below is a list of the dispersible second-line products that are currently available via the GDF

Product Name	Status of WHO or ERP Approval
Pyrazinamide 150 mg DT	WHOPQ
Ethionamide 125 mg DT	WHOPQ
RH 75/50	WHOPQ
RHZ 75/50/150	WHOPQ
Levofloxacin 100 mg DT	WHOPQ
Moxifloxacin 100 mg DT	WHOPQ
Cycloserine 125 mg capsules	WHOPQ
Ethambutol 100 mg DT	WHOPQ

*DT=dispersible tablet, WHOPQ= WHO prequalified; ERP= Expert Review Panel

In addition, the following products will hopefully be available soon.

Isoniazid 100 mg DT	Not yet filed for WHOPQ
Linezolid 150 mg DT	Not yet filed for WHOPQ

Others, for example, may only wish to procure some of these products, depending on their implementation plans for the 2018 WHO guidelines.

Countries that are treating DR-TB infection in children (i.e. “prophylaxis” or “preventive therapy”) can also procure these products.

Step 2: Forecast pediatric treatment needs for the next 12 months

Because most countries treat a small number of children with DR-TB disease or infection and because in the absence of pediatric products, programs have used adult tablets, there has been limited experience forecasting specific drug needs for children.

A forecasting approach developed by the Sentinel Project can be used to make initial estimates. Because these products have short shelf-lives (24 months, as is common with dispersible tablets), it is recommended that countries be ambitious but realistic about what their actual consumption will look like. Close monitoring of consumption can help refine future forecasts. If there are “stock outs” of the novel pediatric formulations, programs can temporarily revert back to using the adult tablets while waiting for new stocks of the pediatric formulations to arrive.

The first stage of forecasting is to *look back over the past three years and see how many children were treated for DR-TB each year.* The novel formulations will be most beneficial in children who are 25kg and below, which roughly translates into children ages 10 years and under (although in children with DR-TB who experience weight loss/wasting/stunting, there may be children as old as 18 who might

benefit from access to the pediatric formulations). The age break downs and numbers treated from the last three years can be used to estimate the number of children who will be treated in 2018. However, if there is a clear upward trend in the number of children started on treatment, it may be best to only use the numbers from 2017 for forecasting.

If only ages are known, then estimates can be made based on age. If weights are available, then weight based forecasting can be used as well. The following table, which lists the number of tablets per child per 12 months, assuming dosing takes place 6 days a week, can be used to guide forecasting.

Drugs	< 2 years	2-5 years	6-7 years	8-10 years
Ethio 125mg	300	600	900	1200
Cycloserine 125mg	300	600	900	1200
Levoflox 100mg	600	900	1200	1500
Moxi 100mg	300	450	600	750
INH 100mg	300	600	900	1200
EMB 100 mg	600	900	1200	1500
PZA 150mg	600	900	1200	1500
Linezolid 150mg	300	600	900	1200

If possible, the precise number of children in each age or weight category should be calculated. If this is not possible, we recommend that countries assume that 12.5% of children are < 2 years, 12.5% of children are ages 2-5 years, 25% of children are ages 6-7 years and 50% of children are ages 8-10 years.

While there can be great variability in the treatment of pediatric DR-TB, we also recommend that countries review the types of regimens being used in children. Countries treating children with DR-TB infection (i.e. “prophylaxis” or “preventive therapy”) should also forecast needs for these children based on the number of children receiving such treatment in past years.

Countries may also want to consider adding 5% to the order placed for each product given that there may be some other populations needing these tablets (i.e. adults who are obtunded or with nasogastric tubes, adults who cannot swallow tablets).

Step 3: Secure funding for the products

The prices for the pediatric formulations are available on the GDF website in the second-line drug, oral formulation section (http://www.stoptb.org/gdf/drugsupply/pc2.asp?CLevel=2&CParent=4). These prices depend on order volumes, and thus countries are encouraged to order early so the GDF can pool and coordinate orders. Global Fund grant monies can be used to purchase these products. It is anticipated that the use of these formulations will result in overall cost savings to programs. These savings will come from the decreased need for prolonged hospitalization for children—which was often necessary since preparation of medications using the adult tablets—and from decreased personnel time needed to prepare the adult medicines to give to children.

Step 4: Verify mechanism for import of the products

Since these formulations are not likely to be registered in any of the countries using them over the next few years, import mechanisms will need to be verified. Most countries have identified mechanisms for importing products that are not yet registered, especially if they will be used for treating public health emergencies like DR-TB. Most countries used these mechanisms to import other DR-TB innovations such as Xpert MTB/RIF™ cartridges, bedaquiline, and/or delamanid. Similar mechanisms should be used to import these pediatric formulations.

The Global Drug Facility can provide information and assistance with import waivers.

Step 5: Place an order with the Global Drug Facility

The dispersible tablets and other pediatric products are available through the GDF and should be ordered using the standard GDF order form. The ordering form is available here:

http://www.stoptb.org/gdf/drugsupply/procurement_forms.asp

It is highly recommended the order for these products be placed as soon as possible and not wait until the usual procurement cycles followed in the country. It is also recommended that these pediatric products be ordered annually (or possibly even every six months) given their short shelf life.

Step 6: Prepare for implementation while waiting for shipment to arrive

From the time the order is placed until there is drug available in the country, there is usually a time lag of 4-6 months but the time period may be longer if only small orders are placed due to the relatively large minimum order quantities for these products which will require pooling procurement across multiple countries. During this time period, the program should begin planning for optimal use of these novel products. This would include development of standard operating procedures, refresher trainings for pharmacy and health care staff, development of materials for caregivers and children, plans for assessing the acceptability of the products, and procedures for monitoring consumption. The Sentinel Project has developed a number of SOPs that can be provided for countries to adapt to their individual needs. For a list of these SOPs and to have the materials sent to you, please contact the Sentinel Project (tbsentinelproject@gmail.com). Sites where the products will be stored should be identified as well as a mechanism for distribution to the sites where the drugs will be used.

Step 7: Begin using the products

Once the products arrive, they should be deployed for use in the field immediately, especially given their short shelf lives. The novel pediatric formulations can be given immediately for children already on treatment and for children who are newly diagnosed.

Step 8: Assess the acceptability of the products

While it is widely anticipated that these dispersible tablets will be a major improvement in the treatment of children with DR-TB disease and infection—and preliminary data from acceptability assessments of the levofloxacin dispersible tablets in Cape Town support this—it will be important to understand any

barriers or challenges to their use among children, caregivers and providers at all levels. Each country can decide how best to assess this in their contexts and settings. A generic assessment protocol and tools are available from the Sentinel Project and can be obtained by contacting the Sentinel Project (tbsentinelproject@gmail.com).

In addition to assessing the acceptability of the products, pharmacists and providers should note any problems with the drugs themselves (i.e. change in color, broken tablets, etc.) and report these quality issues to the GDF.

Step 9: Monitor consumption to refine forecasting needs

Because small numbers of children are being treated with these novel second-line formulations, it is important that actual consumption of product is closely monitored (i.e. on a quarterly basis) so that better forecasting and procurement can be done in the future. This monitoring will not involve collecting additional data beyond what is routinely available for patient care. Basic monitoring variables will include: stock levels of drug product, numbers of children currently on treatment, numbers of new children started on treatment, and the treatment regimens being used. Some programs may also wish to collect data on how weights change during treatment, how many children discontinue drugs due to adverse events, how many children die, and how many children are lost to follow up. A sample of a quarterly update form is available from the Sentinel Project (tbsentinelproject@gmail.com).

Step 10: Addressing other gaps in pediatric DR-TB

The novel pediatric formulations of the second-line drugs are a major breakthrough in treatment of children with DR-TB disease and infection. Their availability alone, however, will not have much impact on the lives and health of children affected by this disease unless they are coupled with other interventions to prevent, diagnose and treat children with DR-TB infection and disease. Globally it is estimated that there are between 24,000 and 30,000 children who become sick with DR-TB and fewer than 5% of these children are ever diagnosed or started on treatment. Each year approximately 1.2 million children are infected with DR-TB yet almost none of them receive targeted interventions or access to treatment of infection. These gaps must be addressed if there is to be a significant impact on the problem of pediatric DR-TB. “One way to diagnose and treat more children with DR-TB is to thoroughly investigate the household contacts of adults newly diagnosed with DR-TB.”The novel formulations of the second-line drugs are an important intervention and will greatly improve the care of children with DR-TB. To maximize their potential, however, they must be coupled with broader efforts to diagnose, prevent, and treat DR-TB in children.