The Global Fund / Vincent Becker

The TB Quarterly Update
Innovations

NOVEMBER/DECEMBER 2024

THE GLOBAL FUND

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About the TB Quarterly Update

The TB Quarterly Update is produced by the TB team at the Global Fund to share best practices, lessons learned and information from countries supported by the Global Fund, partners and other stakeholders, as well as updates on new innovations and tools coming onto market. If you have any information you would like to share, please reach out to TBQuarterlyUpdate@theglobalfund.org.

1. What's New

WHO Global Tuberculosis Report 2024

WHO recently released the Global Tuberculosis Report, which highlights recent progress in the fight against the disease. Notably, the number of people dying from tuberculosis (TB) each year continues to fall, while a record number of people with TB were notified in 2023. Gains have also been made in TB treatment globally—including increases in access to TB treatment and steady improvements in treatment outcomes for people with drug-resistant TB. While an estimated 10.8 million people fell ill with TB in 2023, an increase from 10.7 million in 2022, the rise (due to the effects of COVID-19) has slowed down and is starting to stabilize. Despite significant progress, TB remains one of the top 10 leading causes of all deaths globally. Advancements in TB prevention, diagnosis and treatment offer critical pathways to close gaps and translate global commitments into action, but much more investment is needed. In a statement on the WHO Global Tuberculosis Report, Peter Sands, the Executive Director of the Global Fund, emphasized, "We must invest more vigorously in the fight against this disease. Above all, we must tackle deep social inequities that make people more vulnerable to the disease and less able to access care. That is the surest way to end this disease as a public health threat." The 2024 WHO Global Tuberculosis Report can be found here.

United National General Assembly 2024

From 23 to 27 September 2024, the Global Fund joined heads of state, policymakers, donors, affected communities, civil society organizations and other stakeholders in New York for the 79th session of the United Nations General Assembly (UNGA). The Global Fund spotlighted the organization's Results Report and its role in Antimicrobial Resistance (AMR), among other key areas. During the High-Level Meeting on AMR, Marijke Wijnroks, Head of the Strategy, Investment and Impact Division at the Global Fund, highlighted the organization's role as the largest external funder for drug-resistant TB, as well as its investments in AMR through health systems strengthening. The event concluded with global leaders committing to decisive action on AMR, including reducing the estimated 4.95 million deaths associated with bacterial AMR annually by 10% by 2030. See the political declaration on AMR here.

The Stop TB Partnership (Stop TB) also successfully co-convened three side-events during the week with the United States Agency for International Development (USAID), Japan's Ministry of Health, Labour and Welfare, Indonesia's Ministry of Health, the Philippines' Department of Health, and Tajikistan's Ministry of Health and Social Protection of Population. These included a dialogue aimed at increasing awareness of the need for TB vaccine development and delivery, a side-event on advancing action on AMR, and the launch of a new report on the need for improved governance of national TB responses. More information is available at the Stop TB website.

2. Knowledge Sharing and Learning Resources

Case Study: Programmatic roll-out of BPaL/BPaLM for multidrug-resistant TB (MDR-TB) patients in Sierra Leone

Background

Sierra Leone is a high TB-burden country with approximately 24,000 TB cases annually. Programmatic management of multidrug-resistant TB (MDR-TB) started in 2017 with injectable regimens. In 2020, the TB program changed the treatment protocol to all-oral regimens. Sierra Leone was the first country to adopt the recently recommended bedaquiline, pretomanid, and linezolid/bedaquiline, pretomanid, linezolid and moxifloxacin (BPaL/BPaLM) regimens at a national scale without the experience of operational research. The six-month regimen was introduced as a first-line option for all MDR-TB patients in 2022.

Implementation

In January 2023 the BPaL/BPaLM regimen was available in all three drug-resistant TB (DR-TB) treatment sites in Sierra Leone. The intervention included a two-month preparation phase with technical support from Médecins Sans Frontières (MSF) Holland, which involved several meetings with stakeholders and DR-TB clinicians to determine the feasibility of the intervention. Following this, the TB program revised country TB guidelines to include specific BPaLM guidance, created implementation tools, and reviewed monitoring and evaluation (M&E) tools. The TB program also developed an M&E data tool to perform individual patient analysis. International experts from MSF and Partners in Health supported trainings for staff involved in DR-TB across all three DR-TB sites. Training included a pharmacovigilance review.

The only drug not available from the BPaL/M regimen was pretomanid, which was initially provided by MSF Holland and then the Global Fund via the Global Drug Facility. The first patients were started on the BPaLM/BPaL regimen in October 2022, with full roll-out by January 2023.

Innovations included:

- **Rapid implementation:**
  Instead of piloting the treatment in selected sites, the national TB program immediately rolled it out across all treatment sites. This approach ensured that the benefits of the new treatment reached a larger population in a shorter timeframe.

- **Context-specific adaptation:**
  The TB program adapted the protocol to the country setting. This involved modifications to local health system capacities, stakeholder engagement and operational constraints. By customizing the approach, the TB program ensured the treatment was not only effective, but also feasible and sustainable in the country context. This allowed equitable access to the new treatment for all TB patients in the country, demonstrating an inclusive approach that ensures no region or population was left behind.

- **Evidence generation:**
  Rolling out the treatment across all sites generated additional operational evidence on the effectiveness of the regimens outside of controlled research environments. This allowed for real-world data that could be used to further validate and refine the treatment for use in similar settings globally.

Results

Since its introduction, over 45% of MDR-TB patients have been managed using the BPaL/BPaLM regimens. Results have been encouraging, with high treatment success rates, even for late presenters with extensive lung disease.

Table 1: Results from roll-out of BPaL/BPaLM in treatment sites

Source: The National TB Program

Characteristic	2022	2023	Jan-June 2024	Total	% (n=128)*
Registered	15	86	72	**173**	-
Completed treatment	12	73	13	**98**	**77%**
Loss to follow-up	1	4	1	**6**	**4.7%**
Failed	0	0	1	**1**	**0.8**
Died	2	9	12	**23**	**18%**
On treatment	0	0	45	**45**	-

* This number reflects the total without those still on treatment.

Lessons learned and next steps

Initially, there was some hesitancy from clinicians because chest X-ray advanced disease was not a WHO exclusion criterion for BPaL/BPaLM regimens as it is for other all-oral short regimens. As a result, the clinical team selected these patients on a case-by-case basis, and they were monitored more closely for signs of non-response to treatment. In addition, no changes were made to the bedaquiline dose (200 mg three times per week, not 100 mg daily), as nurses and clinicians were already familiar with this dose.

Patient monitoring has been challenging in the national TB reference lab with frequent disruption in liquid and solid culture as there is no mycobacteria growth indicator tube (MGIT) functionality. Bedaquiline or linezolid drug susceptibility testing (DST) were also not available locally. The alternative option of sending specimens abroad is costly and couriers do not always accept to transport them. The high cost of pretomanid has had significant budget implications. Procurement for the first phase was done with reprogrammed Global Fund financing and included in the subsequent grant. Further challenges include the management of DR-TB limited to the three facilities and inadequate funding for TB prevention and management.

Next steps include:

- Strengthening the lab structures for timely diagnosis of further resistant patterns and to efficiently monitor treatment progress.
- Investing in MGIT and making all second line DSTs available in country.
- Training a greater number of staff, including pharmacists, lab technicians and additional nurses.
- Providing refresher trainings after implementation.
- Strengthening the community support for treatment adherence.
- Establishing a sample transportation system to GeneXpert sites and to the reference lab.
- Establishing structures for scale-up of a fully ambulatory treatment arm.
- Including a comprehensive package of care (nutritional, psychosocial, commodity management, etc.) as part of TB care in the country.

Case study: Using an innovative people-centered design (PCD) process to re-imagine TB care in Uganda and Viet Nam

Background

The Re-imagining TB Care (RTC) initiative aims to transform when, where and how TB services are accessed and delivered in TB-affected countries. The first step to achieving that vision is to enable countries to co-create innovations through early and active conversations with a broad spectrum of stakeholders.

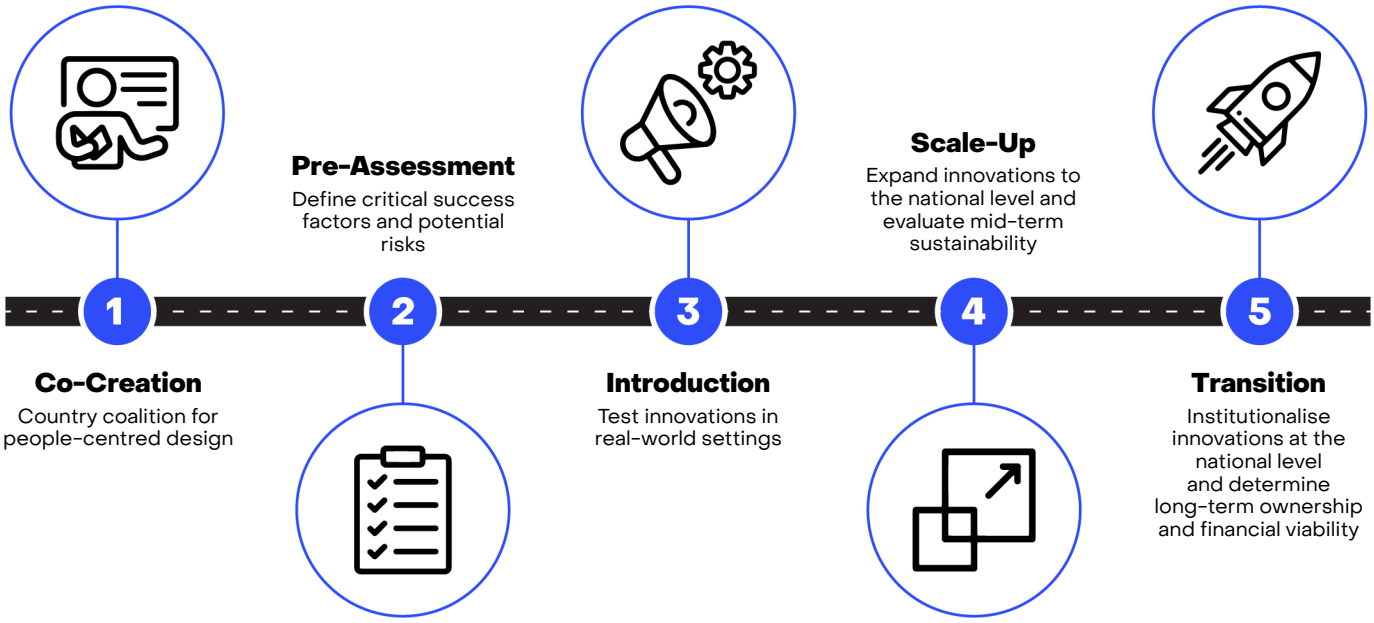
The Stop TB Partnership, in collaboration with its RTC stakeholders and partners, are advocating for a people-

centered design (PCD) process to make investments that can optimally increase the introduction, scaling or transition of an innovation. This investment can be in time, effort and funding, and should be early and proactive, beginning at the outset of an innovation's roll-out. This approach is similar to how many well-known private sector companies use a human-centered design (HCD) process to design and deliver innovations—rooted in a rigorous, measurable and established user-centric methodology.

Therefore, to support an iterative PCD process, Stop TB supported a complete set of stakeholders to come together to co-design an intervention to address critical challenges in the delivery of TB services in Uganda and Viet Nam in 2023. The PCD process described below is the first stage of the RTC initiative's five-stage innovation pathway framework to scale innovations (see Figure 1 below). The framework helps structure a scale-up plan through five stages: co-creation, assessment, introduction, scale-up and transition.

Figure 1: The RTC initiative's five-stage approach to scaling innovation

Source: The Stop TB Partnership



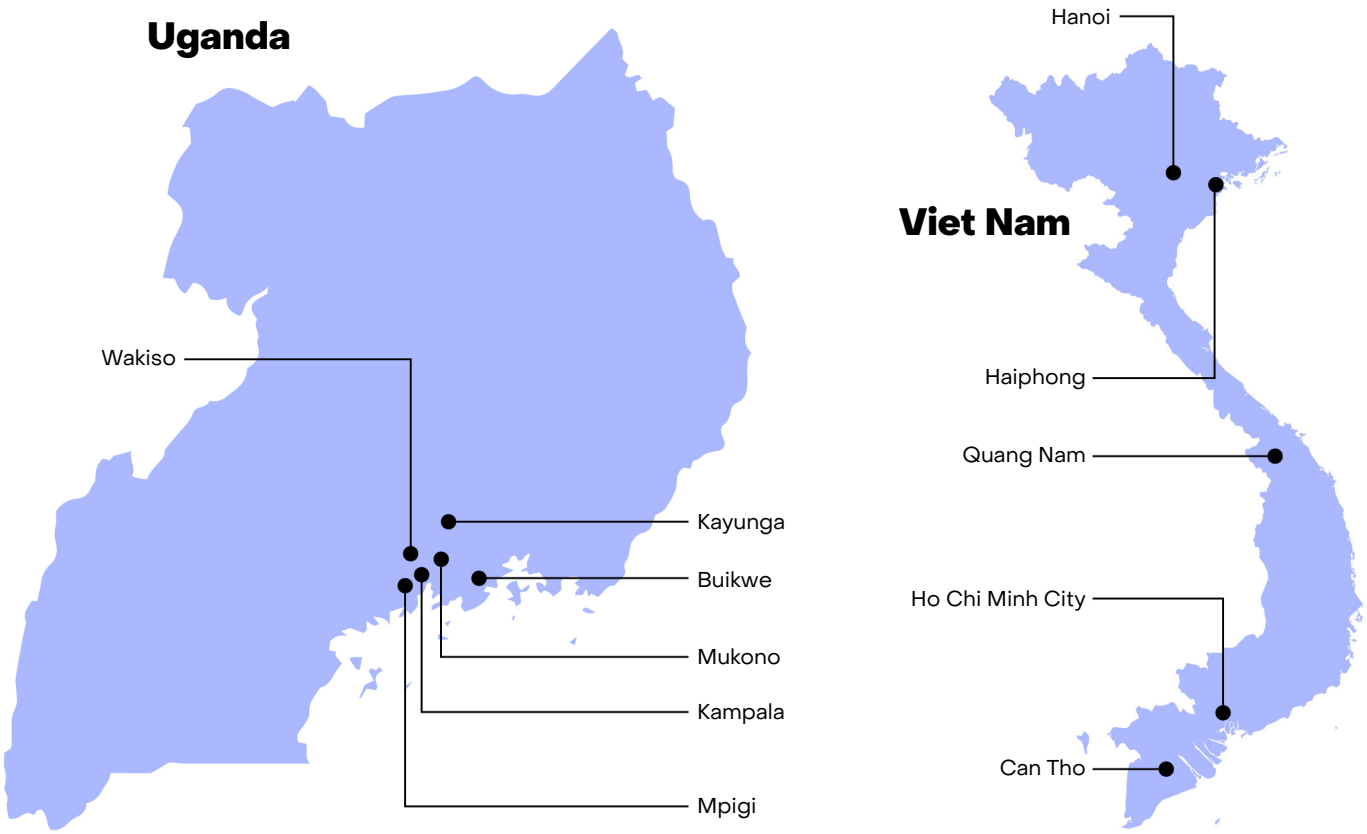
Implementation

The aim was to build a coalition of stakeholders (including TB-affected people, healthcare workers and policy-makers) to decide which problems to solve and which innovations to introduce in order to solve the selected problems. From March to November 2023, Stop TB worked with local partners in Uganda (WALIMU) and Viet Nam (FIT) to implement the PCD process, alongside a coalition of stakeholders to help evaluate, prioritize and ultimately decide what innovation to introduce. Target beneficiaries included TB-affected people and their families, community healthcare workers and national TB program staff.

The objective of the process was to create an RTC Leadership Group composed of representatives from different stakeholders in TB care, working with that group to brainstorm, filter and ultimately select an innovation to implement in each country. The hypothesis was that ideas co-designed and selected by all partners would be more appropriate, effective and scalable.

Figure 2: Locations across Uganda and Viet Nam in which the PCD process and interviews took place

Source: The Stop TB Partnership

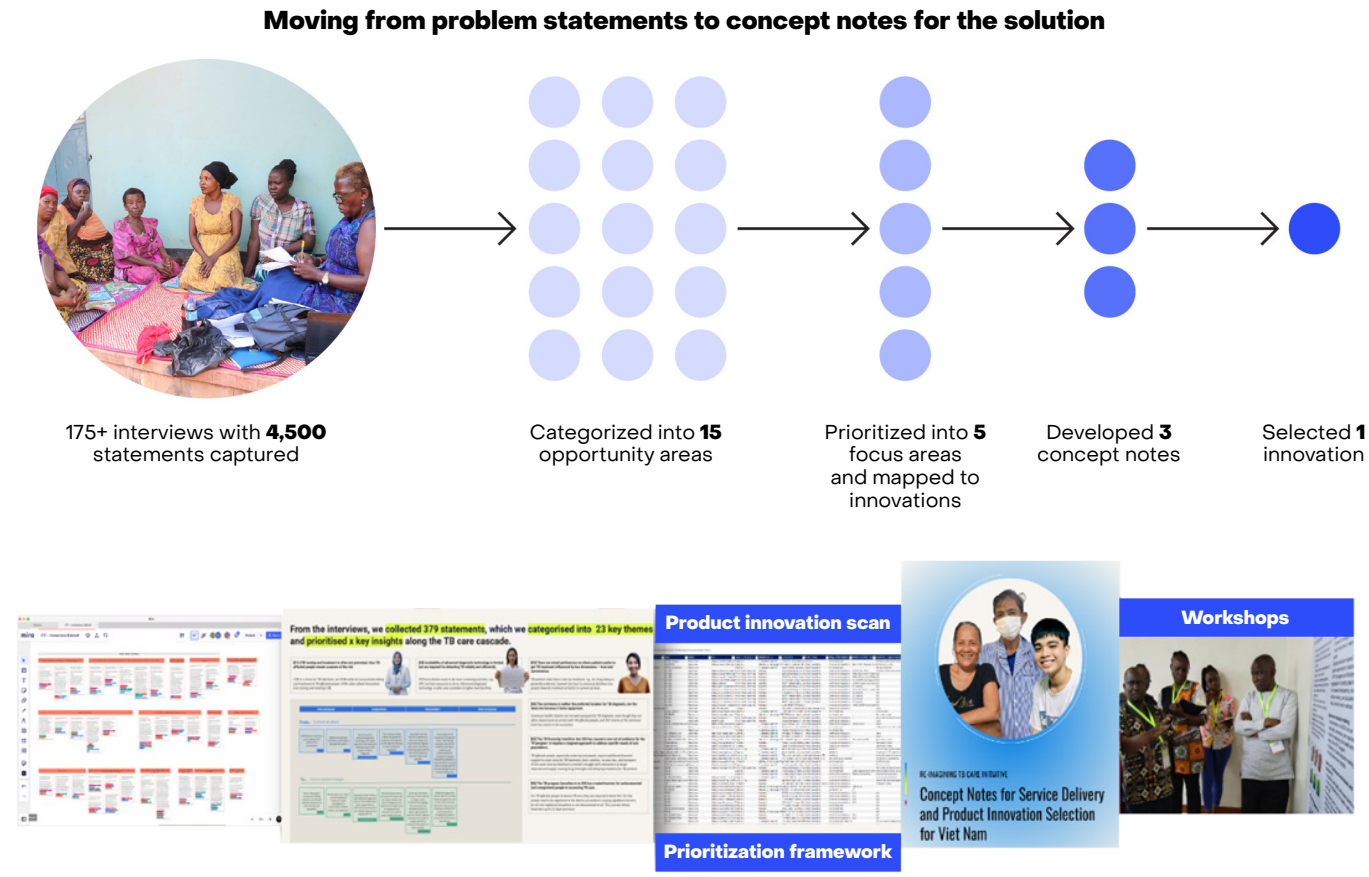


The RTC process began with an initial workshop where the PCD concept was introduced, the Leadership Group was convened and participants collectively defined how they would prioritize product innovations. This included categorizing innovations into three themes: desirability, fit and potential impact. The entire PCD process involved five key steps (see Figure 3):

1) Each local partner conducted approximately 90 interviews with TB-affected people and stakeholders to better understand their needs.
2) Interviews were summarized, translated and synthesized into 15 opportunity areas organized along stages of the care cascade: prevent, search, diagnose and treat.
3) In the first of three workshops, the in-country teams presented the 15 opportunity areas to the Leadership Group and as a group they ranked the five identified as most critical. Participants included TB survivors; TB-affected people; healthcare workers; the Ministry of Health; and NTP staff and managers, CSOs and NGOs.
4) A product innovation scan (InnoScan) was developed and mapped more than 450 innovations against those five prioritized opportunities. Those opportunity areas were presented in the second workshop, and the Leadership Group selected three opportunity area/innovation pairs to evaluate further and develop tentative implementation plans.
5) The team developed concept notes on each of the three areas, which were presented in the third workshop where the teams selected the final innovation to be introduced.

Figure 3: The filtering process through consecutive workshops and voting to select the highest priority innovation in each country

Source: The Stop TB Partnership

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A PCD focus group discussion during the data collection process around opportunities to improve TB services in Uganda


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PCD expert from FIT interviewing a healthcare provider in Can Tho, Viet Nam, to understand how to improve service care delivery

While the three workshops involving critical decisions were held in-person, the in-country teams had several discussions, pre-workshop meetings and online discussions to engage the Leadership Group throughout the process.

One participant from Viet Nam shared:

> *"This is the first time I've seen a project that facilitates close collaboration between TB-affected people, healthcare workers and policy-makers."*

Critically, the PCD process convened a diverse group of stakeholders to co-select an innovative approach to addressing the highest priority challenges facing people with TB in a specific context. Rather than simply giving feedback on a plan, TB-affected people co-designed the intervention alongside the NTP as equal participants. Many projects are either donor or government directed, and while they aspire to address real challenges, they may not be directly linked to what people truly need. While initiatives in global health often say they are "people centered", this process brought rigor and quantifiable metrics to demonstrate consistent and dedicated engagement in the decision-making process from all stakeholders.

Simultaneously, materials were developed to enable other organizations to replicate the process in the PCD Toolkit. While only one of the prioritized and selected innovations could be funded, the process produced many other exciting ideas that the countries are already proposing to other funders, citing the PCD process as evidence that there is demand. The InnoScan also helped identify new innovations that the countries were not aware of, including over 90 from high TB burden countries (i.e. Uganda, Viet Nam, India and South Africa).

Lastly, the advance mapping of the entire Five-stage Innovation Pathway also helped both country teams plan for what data they need to capture in order to influence national strategic plans, what funding would be required to scale and sustain these innovations and what levels of engagement/approval they would need from not only the Ministry of Health, but other related ministries like finance or technology/innovation. While teams often focus solely on implementation without investing in either a PCD process or mapping out the roll-out plan, this advance planning helps anticipate challenges and increase the likelihood of scale.

Results

The selected innovation in each country was as follows:

Uganda

In Uganda, the country will be deploying **digital and AI-enabled solutions to empower community health workers** to conduct integrated screening, awareness and support. The team will be integrating TB care modules into existing tools (eCHIS, eCBSS, LabXpert) and enabling data sharing across each application. The team will also be exploring AI-enabled support tools for healthcare workers to enable them to ask questions, get advice and assistance with their outreach efforts.


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Vietnam

In Viet Nam, the country will be developing **digital tools to address the financing gaps left by Viet Nam's Social Health Insurance (SHI) scheme** and social assistance systems by providing timely financial assistance for the most economically vulnerable people with TB through an existing national fund. The team will digitize the process to identify economically vulnerable people, register them with the PASTB fund, and process payments using traditional and electronic banking/wallets.

Fundamentally, people felt more included and heard, especially TB-affected people, as the selected innovation in each country was the one that better represented the needs of TB-affected people and they had an active role in it.

In the words of one participant from Viet Nam:

> *"I feel that I am encouraged to express myself here. My experiences and opinions are respected, and I feel that they are valued. I find it very satisfying and enjoyable."*

At the same time, senior government leadership also felt the process improved their ability to develop strategy and introduce innovations.

Dr. Stavia Turyahabwe, then Assistant Commissioner, Tuberculosis Leprosy Control, Ministry of Health Uganda, stated:

> *"Having people at the center of the design of TB interventions, and any other intervention is key in making sure that you achieve your intended goal and objective."*

Prof. Nguyen Binh Hoa, Vice-Director, National Lung Hospital, Viet Nam, shared:

> *"This is also the first time I have been directly involved in such a meaningful co-selection process. We had the opportunities to listen to inputs from all key stakeholders, including TB-affected individuals, healthcare providers from all levels, from local and national, and people's voices had the same importance and weighed the same."*

Lessons learned and next steps

There were initial challenges understanding the process and goals of a PCD process and co-selection of an innovation. Some TB-affected people did not feel comfortable sharing their opinions with government representatives and doctors present. The Leadership Group members organized workshops to build trust

and overcome these difficulties. As one example of how to facilitate these interactions, the WALIMU team in Uganda used small group breakouts that allowed people to express their opinions and input.

Both teams learned how to plan and structure these discussions better, how to relate the goals and innovation concepts to non-technical audiences and how to effectively present options and make decisions without the groups losing focus. In Uganda and Viet Nam, both teams strongly advocated for advance planning and continuous engagement with the Leadership Group throughout the process, rather than only at strategic moments such as workshops or dissemination events.

Reflecting on the entire process, Prof. Nguyen Binh Hoa from Viet Nam stated:

> *"We are in favor of this approach. I think to design a program, a project or a policy that meets people's needs and hopes, the time and effort spent on the whole process is worth it. I personally will advocate for this approach to be applied more widely, especially in the policy making process in Viet Nam. And I believe that with the PCD approach, with efforts made by the community as a whole, we can collectively drive positive change in TB care and treatment."*

After concluding the PCD process in 2023, partners in Uganda and Viet Nam have since gone through stage two (assessment) and are now beginning stage three (introduction) of their innovation roll-out strategy. While the innovation stages have been presented as sequential, it is not necessary for one stage to start only when the prior stage concludes. Activities from one stage may, and often do, overlap with activities in another stage or happen in parallel depending on the context. As of September 2024, the teams have devised systematic roll-out plans and evaluation studies, and are starting the digital development/integration of the system, including gathering early user feedback. Initial roll-outs are expected to start by the end of 2024. Scale up, analysis and incorporation of study results into national strategic plans and discussions are anticipated in 2025.

More information about the process can be found in the toolkit here, in case studies on the experience here, and RTC's website here. RTC is generously supported by KOICA's Global Disease Eradication Fund and CDC's Global TB team.

CASE STUDY: Cost, cost-effectiveness and efficiency gains of introducing modified short treatment for multidrug or rifampicin-resistance TB in Belarus, Georgia, Kazakhstan and Moldova

Background

In the Eastern European and Central Asian (EECA) region, financing mechanisms have historically encouraged inpatient hospital care for TB. High rates of drug-resistant TB in EECA amplify the disadvantages of hospital focused care, such as the risk of nosocomial transmission and higher treatment costs. WHO guidelines now recommend innovative, simplified six- and nine-month treatment regimens for drug-resistant TB. In GC6, the Global Fund supported the introduction of modified fully oral shorter treatment regimens (mSTR)[1] across 11 EECA countries. A cost-effectiveness analysis from four representative country case studies was conducted to help policymakers assess whether mSTR provides good value for money compared with standard drug-resistant TB care.

Implementation

Data were collected in collaboration with the WHO Regional Office for Europe and national TB programs in four countries: Belarus, Georgia, Kazakhstan and Moldova. Data on treatment outcomes and provider costs were analyzed using a Markov model to estimate average costs and quality-adjusted life years (QALY) gained with mSTR versus standard care. Differences in cost and QALYs gained between mSTR and standard

[1] The regimen consisted of Levofloxacin, Bedaquiline, Linezolid, Clofazimine and Cycloserine for a duration of 39 weeks. Cycloserine was replaced with Delamanid for patients with suspected resistance or intolerance.

care were summarized as an average incremental cost per QALY gained. Uncertainty around the results was estimated by varying key assumptions and model parameters.

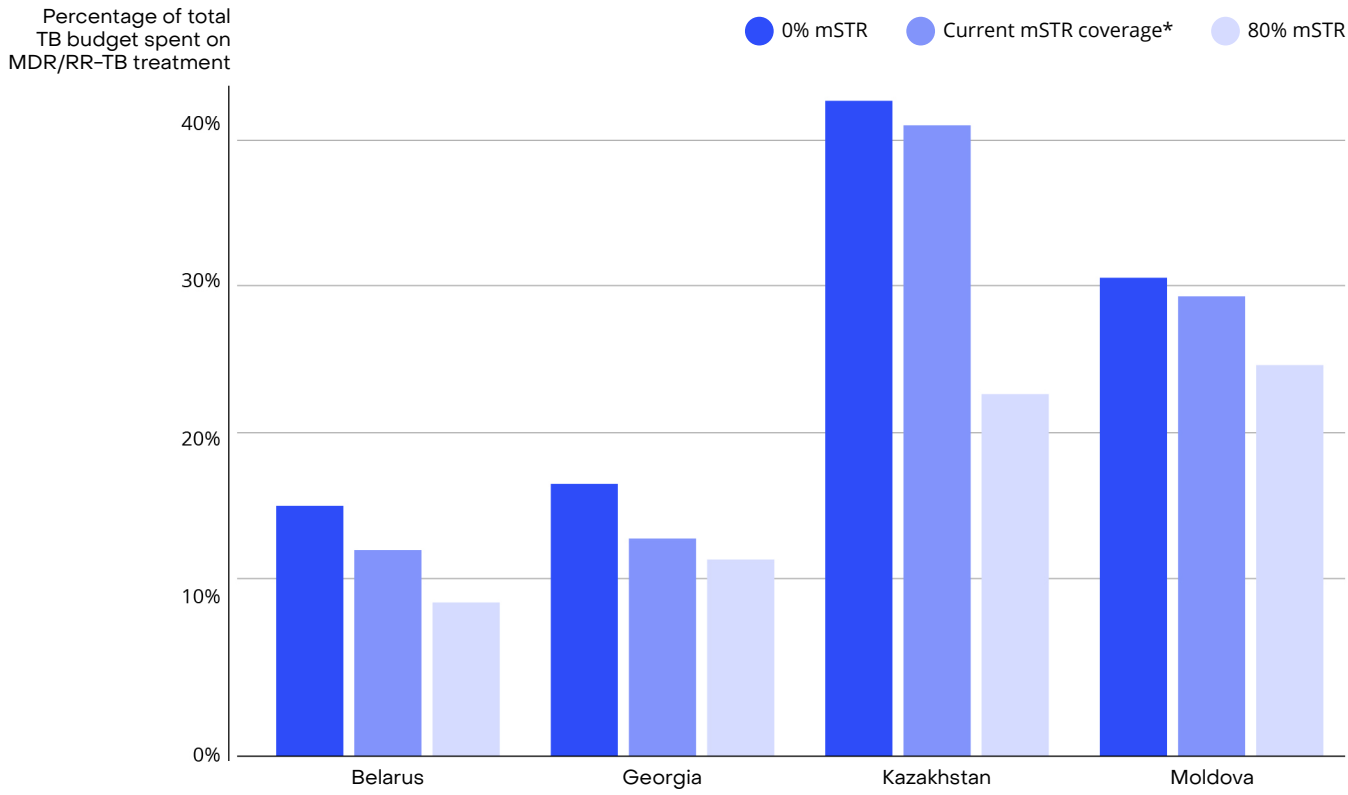
Results

Inpatient costs accounted for the largest proportion of the total treatment cost for both mSTR and standard care, except in Georgia. Total treatment costs per patient receiving mSTR were estimated to be US$7,682, US$7,161, US$5,711 and US$6,251 respectively in Belarus, Georgia, Kazakhstan and Moldova. This is between 23% and 47% lower than total treatment costs per patient for standard care in these settings, while drug costs for mSTR were between 39% and 74% lower than for standard care. Switching to mSTR from standard care would generate cost savings in all four countries of between US$3,596 and US$8,174 per patient, along with additional health gains of between 0.56-2.69 QALYs per patient in base case analyses. The mSTR treatment regimen remained cost-saving, with higher generated health gains compared with standard care in almost all scenarios. These results imply that mSTR likely provides better value for money than standard care in all four countries, with lower costs and greater health gains.

The impact of mSTR regimens on overall TB expenditure was also considered. Scaling up mSTR to a maximum of 80% of multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) patients in each country could result in cost savings of 3%, 1%, 17% and 4% of total annual TB budgets in Belarus, Georgia, Kazakhstan and Moldova respectively (Figure 4).

Figure 4: Impact of mSTR scale-up on MDR/RR-TB treatment expenditure

Source: WHO



* Current mSTR coverage is based on country level estimates (Belarus=34%, Georgia=57%, Kazakhstan=6%, Moldova=19%). An 80% upper limit for mSTR scale-up was assumed to reflect eligibility criteria, with the remaining 20% of notifications assumed to receive SOC. Similarly, 0% mSTR scenario assumes 100% coverage of SOC. Total TB budgets in each country were sources from WHO estimates.

Lessons learned and next steps

- This study found that the mSTR regimen for MDR/RR-TB was both more effective and less costly than standard care comparator regimens (drug treatment for 18-20 months comprising of Group A, B and C drugs, including injectables) in Belarus, Georgia, Kazakhstan and Moldova. Short course regimens containing Bedaquiline can be highly effective, reduce costs and reduce burden on patients. Such regimens are likely to be more acceptable to patients, given reduced disruption to their lives from a substantially shorter treatment duration.
- Further significant cost-savings at scale were found if adherence to mSTR treatment is improved, especially among countries with the lowest mSTR coverage (e.g., Kazakhstan and Moldova).
- Although social analyses were not conducted due to data limitations, shorter treatment courses would likely also lead to reduced societal costs and higher benefits, and these results therefore likely underestimate the cost-effectiveness of the mSTR treatment regimen.
- Reducing overall treatment duration is one aspect of increasing treatment acceptability and patient-centred care. However, long initial hospitalization periods also impact patients negatively and remain a substantial cost driver in the EECA region.
- Ideally, any cost savings from implementing mSTR should be retained and used by national TB programs to increase access to TB services, improve quality of care or reduce costs incurred by patients. This can help to ensure continued progress towards national and international TB control targets.

3. Other Updates

Supporting, mobilizing and accelerating research for tuberculosis elimination (SMART4TB) drug-resistant TB update

SMART4TB is a consortium that brings together experts in TB tools development, implementation science, capacity strengthening, civil society engagement and policy translation. Funded with support from USAID, the consortium is led by Johns Hopkins University and includes the University of California, San Francisco, the Elizabeth Glaser Pediatric AIDS Foundation, KNCV Tuberculosis Foundation and Treatment Action Group. SMART4TB's projects focused on drug-resistant TB include the PRISM-TB trial, which seeks to learn if shortened treatment of drug-resistant TB using a stratified medicine approach is as effective as the current standard of care. The trial will start enrollment in South Africa in the coming months with Moldova, Mongolia, Peru, the Philippines and Vietnam to follow. SMART4TB is finalizing plans for a related study in children, PRISM Kids. In partnership with the Building Expertise on Treatment of TB with Expanded Resistance (BETTER) project, SMART4TB also organized a workshop in Johannesburg, South Africa, gathering frontline providers, policymakers, implementers and affected communities to develop a field guide for treating rifampicin-resistant TB with expanded resistance to bedaquiline, linezolid, or the nitroimidazoles. Finally, the 1/4/6x24 campaign is rallying around WHO's DR-TB treatment guideline updates to expand access to shorter treatment regimens for drug-resistant TB and plans to release a related statement soon. Since the mid-campaign report was released, SMART4TB regional community advisory boards ECAT Afrocab and APCASO held regional launches to promote uptake of shorter regimens. To learn more about when SMART4TB trials launch or to follow news about the field guide and the 1/4/6x24 campaign, sign up for updates here.

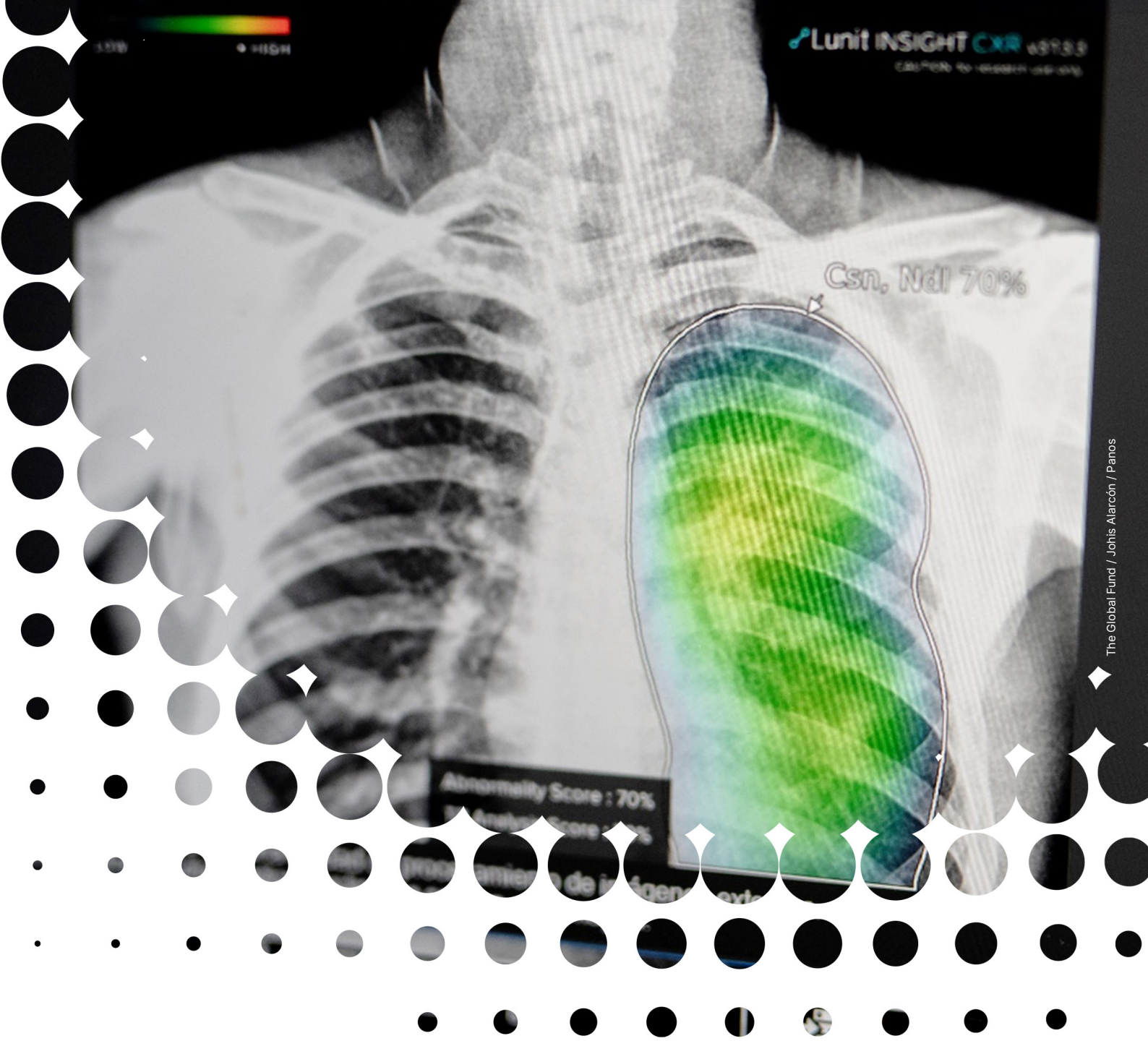
4. Voices

"Innovations in MDR-TB care should not only include better diagnostics and digital tools but should prioritize empowering patients to take an active role in their treatment. By listening to patients' voices and involving them in their own care, we are transforming outcomes and ensuring more compassionate, effective solutions for MDR-TB."

Dr. Mariama Mahmoud
Programme Manager
National Leprosy and Tuberculosis Control Programme, Sierra Leone

"The shorter DR-TB treatment regimens treated me really well. Once you choose hope, anything is possible."

Yondela Kolweni
DR-TB survivor
South Africa



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About the NextGen Market Shaping Strategic Initiative
The NextGen Market Shaping Strategic Initiative, financed by the Global Fund, will support the implementation of innovative approaches and mechanisms for the introduction and scale up of new tuberculosis tools in Global Fund-supported countries. This initiative is part of the Global Fund NextGen Market Shaping approach, which outlines a holistic set of interventions to shape innovation and accelerate new product introductions at scale, promote capacity building for regional manufacturing and drive environmentally sustainable procurement and supply chains.