SCALING LIFE-SAVING INTERVENTIONS FASTER

Case Studies Series

Explore the pathways and important factors that contribute to the development and uptake of global health interventions—from proof of concept to scale-up.

NOVEMBER 2020

LAUNCH & SCALE SPEEDOMETER

Duke GLOBAL HEALTH Innovation Center

Contents

EXECUTIVE SUMMARY 1

CHILD-FRIENDLY PEDIATRIC TUBERCULOSIS TREATMENT 6
Anshula Nathan, Elina Urli Hodges, Diana Silimperi

EVERY SECOND MATTERS FOR MOTHERS AND BABIES™ –UTERINE BALLOON TAMPONADE (ESM-UBT) 12
Dzidzai Muyengwa, Elina Urli Hodges, Diana Silimperi

LONG-LASTING INSECTICIDE-TREATED NETS 16
Kelly Kilburn, Elina Urli Hodges, Diana Silimperi

SAYANA® PRESS (DMPA-SC) 22
Dzidzai Muyengwa, Elina Urli Hodges, Diana Silimperi

XPERT® MTB/RIF 27
Ernesto Ortiz, Elina Urli Hodges, Diana Silimperi

ABOUT US

The Launch and Scale Speedometer, led by the Duke Global Health Innovation Center, seeks to understand key factors for successful and fast launch and scale of global health interventions to help save lives.

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Executive Summary

Every year, millions of lives—especially in low resource settings—are at stake because we have not scaled up proven, effective solutions. The Launch and Scale Speedometer initiative seeks to build an evidence-base, both quantitative and qualitative, to understand the time it takes for lifesaving interventions, in low- and middle-income countries, to advance from proof of concept through development to scale-up. The initiative also aims to describe the barriers and drivers or enablers to scale-up. The following in-depth case studies describe the launch and scale stories of five interventions: long-lasting insecticidal nets (LLINs) for malaria prevention, Xpert®MTB/RIF for tuberculosis diagnosis, Sayana Press for pregnancy prevention, Every Second Matters for Mothers Uterine Balloon Tamponade (ESM-UBT) for treating postpartum hemorrhage, and child-friendly pediatric treatment for tuberculosis (TB). We selected these interventions to build on learnings from our first year of exploratory data collection on LLINs, Xpert MTB/RIF, and Sayana Press; we selected ESM-UBT and child-friendly pediatric TB treatment to better understand the launch and scale of two maternal and child health specific interventions, given our focus on maternal and child health for the initiative in 2020. A high-level overview of each of these interventions and the status of their current scale up is described in the table below.

Intervention	Type of Intervention	Time from Proof of Concept to Current Scale	Global Burden	Global Scale Up Levels (from the Launch and Scale Speedometer framework)								
				Policy (e.g. guidelines)			Supply (e.g. procurement)			Demand (e.g. use)		
				20%	50%	80%	20%	50%	80%	20%	50%	80%
Long-Lasting Insecticidal Nets	Vector Control / Prevention	17 years	200M cases of malaria per year in Africa					●[1]			●[2]	
Xpert MTB/RIF	Diagnostic	7 years	10 million new cases of tuberculosis per year		●[4]			●[3]				
Sayana Press	Drug / Device	14 years	190 million women with unmet need for contraception	●[5]			●[6]					
ESM-Uterine Balloon Tamponade	Device	5 years	14 million postpartum hemorrhage cases per year				Available in 22 countries					
Child-Friendly Pediatric TB Treatment	Drug	5 years	>1 million pediatric TB cases per year				●[7]					

1. Bed net distribution per year in sub-Saharan Africa (150M) out of total cases of malaria in sub-Saharan Africa (200M) (75%)
2. Percentage of population at risk sleeping under an ITN, sub-Saharan Africa (50.1%); sourced from World Malaria Report 2019
3. Total countries in the world that have procured Xpert MTB/RIF cartridges (125) out of total countries in the world (195) (64%)
4. High-burden countries that have Xpert MTB/RIF in their national policy (32) out of high-burden countries (48) (67%)
5. Number of FP2020 focus countries that have permitted self-injection of Sayana Press (20) out of total number of FP2020 focus countries (69) (29%)
6. Number of FP2020 focus countries that have Sayana Press available (30) out of number of FP2020 focus countries (69) (43%)
7. Total pediatric TB treatments procured since they were available on market (1,022,922) out of total number of pediatric cases since they were available on market (approx. 4M) (26%)

Enablers of Scale

We identified four themes that enabled the launch and scale up of nearly each intervention.

1. MULTI-STAKEHOLDER PARTNERSHIPS AND CHAMPIONS ACROSS DEVELOPMENT SPECTRUM:
Each intervention launched or scaled with the support of at least one kind of partnership, whether public-private, private-private, coalition, or alliance. These partnerships are made up of a variety of organizations representing the private sector, nonprofits, academics, advocacy, global development, funders (philanthropic and government), and public sector. For successful launch and scale, these partnerships also exist and shift along the continuum from introduction to uptake. Additionally, public sector involvement and clear national champions or commitment early and continuously in the process, to address policy, training, integration into supply chain—prime the pump, drive demand, and ready the system for uptake, scale and sustainability.

2. GLOBAL DEVELOPMENT FUNDERS AND BELOW-MARKET PRICING:
Donor funds, whether philanthropic or government-backed, have covered the development and scale-up of most of the interventions studied. LLINs, for example, are primarily externally funded by global donors which thus enable low- or no-cost distribution to populations at risk in sub-Saharan Africa. Price negotiations and buy-down arrangements are also key to bringing the price of each intervention to a level that enables procurement by the public sector in LMICs.

3. STRONG EVIDENCE OF IMPACT:
Understanding the evidence of impact, effectiveness, and safety of an intervention drives regulatory approvals, guidelines, and recommendations by organizations like the WHO and others. Evidence also drives private sector action and can make the business case for hesitant agencies to move forward with intervention development, as was the case for child-friendly pediatric TB treatments. Significant research, including pilot studies and gold standard randomized control trials, also contribute to program and policy decisions, particularly by national governments in their efforts to introduce new interventions.

4. FACILITATED TECHNICAL ASSISTANCE:
Targeted country level preparation alleviates bottlenecks and prepares a country for accelerated uptake. Examples of preparation include support for procurement, shaping the supply chain, technical assistance for national programs, providing comprehensive training programs, building laboratory capacity.

Barriers to Scale

In looking across these interventions we have identified several barriers to their scale-up:

1. UNCLEAR, UNPREDICTABLE TIMELINES AND CRITERIA FOR APPROVALS, GUIDELINES, RECOMMENDATIONS:
In two of the case studies, the World Health Organization's timelines for updating guidelines or recommendations have led to potential scaling delays of up to 10 years. Additionally, the lack of regulatory approval for using an intervention like Sayana Press as a self-injectable, also serves as a barrier to its scale among women.

2. HIGH COMPLEXITY OF INTERVENTION FEATURES OR COMPONENTS:
Reliance on stable electricity and air conditioning, requiring trained providers or skilled laboratory staff, reliance on consumables, maintenance, and other features not suitable to certain environments in low- or middle-income countries, have been shown to limit scale-up. Interventions that are recommended as second line treatments may also not scale quickly, particularly if countries are unable to secure even first line treatments, like those for postpartum hemorrhage. Additionally, interventions or topics that are not "in the spotlight" of the global community may have difficulty attracting funding and attention.

3. MARKET PRICING:
Not only are the original prices of the products too high for LMIC contexts and must be negotiated lower, but the negotiated prices are typically only available to the public sector or in public sector facilities. This means that populations relying on the private sector for their care, are going to pay exorbitantly higher prices for these interventions.

4. IMPLICIT BIAS AGAINST INNOVATIONS FROM LMICS:
Current funding mechanisms for innovation favor entrepreneurs in high income countries who have teams dedicated to grant sourcing and have other means for securing funding for research, development, and scaling. We are thus potentially missing the majority of frugal, high quality innovations developed in LMICs due to their location, connections, and capacity.

5. BEHAVIOR CHANGE REQUIRED FOR UPTAKE:
Changing individual behavior is hard. Interventions that rely on an individual – a healthcare provider, a child, a woman, a person – can have challenges in scale-up as ultimately the end user must change their perspective or way of doing something. In the examples of Xpert MTB/RIF and the new child-friendly pediatric TB treatment, providers must change their reliance on traditional methods of diagnosis and treatment respectively. In the case of LLINs, community members must change their perspective on malaria and must diligently care for and properly use the nets to reduce the risk of transmission. These individual factors have a significant role to play in the scale-up of life-saving interventions.

6. LIMITED ADDRESSABLE MARKET:
The end user or recipient may matter for launch and scale speed and coverage. The addressable markets for Sayana Press, child-friendly pediatric TB treatments, and ESM-UBT are specifically focused on women and children and smaller than those for LLINs and Xpert MTB/RIF, which focus on all populations at risk or with presumed tuberculosis respectively, thus potentially generating less interest in scaling greater or faster from product developers or manufacturers given the market size. These three interventions have only scaled to the 20% range in terms of availability and supportive policies, whereas LLINs and Xpert MTB/RIF have scaled to at least 50%, if not much closer to 80%, in actual use, availability, and policy. On the other hand, the global partnerships and funding that came together because of the worldwide calls to specifically help women and children in need in LMICs, drove the scale up of LLINs (originally recommended just for pregnant women and children), Sayana Press, and the launch of child-friendly pediatric TB treatments.

Further Research

The Launch and Scale Speedometer initiative will continue to research these interventions and others to build the evidence-base for introduction and uptake. Country level milestones and additional scale measures will be primary focus areas. For more information about the initiative, read insights, interact with visualizations, and download data on each intervention, visit https://launchandscalefaster.org.

LAUNCH & SCALE SPEEDOMETER

Child-Friendly Pediatric Tuberculosis Treatment

Photo from TB Alliance, 2017

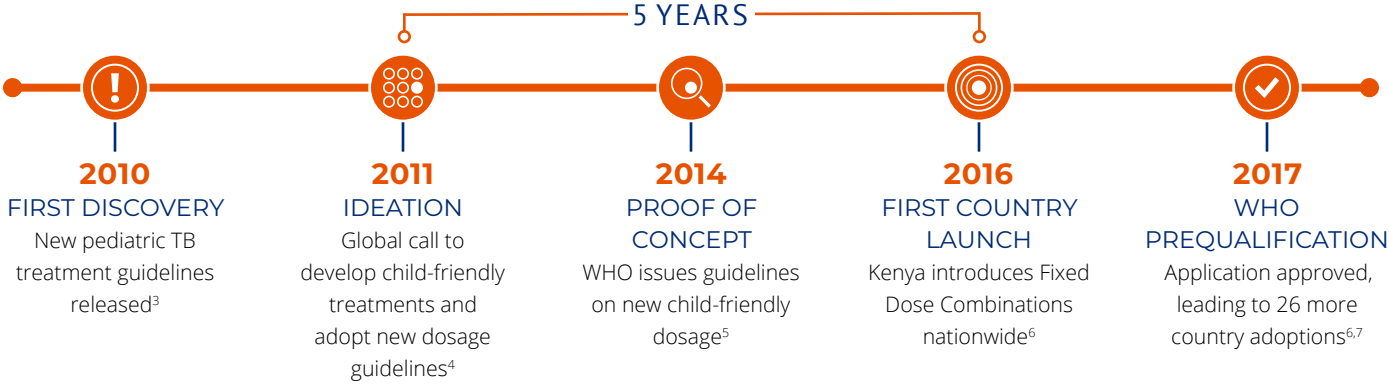
Child-friendly treatment for tuberculosis that dissolves in water with proper dosage and palatable flavoring.

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]

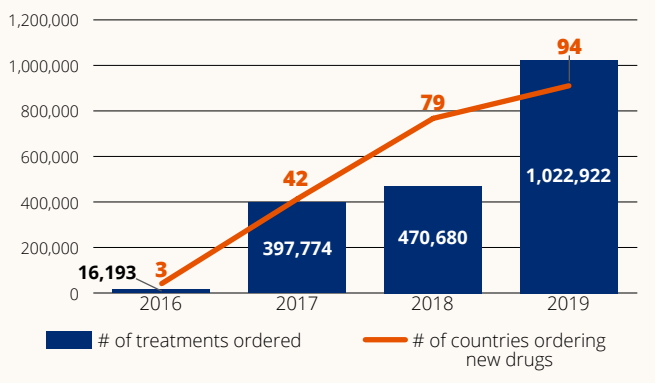
Prior to the launch of the new fixed-dose formulations, the STEP-TB project also implemented focused stakeholder engagement strategies to increase demand in high-burden countries.[6] Most notably, STEP-TB extended their partnership to UNICEF in March 2015 to expand their reach beyond the TB community 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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LAUNCH & SCALE SPEEDOMETER

Every Second Matters for Mothers and Babies™–Uterine Balloon Tamponade (ESM-UBT)

Photo from MGH Division of Global Health and Human Rights, Department of Emergency Medicine

ESM-UBT is a low-cost device that stops postpartum hemorrhage.

GLOBAL BURDEN OF POSTPARTUM HEMORRHAGE: 14 MILLION CASES ANNUALLY (2015)[16]

TIME FROM PRODUCT IDEATION TO FIRST IN COUNTRY LAUNCH: ~4 YEARS

NUMBER OF COUNTRIES WHERE INTERVENTION HAS BEEN INTRODUCED: ~22 COUNTRIES (2018)[11]

NUMBER OF DEVICES THAT HAVE BEEN USED GLOBALLY: 670[5]

Postpartum hemorrhage (PPH), severe and uncontrolled bleeding after childbirth, is the most common cause of maternal mortality accounting for an estimated 130,000 maternal deaths each year.[1] Another 2.6 million women, who experience PPH, are left disabled.[2] Many of these mortalities and morbidities (94%) occur in contexts where poverty is endemic and as the result of inadequate healthcare and resources.[3]

In 2012, the World Health Organization (WHO) put out a series of updated prevention and treatment guidelines for PPH. The recommendations called for uterotonics (drugs to induce contractions) as well as other therapeutic options, as a first line of treatment; a second line of treatment included surgical interventions and uterine balloon tamponades (UBTs).[4] In the developing world, uterotonics and surgical interventions are often inaccessible. UBTs can cost upwards of $400 each, a steep price for a device that can be used only once.[5]

In 2009, a team from Massachusetts General Hospital (MGH) began to develop a low-cost UBT for the developing world. Borrowing from "Sayeba's Method" and other UBT designs, they developed the Every

Second Matters for Mothers and BabiesTM -Uterine Balloon Tamponade (ESM-UBT).[6] This device costs less than $5 USD and is fashioned from a condom attached to a Foley catheter. When a woman is experiencing uncontrolled PPH, the ESM-UBT is inserted into the uterus. The condom/balloon is filled with water, applies pressure to the uterine wall, and stops bleeding. This life-saving technology can be used by lay midwives, community health workers (CHW), health aides in non-surgical health facilities, and even at home.[7]

In 2012, the MGH team conducted preliminary research into the feasibility of using UBTs in South Sudan. This study provided evidence to show that training CHWs on UBTs was feasible and effective.[8] In 2013, the MGH team received a grant from the Saving Lives at Birth Grand Challenge that enabled them to introduce the ESM-UBT in other low-resource settings. Additionally, with the help of their partners (ministries of health, USAID, PATH), they published a study in 2015 that demonstrated the safety and effectiveness of the ESM-UBT in stopping hemorrhage.[9] Research indicated an overall survival rate of 97%, rising to 100% if the ESM-UBT is placed before a woman goes into advanced shock.[11,12]

By 2017, more than 20 countries in Africa and Asia had introduced use of the ESM-UBT, but only 670 devices had actually been used![5,11] This is because despite rapid acceptance at country/MOH level, other factors influenced use of ESM-UBTs.[11] First, UBTs are a second line of treatment and thus, only used when the first line is not available or effective. Additionally, although the WHO encourages the use of UBTs, the recommendation for use is described as weak, with very low-quality evidence. It has taken eight years for the WHO to prioritize an update to its recommendations on UBTs, including the newer evidence of their safety and effectiveness.[13] Another disadvantage is the need to put together an ESM-UBT before use, unlike the Ellavi UBT, which is preassembled for ease and rapid use. The ESM-UBT business model relies on a regional or local business to distribute and package items that are used to assemble the ESM-UBT devices. This means that countries lacking such a company cannot mass produce and scale this device.[14] Other factors limiting uptake have been country specific. For example, Sierra Leone was ready to implement a national program to scale-up the use of the ESM-UBT when the Ebola epidemic hit. This forced the Ministry of Health to funnel funds slated for the ESM-UBT program towards the fight against Ebola.[7]

Overall the ESM-UBT has been proven to be effective in treating PPH, and has the potential to save lives, especially in low-resource settings. WHO should be encouraged to update its recommendation. It is time for champions to develop the business case for this low cost, live-saving device and for it to be included in the essential equipment list for maternal care. Global advocacy and inclusion in global development projects would help expand use of this valuable device in places where it is needed the most.

KEY INSIGHTS TO LAUNCH AND SCALE

WHO recommendations are guideposts for Ministries of Health in many countries, but delays in updating its recommendations to include the latest research in may significantly hinder the use of available, proven and life-saving devices such as the ESM-UBT. If WHO only updates its PPH guidelines every 5 years, we may not see changes in UBT recommendations until 2020, 10 years after the device was first recommended.

A key feature of the ESM-UBT is its accessibility to lower level health facilities, where millions of women deliver their infants. Such a low cost, life-saving intervention could be an essential element in primary health care and community-based delivery kits.

New mechanisms to invest in innovations from the global South are needed. Sayeba Akhter, a physician in Bangladesh, developed the first UBT using readily available hospital items in 2000. The MGH team used her idea as the basis for the ESM-UBT. It was only after introduction by the MGH team, that the UBT got global traction and funding. Current funding mechanisms for innovation favor entrepreneurs in the global North who have teams dedicated to grant sourcing and writing. Thus, we may be missing many frugal innovations developed in LMICs and the global South.

COUNTRY RESEARCH INSIGHTS FROM INDIA AND ETHIOPIA[15]

In Ethiopia: The ESM-UBT has been introduced but is still in the testing phase because there is no real implementation support (not enough trainers, material being imported). UBTs would require more advocacy to scale in Ethiopia. Currently, there is no system to train newcomers and turnover rates at health facilities are high.

In India: Due to COVID-19, the main manufacturer for the ESM-UBT has now been redirected to focus its manufacturing on PPEs for the country. This has indefinitely delayed the introduction of ESM-UBT at the national level.

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LAUNCH & SCALE SPEEDOMETER

Long-Lasting Insecticide-Treated Nets

Photo from U.S. President's Malaria Initiative

Long-lasting insecticide-treated nets (LLINs) are bed nets that kill mosquitos carrying the parasite that causes malaria, thus preventing malaria.

GLOBAL BURDEN OF DISEASE: ESTIMATED 228 MILLION CASES IN 2018

TIMELINE FROM IDEATION TO 50% GLOBAL SCALE UP: 24 YEARS (1993 TO 2017)

TREATMENTS DISTRIBUTION:
578 MILLION INSECTICIDE TREATED NETS (ITNS), THE MAJORITY OF WHICH WERE LLINS, WERE DISTRIBUTED IN 2016-2018 (WITH 197 MILLION DELIVERED IN 2018 ALONE)

Malaria is a serious disease transmitted to humans through mosquitos infected with Plasmodium parasites. The disease can cause fever, chills, and other flu-like symptoms. If left untreated, it can be life-threatening. In 2018, there were an estimated 228 million cases of malaria and 405,000 deaths worldwide.[5] Sub-Saharan Africa is the most affected region with six countries accounting for more than half of all malaria cases worldwide. It is a particular burden for pregnant women and children in terms of infection and death. Mothers with malaria during pregnancy are more likely to have premature and low birth weight babies, while children under age 5 accounted for 67% of malaria deaths in 2018.[5]

One way to prevent malaria is to sleep under long-lasting insecticidal (bed) nets (LLINs), a category of insecticide-treated nets (ITNs), which, when used correctly, are designed to physically block mosquitoes and kill them before they can bite a person. The first ITNs were developed and tested in the 1980s. Since individuals regularly wash their nets along with their bed linens, these original ITNs were only effective for several months, after which they needed to be re-impregnated with insecticide. LLINs were developed to be more sustainable and cost-effective; even with washing, they last about three years.[6]

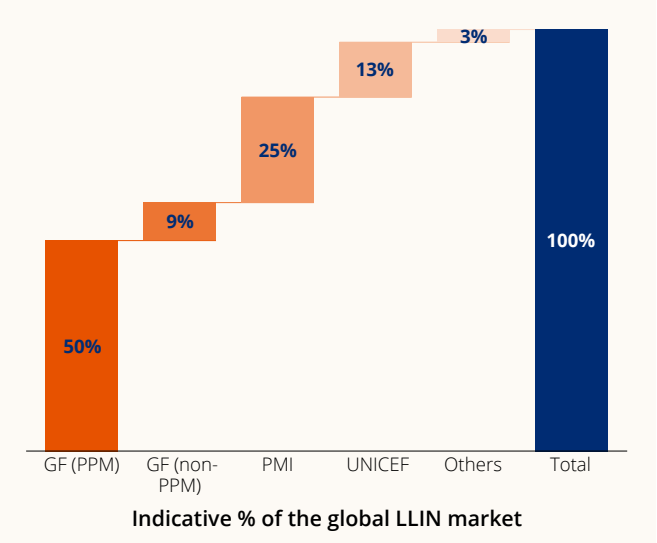
Around the turn of the 21st century, the world increasingly focused on reducing and eradicating

malaria. In 1998 and 2000, the Roll Back Malaria partnership and the United Nations Millennium Development Goals (MDGs) respectively, set ambitious goals to reverse the incidence of malaria by 2015 through the use of new tools, strengthening health systems, and engaging cross-sector partners.[28] In 2002, The Global Fund to Fight AIDS, Tuberculosis, and Malaria was founded to serve as a financing mechanism for the international effort to combat these diseases and continues to serve as a primary purchaser of malaria control interventions. Early on in the eradication fight, LLINs became a key component of a multi-faceted approach to malaria control, which includes additional prevention mechanisms like indoor residual spraying (IRS), environmental control to eliminate breeding, and prophylactic antimalarial medicines; diagnostic testing and treatments for confirmed malaria cases; and national surveillance for targeted deployment of interventions.[5]

In 2001, the World Health Organization Pesticide Evaluation Scheme (WHOPES; now the WHO Prequalification Team for Vector Control (PQT-VC)) evaluated one of the newest tools in the malaria control toolbox at the time, LLINs, and gave Sumitomo's Olyset net the first certification for quality, safety, and efficacy, allowing it to be widely procured and distributed.[3] According to the WHO, in order for a bed net to be an LLIN it had to "retain its effective biological activity without retreatment for at least 20 standard WHO washes under laboratory conditions and three years of recommended use under field conditions."[7] A recent analysis indicates that LLINs have been found to reduce the incidence of malaria by 56% when compared to no net use.[17] There are now 22 LLINs prequalified by WHO for their safety, quality, and efficacy, and available globally.[9]

In 2007, the WHO recommended that all countries purchase only LLINs and that these nets be provided free or be highly subsidized for all populations, not just pregnant women and children under five years old as previously recommended.[6] While country governments are responsible for malaria policies and the distribution of bed nets, international organizations have been instrumental in increasing access to LLINs by providing funding to national malaria programs, technical assistance for behavior change approaches in populations, distribution, or supply chain management, and centralizing purchasing through pooled procurement. The Global Fund, the President's Malaria Initiative (PMI), and UNICEF, among others, purchase most of the bed nets for highly burdened countries, particularly those in sub-Saharan Africa (see Figure 1).[5,16] These organizations have also succeeded in negotiating lower prices with LLIN manufacturers. For example, the Global Fund's Pooled Procurement Mechanism for LLINs lists reference prices ranging from $1.90 to $2.95 per net for country or grant budgeting purposes in 2020 – an 11% and 16% respective decrease from January 2016 reported prices.[12,13]

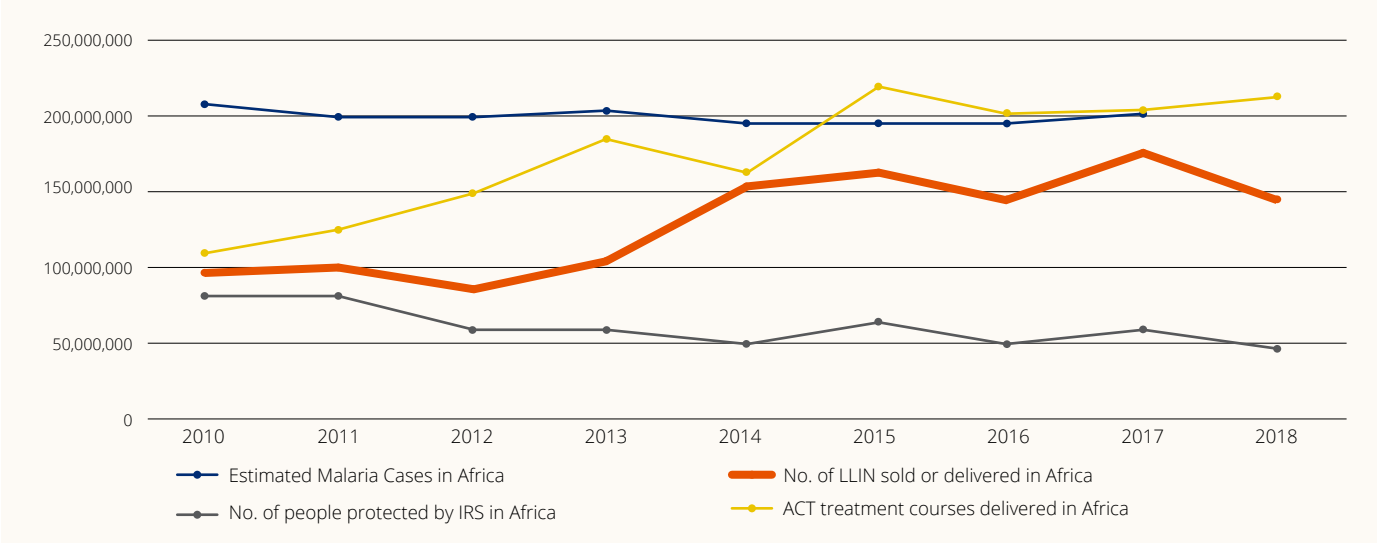
Figure 1 **Indicative % of the global LLIN market by purchaser.**



Sources: The Global Fund. Long-lasting Insecticidal Nets Supplier & Partner Consultative Meeting. September 2019

This support has led to a vast scale-up of LLINs primarily through mass distribution campaigns, albeit over a timeframe of nearly two decades. Millions of these nets (mostly LLINs) are typically delivered and distributed on a three-year universal campaign cycle, with some 197 million distributed in 2018 alone.[5] About 2 billion nets (ITNs and LLINs) have been delivered worldwide since the start of distribution campaigns in the early 2000s.[8] The African region, where 80-90% of the global malaria burden exists, has experienced approximately a 50% increase in net sales or deliveries since 2010 (see Figure 2). Overall, ITNs, IRS, and artemisinin-based combination therapies (ACTs) have reduced cases of malaria in Africa between 2000 and 2015 by 68%, 22% and 10% respectively.[23]

Figure 2. **Malaria Incidence and Intervention Coverage in Africa**



Sources: World Malaria Reports 2012, 2015, 2017, 2019 and WHO Global Observatory Data

Still, in 2017, only half of the population at risk for malaria in sub-Saharan African countries slept under bed nets and distribution of nets has remained around 150 million per year since 2014.[5] The total estimated cases of malaria in Africa has also decreased little since 2010 (Figure 2), leaving questions about the effectiveness of preventive vector control methods since that time. In order for bed nets to be effective, people must use them correctly and sleep under them every night. As the data shows, many people with nets do not sleep under them every night; individual reasons for not using a bed net range from the hot, humid climate making the nets uncomfortable, to not using them during the dry season when there are fewer mosquitos.[17] Also, as malaria is seen as a common, unavoidable disease in many places, the value of net use may be underestimated or not understood.[17] Other reasons for reduced use are excessive washing, tears, and even loss of the nets. A recent commentary has called for more nets to be delivered and continuous net distribution, to reduce malaria morbidity during the three-year period in between campaigns, when net use declines.[10] Continuous distribution may be supported by increased engagement from the private sector in the sale of LLINs to supplement existing public sector campaigns. A recent study has shown that households are turning to the private sector to purchase nets, particularly urban, wealthier households and households that are either seeking to fill an access gap or desiring custom features that are not available in the publicly distributed versions.[14]

There is also growing concern about resistance to pyrethroid insecticides, the only insecticide recommended by WHO for ITNs and also commonly used in IRS campaigns, as 81% of malaria-burdened countries report pyrethroid resistance.[24] Manufacturers are beginning to address this concern by using piperonyl butoxide (PBO) in the nets, in addition to the pyrethroid insecticide. PBO is a chemical that inhibits the ability of the mosquito to detoxify the insecticide before it takes effect.[20] In 2008, WHOPES recommended the first PBO net to combat insecticide resistance.[21] Seven years later, in 2015, the WHO Evidence Review Group, recognizing that PBO LLINs may be beneficial in certain settings with pyrethroid resistance, recommended that pilot studies should be conducted to understand their benefit in various settings and to continue to build the evidence base for their use.[20] In 2017, following the results of one study in Tanzania, WHO gave conditional endorsement of pyrethroid-PBO nets as a "new class of vector control products" and recommended that national malaria control programs deploy PBO nets in specific situations with confirmed, intermediate-level pyrethroid resistance.[15] This conditional recommendation for use of PBO nets is included in the 2019 WHO Guidelines for Malaria Vector Control.[22]

Adding to the evidence base of the effectiveness of pyrethroid-PBO nets, a recent large study in Uganda that distributed more than five million nets, showed that nets treated with PBO reduced parasite prevalence more effectively than pyrethroid-only LLINs.[19] Given increasing evidence of effectiveness, the demand for PBO nets is increasing, making up approximately 15-20% of the overall demand for LLINs in 2020, and potentially up to 25% in 2021 according to The Global Fund.[16] As of August 2020, WHO has prequalified six PBO nets.[9] Growing concerns over increasing insecticide resistance has also evoked at least one call to action to develop more durable and insecticide-free nets, which could be manufactured locally in Africa at competitive scale and prices, unlike today's nets which are primarily produced outside the continent.[18]

In sum, LLINs have scaled to the regions of the world that need them most and contributed to the achievement of the Millennium Development Goal that reduced global malaria incidence by 37% by 2015.[11] Bed nets will continue to be an important component of malaria control efforts and finding innovative ways to combat insecticide resistance and encourage greater use, primarily in endemic regions of sub-Saharan Africa, will be key to their ultimate success.

KEY INSIGHTS TO LAUNCH AND SCALE

Global partnerships like Roll Back Malaria and the UN MDGs brought visibility to malaria control and, when aligned with the evidence of LLIN effectiveness, built the political will to introduce and scale up the distribution of LLINs. Early efforts to primarily protect pregnant women and children under five were modified when new evidence that mass distribution could protect all community members emerged, leading to a revised WHO recommendation. International development aid organizations like the Global Fund, USAID/PMI, and UNICEF also were critical in negotiations for pooled purchasing and lower net prices. The alignment of global partnerships, visibility, evidence and political will were critical to the scaling of LLINs.

External donor funds backed the procurement of the majority of LLINs for universal distribution at low- or no-cost to populations, leading to significant scale-up. However, given the current potential for global economic volatility, domestic resources must also be mobilized for countries to maintain or expand LLIN use. Given the strong business case for malaria control and the cost-effectiveness of LLINs, global malaria leadership can advocate and assist governments to increase domestic resource mobilization for malaria, as they have done for HIV. The cost savings and health outcomes from eliminating malaria are substantial for countries like Ghana, whereby mobilizing USD $961 million to eliminate malaria over the next decade would produce a 32-fold return on the country's investment from cost-savings and health and economic returns.[25] There is a need for similar investment cases to be made for other high burden countries.

Significant research, including gold-standard randomized control trials and strong surveillance systems, continue to be the basis for program and policy decisions for LLINs and other vector control interventions. Use of high quality vector control/malaria data from surveillance and global malaria programs has been instrumental in monitoring and evaluating the effect of scaling LLINs, changing course with new insecticides to combat resistance, and evaluating the cost and effectiveness of diverse malaria control interventions.

Despite impressive scaling, only 50% of populations at risk sleep under a net in sub-Saharan Africa and distribution in Africa has stagnated at around 150,000,000 nets per year. It is clear that new research and behavior change approaches are needed to break the impasse in net use globally. Persuasive technology tactics applied through social media could target bed net use, and locally made nets might increase availability and access in hard-to-reach areas. But as noted in more detail below, increasing and broad private sector commitment will be critical.

The public sector has driven the advancement of LLINs, with primary responsibility for leading national malaria control programs, but to further extend the reach and use of LLINs, the private sector will need to be increasingly mobilized. Research has shown that the private sector is playing an important role in providing access to LLINs on a regular basis outside of the three-year campaign cycles run by the government. People are willing to purchase nets, especially if they lose access to a net in between campaign cycles or if

they are wealthier, more educated households. The private commercial sector also provides nets that are suited to customer preferences, rather than the standard ones manufactured specifically for global donor programs. In addition, the private sector is critical in the development of new insecticides and new methods of malaria control, including insecticide impregnated garments and housing materials.

Insecticide resistance is a growing challenge which requires innovation and the evolution of next- generation bed nets. It took almost 10 years for the WHO to include PBO nets in malaria control guidelines and in that time resistance to pyrethroids markedly increased. New and continued partnerships between public, private and academic centers are needed to address growing insecticide resistance, and to advocate for more rapid changes in global guidelines. The private commercial sector in partnership with global development agencies could be critical in leading needed innovation.

COVID-19 IMPACT ON LLIN DISTRIBUTION EFFORTS

According to Sherrard-Smith et al., 27 of 47 malaria-endemic countries in sub-Saharan Africa have bed net distribution campaigns scheduled to take place in 2020.[26] Unfortunately, the typical distribution mechanisms that involve large gatherings of people collecting the nets, are not advised during the pandemic. The nets that were distributed three years ago in these countries are now nearing the end of their effectiveness. A recent study found that "if malaria prevention efforts are halted, the malaria burden in 2020 could be more than double that of 2019."[26] It is imperative that governments do their utmost to safely and effectively continue to distribute LLINs to communities in need. The Alliance for Malaria Prevention advocates for the continued distribution of nets during the COVID-19 crisis, with guiding documents for safe distribution developed for countries.[27]

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LAUNCH & SCALE SPEEDOMETER

Sayana® Press (DMPA-SC)

Photo from PATH/Gabe Bienczycki

An easy-to-administer three-month injectable contraceptive (depot-medroxyprogesterone acetate, DMPA-SC) administered into the fat below the skin.

GLOBAL BURDEN: 190 MILLION WOMEN WITH UNMET NEEDS FOR CONTRACEPTION[1]

TIME FROM PRODUCT IDEATION TO FIRST IN COUNTRY LAUNCH: 19 YEARS

TOTAL DISTRIBUTION : AVAILABLE IN > 30 FAMILY PLANNING 2020 COUNTRIES (2019)[2]

PRICE: $0.85 USD PER DOSE FOR QUALIFIED BUYERS (FAMILY PLANNING 2020 COUNTRIES) FROM MAY 2017 TO 2022[3]

9 YEARS

1995
IDEATION
Effort to deliver DMPA in disposable, single dose syringe begins[4]

2005
PROOF OF CONCEPT
DMPA-SC demonstrated effective as a contraceptive method[4]

2011
REGULATORY AUTHORITY APPROVAL
UK Medicines and Healthcare Products Regulatory Agency (MHRA)[5]

2014
FIRST COUNTRY LAUNCH
Sayana® Press launched for commercial use in Burkina Faso[6,7]

2015
WHO POLICY
Recommendation of DMPA-SC for use as a contraceptive[8]

An estimated 190 million women in low- and middle-income countries (LMICs), have unmet needs for contraception despite the availability of a wide range of options.[1] This unmet need is due to a variety of factors that affect women in LMICs differently than in other parts of the world. Many women in LMICs cite the great distances they must travel to clinics, stock shortages at facilities, and a lack of support in their family planning decisions as barriers to accessing contraception.[9]

Injectables are a popular contraceptive choice in LMICs. In Sub-Saharan Africa (SSA), 47% of modern contraceptive users choose injectables.[10] Unfortunately, access to these injectables is plagued by many of the aforementioned barriers. The most common injectable is depot medroxyprogesterone acetate or DMPA. Traditionally, DMPA required the services of a healthcare provider, who had access to the necessary vials, syringes and needles, and was trained to do the intramuscular injection.[11] This meant

that women had to find transportation to clinics multiple times a year. Not surprisingly, this proved to be a difficult task.[12]

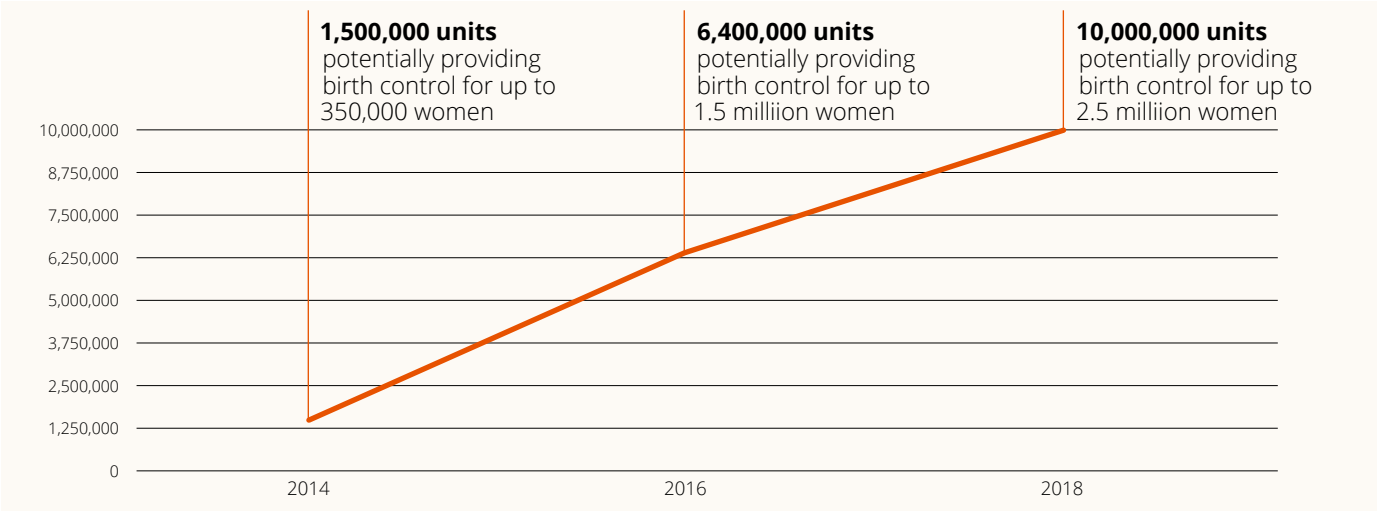
This challenge led PATH and partners to champion development of DMPA-SC under the brand name Sayana® Press (SP). SP can be injected subcutaneously with the BD Uniject™, a single-use, prefilled injection system named for licensee Becton Dickson & Company.[13] With little training, physicians, nurses, community health workers (CHWs), pharmacists, and even the women themselves (in countries where self-injection is approved) can administer the correct dose to prevent pregnancy for at least three months. Because CHWs and women can administer the contraceptive, SP is a game changer that has brought injectables from "the clinic to the home."[14] The injectable is safe, effective, and it affords women full access to birth control, while preserving their choice and privacy.[6,4]

SP's story began in the 1980s when PATH developed the uniject system it then licensed in the 1990s to Becton Dickson and Company (BD), a global medical technology company. That same decade, PATH partnered with USAID and Pfizer Inc. in an effort to deliver DMPA in the all-in-one injectable system. This partnership combined BD's expertise in medical technology and Pfizer's expertise in pharmaceuticals and product commercialization.[6] Pfizer completed clinical trials to prove the efficacy of SP in the mid-2000s.[6] In 2011, the contraceptive received regulatory approval from the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA).[4,5,6]

The following year, FP2020, a public-private partnership began funding efforts to provide 120 million more women in 69 countries with access to contraceptives.[15] This global consortium was aimed at focusing the family planning agenda and supporting the fertility rights of women and girls. It became a critical enabler of the scale-up of Sayana® Press. Pfizer committed to manufacturing SP and registering it in various markets, while FP2020 partners (PATH, UNFPA, DFID and USAID) would be in charge of in-country distribution and implementation.[16,17] These partners committed to launching SP in sub-Saharan Africa and South Asia, and to disperse 12 million doses of SP by 2020.[18]

In 2013, acceptability studies began in Ethiopia, Uganda, and Senegal, and pilot projects introduced the contraceptive in Burkina Faso, Niger, Uganda, and Senegal in 2014.[6,19] PATH led some of these efforts with funding from USAID, UNFPA, BMGF, and others.[20] The pilot projects, which focused on CHW administration of SP, were done in partnership with the ministries of health in each country.[11] This led to a smooth transition to scale a year to 18 months after the contraceptive was introduced, highlighting

Figure 1 **Sayana® Press Scale: Units shipped to 20 LMICs since pilot introductions in 2014**



Data for chart from sources 21, 24

the importance of country-level coordination and buy-in. Additionally, the introduction and delivery of SP marked a change in policy and scope/norms of practice with non-clinical CHWs becoming key providers of SP and bringing contraceptives closer to home.[11] SP also showed promise among new contraceptive users and young women (women and girls < 25 years) with uptake ranging from 30% to 70%, amount to 44 % of all doses.[11] During this time, researchers also explored the feasibility of self-injection.6 In 2016, a label update for self-injection was approved by the MHRA. Now, self-injection is permitted in 20 FP2020 countries.[6,2]

From 2014 through 2018, "10 million units of Sayana Press were shipped to 20 developing world countries, potentially reaching more than 2.5 million women" (See figure 1 for SP scale over the years).[21] This meant a 614% increase in four years and amounted to 83% of the 12 million dose commitment with two years to spare.[18,21] In 2017, the Access Collaborative (BMGF, Pfizer, and the Children's Investment Fund Foundation), negotiated a lower price for qualified buyers at $0.85 USD per dose (from $1 USD), which made the cost competitive with intramuscular forms of DMPA.3 In 2019, SP was available in nearly half (>30) of the FP2020 focus countries.[2]

Despite continued success, the introduction and implementation of SP has not been without challenges. Part of the problem is fear of side effects and the issue of who delivers the injections.[22,23] Some governments are hesitant to change norms or policies about who can administer contraceptives for fear that the injections will not be done correctly or safely, that follow-up will be more difficult.[23] These reasons are why only 20 out of 30+ countries where SP is available have approved self-injection.

Overall, SP has expanded access to contraceptive methods available to women in LMICs (especially among young women and new users).[11] In places where women lack empowerment to make their own family planning decisions, this discrete contraceptive gives them the ability to decide if, when, and how many children to have. Getting SP into women's hands for self-injection de-medicalizes family planning and will ultimately lead to healthier and more prosperous families and communities.

KEY INSIGHTS TO LAUNCH AND SCALE

Sayana Press (SP) is a game changer in family planning, shifting care from clinics to community and homes and in so doing, "de-medicalizing" family planning. Furthermore, with the approval of self-injectable SP, for the first time in history, women themselves have effective control of their reproductive decisions.

- Approval of self-injection in more countries is essential for more women to access SP. SP helps address the challenges (distance to health facilities, lack of family or partner support) underlying unmet needs for contraception.
- SP provides an opportunity to task share with community providers and reduces the burden on medical facilities, while it also shifts FP care to non-clinical settings and the homes of women themselves.
- There is growing evidence that self-injection may help decrease the rates of discontinuation among young women.

Organizational partnerships and a global consortium made the development, financing and scaling of SP possible.

- Collaborative partnership between profit and nonprofit companies with different areas of expertise (global health research, medical technology, pharmaceuticals and product commercialization) were essential for the development and advancement of SP. One company (PATH) also played a pivotal brokering role, bringing the companies together, and then obtaining the financial support of a FP global champion and investor, USAID.
- Another trajectory-changing public-private partnership, the FP2020 Global Consortium was largely responsible for setting a global agenda, catalyzing funding, and negotiating lower prices to assure access to SP in nearly 70 countries
- Division of roles enabled the Consortium to utilize their diverse strengths to advance development, funding, distribution and uptake – to achieve clear distribution goals by 2020

- However, a note of caution: over-reliance on global champions can mean that global health issues or products not in the "initiative spotlight" may have difficulty attracting funding and attention

Country uptake was accelerated by support from both public and private sectors.

- Simultaneous with product development and efforts to gain regulatory approval, acceptability and research pilot studies were undertaken in conjunction with Ministries of Health in multiple countries, thus preparing their health systems, policies and providers for rapid implementation
- Global organizations championed the use of SP and advocated for low-price agreements, as well as providing funding for research, and advocating for policy changes
- Partnerships with Ministries of Health shaped introduction and scale strategies making it easier to integrate SP into the public supply chain and eased the transition from pilots to scale.

COVID-19 IMPACT

Concerns over the spread of COVID-19, have led to decreased access to health services like family planning as many women in LMICs are under lockdown or quarantining and have limited access to healthcare providers. Self-injection or CHW provided injection is possible even in these extreme circumstances. Ironically, the COVID-19 crisis may increase the demand for Sayana® Press.

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LAUNCH & SCALE SPEEDOMETER

Xpert® MTB/RIF

Ernesto Ortiz, Elina Urli Hodges, Diana Silimperi

Photo ©John Rae

The Xpert® MTB/RIF, is a fully automated molecular test to diagnose tuberculosis (TB), including its most resistant form rifampin (RIF), in less than 90 minutes and with minimal laboratory expertise.

GLOBAL BURDEN OF DISEASE: APPROXIMATELY 10 MILLION NEW CASES AND 1.2 MILLION TB DEATHS IN 2018[1]

PROOF OF CONCEPT TO 50% GLOBAL UPTAKE: 8 YEARS

TOTAL DISTRIBUTION:

- 34.4 MILLION XPERT® MTB/RIF CARTRIDGES PROCURED BY COUNTRIES ELIGIBLE FOR CONCESSIONAL PRICING AT THE END OF 2017[2]
- 67% OF HIGH BURDEN COUNTRIES (HBC) INCLUDED XPERT® MTB/RIF IN THEIR NATIONAL POLICY (2017) UP FROM 31% IN 2015[2,4]

PRICE: $9.98 PER CARTRIDGE, FOR THE PUBLIC SECTOR IN 145 HIGH-BURDEN AND DEVELOPING COUNTRIES5

8 YEARS

2009
PROOF OF CONCEPT
Xpert® MTB/RIF proven effective through clinical validation trial[7]

2009
REGULATORY AUTHORITY APPROVAL
European CE Marking approval[8]

2010
WHO POLICY
WHO endorsed Xpert® MTB/RIF[10]

2011
FIRST COUNTRY LAUNCH
Xpert® MTB/RIF launches in South Africa[9]

2017
50% GLOBAL SCALE
More than half (67%) of HBCs include Xpert MTB/RIF in national policies

Tuberculosis (TB) is among the leading causes of morbidity and mortality worldwide. In 2018, an estimated 10 million individuals contracted TB, and 1.2 million died from it.[1]

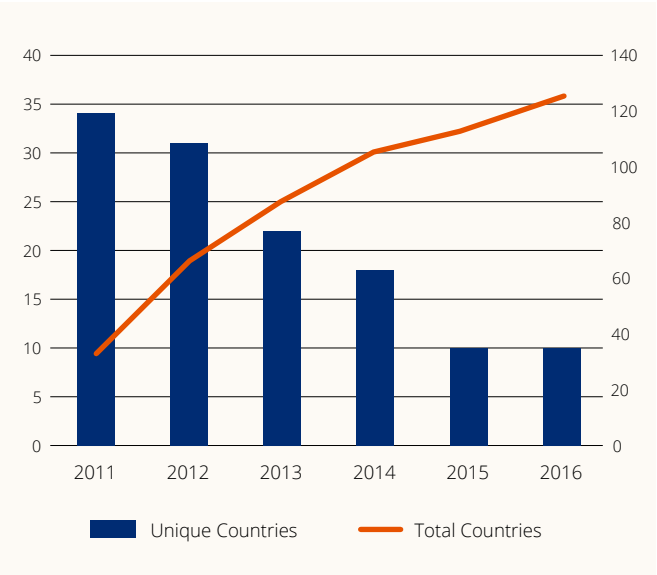
Multidrug-resistant TB (MDR) and extensively drug-resistant TB (XDR) are an increasing global public health concern.[1] Rapid diagnosis and timely and appropriate treatment initiation are fundamental to reduce the burden of TB. Delays in diagnosis and treatment lead to higher morbidity, mortality and transmission. Conventional diagnostic methods (e.g. sputum smear microscopy, culture and drug susceptibility testing (DST)) for TB are slow (6-8 weeks for bacterial growth from samples to be detected), technically demanding, and are not very accurate – resulting in patients going undiagnosed, or diagnosed too late, and not receiving treatment or receiving inappropriate treatment.[13]

The limitations of conventional TB diagnostics and the pressing need to improve diagnostic capabilities at the point of care drove the Foundation for Innovative New Diagnostics (FIND) to facilitate a partnership between industry (Cepheid) and academia (UMDNJ/Rutgers) in 2006 to improve diagnostics for drug-resistant TB.[8] This effort was funded by the U.S. National Institutes of Health and the Bill & Melinda Gates Foundation (BMGF). The resulting innovation from this partnership, named Xpert® MTB/RIF, is a fully automated molecular rapid test to diagnose tuberculosis and rifampin-resistant TB. The test provides a diagnosis in less than 90 minutes and with minimal laboratory expertise. It uses a cartridge with the patient's sample (i.e. sputum, nasopharyngeal aspirate, gastric aspirate and stool (pediatric diagnosis)), and the test is automatically performed by the multi-disease diagnosing platform GeneXpert®.

The development of Xpert® MTB/RIF has been a landmark event in the fight against TB, and is used as an example of a relatively fast pathway from development to scale up. In December 2010, a dynamic policy development occurred in which WHO assessed published and unpublished data on Xpert® (shared before publication thanks to nondisclosure collaborative agreements) and endorsed Xpert® MTB/RIF.[10] Subsequently in 2011, a WHO policy statement recommended the use of Xpert® MTB/RIF as the initial diagnostic test in individuals suspected of MDR-TB or HIV-associated TB.[10] Following these endorsements, the political will of several institutions (public and private) and multiple countries changed. Xpert® began to roll-out worldwide, primarily in TB-affected regions in low- and middle-income countries. In March 2011, South Africa, which then had the second largest number of cases in the world, "announced a rapid, nationwide scale up of access to Xpert, to be achieved within a 2–3 year period", and by the end of the year 33 additional countries were providing the diagnostic (Figure 1).[9]

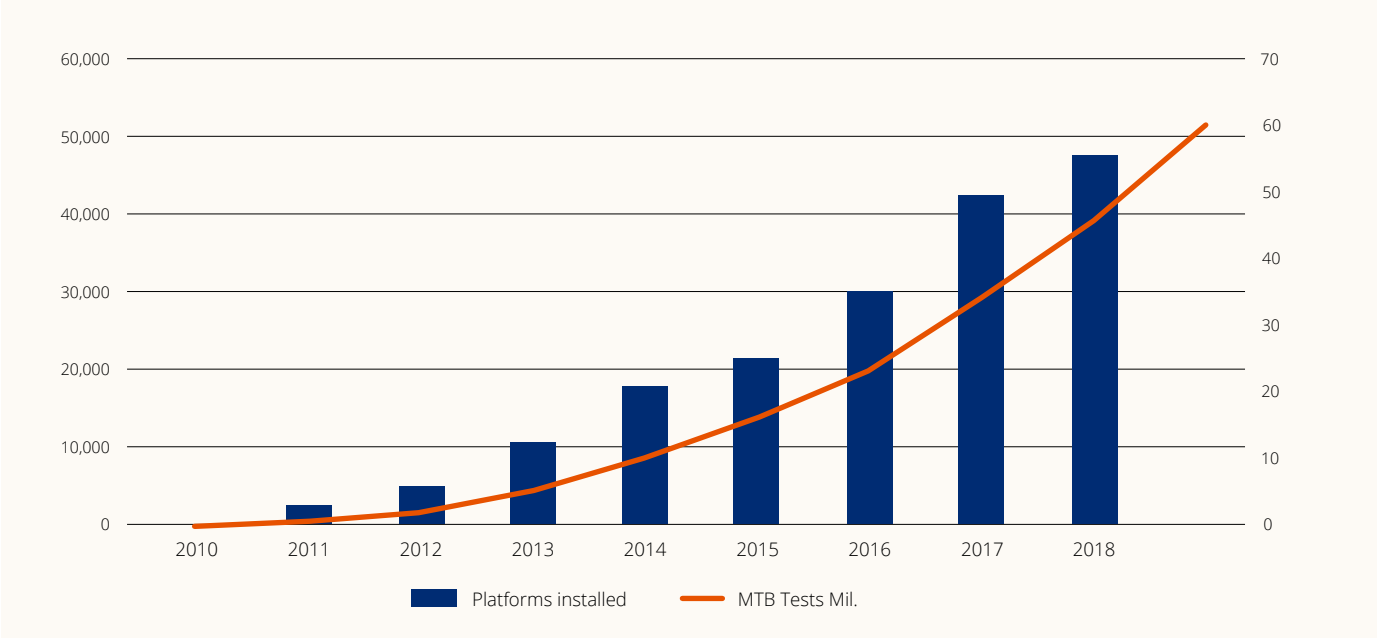
Other key events sped the scale up of Xpert® MTB/RIF worldwide. Prior to launching Xpert, FIND also negotiated prices with the industry to significantly reduce the upfront cost of both the GeneXpert platform and the Xpert MTB/RIF cartridges for LMICs.[14] In August 2012, a public-private partnership made up of PEPFAR, USAID, UNITAID, and the Bill & Melinda Gates Foundation negotiated a buy-down arrangement that resulted in an additional 40% price reduction of Xpert® MTB/RIF cartridges from USD$16.86 to $9.98 for 145 high-burden and developing countries, guaranteed until 2022.[5] Less than a year later, in 2013, after reviewing new scientific evidence, WHO updated its policy and recommended the use of Xpert® MTB/RIF as the initial diagnostic test for all individuals (adults and children) presumed to have

Figure 1 **Country Provision of Xpert MTB/RIF**



Data provided by GDF of public data from Cepheid 2010-2017 (email communication)

Figure 2. **MTB Tests Delivery Trend vs GeneXpert Platforms Installed**



Graph provided by Cepheid on an email communication in 2019

TB, thus increasing the potential market size for the intervention.[11] These events had a strong impact on the rollout and scale up of Xpert® MTB/RIF worldwide, with the majority of countries providing the diagnostic by 2014 (see Figure 1). Also by 2017, 32 out of the 48 (67%) countries listed as a high TB-burdened country (HBC) included Xpert® MTB/RIF in their national policy as the initial diagnostic test for all people suspected of having pulmonary TB, a 113% increase from 2015.[2,4] Countries eligible for concessional prices procured 6.2 million cartridges in 2015, up from 550,000 in 2011.[2,4] By the end of 2018, 46 million cartridges had been delivered to high TB-burdened countries (HBC) (see Figure 2).[3]

Xpert® MTB/RIF has advanced point-of-care diagnosis, however, its drawbacks include a relatively high cost, reliance on sophisticated hardware to perform the diagnosis (GeneXpert® platform), a stable connection to an electrical power grid, air-conditioned temperatures to operate effectively, a reliable cold chain for storing the cartridges (2-28°C), and trained laboratory staff. These drawbacks all pose critical challenges in remote locations, especially in those with hot climates.[13] The shelf-life of the Xpert® MTB/RIF cartridge is only 16 months, which necessitates efficient procurement and distribution to assure a reliable supply of cartridges. Additionally, the lack of uniformity in country procurement processes pose another barrier to scale up. To address this, the Stop TB Partnership's Global Drug Facility (GDF) provides technical assistance to countries to improve their procurement mechanisms and has a pooled procurement mechanism that allows countries to get better prices for TB drugs and diagnostics.[18]

In order to overcome some of these obstacles as well as to improve its diagnostic capabilities, this innovation continues to evolve. In 2015, a plan to bring this diagnostic tool even closer to the most remote point-of-care settings (primary health posts and centers)—the GeneXpert® Omni—was unveiled. This platform consists of a mini-portable, battery operated GeneXpert® system that will not require an air-conditioned environment and a computer, just a mobile device to transmit data that enables its use in the most remote healthcare settings. However, several technical challenges have delayed the Omni's launch. In response to this delay, in 2018 Cepheid launched the GeneXpert Edge as an interim solution. The Edge is a portable, battery operated platform, but still relies on air-conditioned temperatures and computer, which prevent it from being used as real point-of-care diagnostic.[17]

In 2017, Cepheid launched a new updated version of the Xpert® MTB/RIF cartridge, the Xpert® MTB/RIF ULTRA which has a better TB detection capability (increased sensitivity) and a more definitive identification of RIF susceptibility and resistance. In March of that year, the WHO recommended Xpert® MTB/RIF ULTRA as a replacement for the current Xpert® MTB/RIF cartridge.[14]

In recent developments, in June 2020, the WHO consolidated guidelines on tuberculosis and recommended that Xpert® MTB/RIF and Xpert® ULTRA should replace the traditional smear microscopy/ culture and drug susceptibility testing (DST) as the initial diagnostic test for TB and rifampicin-resistance detection.[12] In July 2020, FIND and Cepheid launched their new Xpert® MTB/XDR test that is able to detect TB that is extensively drug-resistant, the most complicated form of TB (resistant to multiple first-and second-line TB drugs), in anticipation of a review and recommendation by WHO by the end of 2020.[16] At the same time, market competition in LMICs is increasing for Xpert® MTB/RIF, with new diagnostic tests, TruenatTMMTB and Truenat MTB Plus, developed by FIND, Molbio Diagnostics, and the Indian Council of Medical Research (ICMR), endorsed by WHO in July 2020.[20]

Xpert® MTB/RIF has revolutionized TB control by bringing a rapid, reliable diagnostic nearly to the point-of-care. But in countries where weak and dysfunctional health systems and inadequate infrastructure are highly prevalent, having this tool available does not solve the problem of poor-quality TB services. In order to effectively address the disease burden of TB, a more comprehensive approach is needed. An approach that not only involves expanding the coverage of screening, diagnostics, and treatment services, but also improves the quality and timeliness of those TB services through health system strengthening.[19]

KEY INSIGHTS TO LAUNCH AND SCALE

Global public and private sector partners were involved at every stage of the development and scale up of Xpert MTB/RIF catalyzing the speed of uptake and coverage. These collaborative partnerships were key for research, development, and funding which contributed to the generation of the scientific evidence that resulted in WHO's endorsement. Numerous implementation partners worked with the governments (national and sub-national levels) assisting with the integration of Xpert® MTB/RIF into national TB programs, providing comprehensive training programs, building laboratory capacity, and offering technical support.

Initial price negotiations by FIND and the buy-down arrangements, that reduced the price to less than USD $10 a test, had a strong impact on making this technology available in the countries most impacted by TB. However, this pricing is only available to the public sector and anyone seeking care in the private sector continues to pay significantly higher prices, estimated to average US$68.73 per test, for their diagnosis.[21] Going forward, including high quality private sector providers in lower pricing negotiations could be considered, especially in urban environments where they provide care for significant proportions of the population.

Although product features limited scalability in certain environments, continuous innovation and improvement played an important role in expanding scale and ultimate uptake. Such innovation is necessary to ensure access closer to the point-of-care and to reach remote locations**.** Limited shelf-life required faster procurement, delivery and distribution processes; cold chain transportation and storage made it more challenging in hot climates and remote locations. Relatively high cost, reliance on sophisticated and expensive hardware, a stable supply of electricity, and skilled laboratory staff, are all factors which pose ongoing challenges to scaling, and are being addressed through ongoing improvements in the product.

A comprehensive approach to TB care is needed. Integrating TB care – screening, diagnosis, and treatment – within primary health care would be an important step forward. Xpert® MTB/RIF is a critical diagnostic tool which will only reach its full potential when it can be used across the health system, including the most distal points of primary care. As Dr Tedros Adhanom Ghebreyesus, WHO Director-General, said during the launch of WHO's latest Global TB Report: "Sustained progress on TB will require strong health systems and better access to services. That means a renewed investment in primary health care and a commitment to universal health coverage."[22]

COVID INSIGHT

The COVID-19 pandemic has brought some opportunities and challenges to the scaling of the GeneXpert platform and the Xpert® MTB/RIF cartridges. Cepheid launched a rapid molecular test for COVID, the Xpert Xpress SARS-CoV-2 cartridge, which uses the same GeneXpert machines used for TB diagnosis. This opens the opportunity to scale the deployment of more GeneXpert platforms and likewise the possibility to scale the Xpert MTB/RIF cartridge. This has also triggered some concern among the TB scientific community because of the potential disruption of TB diagnoses due to the re-purposing of testing systems like GeneXpert platforms for COVID. [23]

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