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CHALLENGE TB

TECHNICAL HIGHLIGHT

(Photo Credit: Warren Zelman)

Introduction of New Pediatric TB Drug Formulations in Ethiopia

BACKGROUND

Tuberculosis (TB) is a major cause of morbidity and mortality among children.[1] Ethiopia has reported more than 15,000 pediatric, drug-sensitive TB cases in 2017/18.[2] However, there were no appropriately dosed TB medicines for children. Recognizing the need for higher doses of medicines for children (relative to their body weight than an adult would need), the World Health Organization (WHO) revised the appropriate therapeutic dosage of first-line TB medicines in the 2010 childhood TB guideline. Gaps in medicines that conform to global standards remained a challenge and may render TB treatment ineffective and lead to increasing rates of drug-resistant TB in children.

The existing medicines for drug-sensitive TB treatment are rifampicin 60 mg + isoniazid 30 mg + pyrazinamide 150 mg (RHZ), which is used for the first two months of the intensive phase and rifampicin 60 mg + isoniazid 30 mg (RH) for the four months of the continuation phase. However, according to the new WHO recommendation,[3] these formulations are not appropriately dosed and carry the risk of poor treatment outcome and development of resistance to treatment. This warranted a change to new formulations that are correctly dosed for drug-sensitive TB according to WHO.

Benefits of Child-Friendly TB Formulations

- The right medicines in the right doses will increase adherence and save more lives.
- Child-friendly medicines improve the daily lives of children and their families struggling with TB.
- Good medicines prevent the risks of poor response to treatment and developing drug resistance.
- Simple TB medicines for children ease the burden on the TB control program.

WHO with its partners have worked to make available quality, affordable, child-friendly medicines in the correct internationally recommended dosages for drug-sensitive TB through the Global Fund that can be adopted by countries with endemic TB. The tablets are fixed-dose combinations (FDCs) that contain multiple drugs at the proper doses for children. These include rifampicin 75 mg + isoniazid 50 mg + pyrazinamide 150 mg, which is used for the first two months of treatment, followed by rifampicin 75 mg + isoniazid 50 mg for an additional four months, both of which are available in fruit flavors that are palatable for children. In addition, the medicines dissolve in water in just a few seconds.

ETHIOPIA

Given that the medicines became available through global mechanisms in 2016, the National TB Program (NTP) adopted the guidance and planned to introduce these new pediatric formulations and phase out the existing ones, particularly for the benefit of the pediatric cases. The introduction process started around August 2016; for a smooth transition in the context of different scenarios, it was decided to start treatment with the new formulations at health facilities in January 2018. The USAID-funded Challenge TB (CTB) Project has supported the NTP and other government organizations at different levels on introducing and transitioning to the new medicines.

FIGURE 1. Steps for introducing pediatric TB drug formulations

STRATEGIC RESPONSE

Introducing the WHO recommended drugs required a series of coordinated activities that avoided supply risks, such as stock-out and wastage, while also phasing out previously procured medicines in a way that mitigates wastage.

There are important issues to address during the introduction of new drugs into a health system, for example, when to introduce, how to introduce (pilot approach, phased approach, or complete shift), what to do with the existing medicines, and so forth. The introduction modality used in Ethiopia was to shift completely all at once. Once the drugs were procured and available, they were distributed to all health facilities. All children already on treatment continued with previous stock and shifted to new formulations based on the available of that stock. All new cases shifted to using the new formulations. CTB supported the NTP in all steps required for introduction.

IMPLEMENTATION

The major activities were implemented across the health system are described below (see figure 1).

Transition plan: A national transition plan was developed to prepare for and guide the implementation for a smooth transition to the new formulations. The plan explained the modality of the transition and how to prevent stock-out at health-facility levels and forecasted the resource requirements for the program.

National policy guidance: As the initial step to meet the minimum requirements set by the WHO/Global Drug Facility (GDF) for introducing new formulations of medicines, the NTP endorsed the shift and incorporated

the necessary guidance in the sixth edition of the national tuberculosis, leprosy, and HIV (TBL/HIV) guidelines and training curriculum.

Registration and regulation: The NTP asked for permission to waive product clearance while the registration process is underway.

Situational and feasibility analysis: The NTP, in collaboration with partners, conducted a feasibility analysis of the transition, taking into consideration the minimum country-level requirements, the current national stock level of existing pediatric formulations, morbidity data, and the enrollment plan of children with TB. It also considers different national and subnational systems and structures that could affect the shift.

National dialogue with stakeholders: The NTP held national-level dialogues with national technical working groups, regional health bureaus, and developmental partners on introducing these new improved formulations.

Capacity building at different levels of the health system: NTP organized a national event to disseminate information and build capacity at the lower management and patient-care levels and to exercise a regional implementation plan for the transition process.

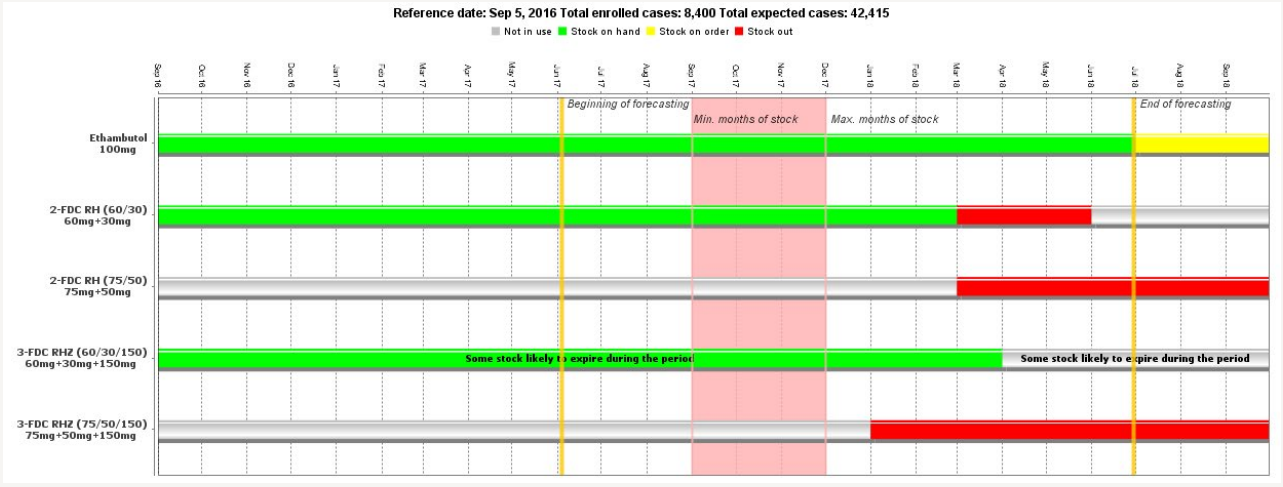
Provider toolkits: Posters, desk references, patient leaflets, and other job aids and information, education, and communication materials were developed to assist the transition process.

Quantification, forecasting, and supply plan: Quantification of the new pediatric TB formation was conducted using recent logistics and morbidity data considering lead time and minimum and maximum stocks as inputs. The quantification was done using the QuanTB tool and the result showed that the existing stock would last until March 2018. Figure 2 shows how long the existing medicines (RH 60/30 and RHZ 60/30/150 in green) will last and when new ones (RH 75/50 and RHZ 75/50/150 in red) will be introduced to maximize resources and benefits to children.

Monitor the transition: The introduction of new pediatric TB drug formulations was aligned with the Ethiopian Pharmaceutical Supplies Agency (EPSA), which is responsible for procurement and distribution through subregional hubs to health facilities. Pharmacy professionals at health facilities provided stock updates to higher levels on a monthly basis using a drug reporting and requisition form. Subregional hubs updated the status of drugs to the EPSA on monthly basis to follow the stock and make procurement and shipment decisions. On the basis of stock monitoring reports, actions were taken to maintain adequate stock in both the subregional hubs and the national level.

Based on the above considerations and the trade-off between minimizing wastage and respecting patient-centered care, the NTP decided to initiate treatment with new formulations as of December 2017 all at once. All patients on treatment shifted to the new formulation, and all new patients would start treatment with the new formulation once available at the facility level.

FIGURE 2. Dashboard of the quantification result from QuanTB



RESULTS AND ACHIEVEMENTS

By February 2018, all children shifted to the new formulation successfully and no supply interruptions (stock-outs) were reported during the transition at facility level. No wastage of previously available pediatric medications was reported.

Secure grant and place drug order: Quantities of the new medicines were procured through the quantification process, and the necessary funding for the new formulations was secured from the Global Fund's new funding model allocated for year 3; PFSA made the first procurement through GDF. The procurement order for the new pediatric TB formulations was placed in February 2017 and was delivered as expected in September 2017.

Distribution plan to health facilities shift to the new formulations: The medicines were distributed in December 2017 and distribution to the hubs started in January 2018. By February 2018, all hubs had finished distributing the medicines to all health facilities.

Shift to new formulations at health facilities: The shift to the new medicines started in January 2017 at health facilities. By March 2018, the treatment of existing and new pediatric TB cases at all facilities shifted to the new formulation, and no significant problems occurred during the shift, thanks to the meticulously designed transition plan and collaboration of stakeholders and partners.

Table 1 shows the formulations' properties that are used to manage stock at different levels.

TABLE 1. Product description of the new formulations

PRODUCTS	▪ RHZ 75/50/150 (2-month IP—intensive phase) ▪ RH 75/50 (4-month CP—continuation phase)
FORMULATION	▪ Tablets come in fruit flavors. ▪ Tablets are dispersible in 10 seconds when mixed in 50 ml water. ▪ Once reconstituted, dispersion should be taken within 10 minutes.
ADMINISTRATION	▪ Transition to new products can occur at any time during the treatment course. ▪ FDCs should be dissolved in 50 ml water, and child should take the entire 50 ml on an empty stomach within 10 minutes of dissolution.
SAFETY PROFILE	▪ Products are not new drugs, but are new formulations of existing first-line drugs and have a comparable safety profile to FDCs currently on the market.
PACKAGING	▪ Similar to current FDCs but different color coding on package and foil for both FDCs ▪ Aluminum foil blister pack; 28 tabs per blister × 3 blisters per pack ▪ Total of 84 tabs per box
SHELF LIFE/STORAGE	▪ Shelf life of 2 years ▪ Cold chain not required.
COST	▪ RHZ 75/50/150—USD 2.95/pack ▪ RH 75/50—USD 2.41/pack ▪ Average price of USD 15.54 for a full 6-month treatment

LESSONS LEARNED

Global guidance in shifting or transitioning treatment regimens whenever better options are available is important for successful disease prevention and control. Successful transitioning requires effective preparation, which includes prior planning for the transition in close collaboration with stakeholders. Collaboration maximizes partnership and facilitates shared responsibilities to support prior preparation at different administrative levels, resulting in a smooth transition without compromising patient care and preventing stock-outs and wastage.

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What is QuanTB?

QuanTB is a downloadable forecasting, quantification, and early warning tool for TB medicines that is designed to improve procurement processes, ordering, and planning for TB treatments. It allows forecasting of needs for any type of TB treatment regimen or combination of medicines for any period of time.

Access QuanTB: Download as desktop application for PC and Mac: http://siapsprogram.org/tools-and-guidance/quantb/

Use QuanTB: Self-paced course for health professionals on how to use QuanTB: https://leadernet.org/groups/courses/quantb/

WAY FORWARD

The transition to new pediatric formulations for children in Ethiopia was successful at preventing interruption of medicines and wastage. The lessons gained through this process may be applied to other drug introduction efforts in Ethiopia such as shifting of second-line drugs for drug-resistant TB treatment. Efforts such as the experience detailed can be sustained through continuous monitoring of drugs and supplies under the umbrella of the larger national drugs and supplies management system.

References

1 World Health Organization (2010). Rapid advice: treatment of tuberculosis in children. Available at: https://www.who.int/tb/publications/tb-children-rapidadvice/en/

2 District Health Information System available at: https://district-health-information-system.soft112.com/

3 WHO, Guidance for national tuberculosis programmes on the management of tuberculosis in children, second edition.

4 Access QuanTB: Download as desktop application for PC and Mac: http://siapsprogram.org/tools-and-guidance/quantb/

5 Use QuanTB: Self-paced course for health professionals on how to use QuanTB: https://leadernet.org/groups/courses/quantb/

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