



Child-Friendly Pediatric Tuberculosis Treatment



Photo from TB Alliance, 2017

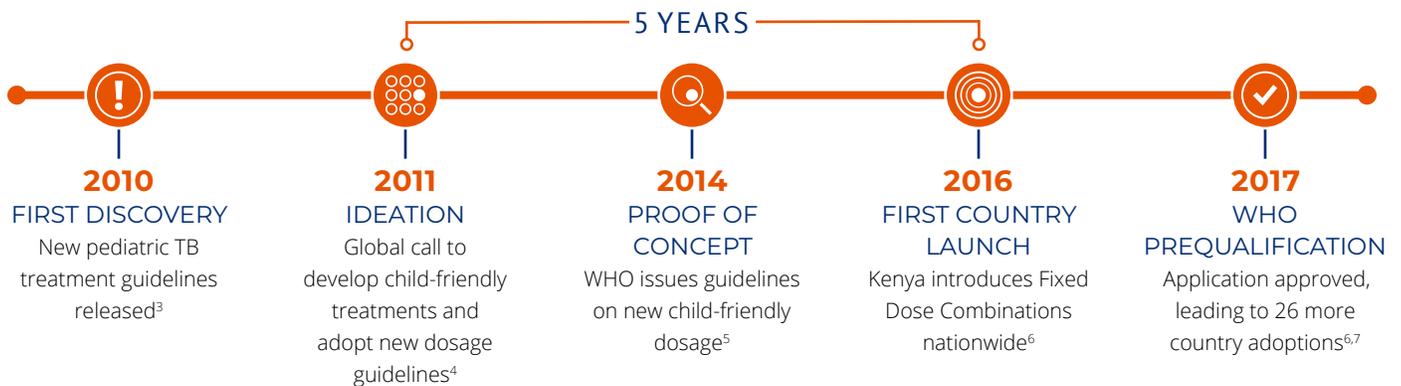
Child-friendly treatment for tuberculosis that dissolves in water with proper dosage and palatable flavoring.

GLOBAL BURDEN OF PEDIATRIC TUBERCULOSIS: >1 MILLION CHILDREN (2018)¹

TIME FROM PRODUCT IDEATION TO FIRST COUNTRY LAUNCH: 5 YEARS

TREATMENTS ORDERED: 1,022,922+ COURSES PROCURED GLOBALLY (2019)²

TOTAL COUNTRY PROCUREMENT:
116 COUNTRIES, COMPRISING 75% OF THE GLOBAL TB BURDEN (2020)⁸



Tuberculosis (TB) is considered one of the world's most fatal infectious diseases, causing 4,109 deaths per day worldwide.¹⁷ Each year, more than 1 million children are estimated to become ill with TB, which accounts for 11% of the global burden.¹ Traditional methods of diagnosing and treating TB are not suited for children, contributing to more than 200,000 child deaths from TB per year.⁸ Furthermore, due to inadequate TB case-detection systems, approximately 64% of the 1 million children contracting TB each year are either incorrectly diagnosed or missed completely.⁶ Prior to 2016, children diagnosed with TB were typically treated with six months of crushed, bitter-tasting,

fixed-dosage (FD) combination treatment courses, which necessitated an imprecise "splitting" of the FD pills to approximate appropriate dosages.^{6,13} Though pediatric diagnostic procedures need improvement, there was a critical need for simplified, child-friendly pediatric TB treatments with accurate dosages. This case study presents an overview of key elements that determined the pace of development and uptake of the first child-friendly treatments for TB. These innovative treatments are two courses of fixed-dose combination tablets that can quickly disperse in liquid with a palatable fruit flavor.

In 2010, the World Health Organization (WHO) revised pediatric TB treatment guidelines by changing the dosages for children based on new evidence.³ The WHO expressed the critical need to engage the pharmaceutical industry in developing child-friendly formulated, effective treatments.³ Despite the expressed urgency, the ill-defined pediatric TB market and poor global demand stifled a response from the pharmaceutical industry.^{6,10} Without the appropriate diagnostics implemented in the TB care continuum, the epidemiological data was not reflective of the true global burden of pediatric TB, thereby supporting the perception of a relatively small pediatric TB market that would not be commercially viable.¹³ In 2011, the WHO and Stop TB Partnership issued a call to action during the International Childhood Tuberculosis Meeting to prioritize and bring attention to the severity of this problem and catalyze the pharmaceutical sector to research innovative child-friendly treatment options.⁴ Although this call sparked the attention of child health advocates and providers in the global TB community, the pharmaceutical industry remained silent, presumably due to the limited understanding of market size and demand.⁶ As time passed, absence of an appropriate pediatric formulation complying with the new dosage recommendations could not be ignored. Clinicians had no choice but to continue prescribing bitter-tasting pills that required splitting and crushing, or combining outdated treatments to estimate the new dosing.¹³

In December 2012, Unitaid sought to address this pressing need and invested USD\$16.7 million in TB Alliance to initiate the development of the appropriate formulation and dosage for pediatric TB treatments.¹⁰ In August 2013, the 'Speeding Treatments to End Pediatric Tuberculosis' (STEP-TB) project was launched to understand the pediatric TB landscape, better define the pediatric market, and develop new TB treatments for children.^{6,10} The project, led by TB Alliance and the WHO, received additional funding from other donors, such as USAID. Within one month of the project's start, 50 subject-matter experts, including research partners, donors, and technical contributors, convened to work together to better comprehend the pediatric TB market size and treatments.⁶ They conducted a series of studies to build the evidence base of the pediatric TB market, make the business case for the introduction of child-friendly TB treatments, and to catalyze successful collaboration with the pharmaceutical sector.⁶ These

studies indicated that the estimated pediatric TB case numbers was double the figure commonly accepted, from an estimated 500,000 cases globally in 2013 to an estimated 1,000,000 cases globally in 2014.⁶ Additional insights from this convening included a deeper understanding of national procurement and regulatory pathways. This collaborative convening of STEP-TB partners resulted in a strategic market plan coupled with a compelling business case.

After several years of failed attempts to engage the pharmaceutical industry, the newly developed market data and business case quickly motivated the sector to act. Three companies, Lupin, Svizera, and Macleods Pharmaceuticals Ltd, indicated interest in developing pediatric formulations for TB treatments.¹⁰ Macleods, based in India—the world's largest TB market—is a leading manufacturer of TB medicines. During this time, nearly one-third of WHO-prequalified TB medicines were developed by Macleods. Additionally, they had supplied previous pediatric fixed-dose combination treatments to Stop TB's Global Drug Facility (GDF). Fittingly, Macleods was the only manufacturer who was able to receive a financial incentive and meet the STEP-TB criteria: 1) current manufacturer of existing TB drugs; 2) ability to obtain WHO Prequalification (PQ) regulatory approval with the ability to export the product; 3) have capacity to meet the market demands and necessary scale; 4) experience with drug formulation; and, 5) regulatory track record at a country-level in high-burden countries.^{10,6} By March 2014, Macleods entered into a manufacturer cooperation agreement with TB Alliance, that led this component of the STEP-TB project. TB Alliance offered advisory support throughout product development by providing evidence that supported the parallel study of pediatric cohorts along with adult cohorts after promising Phase II data.^{6,12} Within a year, Macleods developed two fixed-dose combination (FDC) treatments that quickly dissolved in water and were palatable to children.⁶

Prior to the launch of the new fixed-dose formulations, the STEP-TB project also implemented focused stakeholder engagement strategies to increase demand in high-burden countries.⁶ Most notably, STEP-TB extended their partnership to UNICEF in March 2015 to expand their reach beyond the TB community and into intersecting global health fields, such as maternal and child health, HIV, pneumonia, and nutrition. By leveraging UNICEF's in-country

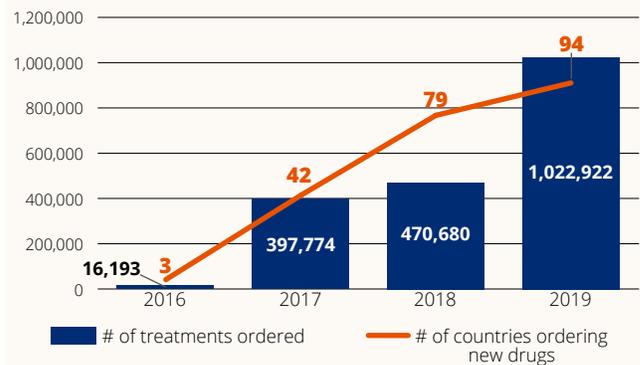
presence and capacity, STEP-TB was able to identify entry points to prioritize and promote the new pediatric TB treatments. In efforts to maximize global reach, the project partners worked closely with key donors and national governments to prepare for adoption of the new products. WHO led a series of technical support activities, such as region-specific information sharing meetings, the development of the “National Tuberculosis Programmes on the Management of Tuberculosis in Children” guidelines, and in-country trainings to promote practice change for pediatric TB care and increase adoption of the WHO 2010 recommendations.^{5,6} Targeted country preparation and mobilization efforts were critical to ensure national systems were primed for product adoption. As a STEP-TB partner, Management Sciences for Health (MSH) offered technical assistance to guide early adoption efforts for 12 countries.⁶ These activities included consensus building, updating national dosage requirements and essential medicines lists, as well as developing transition plans.⁶

By December 2015, the treatments were available for purchase through GDF, ahead of the planned timeframe, with an agreed-upon average price of US\$15.54 for a full, six-month course.¹⁰ By adhering to the revised dosage requirements, Macleod’s applied for WHO Prequalification a month later.¹⁰ Despite the urgent need for these treatments, it took almost two years for WHO to prequalify the child-friendly FDC treatments.⁷ However, GDF worked closely with the Global Fund’s ad-hoc Expert Review Panel to approve the newly formulated FDCs, in order to support country adoption during the waiting period.¹³ The Expert Review Panel approval served as a trusted endorsement and enabled procurement efforts to proceed, while waiting for the WHO prequalification process to be completed. Additionally, WHO and UNICEF issued a joint statement to replace older treatments with the new medicines in March 2017.¹⁵

In October 2016, Kenya became the first country to introduce the child-friendly treatment courses nationwide as a result of MSH’s targeted technical support efforts.⁶ Between the first country launch and the end of 2019, more than 90 countries had procured the child-friendly treatment courses (figure 2).² Comprehensive technical support from GDF enabled a significant leap in the number of countries procuring the treatment courses—from 36 to 62 countries—in 2017.⁶ This support included supply planning, forecasting and quantification, and phasing

out old medicines.¹³ GDF also developed a tool that allowed countries to adjust their Global Fund grants by estimating the value of wasting existing stock of old medicines and comparing it to the value of purchasing new treatments. This tool expedited procurement and uptake efforts. Additionally, the STEP-TB project ran effective marketing campaigns to build momentum for change and heighten awareness on the once-neglected topic of childhood TB.^{6,10} For example, the “Louder than TB” campaign recruited participation from Unitaid, WHO, UNICEF, and over 50 other organizations, to generate awareness of pediatric TB, resulting in increased uptake of the new FDCs.⁶

Figure 1. **Cumulative Child-friendly Pediatric TB Treatment Uptake (2016-2019).**



Data from TB Alliance^{2,6}

The STEP-TB project formed a catalytic coalition that successfully engaged the pharmaceutical sector and galvanized diverse collaboration across public and private sectors, resulting in the first child-friendly formulated TB treatments. Most critically, the project prioritized, simplified, and improved treatment options for children living with TB. But, challenges still remain, and progress will be limited without addressing gaps embedded in the current systems of care. Case-detection, notification, treatment initiation and adherence must be strengthened in order to improve TB outcomes in children.¹⁰ Additionally, countries must continue to supply a minimum of one million treatment courses per year to address the estimated burden of childhood TB—a number that was only cumulatively reached in 2019 after four years of availability.^{2,8} With a newly defined pediatric TB market, there may be more private sector interest and innovation to support and protect children’s health across the world.

KEY INSIGHTS TO LAUNCH AND SCALE

Global collaboration across sectors was critical to accelerate development, introduction, and scale of the first child-friendly TB treatments. By having significant champions in TB Alliance and WHO— along with support from several prominent organizations such as, UNICEF, USAID, the Global Fund, and Unitaid — children living with TB were prioritized across the globe. The STEP-TB project was able to break down silos in the once fragmented field by catalyzing coordination and alignment across a diverse array of partners (academics, donors, clinical providers, nonprofit organizations, public sector, technical/research groups, pharmaceutical companies and regulatory partners). Most notably, public-private partnerships accelerated the development of pediatric treatments; generated buy-in and prepared countries for their introduction; and catalyzed adoption of the new fixed-dose pediatric formulation in 116 countries within 5 years. With this diverse partnership, the project was able to maximize global reach by optimizing the specific expertise of each partner, identifying linkages across networks, and establishing opportunities for integration across sectors.

The development of a compelling business case, grounded in data, successfully engaged the pharmaceutical sector. With limited market data, there was a misconception that the pediatric TB treatment market was commercially unviable. Building a stronger evidence base by improving clinical data, developing disease burden estimates, and defining market size and demand helped mitigate the risk for pharmaceutical companies to develop pediatric treatments. Additionally, these efforts supported demand generation. These endeavors catalyzed the once unengaged pharmaceutical sector, and generated product development opportunities for future innovations to support pediatric treatments globally.

Timely and strategic investments enabled a sustainable pathway for the development and introduction of innovation. After three years of unsuccessful pharmaceutical engagement, Unitaid's funding commitment catalyzed the global collaboration that engaged Macleods Pharmaceutical Ltd., resulting in the first child-friendly pediatric TB treatment courses. Additionally, Macleods was the only pharmaceutical

company to receive a financial incentive and meet STEP-TB's criteria to develop the treatments. Working with key donor agencies and national stakeholders to develop financial plans to invest in these treatments was also critical to country uptake.

Targeted country-level preparation accelerated both uptake and scale, and was critical to achieving broader global reach. In-country preparation—including adoption of WHO dosage guidelines, WHO national TB program guideline implementation, and supply chain strengthening— alleviated adoption barriers. Leveraging WHO and MSH country presence, the STEP-TB project was able to engage national government stakeholders to generate demand, integrate the new treatments into national TB guidelines, and support national procurement functions. UNICEF's demand generation efforts further expanded the reach outside of the national TB programs and into the maternal and child health sector.

Catalytic technical support alleviated bottlenecks with procurement. Procurement barriers started delaying country uptake efforts. To resolve this issue, GDF's technical support eliminated procurement barriers and catalyzed a major leap with country adoption. While WHO took two years to approve the PQ application, GDF worked with the Global Fund's Expert Review Panel to obtain their approval which enabled country procurement efforts to continue until the WHO prequalification process could be completed. Additionally, GDF worked closely with the Global Fund to develop a tool that supported budgeting efforts and expedited access to the new treatments.

COVID IMPACT

There is a growing concern of the adverse impact of COVID-19 on TB care. It is estimated that COVID-19 will bring a lasting impact on TB in high-burden settings, primarily disrupting TB diagnosis and treatment.¹⁸ Estimates suggest this disruption could result in an additional 6.3 million cases and 1.4 million deaths between 2020-2025. It is critical to secure uninterrupted access to quality TB services for all throughout the pandemic.

ABBREVIATIONS

- FDC:** Fixed dose combinations
GDF: Stop TB's Global Drug Facility
MSH: Management Sciences for Health
STEP-TB: Speeding Treatments to End Pediatric Tuberculosis project
UNICEF: United Nations Children's Fund
USAID: United States Agency for International Development
WHO: World Health Organization
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REFERENCES

- World Health Organization. (2019). Global tuberculosis report 2019. Geneva: World Health Organization; 2019. License: CC BY-NC-SA 3.0 IGO Retrieved from: <https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf?ua=1>
- TB Alliance. (2019). Accessing Improved TB Medicines for Children. Update from the STEP-TB Project. https://www.tballiance.org/sites/default/files/assets/TB-Alliance_Child-Friendly-Medicines_brochure_2020_0.pdf
- World Health Organization. (2010) Rapid Advice: Treatment of Tuberculosis in Children. ISBN 978 92 4 150044 9. Retrieved from: https://apps.who.int/iris/bitstream/handle/10665/44444/9789241500449_eng.pdf;jsessionid=36644AEC6B239207FD896E5EF6A20AC4?sequence=1
- Stop TB Partnership. (2011). Call to Action for Childhood TB. Retrieved from: http://www.stoptb.org/getinvolved/ctb_cta.asp
- World Health Organization. (2014). Guidance for national tuberculosis programmes on the management of tuberculosis in children: Second Edition. ISBN 978 92 4 154874 8. Retrieved from: https://apps.who.int/iris/bitstream/handle/10665/112360/9789241548748_eng.pdf?sequence=1
- TB Alliance. (2017). New Pathways for Childhood TB Treatment: Lessons from the STEP-TB Project. Retrieved from: https://www.tballiance.org/sites/default/files/child-resources/New_Pathways_for_Childhood_TB_Treatment.pdf
- World Health Organization. (2018). WHO PUBLIC ASSESSMENT REPORT (WHOPAR) Part 1. *WHO Prequalification Programme*. Retrieved from: <https://extranet.who.int/prequal/sites/default/files/TB309part1v1.doc.pdf>
- TB Alliance. (2019). Child-friendly medicines. Retrieved from: <https://www.tballiance.org/child-friendly-medicines>
- World Health Organization. (2018). Roadmap towards ending TB in children and adolescents, second edition. Geneva. License: CC BY-NC-SA 3.0 IGO. Retrieved from: <https://apps.who.int/iris/bitstream/handle/10665/275422/9789241514798-eng.pdf?ua=1>
- Euro Health Group. (2017). Global Alliance for TB drug development (TB Alliance) Speeding Treatments to End Paediatric Tuberculosis (STEP – TB) End of Project Evaluation. Retrieved from: <https://unitaid.org/assets/UNITAID-STEPTB-Final-Evaluation-04July2017.pdf>
- Graham, S. M., Grzemska M., & Gie R. P. (2015). The background and rationale for a new fixed-dose combination for first-line treatment of tuberculosis in children. *The International Journal of Tuberculosis and Lung Disease*. Retrieved from: https://www.tballiance.org/sites/default/files/child-resources/Background_rationale_new_FDC.pdf
- Nachman S., Ahmed A., Amanullah F., et al. (2015). Towards earlier inclusion of children in tuberculosis (TB) drugs trials: Consensus statements from an expert panel. *Lancet Infect Dis*. 2015 June;15(6):711-720. doi: 10.1016/S1473-3099(15)00007-9

13. World Health Organization. (2018). Best practices in child and adolescent tuberculosis. License: CC BY-NC-SA 3.0 IGO. Retrieved from: <https://apps.who.int/iris/bitstream/handle/10665/274373/9789241514651-eng.pdf>
14. UNICEF. (2018). Change the Game: An agenda for action on childhood tuberculosis. [PDF]
15. World Health Organization, UNICEF. (2017) Statement on the use of child-friendly fixed-dose combinations for the treatment of TB in children. Retrieved from: https://www.who.int/tb/areas-of-work/children/WHO_UNICEFchildhoodTBFDCs_Statement.pdf?ua=1
16. Caminero J. A., Scardigli A. (2016). Tuberculosis in children. Challenges and opportunities. Anales De Pediatria. DOI: [10.1016/j.anpede.2016.10.002](https://doi.org/10.1016/j.anpede.2016.10.002)
17. TB Alliance. (2020). TB is a Pandemic. Retrieved from: <https://www.tballiance.org/why-new-tb-drugs/global-pandemic>
18. STOP TB. (2020) The Potential Impact of The Covid-19 Response On Tuberculosis In High-Burden Countries: A Modelling Analysis. Retrieved from: http://www.stoptb.org/assets/documents/news/Modeling%20Report_1%20May%202020_FINAL.pdf