New Pathways for Childhood TB Treatment

Lessons from the STEP-TB Project

TB ALLIANCE

Unitaid
Innovation in Global Health

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Project Partners

Imperial College London, Janssen, Lupin Limited, Macleods Pharmaceuticals Limited, Management Sciences for Health (MSH), RTI International, U.S. Fund for UNICEF, UNICEF, University of Sheffield, University of Stellenbosch Desmond Tutu TB Centre, USAID, and Yale University.

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Louder than TB Coalition
www.louderthantb.org/our-coalition.html

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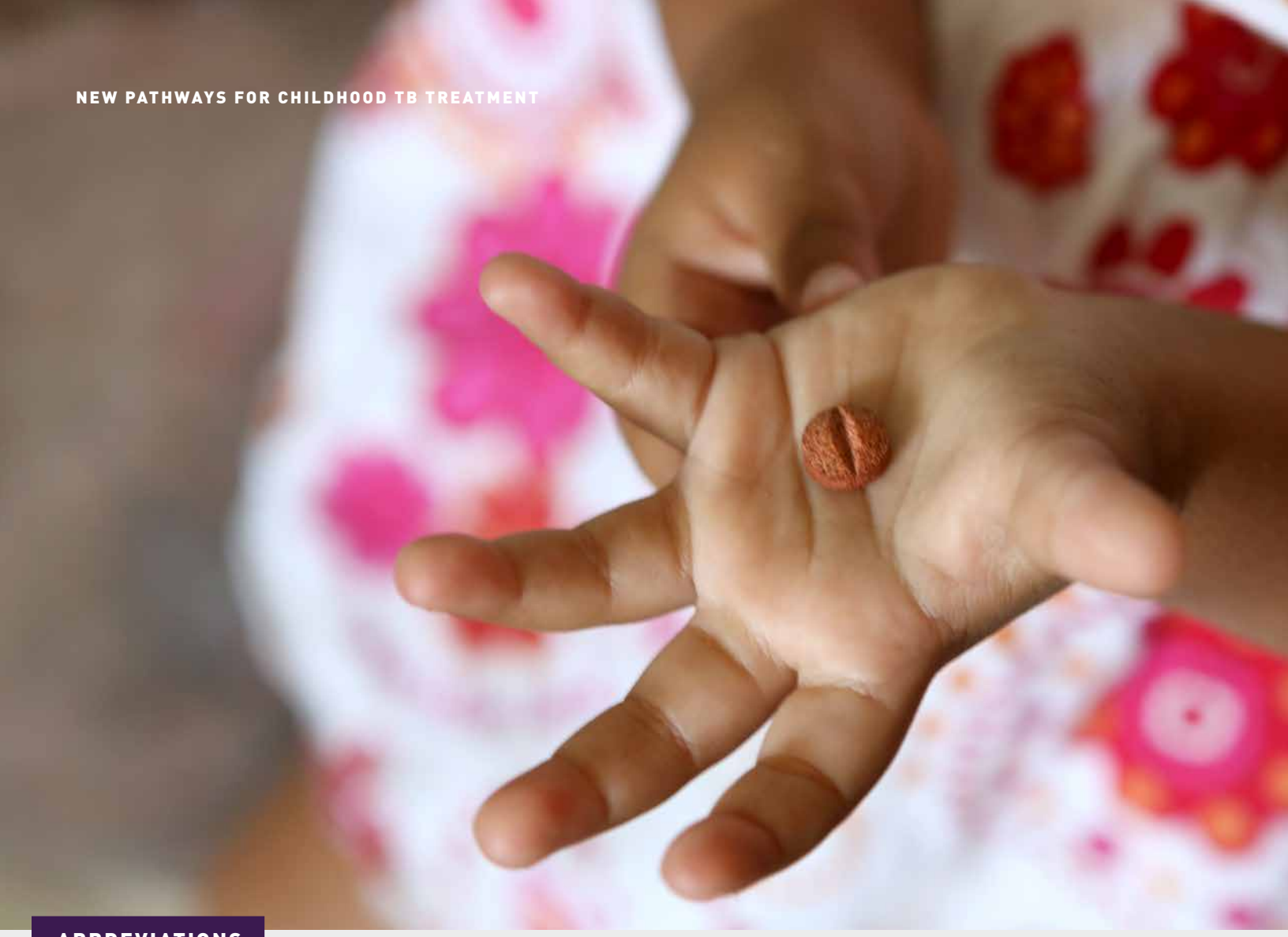

ABBREVIATIONS

BE Studies—Bioequivalence Studies
DND*i*—Drugs for Neglected Diseases *initiative*
EML—Essential Medicines List
EMB—Ethambutol
FDC—Fixed Dose Combination
GDF—Stop TB Partnership's Global Drug Facility
HBC—High Burden Country
HIV—Human Immunodeficiency Virus
ICH—International Conference for Harmonization
INH—Isoniazid
KNCV—KNCV Tuberculosis Foundation
MAP-IT—Model for Assessment of Pediatric Interventions for Tuberculosis
MCH—Maternal and Child Health
MDR-TB—Multidrug Resistant Tuberculosis
MSF—Médecins Sans Frontières
MSH—Management Sciences for Health
NTP—National TB Program
PDP—Product Development Partnership
pK—Pharmacokinetic
PSI—Population Services International
PZA—Pyrazinamide
RIF—Rifampicin
SIAPS—Systems for Improved Access to Pharmaceuticals and Services Program
STEP-TB—Speeding Treatments to End Pediatric TB Project
TAG—Treatment Action Group
TB—Tuberculosis
Global Fund—The Global Fund to Fight AIDS, Tuberculosis and Malaria
The Union—The International Union Against Tuberculosis and Lung Disease
UNICEF—United Nations Children's Fund
USAID—United States Agency for International Development
WHO PQ—World Health Organization Prequalification
WHO—World Health Organization
XDR-TB—Extensively Drug-resistant Tuberculosis

Foreword 1

Tuberculosis (TB) kills around 210,000 children a year, making it one of the top 10 causes of pediatric deaths. But until recently, national pediatric TB programs relied on outdated, imprecise diagnosis and treatment methods that failed many patients, and had no chance of subduing the epidemic. Bitter-tasting pills for adults were the only drugs available for children. Clinicians and caregivers would break them in pieces and guess at the correct dosage for their adolescent patients.

Although the World Health Organization (WHO) revised its dosing guidelines for pediatric TB in 2010, practical barriers kept the most affected countries from following them. Countries and drug manufacturers needed help to gauge the number of children with TB and estimate the disease burden—a step integral to persuading donors, governments, and other key players to get involved.

In 2013, Unitaid in partnership with TB Alliance, the WHO Global TB Programme, and Department of Essential Medicines and Health Products, launched the STEP-TB project to overcome those obstacles.

STEP-TB gave drug manufacturers an incentive to develop properly dosed and affordable pediatric medicines, and cleared a path between those medicines and the patients whose survival depends on them.

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TB Alliance and partners delivered their results ahead of schedule, having pooled their expertise on clinical development, registration, market research, and product launch. WHO's global reputation and technical know-how proved vital to the project, connecting STEP-TB with global experts, countries, opinion leaders, and other stakeholders.

Without STEP-TB, the pediatric TB treatment landscape would have remained fragmented and stagnant. Few companies, if any, would have been willing to invest, innovate, and enter this critical market.

By early 2017, more than 50 countries had ordered treatments, and the numbers are rising. But the fight against childhood TB is far from over. We need to do a better job of identifying and diagnosing children with TB. Unitaid is committed to sustaining the gains made during STEP-TB, as well as supporting innovative new projects to reach and cure more children. Working with partners, we are determined to reach our global target of a world without TB.

Lelio Marmora
Executive Director, Unitaid

2 Executive Summary

Each day, nearly 600 children die of TB, the world's deadliest infectious disease. Of the 1 million children who are estimated to develop active TB each year, approximately 64% are either missed by doctors or incorrectly diagnosed. Those who are diagnosed have relied on six months of foul-tasting, improperly formulated medicines to fight the disease—until now.

In 2013, the Speeding Treatments to End Pediatric Tuberculosis (STEP-TB) project, led by TB Alliance, marshalled partners around the world in response to this dire situation, engaging with the pharmaceutical industry to develop better medicines for children with TB. In the span of one year of availability, these new medicines have begun to reach children around the world, setting a precedent for future action in the fight against TB. This paper documents the key tactics that allowed for the medicines' rapid and successful introduction, providing lessons for the release of innovative health products in the future.

BY THE NUMBERS

Market research and modelling made the case for private sector investment.

1 million
new cases of active TB in children annually

210,000 deaths
from childhood TB each year

53 million
latently infected cases

2.1 The Situation

TB is a leading cause of illness and death among children, especially in low- and middle-income countries. Despite this, children with TB have long remained a low priority for stakeholders in both the TB and global health areas. In recent years, this neglect was evidenced by a lack of market action in response to a global policy change by the World Health Organization (WHO), which called for anti-TB medicines in higher doses to effectively treat children with TB.

2.2 STEP-TB

In 2013, Unitaid responded to this urgent need with a major investment to establish the STEP-TB project, led by TB Alliance with WHO. STEP-TB sought to make significant progress in the health of the market for childhood TB medicines.

One of the critical rate determining steps achieved by the project was the engagement with pharmaceutical companies to develop the required medicines and co-invest in ensuring global availability, leading to regulatory filings across TB endemic countries, including South Africa and India.

STEP-TB facilitated early availability and uptake of child-friendly formulations through the Stop TB Partnership's Global Drug Facility (GDF). The new medicines were designed to be dissolvable in water, palatable to children, and in the right doses. At an average price of US$15.54 for a full, six-month course of treatment, affordability was key to ensuring widespread access for those who needed it most.

To support these efforts, market research and modelling work conducted by STEP-TB improved the understanding of the global burden. These findings, which for the first time accounted for children coinfected with HIV, reduced the potential business risk for pharmaceutical companies. Improved market intelligence, along with in-country research on procurement processes and regulatory pathways, also helped technical partners work with countries to plan effectively for procurement.

Collaboration with a wide range of partners was essential. STEP-TB worked closely with national TB programs, including WHO, MSH, the Global Fund, USAID, and GDF among others, leading to the effective implementation of policy changes, product transition planning, registration strategies, and rapid uptake.

2.3 Impact

The project made significant headway in revitalizing the pediatric market. New products were made widely available at an affordable price, and children around the world began to take better TB medicines in the right doses. Ultimately, these medicines can improve adherence and outcomes, and slow the spread of drug-resistant TB. At the time of publication, 60 countries, representing approximately two-thirds of the estimated childhood TB burden, have procured these improved medicines. Though the goal of two manufacturers entering the market was not met by the end of the project one manufacturer joined and a second is expected to enter in 2017.

The project achieved broad impact across the field of childhood TB by raising its visibility on the broader child survival agenda and leveraging partner networks, such as UNICEF, to draw global attention to this long-neglected crisis. This was supported by a range of communications efforts, including a project web portal, earned media coverage, and strong support from activists, key opinion leaders, and celebrities.

STEP-TB has reshaped the market for pediatric TB drugs by reducing barriers to entry, engaging in innovative industry collaboration to launch optimized products, and mobilizing strong demand.

2.4 Way Forward

The STEP-TB project's introduction of improved TB medicines for children marks an important first step. Stakeholders must continue the work necessary to fully implement worldwide rollout and secure long-term sustainability of the market.

The experiences and lessons learned from the STEP-TB project are well positioned to serve as a model for the future development and introduction of innovative, life-saving medicines.

STEP-TB TAKEAWAYS

- Improved estimates coupled with comprehensive market intelligence and demand building significantly reduced business risks for pharmaceutical companies; gaps remain between the estimated disease burden and number of children put on treatment.
- Active collaboration with pharmaceutical partners has been key to success; in a small market, ensuring widespread adoption to create adequate scale and avoiding fragmentation contributed to ensuring affordable pricing and sustainable supply of products.
- Country preparation and the link to financial plans and buy-in from donors was crucial. Broad stakeholder involvement at the national level drove guideline and adoption decisions.
- True global availability required a two-fold approach with both central procurement mechanisms such as the GDF and specific national-level strategies contributing to widespread adoption.

2.5 STEP-TB Milestones

Mid-2013

Making the Case

- **August 2013**
  Project initiation
- **September 2013**
  Global consultation
- **October 2016**
  Improved estimates on the impact of TB in children, WHO Global TB Report

Product Development and Availability

- **September 2013–June 2014**
  Commercial partnerships established
- **December 2015**
  FDCs available through Global Drug Facility

MODEL OF MARKET INTERVENTION & PRODUCT INTRODUCTION

- Engaging in an active collaboration with pharmaceutical partners to develop and manufacture improved products for children
- Creating a communication and collaboration network that includes all major market players including commercial companies, countries, procurers, donors, civil society, and policy makers
- Providing country technical support for each product that enters the market

2017 and Beyond

Market Preparation and Mobilizing Demand

- **March 2015**
  UNICEF partnership
- **March 2015**
  "Louder Than TB" campaign launched on World TB Day with a global audience of over 10 million people reached
- **2016**
  Over 19 countries mobilized and prepared for the FDCs

Product Launch and Rollout

- **September 2016**
  First nationwide launch, Kenya
- **September 2017**
  At the time of publication, 62 countries have ordered approximately 400,000 treatment courses

Way Forward

- **2016**
  Development of child-friendly Bedaquiline in Phase 2
- **2017**
  Unitaid scale-up pediatric grants awarded
- **September 2017**
  WHO prequalifies the rifampicin + isoniazid FDC tablet
- **2017**
  Accelerated planning for pediatric development of new regimens
- **2017**
  TB drug taste optimization project for children

- Providing guidance and technical assistance on implementation of policy and practice changes to support country uptake of the products
- Addressing treatment and procurement in sectors outside of the national TB program in certain markets
- Supporting momentum and political commitment among donors and high burden/high volume countries and ensuring transition planning and available financing for the new products at the time of launch

3 Introduction

3.1 The Problem

The WHO revised its dosing guidelines for treatment of children with TB in 2010 based on evidence indicating that children require higher doses of first-line medicines for their TB treatment to be effective.[1,2] After issuing this guidance, WHO invited expressions of interest for appropriately dosed, quality medicines in a child-friendly format. However, no pharmaceutical response was forthcoming. The ensuing lack of properly formulated TB medicines left country programs, clinicians, and caregivers to rely on varying and often imprecise treatment practices. These included splitting or crushing multiple, bitter-tasting pills in an attempt to achieve the recommended dose for children, ultimately contributing to poor treatment outcomes.[3]

There were several commodity access issues which contributed to this situation and to dysfunction in the market, including:

1. The global market estimates for TB medicines for children were missing important information, resulting in a perceived risk among pharmaceutical companies which led them to opt out.
2. The relative advantages of various options for formulating medicines (e.g., optimal flavors, taste masking, and dispersible tablets) for children were not clearly understood; this was necessary to guide pharmaceutical companies in development.
3. Lack of alignment on treatment policies and practices from country to country caused market fragmentation.
4. A delay in the availability of products needed to facilitate implementation of policy resulted when the pharmaceutical industry was nonresponsive and was concerned about investing in a small, ill-defined market.
5. Some national markets emphasized price over quality, which left the market vulnerable to a preponderance of non-quality–assured products, further fragmenting demand for quality-assured products.
6. Procurement of pediatric TB medicines was largely dependent on donor funding for the majority of countries with a high TB burden.
7. Challenging regulatory pathways for pediatric TB products disincentivized the participation of pharmaceutical companies.

Taken together, these factors brought about a reality in which children with TB were the neglected of the neglected.

In addition to market factors, several public health factors contributed to poor demand for child TB medicines. Many countries did not have sufficient information on the number of children affected by TB and did not have systems in place to identify these children. This was in part because children are rarely infectious, and consequently do not substantially contribute to the spread of the disease. Also, the lack of effective diagnostic tests for TB in children contributed to poor country reporting practices. Taken together, these factors brought about a reality in which children with TB were the neglected of the neglected—largely invisible within the TB and larger global health communities.

3.2 A Solution

A group of partners led by the WHO and members of the Stop TB Partnership's Child and Adolescent TB Working Group issued a Call to Action in 2011 at the International Childhood Tuberculosis Meeting in Sweden, calling for increased efforts to meet the needs of children with TB globally.[4] Afterward, a group of child health providers and advocates in the TB community began to draw greater attention to the significant suffering and death in children with TB, and in 2013 published the *Roadmap for Childhood TB*, which provided a complimentary action plan to be taken at both the global and national levels.[5] Despite this progress, significant challenges remained, especially around TB treatment.

▼ Pediatric treatment before the STEP-TB project compared to the new improved treatment with availability of the FDCs.

Inadequate Pediatric Treatment → **Now Available**

During this same period, Unitaid committed a substantial investment of approximately US$17 million to address the lack of appropriate first-line treatment for children and paved the way for new treatments through the STEP-TB project, launched in August 2013. The project, which received additional support from USAID and other donors, was a partnership between TB Alliance and the WHO.

The STEP-TB project set out to reshape the pediatric TB market by reducing market barriers, engaging in innovative industry collaborations to bring optimized products to market, making products available through a global mechanism like the GDF, and mobilizing demand for the products in countries for the long-term health of the market. Without Unitaid's support for the work, the pediatric TB treatment landscape would have remained fragmented and stagnant, with few if any companies willing to invest, innovate, and enter this critical market.

"The availability of correctly dosed, child-friendly TB fixed-dose combinations is a major step forward to addressing care of TB in children, an aspect which has been neglected for so long. It is the result of a very fruitful and dynamic collaboration between the TB Alliance, WHO, and other partners, including UNICEF, on the UNITAID-funded STEP-TB project."

MARIO RAVIGLIONE
Director of the Global TB Programme at WHO

3.3 Intended Impact of the STEP-TB Project

The project's primary goal was increasing access to correctly dosed, properly formulated, affordable, high-quality pediatric TB medicines. The project also intended to establish a sustainable market for these products. To achieve this, the project activities focused on the following outputs:

- Development of appropriately formulated first-line pediatric TB medicines.
- Affordable optimized first-line pediatric TB medicines made available to treat children globally.
- Market barriers that exist from the beginning of the project eliminated or greatly reduced.
- Increased commitment of countries to adopt the optimized medicines for treating pediatric TB.
- Clear pathway delineated for the introduction of new pediatric TB medicines.

The availability of child-friendly TB medicines in the correct doses represented an important initial step toward ensuring widespread access to optimal treatments and improved treatment outcomes for children. By design, the project focused on product development, policy, procurement, and regulatory pathways. It ultimately expanded to include integration and uptake activities, which paved the way for continued efforts by countries, donors, and others. Integrating the medicines into country systems and programs, training providers, and other activities will need to be sustained to ensure improved outcomes for children. The achievements to date provide an important model for innovative market introduction and rapid scale-up for similarly fragile markets.

SPOTLIGHT ON PARTNERS

Stop TB Partnership's Child and Adolescent TB Working Group

The Child and Adolescent TB Working Group strives to promote research, policy development, the formulation and implementation of guidelines, mobilization of human and financial resources, and collaboration with partners from relevant fields to achieve the goal of decreased childhood TB mortality and morbidity. Members of the group include pediatricians, National TB Programme (NTP) managers, mother and child health representatives, technical and financial partners, community TB representatives and WHO staff from headquarter, regional, and country offices. The group was instrumental in promoting research resulting from the project, and helping guide country uptake of the products through implementation of policy and practice changes. Members of the working group provided guidance and technical assistance during a number of project activities, including regional consultations and in-country provider trainings focused on facilitating country transition planning and preparing countries for introduction of the FDCs. The working group served as a unique mechanism for promoting the introduction of the new FDCs and ensuring that countries prioritize childhood TB.

Pediatric Advisory Group

TB Alliance established an international Pediatric Advisory Group at the beginning of the project, whose collective and individual engagement provided guidance and increased integration between childhood TB and the broader maternal and child health sector. Additionally, the membership in this broad-based group crossed traditional boundaries, with members from the Elizabeth Glaser Pediatric AIDS Foundation, Drugs for Neglected Diseases Initiative (DND*i*), Bill & Melinda Gates Foundation, and UNICEF. Operation ASHA, The Union, Janssen Pharmaceuticals, Population Services International (PSI), MSF Access Campaign, the patient advocacy community, and Baylor College of Medicine were valuable in shaping various strategies of the work.

"We've seen firsthand the urgent need for new childhood medicines in India and other countries. I was honored to be able to bring my passion for improving TB treatment to the Pediatric Advisory Group."

SHELLY BATRA

Co-founder and President, Operation ASHA & Pediatric Advisory Group Member

3.4 Value of Partnerships

At the core of STEP-TB was a collaboration between two organizations with complimentary roles:

- TB Alliance, the project's lead implementer, is a not-for-profit product development partnership (PDP). It was well positioned to leverage a global network of public and private partners to effectively advance TB regimen development, bringing an efficient, performance-based approach to the work, with achievable milestones and clear outputs. As well as leading the overall work, TB Alliance applied its core strengths in product development, commercialization partnerships, and market planning.
- WHO, the project's co-implementer, with 194 member states and operations in 147 countries leveraged its normative function, establishing and working with countries to implement policy and best practices. Its global reputation and technical expertise were essential for bringing global experts, countries, key opinion leaders, and other stakeholders into the work of STEP-TB.

In addition, formal and informal relationships with other entities across the work streams of the project were critical to success. These partners included the scientific and academic community, clinicians, international technical and donor agencies, the pharmaceutical and manufacturing sector, nonprofit organizations, governments, policy makers, and regulatory authorities.

▼ Figure 1 outlines each component of STEP-TB, a breakdown of the project implementers, partners and collaborators, and their respective areas of contribution.

FIGURE 1: STEP-TB PROJECT PARTNER LANDSCAPE

Partner Type			Partner Support for the New Pediatric TB Formulations											
	Product Development and Formulation	Development of Regulator/ Registration Plans	Evidence Generation	Commercial Manufacturers (Product Development/ Registration)	National Regulatory Support for Market Approval	Developing Product Phase out/Phase in	Forecasting/ Supply Planning	Securing Budget/Grants	Order Facilitation/ Validation/Import Waivers	National Essential Medicines Lists/Formularies	Policy/Guideline Changes/ Stakeholder Meetings	Advocacy/Awareness	Provider Training	Case-Finding/Treatment Linkages
TB Alliance (Lead Implementer)—overall management and coordination of work streams and contractual relationships														
	●	●	●	●	●	●	●	●	●	●	●	●	●	●
WHO GTB & EMP (Co-Implementer)														
			●	●	●	●	●	●	●	●	●	●	●	●
Project Partners														
The University of Sheffield			●											
Imperial College London			●											
Yale University			●											
Macleods	●	●		●					●					
Lupin	●	●		●					●					
Janssen	●	●		●					●					
MSH						●	●			●	●	●		
RTI			●									●		
University of Stellenbosch Desmond Tutu TB Centre			●								●			
UNICEF											●			●
Key Collaborators														
Stop TB Partnership/GDF						●	●	●	●			●		
The Global Fund								●				●		
Child and Adolescent TB Working Group									●		●	●	●	
MSF Access												●		
TAG												●		
The Union													●	●
KNCV											●		●	●
Baylor College of Medicine													●	●
NTPs in target countries					●	●	●	●	●	●	●	●	●	●
WHO country & regional offices					●	●		●		●	●	●	●	

Note: TB Alliance and WHO (Global TB Programme and Department of Essential Medicines and Health Products) worked across all the activities to support global access of the new pediatric TB formulations.

4 Making the Case

4.1 Evidence Building: Market Sizing and Understanding

Throughout the project, a series of studies were undertaken to help build the evidence base on the size, location, and drivers of the pediatric TB market. The information gathered helped create a business case for commercial, donor, and country stakeholders and mitigate concerns about market risk. The market intelligence data on these key market attributes were essential toward successful collaboration with pharmaceutical companies in developing an introduction strategy, as well as with countries on programmatic and procurement plans.

Due to challenges in confirming the presence of TB in children, as well as a lack of programmatic resources to adequately identify and screen children at risk, childhood TB cases have often gone unreported and uncounted. This reality, coupled with National Tuberculosis Programs (NTP) not disaggregating childhood TB in their reporting, resulted in a significant lack of clarity about the size of the market. Suppliers of TB treatments rely on data from health management and logistics information systems to evaluate the potential return on investment when developing products to serve a market. In this case, pharmaceutical companies were slow to invest in pediatric specific medicines, in part due to a limited understanding of the market size and demand.

Another major commercial concern was low uptake of existing products, in part due to poor adoption of updated treatment guidelines at the country level, which is a key demand-side driver. As seen in 2010 when the WHO issued guidance on optimal dosing for treatment of pediatric TB, the pharmaceutical industry was nonresponsive due to concern about investing in a small, ill-defined market, which resulted in a delay in the availability of products needed to facilitate implementation.

Beyond WHO's initial efforts in 2012 to estimate the burden of childhood TB, there were few ideas and a lack of consensus on how to best strengthen the quality of data to increase confidence around engagement with the market. In light of this, the STEP-TB project made data collection an early priority, organizing a global consultation to define and prioritize gaps and analytical methods relevant to improving the data. In September 2013, some 50 experts including donors, NTP managers, researchers, technical providers, and multilateral institutions met to discuss the market size and other commercial considerations.[6] The key outcome of the meeting was the development of a strategic market research plan (see Figure 2) that was undertaken over the course of the project.

The types of information required to form a clear picture of the pediatric TB treatment market and its dynamics included estimates of the number of children treated within national programs, the number of children treated outside of those programs, the number of children not identified or diagnosed, the number of countries who previously used pediatric TB treatments, and the historical sales volumes of pediatric products. Obtaining and drawing conclusions from these data often required novel and integrated approaches.

AIM

Build evidence base and business case for the pediatric TB medicines market to engage pharmaceutical companies, donors, and governments.

TAKEAWAY

Improved estimates of disease burden resulted in a new estimate of 1 million children with TB, more than double previous estimates. Coupled with a clear understanding of procurement processes and regulatory pathways, this significantly reduced the business risk for pharmaceutical companies.

Significant gaps remain between estimated disease burden and children placed on treatment, with 64% of children undiagnosed and untreated. More attention for this issue is required.

FIGURE 2: STRATEGIC MARKET RESEARCH PLAN

	Research Conducted	Results/Data Generated
Estimation of burden	■ Evaluation and integration of three approaches to modeling pediatric burden.	■ WHO adopted refined methodological approaches for burden estimation to inform official burden estimates. ■ Improved global and country estimates of child TB burden indicating 1,000,000 incident cases of pediatric TB annually; 210,000 deaths; and 53 million latently infected cases of TB disease (estimates include children co-infected with HIV in TB). ■ 80–85% of childhood TB is concentrated in the High Burden Countries (HBCs) and in 60–68% of the HBCs that are lower-middle and upper-middle income (e.g., India, South Africa, Philippines, etc.). **Associated Publication(s):** WHO Global TB Reports published from 2013–2016. Dodd P.J., et al. Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study. *The Lancet Global Health* 2014. Seddon J., et al. Counting children with tuberculosis: why numbers matter. *Int J of Tuberc and Lung Disease* 2015. Kunkel A., et al. Smear positivity in pediatric and adult tuberculosis: systematic review and meta-analysis. *BMC Inf Dis* 2016. Dodd P.J., et al. Global burden of drug-resistant tuberculosis in children: a mathematical modelling study. *Lancet* 2016.
Market sizing and location	■ Analysis of procurement data from GDF and available sales data from pharmaceutical companies with history of supplying pediatric TB products. ■ Inventory studies in 5 countries to assess the number of children treated outside of the national TB programs that go unreported.	■ Burden estimates are a proxy for the ideal market and treatment notifications, and sales data provide insight into the actual or current potential market for a new pediatric product. ■ The procurement analysis of GDF data showed that in 2013, about 25% of pediatric TB treatment products were supplied by the GDF based on the number of notifications of children treated globally. Therefore, most of the market was procuring through other sources. ■ Inventory studies, which were prospective in Pakistan, Vietnam, and Indonesia showed a significant level of cases are treated outside of the NTP, and not reported. **Associated Publication(s):** Scott C., et al. The procurement landscape of pediatric tuberculosis treatment: a Global Drug Facility perspective. *Int J of Tuberc and Lung Disease* 2015. Various publications pending on the result of the inventory studies.

FIGURE 2: STRATEGIC MARKET RESEARCH PLAN

	Research Conducted	Results/Data Generated
Regulatory landscape for new products	■ Landscaping of drug registration requirements across 30 TB endemic countries.	■ Data confirmed that many HBCs (e.g., India, China, South Africa, and Indonesia) have specific evidence requirements and unique regulatory pathways, requiring targeted engagement and country specific regulatory strategies. ■ Regulatory pathways ascertained in target countries fed into negotiations with pharmaceutical companies on where to register the new products. **Associated Publication(s):** Malhotra S., et al. From availability to uptake: planning for the introduction of new, child-friendly anti-tuberculosis formulations. *Int J of Tuberc and Lung Disease* 2015. Murray S., et al. Accelerating clinical drug development for children with tuberculosis. *Int J of Tuberc and Lung Disease* 2015.
Procurement practices and drivers	■ Survey of pharmaceutical companies and procurers concerns around the pediatric TB market. ■ Procurement study in 19 HBCs to understand processes, key stakeholders, and supply/procurement barriers. ■ Consumption studies across 5 HBCs to provide insight into utilization of TB medicines.	■ Gaps and poor practices were identified that could benefit from technical assistance and market intervention to speed adoption of a new product. ■ Procurement and supply chain management systems in many countries do not adequately capture information on TB medicines. The lack of data suggests a weakness that should be addressed to ensure that medicines reach treatment centers. **Associated Publication(s):** Malhotra S., et al. From availability to uptake: planning for the introduction of new, child-friendly anti-tuberculosis formulations. *Int J of Tuberc and Lung Disease* 2015. Usherenko I., et al. Pediatric tuberculosis drug market: an insider perspective on challenges and solutions. *Int J of Tuberc and Lung Disease* 2015. Publication pending on the results of the consumption study in high TB burden countries.

"Working with the TB Alliance as a close collaborative partner has helped to raise the global awareness of pediatric TB and has allowed us to address key clinical research gaps which had not yet been evaluated in children. These key steps as a result of our successful partnership contribute toward improved TB control in children, the most vulnerable yet most neglected amongst research for TB."

ANNEKE HESSELING

Stellenbosch University
Desmond Tutu TB Centre

These findings corroborated what was previously only assumed: TB, a disease that causes widespread suffering in children globally, is largely undiagnosed and therefore most children (approximately 64%) go untreated. In the absence of a reliable diagnostic test that can more accurately confirm active TB disease in children, the field must depend and build upon both novel and existing approaches to monitor and expand the global response to childhood TB and ensure it is established as a priority in child health.

4.2 Evidence Building: Clinical Evidence on Dosing for Children <5 kg

Because of limited data on the use of first-line anti-TB medicines (isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB) in infants, the dosing of these medicines in babies weighing less than 5 kg was a challenge for clinicians, and no WHO guidance was available to inform prescribing decisions.[7] To help ensure optimal treatment of TB in young infants, additional pharmacokinetic (pK) studies were needed to generate representative data on the pK properties and safety of first-line anti-TB medicines. To address this informational gap, TB Alliance engaged the Desmond Tutu TB Centre at Stellenbosch University to conduct a study to determine the key pK parameters of the most commonly used first-line TB medicines in infants—INH, RIF, and PZA. Initial results indicated that exposure to INH and PZA was within acceptable range, while exposure to RIF was highly variable and overall below the target range.[8] Based on these data, a follow-up study was initiated to optimize dosing for RIF, with results anticipated in 2018.

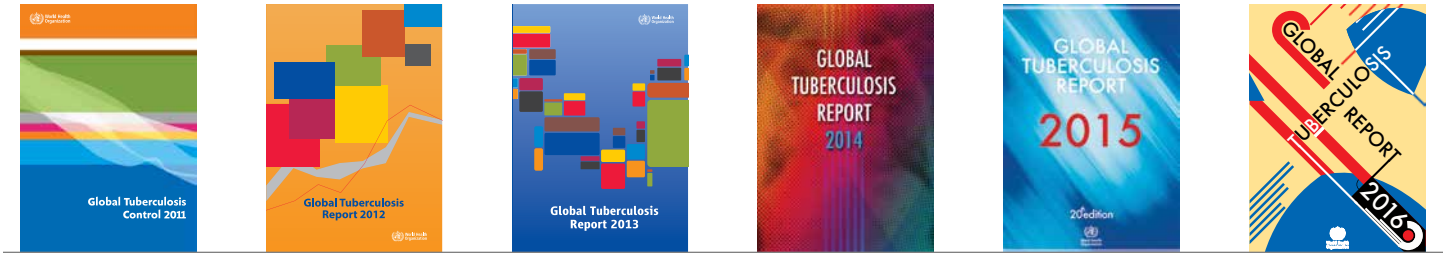
FIGURE 3: A CHRONOLOGY OF TB DISEASE BURDEN IN CHILDREN

Data based on annual WHO TB reports

Number doubled because of a new study

Children with HIV/TB infection were incorporated in 2016 report for first time

2011	2012	2013	2014	2015	2016
No estimate for children	**500,000 cases 64,000 deaths**	**530,000 cases 74,000 deaths**	**550,000 cases 80,000 deaths**	**1,000,000 cases 140,000 deaths**	**1,000,000 cases 210,000 deaths**



SPOTLIGHT ON EVIDENCE BUILDING

Achievements

- Improved TB burden estimate approaches developed, resulting in better global and country burden estimates published in the WHO Global TB Reports.
- Pediatric TB market procurement and regulatory pathways clarified.
- Dosing clarified for INH and PZA treatment in children under 5 kg, with further work under way to verify dosing for RIF.

Lessons Learned

- Gaps remain in market data in childhood TB, and novel methods and collaborations are required to better understand market size and drive the market.
- Market intelligence data on all aspects of the market are critical to the work with pharmaceutical companies on an introduction strategy and with countries on programmatic and procurement plans.
- Filling in gaps in clinical evidence around treatment is critical for policy and implementation efforts.

▲ Before the new fixed-dose combinations, bitter-tasting adult TB medicine had to be chopped and crushed into doses suitable for children.

5 Product Development and Availability

5.1 Identification and Engagement of Pharmaceutical Industry

Given that introducing improved medicines to the market was the cornerstone of the project, without which the overall project could not have succeeded, pharmaceutical companies were essential partners in developing, commercializing, and registering the pediatric TB formulations, and in manufacturing at the scale needed for global availability. Countries changing their treatment practices and adopting appropriate pediatric guidelines were largely dependent on the availability of a product that adhered to WHO recommendations.

In identifying potential commercial partners, TB Alliance looked at the following minimum criteria:

- Current manufacturer of one or more TB medicines, ideally first-line drugs isoniazid, rifampicin, pyrazinamide, and ethambutol.
- Experience with fixed-dosed combination medicines and child-friendly formulation methods.
- Ability to obtain WHO prequalification (WHO PQ) and/or International Conference for Harmonization (ICH) regulatory approval for finished product and the availability to export that product.
- Adequate production capacity and/or ability to scale capacity to meet market demands.
- Regulatory track record at the national level in high burden TB countries.

A pool of prospective partners was identified based on these criteria under the assumption that demonstrated experience, coupled with an interest in expanding an existing TB franchise, would be the foundation. TB Alliance further assessed each prospective partner based on their willingness to invest at risk, to agree to aggressive timelines, to register in HBCs, and to agree to product affordability. Concerns about entering or reentering the market for pediatric TB medicines and options to overcome any perceived market entry barriers were also ascertained. Ultimately, agreements were entered with three pharmaceutical companies, one of whom subsequently became no longer a viable partner due to unrelated issues due to WHO prequalification programs.

At a minimum, each pharmaceutical partner agreed on development and commercialization of the two fixed-dosed combination products (RIF 75 mg + INH 50 mg + PZA 150 mg or RIF 75 mg + INH 50 mg), seeking WHO prequalification, manufacturing at production scale, and making product available through a global mechanism at an affordable price. As part of the collaboration, TB Alliance offered its expertise throughout the product development and commercialization process. These joint efforts included product formulation strategy (e.g., taste optimization), regulatory processes, timelines, defining registration paths and plans, and geographic

AIM

Collaborate with committed pharmaceutical partners to achieve market entry and global availability[9] of optimized child-friendly medicines.

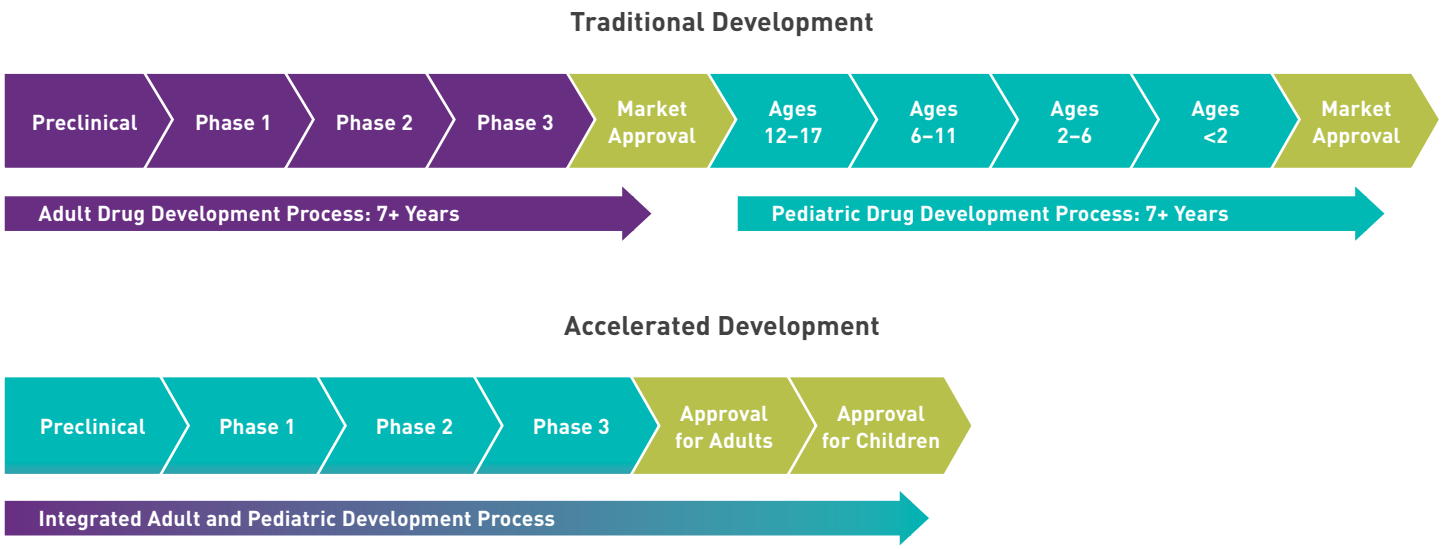
TAKEAWAY

Active collaboration with pharmaceutical partners was key to success, with TB Alliance and the pharmaceutical partner contributing expertise toward jointly established goals in clinical development, registration strategy, market research, demand building, and product launch, resulting in delivering results ahead of schedule. In a small market, creating competition must be effectively balanced to avoid fragmentation and ensure a sustainable source of products.

ACCELERATING AND ENSURING INNOVATION IN PEDIATRIC DRUG DEVELOPMENT

Generally, the development and availability of medicines for children has lagged behind adult medicines by an average of about seven years. The traditional approach for pediatric drug development often waits to initiate studies in children until a later stage or after clinical development in adults and makes use of an age de-escalated approach of enrolling children from descending age groups. TB Alliance has proposed that pediatric studies can be initiated as soon as promising Phase II study data have been generated in adults (see Figure 4).[10] Age groups can be studied almost in parallel without one age cohort having to be completed before the next begins. There have been encouraging signs that TB drug development is moving in this direction. For example, Janssen, in collaboration with TB Alliance, is using this approach to accelerate their bedaquiline pediatric development program by collapsing the two oldest age groups in the Phase II trial in children. With this new approach, there is greater hope that the delays seen in the past will be minimized for new TB treatments, and children will be able to benefit sooner than before.

FIGURE 4: TRADITIONAL DEVELOPMENT VS. ACCELERATED DEVELOPMENT PATHWAY



▲ This accelerated development pathway incorporates juvenile toxicology, formulation work, bioequivalence studies, and simultaneous single- and multiple-dose pK studies in ages 0 through 16. It also considers inclusion of children and adolescents in adult phase 3 studies.

scope. Additionally, TB Alliance committed to both market preparation work, which included conducting the market research needed to characterize demand and regulatory requirements; engaging donor groups to ensure funding for procurement of the fixed dose combinations (FDCs); and working with countries on the adoption of the WHO guidelines, and demand building. Importantly, cost-sharing and other joint efforts as outlined above, resulted in accelerated product development and commercialization, and faster, broader registration in high burden countries.

Macleods Pharmaceuticals was the first company on the market, with a second manufacturer expecting to enter the market within the year. Two manufacturers in the market will ensure a stable and sufficient supply to meet demand, even if countries identify increasing numbers of children with TB.

"Because of this strong partnership, there was rapid uptake and ramping up of demand. Macleods stays committed to improving TB medicines for kids."

VIJAY AGARWAL
Macleods Pharmaceuticals

SPOTLIGHT ON PHARMACEUTICAL COMPANY ENGAGEMENT

Milestones

- Commitments from three pharmaceutical companies for the development of pediatric formulations in the first six months of the project led to early availability of the new child-friendly pediatric FDCs by Macleods.
- Developing an accelerated pediatric development pathway and paving the way for new medicines with early use by Janssen and TB Alliance on bedaquiline.

Lessons Learned

- Risk reduction for pharmaceutical companies by making entry into a small, poorly defined market more attractive through: 1) improved market intelligence; 2) concerted demand generation globally and in early adopter countries; and 3) joint efforts on resolving regulatory hurdles toward market authorization.
- Volumes are key in attracting and keeping suppliers in a small market such as pediatric TB; without adequate volumes, other measures must be taken to allow pharmaceutical companies adequate return on their investment.
- The allocation of national budgets for products and the availability of products in the private sector are dependent on policy adoption and regulatory approvals.
- Active collaboration agreements with pharmaceutical partners favorably impact the ability to achieve the goals of the project within the target timeline.

FIGURE 5: MAP OF COUNTRIES WHERE THE PROJECT SPONSORED, ORGANIZED, OR CONDUCTED ACTIVITIES IN SUPPORT OF PRODUCT AVAILABILITY AND ROLLOUT

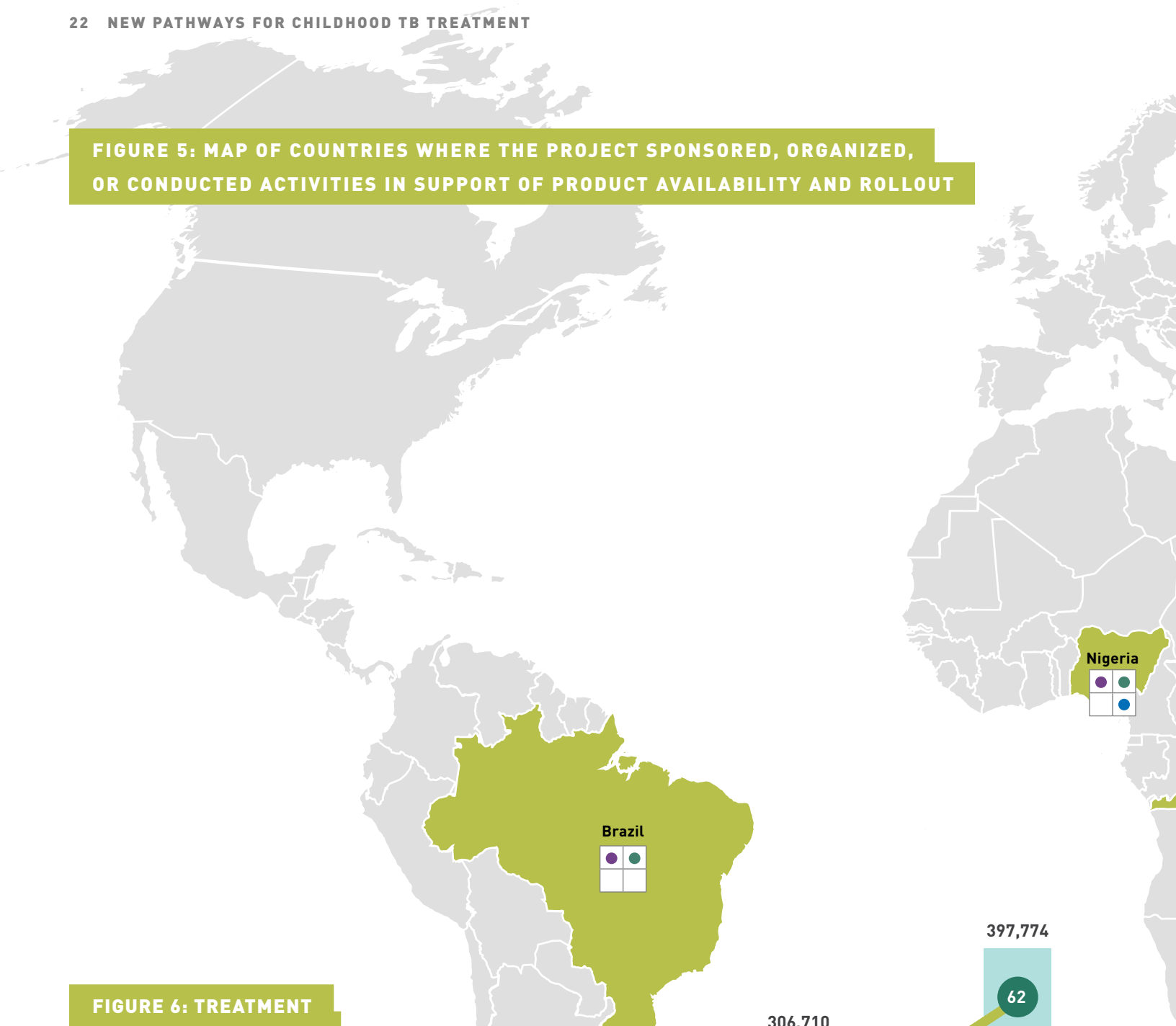
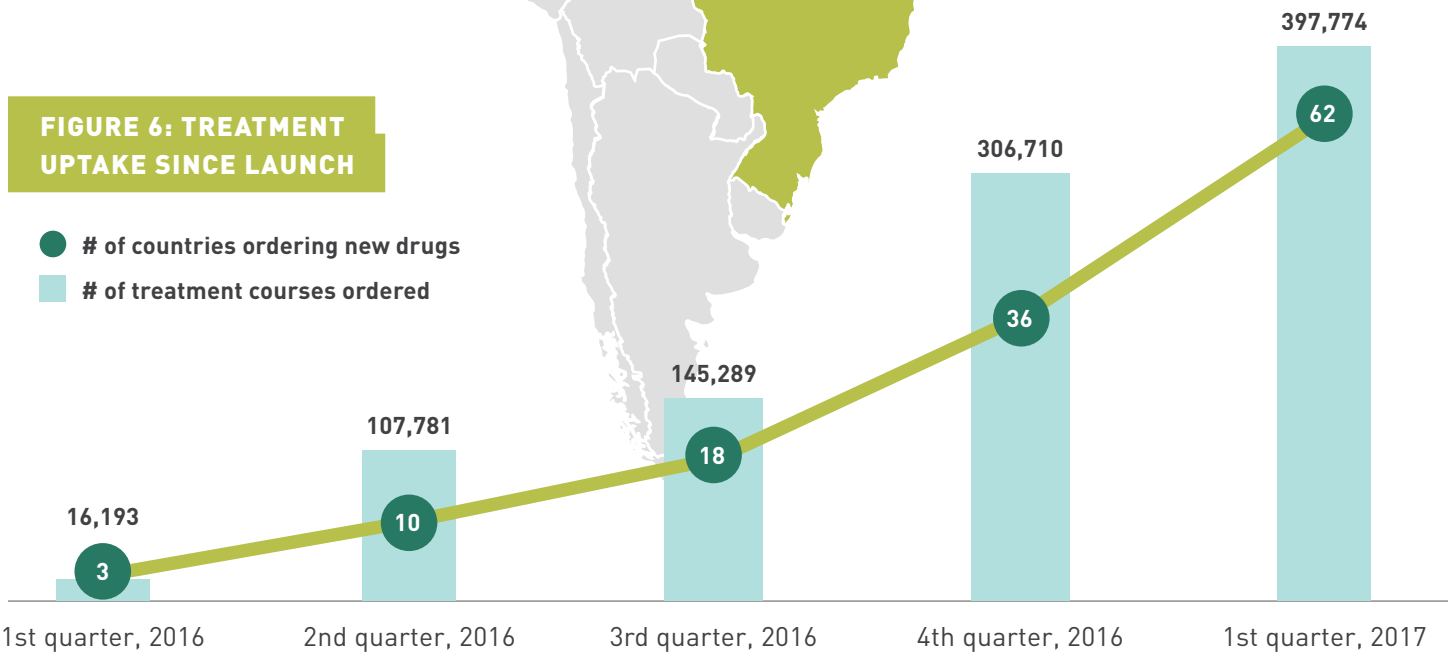
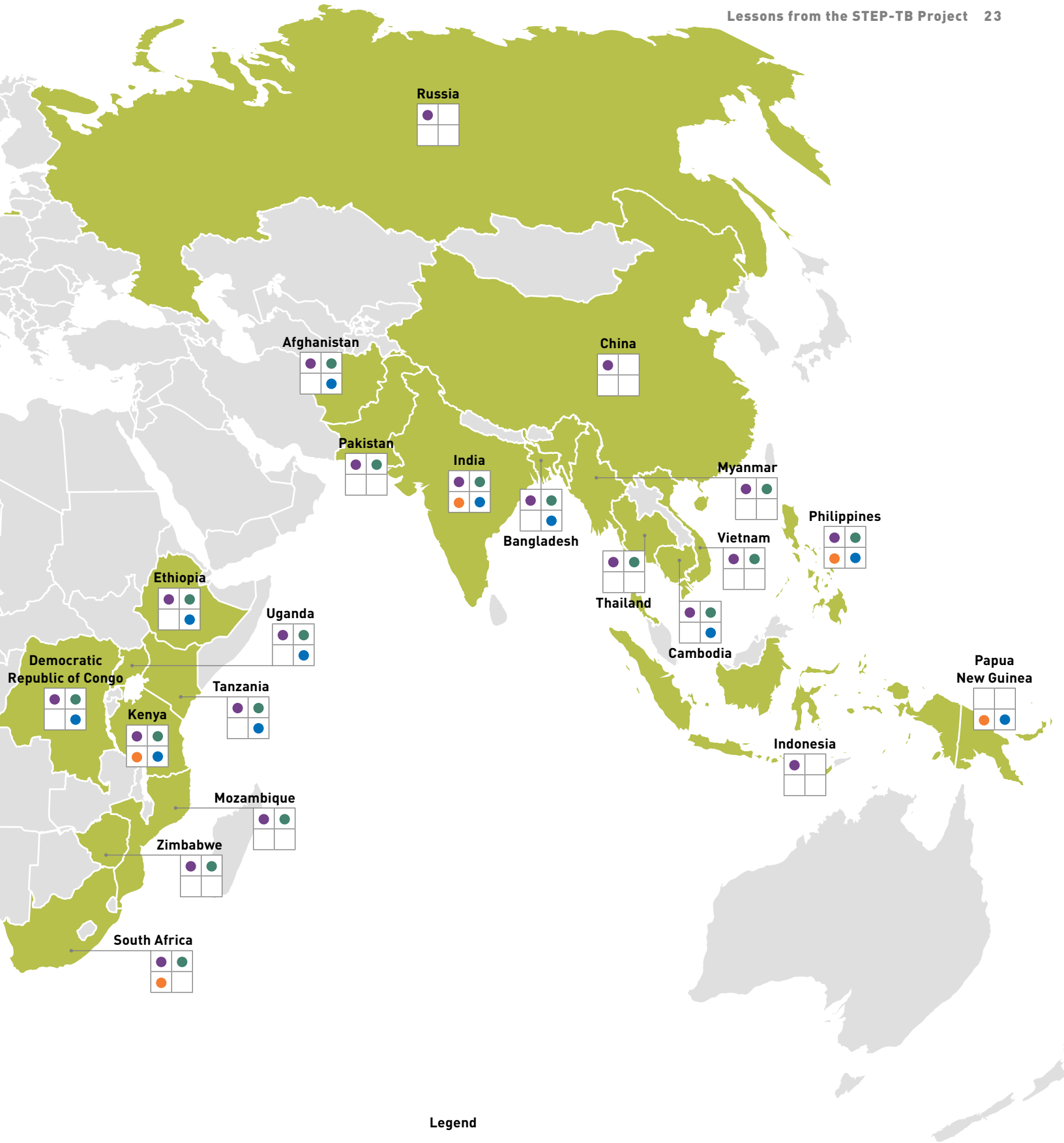


FIGURE 6: TREATMENT UPTAKE SINCE LAUNCH




Russia
Afghanistan
China
Pakistan
India
Bangladesh
Myanmar
Philippines
Vietnam
Thailand
Cambodia
Ethiopia
Uganda
Democratic Republic of Congo
Tanzania
Kenya
Papua New Guinea
Indonesia
Mozambique
Zimbabwe
South Africa
Legend
Market and regulatory research participants
Early preparatory policy adoption/stakeholder engagement
Intensive product launch and registration support
Transition and early uptake support

5.2 High Burden Countries

To maximize the global reach of the pediatric products, the project engaged with high burden countries (HBCs). Since 75–80% of the childhood TB burden is concentrated in the HBCs[11,12] and volume drives companies' ability to recoup their return on investment, it was vital for the project to ensure product availability in these countries. In addition to the countries supported through GDF at the time the project was initiated, a significant amount of the TB burden was in middle income countries. To ensure true global availability, commercial partners wanted to see demand coming from these large markets, which required a unique engagement strategy that included policy change and identifying accelerated registration pathways.[13]

For example, India's national program was not using WHO's dosing recommendations in 2013, instead treating children with a nationally developed policy of intermittent dosing that required different products. The project engaged with the NTP, private providers, and key champions in the country to support evidence-based policy changes to ensure children in India had access to optimized treatment. To this end, the project provided information, contributed to program recommendations, and worked to ensure that registration with national regulatory authorities moved forward for the new formulations. Thus, the government of India shifted its policy to include the new pediatric formulations and daily dosing, becoming one of the first countries to register the products and initiating rollout within the first year of product availability.

Country-specific approaches like this were critical to mobilizing demand and ensuring there was a sufficient customer base to purchase the medicines if they were developed and made available.

SPOTLIGHT ON HIGH BURDEN COUNTRIES

Milestone

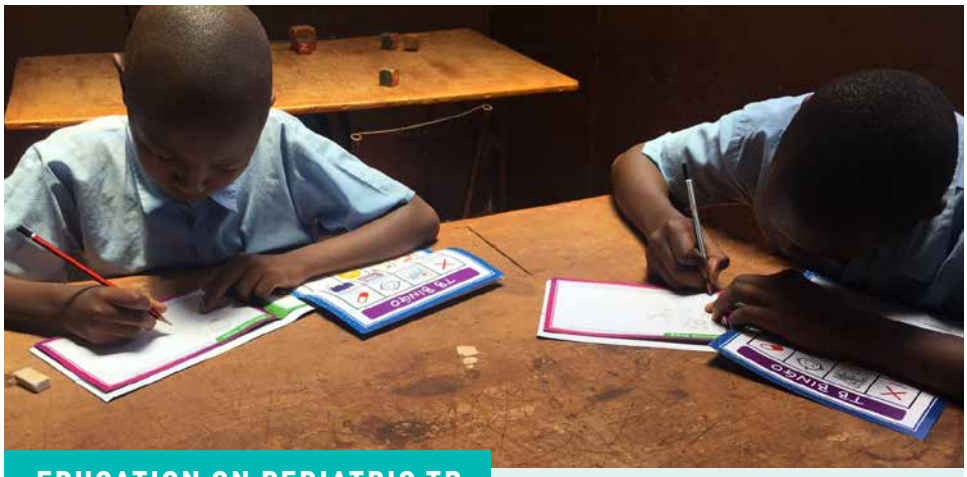
- Through focused efforts to promote adoption of the new pediatric formulations, high volume countries such as India and the Philippines purchased child-friendly FDCs for the first time.

Lesson Learned

- The participation of middle income, high burden countries (e.g., India, South Africa and China) is imperative to create adequate scale with lower volume products.

6 Market Preparation and Mobilizing Demand

▶ TB Alliance developed an activity book for children to learn about TB.



EDUCATION ON PEDIATRIC TB

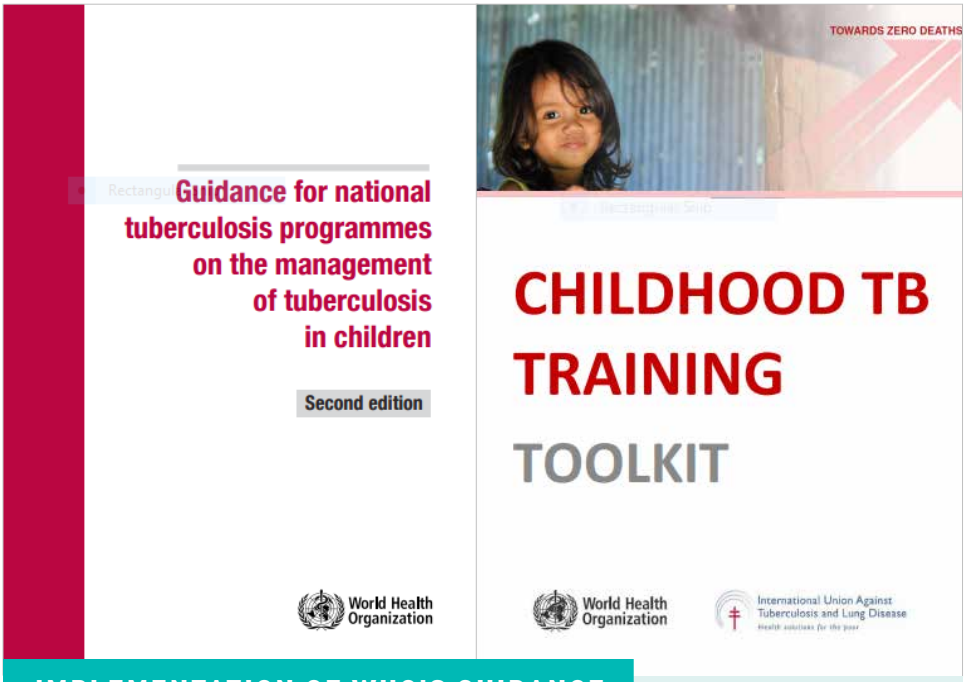
To improve awareness and to increase TB literacy among children and communities, TB Alliance developed educational tools aimed at children, including an activity book, games, educational video, and full manual to enable community members to lead a TB education program aimed at children. These tools were piloted in a school in South Africa, which included a local mural school event to raise awareness of pediatric TB and the need for better medicines. The project partnered with the South African Department of Education to distribute the materials to schools, with interest from other countries to distribute the educational material.

6.1 Stakeholder Engagement for Driving Demand

The project partners worked closely with key donors and countries to drive decisions for adoption of the new pediatric TB formulations and ensure adequate resources were allocated for introduction. The following strategies were applied to build country-level demand and ensure appropriate prioritization for the introduction of the pediatric products:

- Established a pediatric TB information exchange platform with the creation of a web portal[14] to distribute information compiled and data generated on childhood TB and set up forums through webinars and symposia to exchange updates on the project and lessons learned
- In partnership with TB Alliance, WHO organized a series of regional, interregional, and national meetings that:
  - Informed countries of the project and the improved childhood TB medicines coming to market

– Conducted workshops[15] where countries developed action plans that helped to ensure childhood TB was prioritized and included in national strategic plans, as well as to determine the steps required to adopt the formulations
– Ensured donors and countries received information to prepare and allocate necessary funding resources
– Ensured participation across activities of partners outside of the TB sector including HIV, maternal and child health (MCH), and nutrition



IMPLEMENTATION OF WHO'S GUIDANCE ON MANAGEMENT OF CHILDHOOD TB

WHO led a number of activities designed to improve treatment polices and enable uptake of improved medicines at the country level. Among these was the publication of the second edition of the 'Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children' in 2014. This a comprehensive document incorporating all WHO recommendations pertaining to management of childhood TB. This includes the 2010 Rapid Advice, which provided the revised dosing for first-line treatment, information on management of TB/HIV in children, as well as drug-resistant TB in children and integrated care. The document also includes guidance on management of tuberculosis in adolescents, a group that was not specifically highlighted in previous guideline documents. In addition, WHO conducted trainings focused on pediatric TB to help promote in-country practice changes, paving the way for adopting the improved pediatric medicines.

AIM

Engage stakeholders and countries to drive demand for introduction of new pediatric products and ensure global availability.

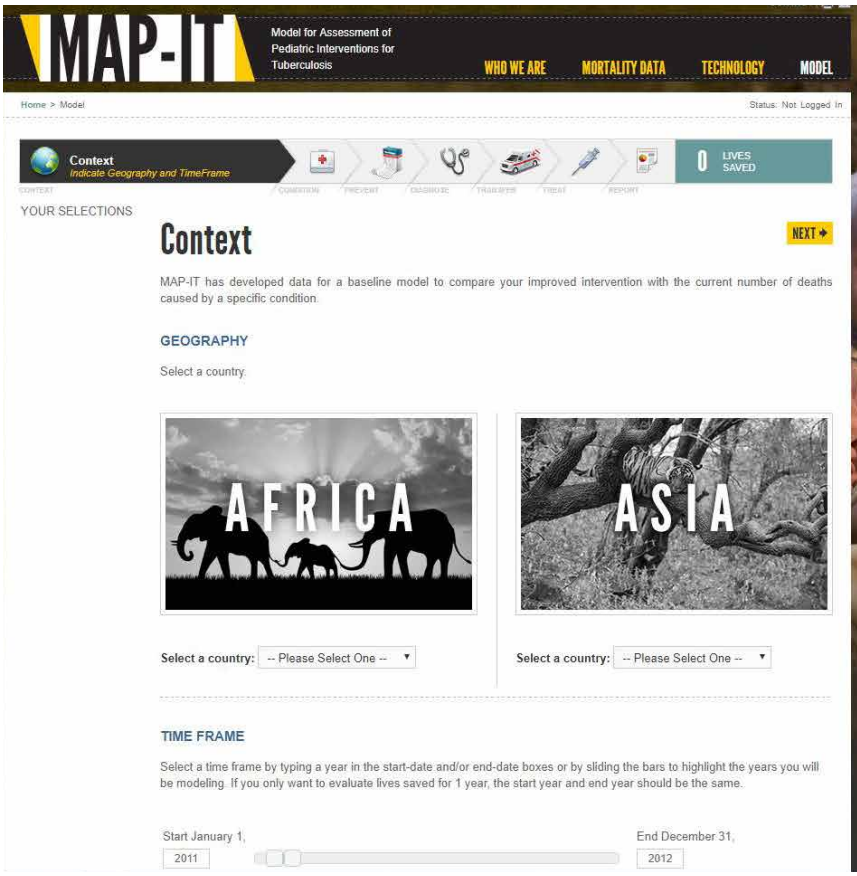
TAKEAWAY

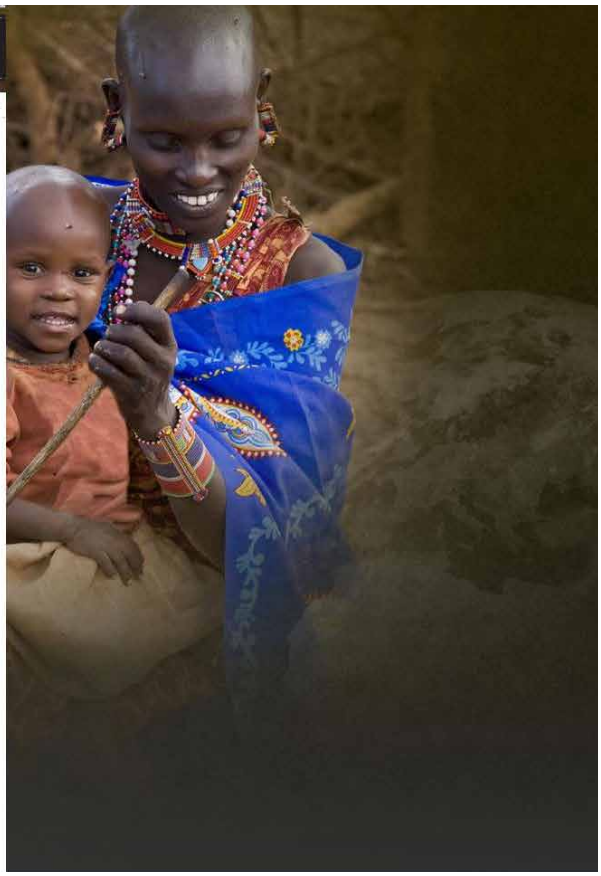
Country preparation was key to success, which included reviewing guidelines, supply chain mechanisms and, crucially, national plans and strategies. The link to financial plans and buy in from donors like Global Fund was imperative, as reprogramming of funding takes considerable time. Broad stakeholder involvement at the national level was needed to drive guideline and adoption decisions.

MAP-IT

The STEP-TB project partnered with RTI International to develop a user friendly, web-based tool to estimate the potential impact of pediatric TB interventions in prevention of pediatric TB incidence and mortality reduction. MAP-IT (Model for Assessment of Pediatric Interventions for Tuberculosis) is a tool that gives decision makers, advocates, and other stakeholders the data needed to make the case and drive the development and adoption of new interventions, such as the FDCs, in key countries. With the capability of demonstrating multiple scenarios in specific countries, such as implementing both the new FDCs and increased contact tracing, the tool can compare the impact of various interventions by adjusting assumptions and inputs. As an example, the MAP-IT model can determine how many lives would be saved if the child-friendly FDCs are available and utilized across all care settings in India. Model results show that one-third of children infected with TB can be saved through this intervention compared to old treatment practices.

Currently, MAP-IT includes data for eight countries: Nigeria, South Africa, Kenya, India, Pakistan, the Philippines, Ethiopia, and Papua New Guinea. MAP-IT is available online at the following link: http://www.mapit4pedstb.org/





- Worked with countries to update their treatment policies and practices to reflect the WHO 2010 recommendations
- Participated in 10 country program reviews (Morocco, India, Pakistan, Vietnam, the Philippines, Zimbabwe, Rwanda, Zambia, Indonesia, and Ethiopia), which allowed engagement with national TB programs and other in-country stakeholders around country preparedness for product introduction
- Developed pediatric TB educational materials to improve awareness of childhood TB and the need for better treatments, which were made available in schools through the educational system in South Africa.

Once the products were available, the project assisted with dissemination of technical information and training of key sectors including pediatricians, health care providers, and community health workers. This was done during national childhood TB stakeholders meetings in several early adopter countries including India, Kenya, and Papua New Guinea.

SPOTLIGHT ON STAKEHOLDER ENGAGEMENT

Milestones

- WHO treatment guidelines adopted in almost all HBCs.
- At least 19 countries engaged by the project expressed a commitment to adopt the new pediatric products and made steps to prepare for their availability.
- Donors and most countries allocated adequate resources to adopt the new products.
- The pediatric portal was used by an average of 10,000 stakeholders annually.
- The announcement of availability of new TB medicines for children generated more than 20 million impressions through social media, and resulted in the publication of approximately 70 original articles.
- Each Thought Leader Webinar brought together an average of 80 active participants.

Lessons Learned

- Countries had unique barriers that informed their decisions around adoption and procurement, all of which had to be identified and considered in offering support or engaging to drive demand.
- Funding and procurement cycles are not always aligned. Therefore, work to influence budget allocation must begin early enough to allow for timely procurement of new products. Alternately, additional investment could provide a bridge mechanism to purchase new products.
- Stakeholders should be engaged continuously through as many avenues as possible to maintain sustained interest and to ensure the necessary actions are taken to adopt a new product once it is available.

"It's exhilarating to think that children who might otherwise have died, or children who might otherwise have gone through months and months of the most painful and nauseating responses to pills they never wanted to take, can now look forward to a medicine that works."

STEPHEN LEWIS
Co-director, AIDS Free World

6.2 Maternal and Child Health and Other Health Sectors

Childhood TB is regularly overlooked and mistaken for other childhood illnesses such as pneumonia and malnutrition. It is also often relegated to the generic category of "other diseases," even though it can cause severe illness and significant mortality, especially in small children and infants. Most children with TB are seen by health care providers outside of NTPs, many of whom do not think to assess a sick child for TB. It is therefore vital to engage partners outside of the TB area. This includes institutions focused on HIV, maternal and child health, pneumonia, and nutrition. TB Alliance also partnered with UNICEF to mainstream childhood TB within the continuum of care for women and children. The U.S. Fund for UNICEF was instrumental in facilitating this partnership.

STEP-TB sought to leverage UNICEF's capacity and in-country presence to identify entry points to address childhood TB and aid in the introduction of the new formulations and drive demand. Through the partnership, UNICEF organized a meeting of key actors working in TB, maternal and child health, HIV, and nutrition to discuss childhood TB and integration. It also organized a three-day interactive online seminar in partnership with USAID's Bureau for Africa on the linkages between tuberculosis and maternal and child health. Due to the STEP-TB project's partnership with UNICEF, TB was included in UNICEF's Strategy for Health 2016–2030.[16]

SPOTLIGHT ON MATERNAL AND CHILD HEALTH AND OTHER HEALTH SECTORS

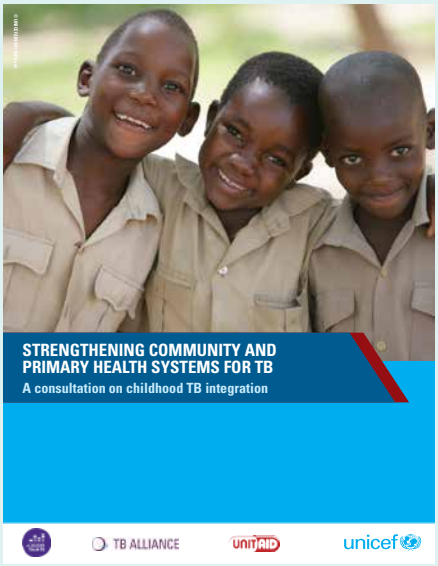
Milestones

- UNICEF/TB Alliance/WHO global consultation on TB integration with 80 experts.
- Tuberculosis included in UNICEF's 2018–21 strategy.

Lesson Learned

- Creating a larger childhood survival platform and leveraging partner networks helped draw needed global attention to the neglected issue of childhood TB.

PARTNERING WITH UNICEF



◀ Publication[17] developed as a result of the Integration meeting organized by UNICEF and the project.

▲ Participants at the consultation on childhood TB integration in New York on June 1–2, 2016.

6.3 Country Preparation for Introduction of New Products

The STEP-TB project worked closely with national governments to efficiently phase out old products while phasing in new products at adequate supply levels. Market preparation to ensure country demand at the time of product availability was essential. Engagement with countries that expressed interest in adopting the new medicines was one way to drive demand. In collaboration with technical agencies, including Management Sciences for Health (MSH), Systems for Improved Access to Pharmaceuticals and Services Program (SIAPS), GDF, KNCV Tuberculosis Foundation (KNCV), the Global TB Program at Baylor University, and The Union, the project helped countries develop plans to introduce the formulations.

TB Alliance leveraged the country network and field presence of MSH to provide extensive technical support with development of product transition plans to several early adopter countries with identified needs. MSH provided targeted technical support to 12 countries[18] for activities that directly facilitated adoption, including consensus building, dosing updates, listing in national essential medicines lists (EMLs), product quantification, and phase in/phase out planning for old and new products. The partnership with MSH resulted in 10 of the 12 countries engaged procuring the products, with the other two expected to follow. Two countries that received support through this partnership, Kenya and the Philippines, became the first to place orders in 2016.

"Having appropriately dosed treatments for children with TB is a major step forward—now we need to address the huge gap in case detection through more decentralized and integrated services to ensure all children can access these life-saving treatments."

ANNE DETJEN
UNICEF

SPOTLIGHT ON STAKEHOLDER ENGAGEMENT

Milestone

- The project engaged 23 countries in preparation for the new formulations. Of those, 16 have purchased the product.

Lessons Learned

- Each product introduced into a program required planning and support involving the ministry of health, national TB program, procurement functions, facilities, community health workers, and technical partners to prevent disruption in TB services and an increased burden on an already overloaded system.
- Countries often lack capacity or have competing priorities that need to be considered and addressed if product introduction and uptake is to be successful.
- One of the rate-limiting factors for product introduction was significant stock of existing, suboptimal pediatric products.

The project conducted technical briefings with the Global Fund and agencies consulting with countries on their Global Fund applications to facilitate the inclusion of funds and activities to support the treatment of pediatric TB. Additionally, WHO partnered with GDF and the Global Fund on the publication of a technical briefing note[19] that provided TB program managers, treatment centers, supply chain specialists, as well as technical assistance providers with a step-by-step plan for transitioning to the new products.

Other key technical support provided to countries included joint missions with WHO and the GDF, specifically assisting countries on forecasting, procurement, and supply chain management. KNCV, the primary implementer of USAID's Challenge TB mechanism, developed a benchmarking tool that included the FDCs; the Baylor University-Global TB Program helped the project's efforts to successfully introduce the products into Papua New Guinea and Tanzania; and The Union, provided technical assistance and training through the Challenge TB mechanism and online Childhood TB Learning Portal.[20]

7 Product Launch and Rollout

AIM

Correctly dosed, dispersible first-line treatments available through a global mechanism at affordable prices and adopted by endemic countries.

TAKEAWAY

Global availability required a balanced approach between central procurement mechanisms, such as the GDF, and specific national-level strategies aimed at HBCs. Even though TB is largely served through government programs, the private sector plays a big role in certain countries and requires specific strategies for supply of products to health care providers.

7.1 Launching an Affordable and Globally Available Product for Children

To ensure that as many endemic countries as possible had access to the products, several mechanisms were used. First, the two dispersible fixed dosed combination products from Macleods, the first manufacturing partner to enter the market (and do so eight months ahead of schedule), received a favorable one year, no objection decision from the WHO External Review Panel, which facilitated a limited procurement while Macleods' dossiers were assessed for prequalification by WHO. Second, GDF was instrumental in accelerating global availability. The GDF's procurement mechanism links demand for medicines to supply and monitoring, as well as grants and TB program performance. GDF became the primary mechanism to achieve global availability of the new quality-assured pediatric formulations, which were listed in their catalog in December 2015.

An affordable and sustainable price for the products were important considerations for both donors and countries. With the new products introduced at an average price of US$15.54 for a full 6-month treatment course, the price was widely accepted as it fell below the median price for the various pediatric treatments that were historically used, which ranged on average in price from US$13.55 to US$22.00 for the 6-month treatment course.

▶ A girl in India with the new FDC dissolved in water.

◀ An interactive mural painting project initiated by TB Alliance called on conference attendees to come together and collaborate in a visible way around the critical need for investment in the development of new tools to help ensure a future free of TB. Yvonne Chaka Chaka, internationally acclaimed South African singer, songwriter, entrepreneur, humanitarian and teacher gave the dedication for the 'TB Free Future' mural in Cape Town, at The Union World Conference on Lung Health in December 2015.

ACTING ON THE CALL: BRINGING CHILDHOOD TB OUT OF THE SHADOWS

A renewed Call to Action was launched at The Union World Conference on Lung Health in South Africa in December 2015 to build momentum around childhood TB to help support uptake of the new FDCs.

No child should die of tuberculosis (TB). Yet each year, at least 1 million children get sick with TB and nearly 400* of them needlessly die, each and every day. TB in children can be prevented, diagnosed and cured, but all too often, children with TB remain in the shadows, uncounted and untreated.

There was broad support for a Call to Action, launched in March 2011 at the International Childhood Tuberculosis Meeting in Stockholm, Sweden, which called for enhanced efforts to meet the needs of children with TB globally. Since then, substantial progress has been achieved, including a strengthening of global political commitment to tackling childhood TB; the development of the Roadmap for Childhood Tuberculosis; creation of guidelines and training materials for national TB programs on the management of TB in children; expansion of programmatic activities at regional and country levels; improved understanding of the TB burden; expansion of research leading to important progress in clinical trials; and now, the introduction of appropriate, child-friendly medicines for drug-sensitive TB.

Despite this progress, significant challenges remain to meet the objective of the Post-2015 WHO End TB Strategy and United Nations Sustainable Development Goals: an end to the tuberculosis epidemic. There is an unprecedented opportunity to address the needs of children and adolescents with TB, and this opportunity must be embraced.

Read more and sign the call at http://www.who.int/tb/areas-of-work/children/call-to-action/en/

Watch the call to action videos: https://vimeo.com/147174852 or https://www.tballiance.org/video/new-childhood-tb-medicines-will-help-save-lives

*Statistics as of December 2015

"We need to cure TB in our lifetime. That can be done. Let's fight this cause together."

YVONNE CHAKA CHAKA
Singer and Humanitarian

FIGURE 7: DOSING TABLE

The number of daily tablets needed to reach the proper dosing, based on the child's weight.

Weight band	Number of tablets	
	Intensive phase: RHZ 75/50/150*	Continuation phase: RH 75/50
4–7 kg	1	1
8–11 kg	2	2
12–15 kg	3	3
16–24 kg	4	4
25+ kg	Adult dosages recommended	

* Ethambutol should be added in the same intensive phase for children with extensive disease or living in settings where the prevalence of HIV or of isoniazid resistance is high.

SPOTLIGHT ON PRODUCT LAUNCH

Milestones

- The new child-friendly fixed-dosed combination products from Macleods were launched eight months ahead of anticipated timelines and were made available through GDF in December 2015.
- Within the first year of launch, 36 countries procured product and more than 300,000 treatment courses were delivered.
- The first nationwide rollout in Kenya was initiated in October 2016.

Lessons Learned

- A global mechanism—such as the GDF—is an effective means to accelerate access to products with little commercial interest but a significant public health need.
- Excitement is contagious. Countries became increasingly open to adopting new medicines as a result of early adopter countries moving faster than anticipated.

7.2 Country Adoption of FDCs

FIRST NATIONAL LAUNCH OF THE FDCS: KENYA

In October 2016, Kenya became the first country to introduce the new child-friendly TB medicines at a national scale.[21] To initiate the rollout, Kenya's National Tuberculosis, Leprosy, and Lung Disease Program, in partnership with TB Alliance, organized a public launch of the new products, consisting of a press conference with national and international media outlets, as well as a stakeholder briefing with public health officials and representatives from other HBCs.

This launch event was followed by a sustained outreach campaign in support of the rollout, including radio spots and training of health care workers. Childhood TB was integrated into the national MulikaTB! MalizaTB! campaign (Swahili for "Find TB, Treat TB") to raise awareness, increase case detection, drive treatment uptake, and improve treatment outcomes. The event and supporting activities not only helped accelerate uptake in Kenya, but provided a model of successful adoption for other countries.

"With appropriate treatments available in our country, we can make rapid progress in finding and treating children with TB, and take a major step toward achieving a TB free generation. Our collaboration with TB Alliance has helped bring childhood TB to the forefront of Kenya's response to the epidemic."

IMMACULATE KATHURE
National TB Program—Kenya

MILESTONE NEWS HEADLINES

BBC

TB drug designed for children launched in Kenya

27 September 2016

Loop Your News Now

New child friendly TB drugs project launched

9 August 2016

THE TIMES OF INDIA

WHO launches flavoured TB drugs made for kids

3 December 2015

The Indian EXPRESS JOURNALISM OF COURAGE

Daily drug regimen for TB patients in 5 states, including Maharashtra, from Sept

5 August 2016

HUMANOSPHERE Give a damn: News and analysis of the fight against inequity

Kid-friendly TB medicine takes advice from Mary Poppins

7 January 2016

THE ASIAN AGE

World's first child-friendly drugs for TB launched

3 December 2015

REUTERS

Child TB deaths set to fall as Kenya launches new drugs

27 September 2016

7.3 Building Momentum

"LOUDER THAN TB" CAMPAIGN

Leveraging pro bono creative direction and support from the advertising firm FCB Health, TB Alliance launched the "Louder than TB" campaign to "change the sound of TB" by raising awareness of TB as a critical issue on the maternal and child health and survival agenda, and helping drive uptake of the child-friendly FDCs. The campaign recruited global institutions to communicate about childhood TB including Unitaid, WHO, UNICEF, Save the Children, World Vision, the World Bank Group and more than 50 other organizations who joined the campaign's coalition of partners.

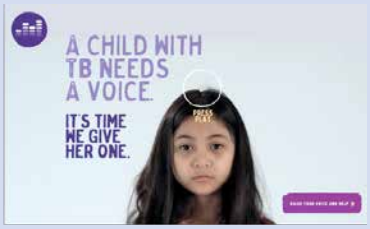
During the launch of Louder than TB on World TB Day 2016, the campaign's messages reached a global audience of over 10 million people. TB Alliance has since leveraged the Louder than TB platform to distribute campaign messages to its partners, primarily through social media, intended for partners to keep childhood TB at the top of minds around influential events and conferences such as Women Deliver, the International AIDS conference, and the World Health Assembly.

▼ Working with countries and communities to raise the messages

▼ Raising the 'sound of TB' at meetings and conferences using innovative approaches including musical exhibits of sound and interactive installations.

▼ Social Media Platforms: Facebook, Twitter, Instagram, Vimeo

▼ The "Louder than TB" campaign's website was launched as part of the campaign.



8 Way Forward

The STEP-TB project's introduction of new TB cures for children in the correct dose and child-friendly forms marks an important first step. Additional progress is expected later in 2017 with the availability of ethambutol and a second manufacturer entering the market. Stakeholders must also continue the work necessary for successful implementation and securing longer term sustainability of the market.

8.1 Achieving Scale-up

For the purposes of the STEP-TB project, "scale-up" refers to the point at which new products are in the hands of providers and caregivers treating children. To reach scale-up, these five requirements must be met: (1) suppliers need a predictable market, ongoing support and incentives; (2) countries should be provided with technical assistance to support product transition, introduction, and use; (3) high-volume countries need to enter and remain in the market; (4) other new medicines, such as the single drug products, must be successfully launched and introduced; and (5) private and child health sectors must play an active role in TB care and work closely with their NTPs.

The recent inclusion of the child TB FDCs in the 2017 version of the WHO Essential Medicines List can also help promote introduction of the products in countries that follow this guidance for decision making.

A sustainable market is necessary for ensuring continued access to the best products for children.

As the STEP-TB project's primary funder, Unitaid enabled the environment necessary for widespread commitment to the needs of children affected by TB. They continue to invest in innovative approaches for wider scale-up and implementation work around the new products. Additional investment and commitment from other partners and donors will be necessary to ensure that the availability of these improved treatments can fully translate into better outcomes for children with TB.

8.2 Ensure Healthy Pediatric TB Drug Market in the Long Term

A sustainable market is necessary for ensuring continued access to the best products for children. The experience and lessons learned from the STEP-TB project can help shape strategies and actions for future development and introduction of innovative products (see Figure 8).

There are many near term opportunities to employ the STEP-TB model for other commodities to improve treatment, prevention, and diagnosis of TB in children. Some of those opportunities include (1) introduction and access of child-friendly medicines for treatment of latent TB infection—dispersible isoniazid 100 mg, a dispersible fixed-dosed combination of isoniazid + rifapentine, and levofloxacin for multidrug resistance tuberculosis (MDR-TB) infection, (2) child-friendly second line drugs to combat the existing threat of drug-resistant TB, (3) additional innovative options for formulating medicines for children, and (4) child-friendly formulations and dosages for new TB medicines and regimens in the pipeline.

FIGURE 8: CRITICAL SUCCESS FACTORS FOR MARKET INTERVENTIONS

Early identification and engagement of pharmaceutical partners	Secured commercial partnership/s through mitigation of risk and with commitments to widespread registration
Secured commercial partnership/s through mitigation of risk and with commitments to widespread registration	Identified the best regulatory pathway, (WHO PQ) including processes that accelerate availability such as the Expert Review Panel which allowed temporary procurement through the GDF until prequalification achieved
Evidence building to improve burden, clinical and market data	Provided data critical to work with manufacturers on introduction strategy and with countries on programmatic and procurement plans
Facilitation of policy implementation in high burden countries	Through a supportive framework, worked with countries to change policy and strategic documents and treatment practices through reallocation of resources and trainings
Leveraging partnerships to drive adoption and scale-up	Convened technical group of key stakeholders to coordinate and delegate roles/responsibilities for launch; integrated launch planning into work plans of existing technical platforms
Momentum building and awareness raising within and beyond TB programs	Sustained an early, comprehensive advocacy and communications strategy to ensure adequate funding, to build excitement and political pressure, and to move the issue to a global scale

Two areas of the pediatric TB market that continue to hinder the ability for greater advancement in childhood TB are diagnostics and case finding. There is an urgent need for improved diagnostic options, and promising innovations in child TB diagnostics urgently need investments to improve rapid detection of TB and potential drug resistance in children. Interventions are needed to improve case finding, such as active household contact screening and integrating TB case-finding strategies into maternal and child health services. Also, a consideration that was not present during the STEP-TB project and has implications to availability of child-friendly medicines are the recent modifications to the WHO prequalification fee structure requiring manufacturers, in addition to the initial filing fee, to pay an annual fee to maintain prequalification status. This new structure may have implications for the availability of some, especially low-volume, pediatric TB treatment products and should be closely monitored.

8.3 Ensuring Treatment for All

Beyond the STEP-TB project, TB Alliance continues to make significant progress in advancing new drug regimens that could significantly impact the TB pandemic by ensuring treatment for all people with TB, including children. Results from the NC-005 trial (which tested regimens consisting of bedaquiline, pretomanid, moxifloxacin, and pyrazinamide in people with drug sensitive and multidrug-resistant TB) and interim results from the Nix-TB trial (testing a regimen of bedaquiline, pretomanid, and linezolid in patients with extensively drug-resistant tuberculosis) point to the possibility of a new treatment paradigm where countries could use just two short, simple regimens to treat all people with TB, no matter their resistance profile or age. TB Alliance continues to advance both treatments toward a new paradigm of short, quick, effective, and affordable treatment for every person with TB, including children.

Endnotes

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