

The procurement landscape of pediatric tuberculosis treatment: a Global Drug Facility perspective

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SUMMARY

Simple, quality-assured, child-friendly formulations of existing first-line anti-tuberculosis (TB) drugs in the correct dosages are now becoming available. Efforts are currently underway by the TB Alliance, the World Health Organization (WHO), and its partners to make appropriate medicines available to treat children diagnosed with TB. The functioning of the current market and the distribution pathways in pediatric TB drugs now require characterization and understanding in order to develop appropriate strategies for delivery of these and other future pediatric TB medicines. The Stop TB Partnership's Global Drug Facility (GDF) plays a major role in supplying pediatric TB medications worldwide.

GDF is considered to be the largest procurer of pediatric TB treatment and the largest supplier to national TB programs of quality pediatric drugs. Between 2007 and 2013, the GDF delivered more than 580 000 treatments to children in over 50 countries, 14 of which are among the 22 high TB burden countries. We analyzed this data set in the context of WHO estimates of pediatric TB as well as other available information to assess the functioning of the current market, lessons learnt from the GDF experience in the market, and opportunities for future products.

KEY WORDS: market; procurement; supply chain; Global Drug Facility

CHILDHOOD TUBERCULOSIS (TB) is a significant public health problem, and ensuring that all children with TB have access to effective medication has become a global priority.¹ Although at least 530 000 children develop TB and more than 80 000 die due to the disease every year (excluding those co-infected with human immunodeficiency virus/acquired immune-deficiency syndrome), child TB has been a neglected area for a long time.² Historically, the process of developing and adopting new global health products has been long, leading to slow or sporadic uptake by countries. The pediatric TB market is no exception. For many years, there were no appropriate pediatric TB treatment regimens, and this neglect helped fuel a dysfunctional and uncertain landscape in the pediatric TB market.³

Child-friendly, correctly dosed, quality-assured products for children with TB are now coming onto the market through efforts spearheaded by TB Alliance and the World Health Organization (WHO), along with other partners; the initiative is funded primarily by UNITAID. There is a need to shape the pediatric TB market to sustain the commitment by manufacturers to produce quality drugs at affordable prices and remove the shadow of neglect of child TB. To obtain optimal availability

and access to affordable, high-quality, adequately dosed and child-friendly formulated anti-tuberculosis treatment, procurement channels in countries affected by TB need to be well understood and aligned with the supply chain, and barriers must be identified and addressed.

One of the key players in facilitating access to anti-tuberculosis treatment is the Stop TB Partnership's Global Drug Facility (GDF) (www.stoptb.org/gdf/). The GDF was founded in 2001 and serves as a global distributor of anti-tuberculosis drugs, including those for children. GDF makes TB products available at reduced cost or for free to countries that cannot afford to purchase them.⁴ GDF has delivered treatments to 133 countries. Because of its global reach, GDF can serve as a consolidator of drug orders to enable countries to acquire small volumes of medicines against competitive wholesale prices. From 2007 to 2014, UNITAID funded the GDF with over US\$10 million to be used to supply high TB burden countries (HBCs), which together account for the majority of childhood TB cases worldwide; pediatric TB drugs were supplied free of charge. Countries were eligible for the grant based on per capita gross national income, among other factors; this allowed

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Table 1 Previous and updated dosing recommendations for pediatric TB treatment

Medication	Previous recommendation mg/kg/day	Current recommendation mg/kg/day
RMP	8–12	10–20
INH	4–6	7–15*
PZA	20–30	30–40*
EMB	15–20	15–25*

* In 2010, the World Health Organization revised its recommendations of the dosing for first-line drugs for TB. In 2014, the recommended dose range for INH was further adjusted to 7–15 mg (from 10–15 mg in 2010), and the maximum doses for PZA and EMB were removed.

TB = tuberculosis; RMP = rifampin; INH = isoniazid; PZA = pyrazinamide; EMB = ethambutol.

17 of the 22 highest TB burden countries to participate.

To understand the procurement landscape more fully, an analysis of past and recent distribution (and presumably administration) of pediatric drugs through the GDF was undertaken. We compared these numbers with the estimated number of children with TB in these countries, as retrieved from the annual WHO global TB control reports. Through interviews with experts in the field and other sources, we also attempted to gain an understanding of how drugs were procured for HBCs that did not receive grant funds. While the picture is still incomplete, our examination of the data provides some initial insights into the pediatric TB market and the manner in which HBCs are currently treating TB in children.

CHANGING SUPPLY IN A CHANGING REGULATORY LANDSCAPE

The WHO revised its treatment guidelines for child TB in 2010,⁵ to increase its recommended dosing for first-line drugs (isoniazid, rifampin, pyrazinamide, and ethambutol); further amendments were made in 2014 (Table 1). As the child-friendly anti-tuberculosis drugs on the market at the time were no longer of the correct strength, practitioners used various ad hoc solutions to administer the recommended doses using a mixture of adult and pediatric fixed-dose combinations (FDCs) and single-dose products which required crushing, dissolving or cutting to achieve the recommended dose. To assist with the implementation of the revised policy guidelines, the WHO outlined the procurement methods for treatments that met recommendations in its 2010 Rapid Advice.⁵ Along with the issuance of the new dosing recommendations, the WHO provided instructions on how to use available products to obtain the correct dosages in children.

The WHO recommends that children be treated with quality-assured dispersible FDCs that have been WHO-prequalified or authorized for use by stringent regulatory authorities, or the WHO Expert Review Panel;⁶ however, quality-assured childhood TB FDCs in the correct dosages are only now becoming

available. Since 2011, the GDF has offered two alternative quality-assured options for countries ordering pediatric treatments: 1) a regimen based on the previous lower dosing, for which dispersible FDCs are available; and 2) a regimen based on the 2010 policy recommendations, for which a mixture of FDCs and single-dose products may be combined.

The dynamics of the pediatric anti-tuberculosis treatment market during the period studied offer important lessons in the introduction of future TB products. Throughout 2007–2012, Macleods, Lupin and Sandoz were the only suppliers of WHO-prequalified dispersible FDCs for children, albeit in formulations aligned with the previous lower dosing recommendations. Macleods supplied their products throughout the reporting period, but Sandoz entered and exited as a GDF supplier in 2008, and Lupin started supplying GDF with pediatric FDCs in 2011. At one point there was only a single supplier, and this led to a doubling in the price of pediatric treatments. The manufacturers entered and exited as suppliers for various reasons, including limited demand (Sandoz) and delays in obtaining certain approvals due to the shift in treatment guidelines during the period (Lupin). Much of the instability around the supply of these products was due to slow uptake by countries and policy changes. This example illustrates the need to generate early demand for new products and maintain a balance in available suppliers—too few suppliers gives rise to monopolies that jeopardize treatment at affordable, competitive prices, whereas too many suppliers may lead to fractured demand that threatens sustainable drug production.

SUPPLY: PEDIATRIC ANTI-TUBERCULOSIS TREATMENT IN 2007–2013

Data on volumes of pediatric TB drugs provided by the GDF offer insight into how demand is met. Our present analysis is centered on the 22 HBCs, which account for approximately 75% of childhood TB case notifications (Figure 1).

Country-specific product procurement data can be used to gauge medication use among patients in these countries and to compare with the overall need for treatments, as judged by the estimated number of pediatric TB cases. GDF product supply data were collected from reports from 2007 to 2013, and covered curative pediatric anti-tuberculosis treatment. The resulting numbers are listed by country and year in Table 2.

From 2007 to 2013, of the 17 HBCs eligible for UNITAID grants for pediatric TB treatment, 14 (64%) received pediatric treatments at least once from the GDF; however, there were no clear patterns in orders. Only 11 HBCs may be considered regular GDF purchasers: Afghanistan, Bangladesh, Cambodia, Pakistan, the Democratic Republic of the Congo

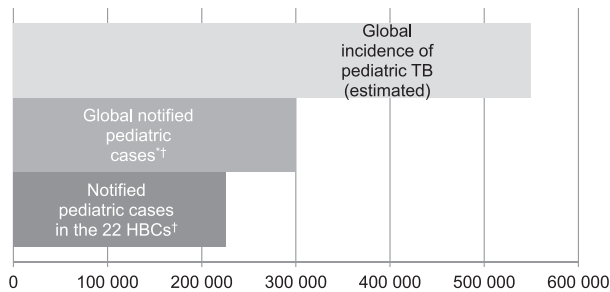


Figure 1 Pediatric TB notifications in 2013.² *Including estimates for countries not reporting age-disaggregated data. [†]New case notifications; relapse case notifications from about half of the HBCs also included. TB = tuberculosis; HBC = high-burden country.

(DRC), Kenya, Mozambique, Myanmar, Nigeria, Tanzania, and Uganda.

During the 2007–2013 period, approximately 60% of pediatric treatments supplied by the GDF were paid for using the UNITAID grant awarded to GDF. The number of procurements allowed under the grant was limited; countries that benefited from this program were expected to graduate to other funding sources at the end of the grant period and continue to procure through quality-assured channels such as the GDF. By 2013, of the 11 countries actively procuring via the GDF (i.e., had an order in the last 3 years), one received its first order with UNITAID funds (DRC), one (Nigeria) continued on the UNITAID grant, five (Pakistan, Tanzania, Bangladesh, Ethiopia, and Cambodia) had some UNITAID funding for procurement, and five (Kenya, Myanmar, Afghanistan, Mozambique, and Uganda) transitioned fully to other funding sources and purchased via the GDF. Among countries that received orders funded through the UNITAID grant, the grant paid for two to three

procurements on average. Cambodia had the most shipments paid for by the grant.⁵ Of the 55 orders placed by HBCs, 35 were paid for by UNITAID.

MARKET ALIGNMENT: SUPPLY VS. DEMAND

Based on 2013 WHO notification data, the 17 HBCs in our analysis contributed 40% of the total estimated case notifications (275 876) for children (age 0–14 years). The countries supplied by the GDF during this year contributed 20% of the total estimated child case notifications, or presumably less than a quarter of the total treatment market. These numbers represent cases that were reported to the NTPs in these countries and do not take into account children treated for TB outside the NTP.

To smooth out discrepancies caused by the year-to-year timing of orders (carry-over effects), we analyzed the combined supply of pediatric treatments and TB notifications over several years (2007–2013). HBCs eligible for GDF grants were included even if they did not procure or ceased procurement from the GDF during this period. Country-by-country numbers for pediatric treatments are compared with pediatric TB notifications in Figure 2. Interestingly, discrepancies go both ways, with an apparent excess in either the number of treatments or notifications. Mismatches between the number of treatments delivered and the number of cases reported are especially apparent in Cambodia, Nigeria, and Myanmar.

Factors that may increase or reduce GDF's estimated share of the pediatric TB drug market through the public sector are: 1) the accuracy of the number of cases used in procurement planning by NTPs, 2) the stockpiling or stock-out of treatments from previous years' deliveries, 3) orders being filled across multiple years, and 4) underreporting of cases in the public sector.

Table 2 Pediatric TB treatments supplied by the GDF to 17 high TB burden countries, 2007–2013

Country	2007	2008	2009	2010	2011	2012	2013
Afghanistan	3 721		6 860		3 162	2 845	Ordered
Bangladesh		8 421	3 146	7 375		8 273	4 799
Cambodia	2 160	2 871	6 761	5 893	3 912	7 696	Ordered
Democratic Republic of Congo							Ordered
Ethiopia*			15 614		9 898	Ordered	
Indonesia*	12 000						
Kenya			5 976		14 424	10 718	9 718
Mozambique			4 092		2 548	5 318	Ordered
Myanmar		29 218	34 272	34 624		16 846	Ordered
Nigeria			7 413	7 792	6 727	6 166	9 472
Pakistan	26 323		18 052	22 361	65	31 174	2 714
Philippines*							
United Republic of Tanzania			4 200	7 923		4 926	Ordered
Thailand*			3 606				
Uganda						9 465	Ordered
Viet Nam*							
Zimbabwe*							

* Countries that did not procure from GDF. Source: GDF database provided to TB Alliance. TB = tuberculosis; GDF = Global Drug Facility.

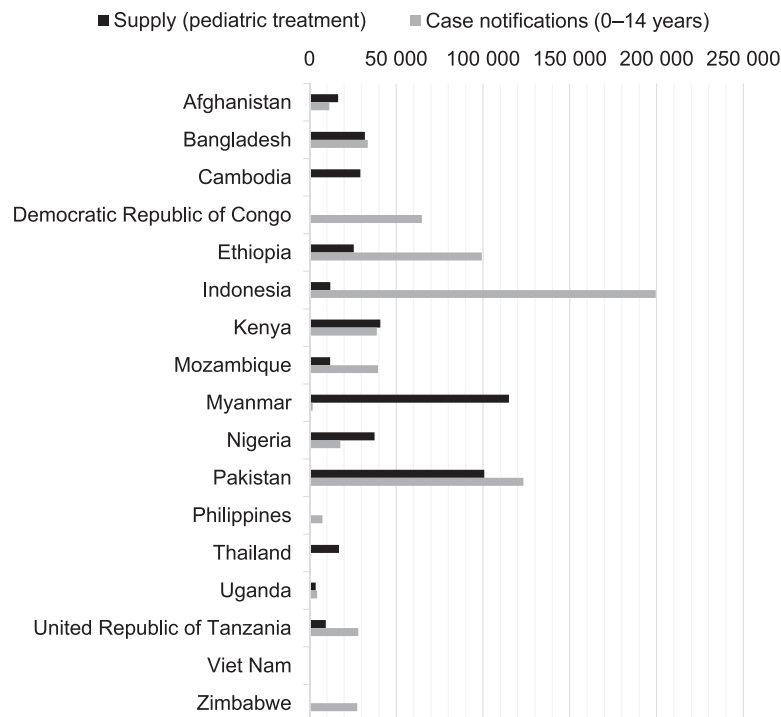


Figure 2 Cumulative pediatric TB treatments delivered (black bars) and new cases notified (grey bars) in 17 HBCs over 2007–2013. (Sources: 2014 WHO Tuberculosis Case Notifications database and GDF data set provided to the TB Alliance.) Note: WHO notification variables changed between 2012 and 2013. Notifications prior to 2013 were a sum of smear-positive, smear-negative and extra-pulmonary TB cases. Notifications since 2013 are categorized as ‘new and relapse cases’, where relapse cases from about half of the HBCs are included. TB = tuberculosis; HBC = high TB burden country; WHO = World Health Organization; GDF = Global Drug Facility.

SUPPLY FROM SOURCES OUTSIDE THE GLOBAL DRUG FACILITY

As the GDF does not presently supply many of the highest TB burden countries, such as China, India, South Africa, and Indonesia, the majority of the pediatric TB market is being supplied by sources outside the GDF, or is not procuring pediatric treatment at all. Furthermore, it is unknown whether the treatment supplied by other sources is quality-assured; it should be noted that GDF product quality is assured through its comprehensive quality assurance policy.

To elucidate the procurement practices in countries with no history of GDF procurement or for countries with no recent orders for pediatric treatments, we interviewed regional officers employed by the GDF and other professionals with extensive experience in treatment/procurement practices in the countries of interest. In the case of Brazil and China (M Grzemska, WHO, personal communication), Thailand, and Viet Nam (D Ngo, Clinton Health Access Initiative, personal communication), NTPs reportedly used ‘adult’ drugs to treat children, while India used national dosing guidelines for children that differed from the current WHO guidelines⁷ (Table 3). Countries that procured pediatric drugs locally were India, Indonesia (since 2007), the Russian Federation,

Philippines, and South Africa (GDF Regional Officers, personal communication). There is limited information available for Ethiopia and Zimbabwe.

DISCUSSION AND CONCLUSIONS

The current market for pediatric drugs is fragmented due to various factors, including 1) changes in treatment policies, 2) the length of time required to adopt policies, 3) lack of adequately dosed pediatric treatment regimens, and 4) uncoordinated procurement with uncertain volumes and multiple procurement channels. For the market to be shaped in a way that results in more children being treated and to sustain manufacture engagement in producing quality drugs, procurement practices in countries affected by TB must be well understood and obstacles identified and overcome.

On the basis of the GDF experience and the funding made available by UNITAID, we believe that offering pediatric products free of charge does not on its own result in countries signing on to procure these drugs for child patients. Although the overall volume of pediatric treatment increased by 70-fold from 2007 to 2012, the UNITAID/GDF project required 5 years to gain the participation of even 70% of the eligible 17 HBCs, and only 12 of these still procure pediatric

Table 3 Procurement policies of the 22 high tuberculosis burden countries

Country	Procurement practice for pediatric anti-tuberculosis treatment
Afghanistan	Currently procures pediatric treatment from the GDF
Bangladesh	Currently procures pediatric treatment from the GDF
Brazil	None; reportedly uses adult-formulated drugs only
Cambodia	Currently procures pediatric treatment from the GDF
China	None; reportedly uses adult-formulated drugs only
Democratic Republic of Congo	Currently procures pediatric treatment from the GDF
Ethiopia	Unknown; has not procured from the GDF since 2012
India	Local procurement; national dosing guidelines differ from 2010 WHO dosing guidelines; uses thrice-weekly intermittent dosing for pediatric treatment
Indonesia	After 2007, local procurement; local manufacturers produce pediatric formulations that meet 2010 WHO dosing guidelines
Kenya	Currently procures pediatric treatment from the GDF
Mozambique	Currently procures pediatric treatment from the GDF
Myanmar	Currently procures pediatric treatment from the GDF
Nigeria	Currently procures pediatric treatment from the GDF
Pakistan	Currently procures pediatric treatment from the GDF
The Philippines	Local procurement and foreign sourced procurement; manufacturing source unknown
Russian Federation	Local procurement; unknown if adult- or pediatric-formulated drugs are available to treat children
South Africa	Local procurement and bidding process; negotiates directly with manufacturers
Tanzania	Currently procures pediatric treatment from the GDF
Thailand	Received a 1-year UNITAID grant from GDF in 2009, but due to wastage problems, the grant was discontinued; uses adult-formulated drugs; in some cases, institutional pharmacies create child-friendly solutions from these drugs
Uganda	Currently procures pediatric treatment from the GDF
Viet Nam	Received GDF grant in 2013 but has yet to procure from the GDF
Zimbabwe	Unknown

WHO = World Health Organization; GDF = Global Drug Facility.

treatment from the GDF. While part of this delay was caused by the need for countries to initiate new pediatric programs, it is apparent that for many countries the purchasing price is only one of the factors that affect procurement decisions.

In addition, reporting and procurement forecasting systems in some countries are not linked. By comparing GDF procurement with case notifications to the WHO, we find clear discrepancies (Figure 2). In some cases, there is close agreement between supply and the number of cases notified (Pakistan, Kenya, Bangladesh); however, other countries report receiving supplies significantly in excess of notified cases, suggesting a severe underestimation of the latter. Obtaining more reliable estimates of the number of children presently accessing treatment for TB is important to enable care givers and governments to procure enough drugs to meet the needs of the patients and avoid wastage. This approach will contribute to sustained product demand, the other half of the equation in a healthy market. It will be important to monitor over the next year or two whether countries that currently procure pediatric drugs through the GDF continue this practice using other sources of funding (external or government), and if other countries begin to procure pediatric treatments through the GDF.

The GDF data presented shed light on the distribution and supply chain for pediatric TB products, which involves less than a fourth of the

treatments needed for pediatric TB in HBCs, and only to the NTPs (i.e., the public sector), in these countries. The next step to filling in the gaps in information on procurement practices in pediatric TB treatment in HBCs, especially those HBCs that do not procure from the GDF, will be to catalogue other buyers, where buyers obtain supplies and for which formulations, and predicted and procured volumes, and identify the basis and criteria for selecting products and suppliers. Ultimately, the completion of the procurement landscape will result in better coordination and forecasting of supply and demand, especially through central procurement mechanisms such as the GDF, in the best interests of both patients and manufacturers.

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RESUME

Des formulations simples, de qualité garantie des médicaments antituberculeux de première ligne, adaptées aux enfants en doses correctes, deviennent maintenant disponibles. Des efforts sont actuellement en cours sous l'égide de TB Alliance, de l'Organisation Mondiale de la Santé (OMS) et de ses partenaires pour rendre ces traitements appropriés disponibles aux enfants chez qui a été identifiée une tuberculose (TB). Le fonctionnement actuel du marché et la distribution des médicaments pédiatriques de la TB requièrent maintenant une caractérisation et une meilleure compréhension afin de développer des stratégies appropriées de distribution de ces médicaments et d'autres médicaments pédiatriques de la TB qui pourraient être disponibles à l'avenir. Le Dispositif Mondial pour l'Approvisionnement en médicaments

(GDF) du partenariat Halte à la TB joue un rôle majeur dans la fourniture de médicaments pédiatriques de la TB dans le monde. Le GDF est considéré comme le plus grand fournisseur de médicaments TB pédiatriques et le premier fournisseur des programmes nationaux TB en médicaments pédiatriques de bonne qualité. Entre 2007 et 2013, le GDF a fourni plus de 580 000 traitements aux enfants dans plus de 50 pays, dont 14 sont parmi les plus touchés par la TB. Nous avons analysé cet ensemble de données dans le contexte des estimations de l'OMS relatives à la TB pédiatrique ainsi que d'autres informations disponibles pour offrir une ébauche d'évaluation du fonctionnement actuel du marché, des leçons apprises grâce à l'expérience de GDF sur ce marché et des opportunités de produits à l'avenir.

RESUMEN

Los medicamentos antituberculosos de primera línea se encuentran ahora disponibles en formulaciones sencillas con garantía de la calidad, en dosis correctas adaptadas a la administración pediátrica. Algunas iniciativas en curso por parte de la Alianza Mundial para el Desarrollo de Medicamentos contra la Tuberculosis, la Organización Mundial de la Salud (OMS) y sus asociados están encaminadas a la obtención de medicamentos apropiados al tratamiento de los niños con diagnóstico de tuberculosis (TB). Es preciso describir y comprender el funcionamiento del mercado y los mecanismos vigentes de distribución de los medicamentos antituberculosos pediátricos, con el fin de elaborar estrategias apropiadas de suministro de los medicamentos existentes y los medicamentos futuros. El Servicio Farmacéutico Mundial (GDF) de la Alianza Alto a la Tuberculosis cumple una función primordial al

proveer medicamentos antituberculosos destinados a los niños en todo el mundo y se considera como el mayor comprador de estos tratamientos y el principal proveedor de medicamentos pediátricos de buena calidad a los programas nacionales contra la tuberculosis. Del 2007 al 2013, el Servicio Farmacéutico Mundial suministró más de 580 000 tratamientos a los niños en más de 50 países y entre ellos, en 14 de los países con mayor carga de morbilidad. Se analizó este conjunto de datos en el contexto de las estimaciones de la OMS sobre la TB en pediatría y otras informaciones existentes, con el propósito de evaluar el funcionamiento del mercado actual, las enseñanzas extraídas de la experiencia del GDF en el mercado y las oportunidades que existen para futuros productos farmacéuticos.
