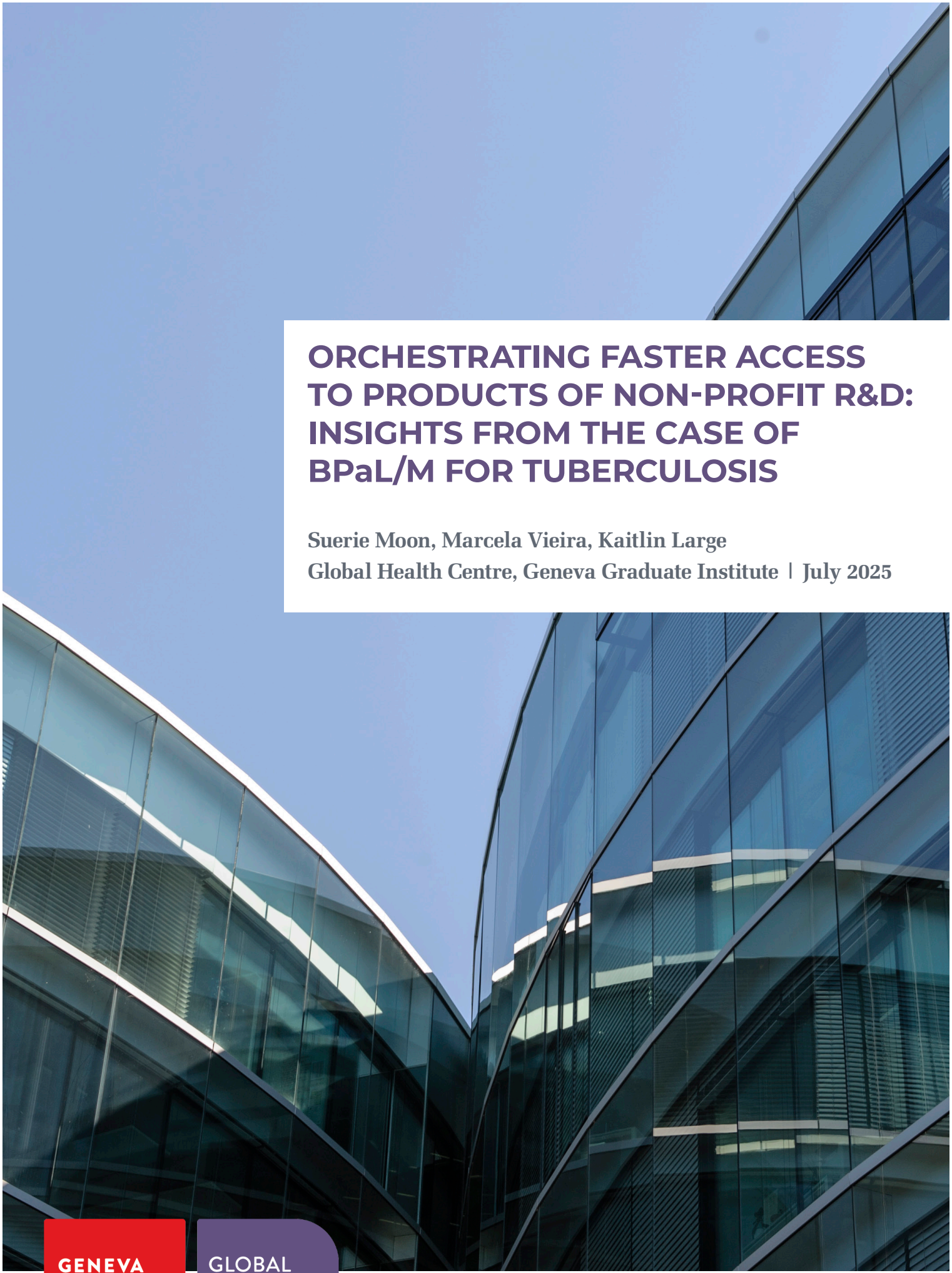

ORCHESTRATING FASTER ACCESS TO PRODUCTS OF NON-PROFIT R&D: INSIGHTS FROM THE CASE OF BPaL/M FOR TUBERCULOSIS

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LIST OF ABBREVIATIONS

ABBREVIATION	FULL FORM
BPaL/M	Bedaquiline, Pretomanid, Linezolid / Moxifloxacin
DALYs	Disability adjusted life-years
DCGI	Drug Controller General of India
DR-TB	Drug-resistant tuberculosis
DS-TB	Drug-sensitive tuberculosis
EMA	European Medicines Agency
EML	Essential Medicines List
ERP	Expert Review Panel
GDF	Global Drug Facility
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
GHC	Global Health Centre
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HICs	High-income countries
ITRC	International Tuberculosis Research Center
JHU	John Hopkins University
J&J	Johnson and Johnson
KNCV	Koninklijke Nederlandse Centrale Vereniging tot bestrijding der Tuberculose
KOICA	Korea International Cooperation Agency
LIFT-TB	Leveraging Innovation for Faster Treatment of Tuberculosis
LMICs	Low and middle-income countries
LPAD	Limited Population Pathway for Antibacterial and Antifungal Drugs
LSHTM	London School of Hygiene & Tropical Medicine
MDR-TB	Multidrug-resistant tuberculosis
MSF	Médecins Sans Frontières/Doctors Without Borders
NGO	Non-governmental organization
NTP	National Tuberculosis Program
OR	Operational Research
PDP	Product Development Partnership

ABBREVIATION	FULL FORM
PeerLINC	Peer-to-Peer Learning for Innovative Cures
PQ	WHO Prequalification
PRV	Priority Review Voucher
R&D	Research and development
RCT	Randomized controlled trial
SLASH-TB	Savings from Leveraging & Adopting Shorter & Highly Effective TB Treatments
SRA	Stringent Regulatory Authority
STBP	Stop TB Partnership
TB	Tuberculosis
TB-PRACTECAL	Pragmatic Clinical Trial for a More Effective, Concise, and Less Toxic MDR-TB Treatment Regimen
TBA	TB Alliance
US FDA	United States Food and Drug Administration
USAID	United States Agency for International Development
USD	United States dollar
WHO	World Health Organization
WHO GDG	WHO Guideline Development Group
WLA	WHO-listed regulatory authorities
XDR-TB	Extensively drug-resistant tuberculosis

EXECUTIVE SUMMARY

INTRODUCTION

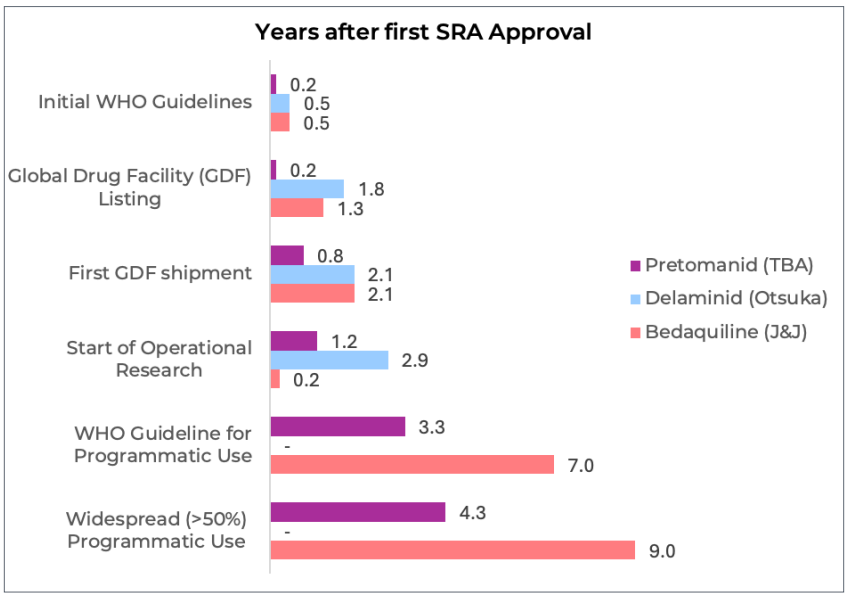
Over the past two decades, non-profit R&D initiatives such as product development partnerships (PDPs) have successfully brought nearly 80 new drugs, vaccines and diagnostics through regulatory approval. However, PDP mandates and funding have traditionally focused tightly on R&D, leaving it unclear which actors can and should ensure that these new products reach the right person at the right time – that is, achieve "access."

This report offers a case study of the role a non-profit PDP, the TB Alliance (TBA), played in rapidly achieving widespread access to a game-changing new treatment regimen it developed for drug resistant tuberculosis (DR-TB). TBA developed the new drug pretomanid as part of a regimen with bedaquiline and linezolid (BPaL), rather than as a standalone drug. This new approach to TB drug development offered the important advantage that evidence on how pretomanid could be used with other drugs was available immediately upon regulatory approval, averting the need for additional trials to answer this key question and enabling faster uptake. BPaL reduced treatment times for XDR-TB from 18+ months down to six, increased cure rates from 20% to 90%, while reducing pill burden up to 95%, lowering side effects for patients and decreasing the footprint on health systems. This regimen was later adapted to BPaL/M with the addition of moxifloxacin for broader use.[1] TBA orchestrated a wide range of interventions with diverse actors across global, national and local levels to achieve widespread access to BPaL/M within five years after first regulatory approval and two years after WHO recommended it for programmatic use.

Based on the academic and grey literature, internal documents, and interviews with TBA and representatives of fifteen other organizations, we summarize the range of access interventions, describe TBA's role and the key attributes that enabled it to play this role effectively, and offer conclusions for ensuring access to the products of non-profit R&D more broadly.

1 In the remainder of this report, we use the acronym BPaL/M to indicate that the regimen may be used with or without moxifloxacin (M). WHO recommends moxifloxacin be dropped from the regimen when there is evidence of fluoroquinolone resistance. See https://www.who.int/publications/i/item/B09123. The regimen was first developed and approved in 2019 as BPaL (that is, without moxifloxacin), with WHO's updated 2022 guidelines adding moxifloxacin. To simplify, we use BPaL/M throughout this report except in cases where the addition or subtraction of moxifloxacin is of substantive importance, such as when calculating regimen prices.

Figure 1. Uptake of three novel TB drugs: Years after first SRA approval



Sources: (1–5). (Figure and data provided by TB Alliance)

RESULTS: WHAT INTERVENTIONS DID TBA ORCHESTRATE FOR RAPID ACCESS TO BPaL/M?

We summarize the complex set of TBA's access interventions into three broad categories :

a. Regulatory and normative guidance:

Recognizing that regulatory and normative guidance can either speed or stall country adoption, key objectives in TBA's access strategy were obtaining regulatory approval from a stringent regulatory authority (SRA) and in TB high-burden countries, and inclusion in WHO TB treatment guidelines.

Regulatory Approvals

TBA's strategy included first filing for regulatory approval with the US Food and Drug Administration (US FDA), an SRA, based on the rationale that it would give confidence to a wide range of stakeholders on the regimen's safety and efficacy, and quickly unlock eligibility for countries to use international donor funds to purchase the new regimen. The US FDA approved pretomanid as part of BPaL in 2019.

Recognizing the importance of quality-assured generic versions of pretomanid, TBA licenses required manufacturers to have approval from an SRA or WHO Pre-Qualification (PQ) and to prioritize filing with national regulatory authorities in TB high-burden countries. By late 2024, pretomanid had been approved by 33 regulatory agencies for use in 62 countries.

Engaging with WHO on TB Treatment Guidelines

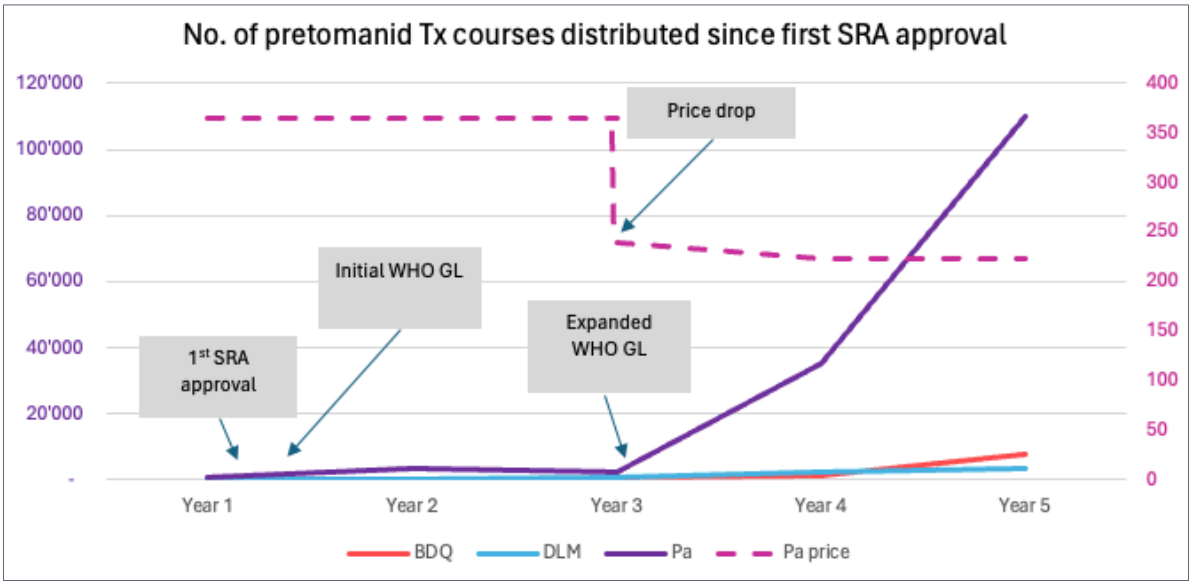
TBA also prioritized engagement with WHO on how the new regimen could be incorporated into its TB treatment guidelines. WHO recommendations can profoundly influence national TB programmes and are often a requirement for international donor funding. In May 2020, WHO released new guidelines recommending BPaL for XDR-TB, but limited to operational research conditions. This first WHO recommendation was based on the results of the Nix-TB trial, a Phase 3 single-arm study on potential use of the regimen for XDR-TB conducted by TBA in South Africa with 109 patients. The 90% cure rate found in this trial generated great

excitement in the TB community. Nevertheless, the WHO Guidelines Development Group raised concerns about the limited evidence provided by this trial and the generalizability of the study findings to all populations and all regions. Additional evidence would be needed to recommend it for programmatic (routine) use.

By 2022, sufficient evidence had been generated by two additional trials as well as operational research (discussed further below) for WHO to recommend BPaL/M for programmatic use. Uptake jumped after this guideline change, with over 100 countries procuring BPaL in quantities to reach nearly 110,000 patients in 2024 alone, about 63% of those on DR-TB treatment worldwide (6). In addition, WHO approved TBA's application to add pretomanid to its Model List of Essential Medicines in 2023.

Some interviewees suggested that the broader WHO recommendation could have been obtained faster with a different clinical trial or regulatory strategy, and urged clearer communication between product developers and WHO on evidence standards for guideline development. That said, the progression from SRA approval (2019) to WHO programmatic guidance (2022) in three years was unprecedented for a new TB regimen, and scale-up outstripped the uptake of previous TB breakthroughs (like bedaquiline or delamanid) in a comparable timeframe (Figure 2).

Figure 2. Number of treatment courses distributed since first SRA approval



(Source: TB Alliance)

b. Market Shaping for affordability and availability:

TBA orchestrated various market-shaping interventions towards making BPaL/M affordable and available, recognizing that the regimen's clinical benefits alone would not be sufficient to ensure country adoption.

Non-Exclusive Licensing to Quality Generic Manufacturers

To expand production and spur competition TBA granted non-exclusive licenses for the LMIC market to three generic producers with track records of quality production. Licenses were also agreed with two other generic manufacturers in China and Pakistan, a strategy to facilitate product uptake and security of supply in those countries.

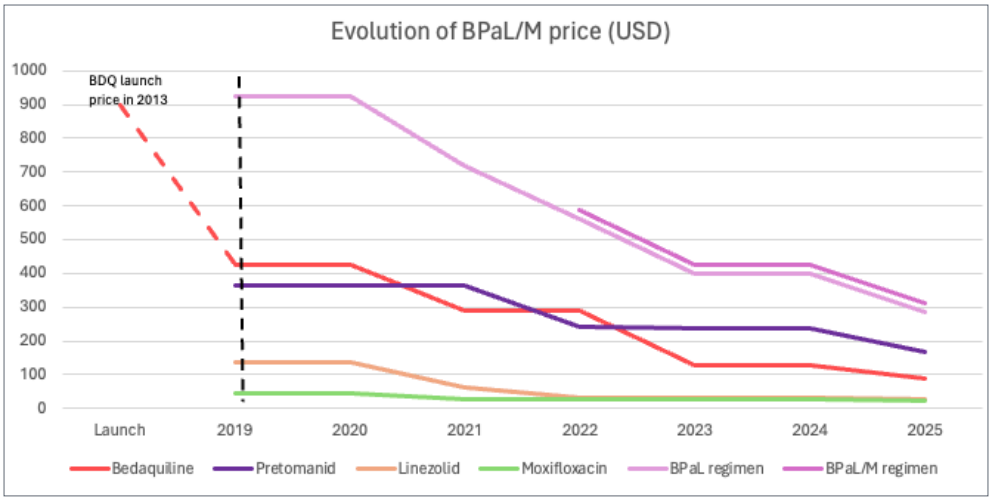
Global Drug Facility (GDF) Listing:

TBA moved quickly to ensure inclusion of pretomanid into existing procurement channels. Notably, pretomanid was added to the Stop TB Partnership's Global Drug Facility (GDF) catalog two months after FDA approval, the fastest inclusion of any TB drug post-SRA approval. By late 2019, countries could order pretomanid (as part of BPaL) through the GDF, the preferred route for many countries and the GFATM for TB drug purchases.

Price Negotiation and Volume Guarantee:

TBA negotiated a launch price of USD 364 for pretomanid with generic manufacturer Viatris, the lowest launch price of a novel TB drug. The BPaL regimen's initial price (~USD 1000) was significantly lower than some prior DR-TB regimens (USD 2,000-8,000), but still far above the target price of USD 500 advocated for by civil society groups. In 2022, anticipating increased demand from the broader WHO recommendation, TBA helped broker a volume guarantee between the global health financing vehicle MedAccess and Viatris, who agreed to cap the price of pretomanid at USD 240 per treatment course. By 2023, price reductions in all three components of BPaL dropped the regimen price to below USD 400, which fell further to USD 310 in 2025.

Figure 3. Evolution of the price of BPaL/M regimens (in USD)*



Economic Evidence for Decision-Makers:

To complement price reductions, TBA invested in economic analyses to demonstrate that adopting BPaL/M was financially feasible and advantageous for countries. To facilitate national-level decision-making, TBA published acceptability/feasibility, cost-savings, budget impact and cost-effectiveness studies for BPaL/M, and engaged in demand forecasting with national TB programs and manufacturers. TBA also developed SLASH-TB, an online tool for countries to estimate their own cost savings from switching to the new regimen, helping to remove budgetary uncertainty as a barrier to uptake.

Concerns Flagged

However, the relatively low-volume DR-TB market was a central challenge for ensuring security of supply and low prices, as economies of scale were difficult to achieve. This issue is also relevant for other small markets such as neglected diseases and pediatric formulations. Views differed on how to balance tradeoffs between the benefits of multiple suppliers (i.e. competition, security of supply) against the risks (i.e. fragmentation, market exit) in a low-volume market. Despite the existence of five generic licensees, Viatris held a

de facto monopoly on the donor-funded pretomanid market from 2019-2024, which some interviewees attributed to long timelines for manufacturers to obtain WHO PQ. Some interviewees also called for TBA's licenses to be made public to improve transparency and facilitate price negotiations, and for better coordination between TBA, GDF, WHO and manufacturers to avert shortages.

Despite these challenges, BPaL has undergone consistent and substantial price cuts over time, contributing to rapid uptake.

c. Country-Level Implementation Support and Knowledge Sharing

The third major area of TBA's orchestration was country implementation. Working with a diverse group of countries, especially those that could serve as examples, TBA co-created and shared knowledge on how BPaL/M could be implemented on the ground, thereby building capacities to switch to the new regimens.

Operational Research and Pilot Projects

Prior to the first regulatory approval, TBA conducted acceptability and feasibility studies to better understand country interest in and capacities for uptake. TBA also later conducted operational research in seven countries, and supported pilot programs in key high-burden countries, which provided evidence that national TB programs could effectively roll out the regimen and achieve outcomes similar to clinical trials.

Guidance and Tools for Implementation

To help ensure learning from early experience, TBA contributed to developing a BPaL implementation guide in collaboration with partners, and funded the creation of country-specific implementation plans. By co-creating these plans with health ministries and TB experts in-country, TBA contributed to local ownership and readiness.

TBA also supported the sharing of knowledge through WHO's BPaL Accelerator Platform, a global forum where countries and experts regularly convened virtually to share experiences, protocols, and troubleshooting tips for BPaL implementation. Separately, it established the PeerLINC Knowledge Hub with partners in the Philippines, a peer-to-peer channel for technical assistance directly from and to those involved with implementation.

Stakeholder Engagement and Advocacy:

Furthermore, TBA engaged TB-affected communities to develop independent feedback loops within their national TB programs. Hearing patient experiences and community perspectives helped address concerns and maintain pressure for rapid uptake. In 2023 when WHO and partners released a high-level "Call to Action" urging countries to adopt new DR-TB treatments, TBA also launched the Fast Track the Cure project, which mobilized communities at the grassroots level to amplify this call. Finally, recognizing that national policy adoption does not automatically translate into patient access, TBA worked directly at province and district levels in some high-burden countries to support sub-national implementation

The fruits of these country-engagement strategies is reflected in 24 of the 30 high DR-TB-burden countries implementing or committing to implement BPaL/M as of end 2024.

DISCUSSION

TBA orchestrated a wide range of initiatives and interventions with partners extending over seven years, working in parallel at global, national and sub-national levels. This complex set of interventions did not necessarily progress sequentially but rather overlapped in time (Figures 4 and 5). They reflect both a purposeful strategy and ad hoc reactivity as needs arose. While TBA did not deliver services directly, it was able to orchestrate – that is, "enlist public or private intermediary actors on a voluntary basis, by providing them ideational and material support" to pursue their goals (7). We identified five attributes that enabled TBA to orchestrate effectively.

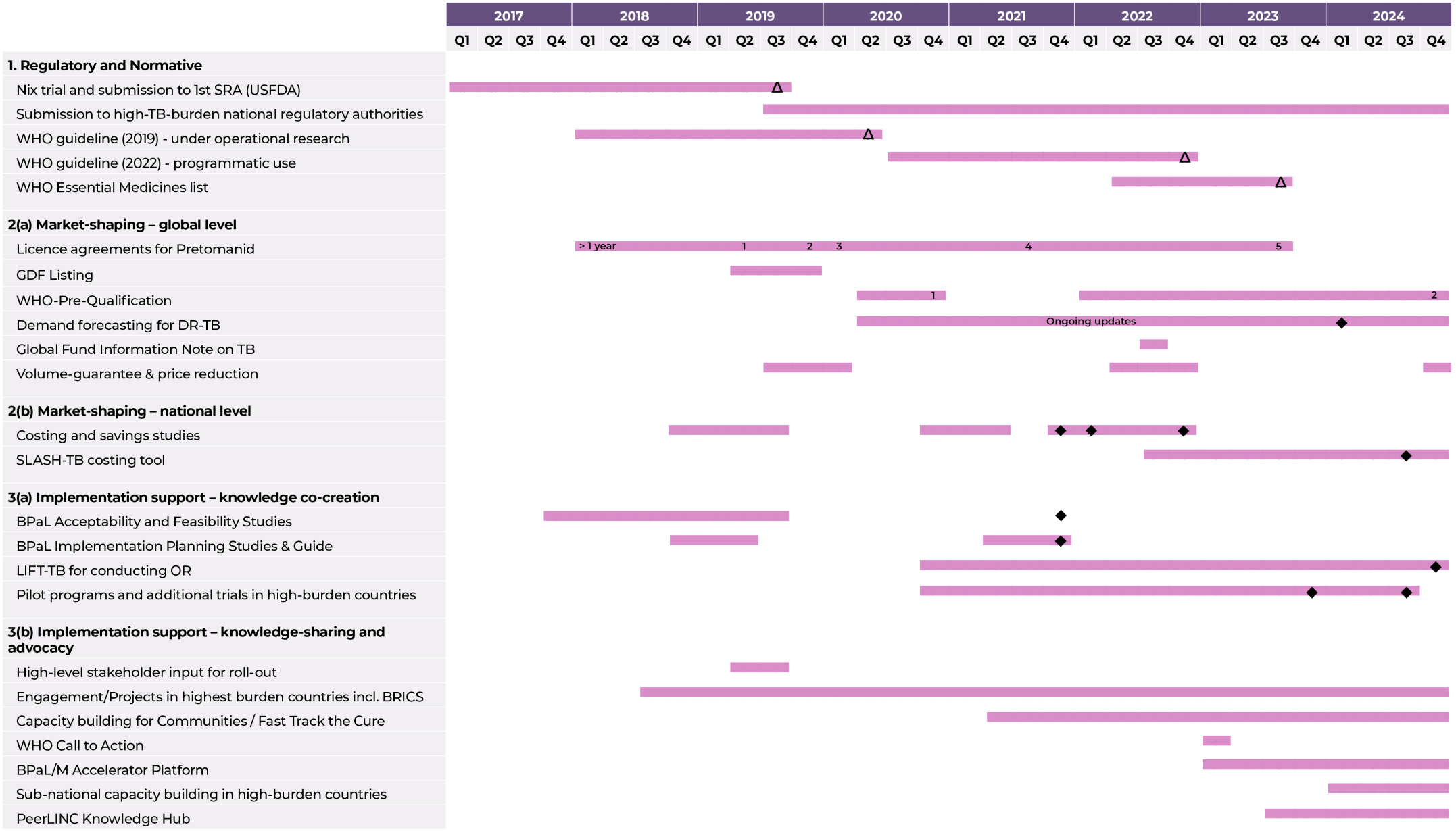
1. **Ability to generate and share knowledge about the product and regimen**. As the developer, TBA's in-depth knowledge of pretomanid and BPaL (e.g. data that had been generated about safety and efficacy) positioned it well to provide authoritative information quickly to regulators, WHO, NTP managers, clinicians and community members. Co-creation of field evidence then generated comfort and buy-in among countries.
2. **Non-profit status** strengthened TBA's legitimacy to orchestrate other actors.
3. **Ability to mobilize material resources for access interventions**, either by funding activities directly or by pro-actively raising new funds.
4. **Pre-existing relationships and/or ability to develop new collaborative relationships** with a wide range of relevant actors.
5. **Intrinsic motivation to see the product reaching people with DR-TB**, a key indicator of how well TBA was achieving its non-profit organizational mission..

Many PDPs have most if not all of these attributes – or could develop them – making them a natural fit to play the orchestrator role. The main counterargument is that they may have a conflict of interest (CoI) in doing so. PDPs do not have the same types of financial CoIs as for-profit firms, but their organizational interest in seeing their products widely used could pose a potential CoI.

Views differed on whether such organizational interests comprised a conflict, and if so, how to manage it. Some interviewees argued that such potential CoIs could be managed by clearly defining and limiting the product developer's role for key policy decisions such as regulatory, WHO guidelines and national adoption decisions. While none of the interviewees expressed concerns that TBA in particular had unduly influenced policy decisions, it remains a general issue that merits attention. Interviewees also suggested that if the product developer is involved in evidence generation or technical assistance, transparency regarding its role and partnering with other organizations is important to mitigate potential COIs.

On the other hand, the non-profit product developer's organizational interest in seeing its product used widely can be a valuable motivator when this interest is aligned with public health objectives. Enduring motivation is necessary to do the hard work of mobilizing financial, human and organizational resources to continue putting in place intervention after intervention until medicines have reached those who need them. We conclude that finding acceptable ways to manage potential COIs is critical, as in some cases there may not be other actors beyond the PDP with the motivation or other attributes necessary to orchestrate access.

Figure 4. Timeline of Access Interventions Orchestrated by TBA



LEGEND		
1, 2, 3	Indicate different actors	Note: for all trials and ORs
◆	Publication	→ shaded till date of enrollment and for follow-up and analysis
Δ	WHO decisions	
*Conducted by country		

CONCLUSIONS: HOW TO ENSURE ORCHESTRATION FOR ACCESS TO PRODUCTS OF NON-PROFIT R&D?

This study found that TBA played a central role in orchestrating rapid access to BPaL/M through its regulatory and normative strategies, market-shaping for affordability and availability, and supporting country implementation through knowledge co-creation, knowledge-sharing, capacity building, and advocacy. The collective impact of these efforts is reflected in the rapid uptake of BPaL/M, which is unprecedented in TB.

The BPaL/M case offers rich lessons for governments, funders, and PDPs to ensure that products emerging from non-profit R&D quickly reach those in need, which we summarize as:

Generate evidence simultaneously for regulatory approval and normative guidance

In the future, access to the products of non-profit R&D could be further enhanced by designing pivotal trials to provide both data sufficient for regulators and the kind of evidence required for national or WHO guidelines to recommend programmatic use. Regularizing and formalizing the current practice of informal exchanges between WHO and product developers could facilitate mutual understanding on the kinds of evidence needed.

Beyond therapeutic value – Address Economic and Country-Level Concerns

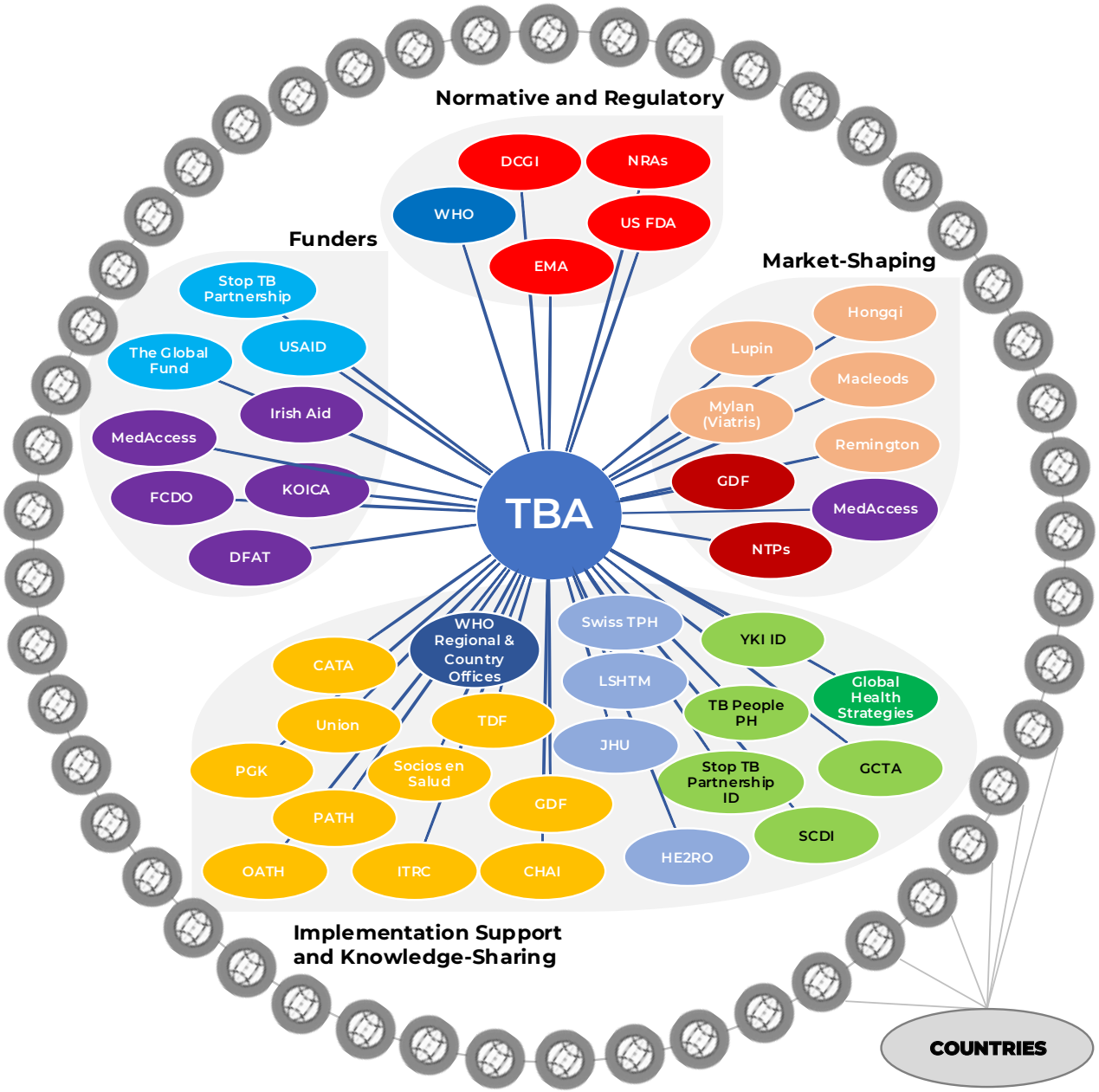
Even in cases of therapeutic game-changers, realizing access requires a strategy to address economic considerations of decision-makers at both global and national levels, and to make cost savings to health systems visible. Access at country level can be accelerated through early and sustained country engagement, including at sub-national levels, and a strategy that coherently links knowledge-building with transnational knowledge-sharing and advocacy.

PDPs can orchestrate access, but need clear mandates and resources to do so

No single organization can be responsible for all the different steps necessary to realize access, but the case of BPaL/M illustrates the critical role of an orchestrator able to steer the efforts of many actors across a complex ecosystem towards a shared goal. If non-profit R&D actors are to orchestrate access effectively, they must be supported to do so by clear decisions mandating access as part of their organizational missions, with relevant political and financial support from governing boards and funders. PDPs have historically been financed primarily through official development assistance (ODA) and philanthropic foundations, but ODA from traditional donor governments is now under severe strain. Funders who have invested in successful non-profit R&D have a stake in getting the job done, and should consider providing sufficient resources for necessary access interventions. In the medium term, it is likely that high-burden countries and emerging economies will need to participate more actively in global access efforts, not just domestic implementation, and institutions (e.g. pooled procurement) should be built to structure and facilitate their cooperation.

Investments are urgently needed to ensure that the growing arsenal of products emerging from non-profit R&D quickly reaches those whose lives are on the line, so that lifesaving medicines do not sit useless on a shelf.

Figure 5. TBA Orchestration of Access Interventions with Partners



ORGANIZATION TYPE
Advocacy
Community engagement; Advocacy
Donor; Advocacy
Evidence Generation
Implementing agency
Knowledge Dissemination, Advocacy
Manufacturer
Normative Guidance
Procurer
Regulator
TBA Donor

1. INTRODUCTION

At the turn of the millennium, concerns were rising about the failure of the mainstream market-driven pharmaceutical research and development (R&D) system to develop medicines for diseases that predominantly affected the world's poorest populations, referred to as the neglected diseases (8). This concern prompted the creation of about two dozen public-private product development partnerships (PDP) to boost innovative efforts into these diseases (9). While non-profit pharmaceutical R&D initiatives were relatively rare at the time, today, they have demonstrated their success, with a growing number of new drugs, vaccines, and diagnostics obtaining regulatory approval and poised to reach those who need them (10). A 2023 report found, for example, that since 2010 PDPs had developed 79 products, including new vaccines for malaria, treatments for sleeping sickness, and a drug and diagnostics for tuberculosis (11). PDPs were mandated and funded to focus on R&D, but once these products are developed, arrangements are unclear for how products will reach patients and what role the PDP should play.

Significant differences exist between how the mainstream commercial and non-profit R&D systems get medicines to people. For-profit pharmaceutical companies often bring a product through regulatory approval and also directly conduct manufacturing, distribution, pricing, marketing, and sales. Successful firms plan their production, regulatory, distribution, and marketing strategies before the R&D process ends to generate sales as quickly as possible, given the costs of capital and time limits on periods of market exclusivity – that is, there are strong reasons to plan ahead and move fast. While they have an in-built incentive to get their products quickly to the most profitable markets, market incentives also mean medicines reach less profitable markets with significant delays – or not at all. Non-profit R&D actors have different objectives and incentives. Their incentive to get their products out quickly is to achieve their missions to address urgent unmet health needs and to have a health impact, and the grant funding on which they rely is often time-limited. However, the mandates and funding of PDPs have predominantly been focused on R&D. Arrangements in the global health system are unclear regarding which actors should get involved to ensure new medicines reach patients and when. Other actors may not get involved until after a product has obtained regulatory approval and been mainstreamed in global policy, resulting in coordination challenges and delays that patients can ill-afford.

For HIV treatments and many vaccines, R&D has largely been led by large multinational firms (with support from the public sector); and global health actors (e.g., USAID, WHO, Global Fund, Gavi, Unitaid, Medicines Patent Pool) have generally focused on expanding and accelerating access in low and middle-income countries (LMICs) after regulatory approval. For a few health conditions that have been a high global priority (i.e., malaria, tuberculosis, maternal and child health) where PDPs have successfully developed new products, in recent years, ad hoc arrangements have emerged among the ecosystem of global actors (e.g., USAID, Global Fund, Unitaid, Global Financing Facility, and international NGOs) on a case-by-case basis to facilitate access. For many neglected diseases, such as sleeping sickness, dengue fever, or schistosomiasis, there is no dedicated set of actors or playbook to facilitate access and uptake. Resultingly, it is not always clear who should play which role, given the many steps and actors required to get the right medicine to the right person at the right time. The lack of clear roles and responsibilities for access to products of non-profit R&D exacerbates the substantial risk that products reach patients after long delays, with lives lost, suffering prolonged, and money wasted.

It is, therefore, instructive to analyze a successful example of how access was accelerated and rapid rollout achieved for a PDP-developed product. The recently-developed tuberculosis (TB) drug, pretomanid, was developed by the TB Alliance (TBA) and procured by over 100 countries in quantities to reach nearly 110,000 patients through 2024, or 63% of global demand. This was five years after obtaining first regulatory approval (6) (see Figure 2) and less than two years after being recommended for programmatic use by the World Health Organization (WHO) as part of a new regimen for multidrug-resistant (MDR) TB treatment, comprised of bedaquiline, pretomanid, and linezolid, with or without moxifloxacin (BPaL/M).[1]

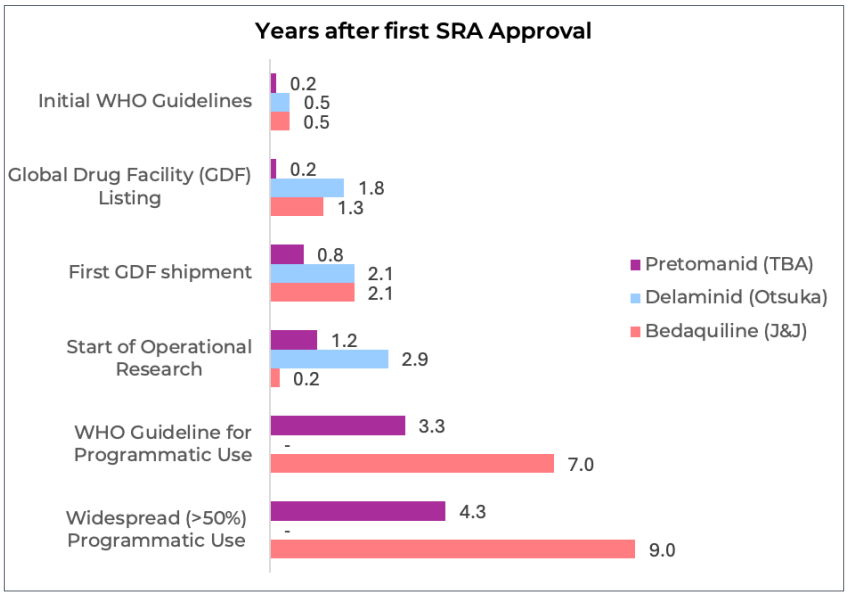
TB is an airborne infectious disease caused by the bacterium Mycobacterium tuberculosis, which primarily affects the lungs and causes flu-like symptoms. Despite being preventable and usually curable, in 2023 alone, approximately 10.8 million people worldwide became sick with TB, and without treatment, the death rate is high (approximately 50%) (12). However, not all TB infections respond to first-line, or even second-line, treatment, with the WHO using five categories to classify cases of drug-resistant (DR) TB[2]. Globally, the WHO estimates that 400,000 people developed MDR-TB in 2023, out of which almost 176,000 were enrolled in treatment (12).

Treatment options for DR-TB have improved remarkably over the past decade, with novel drugs being approved after decades of lack of innovation. In June 2013, the WHO first recommended the novel drug bedaquiline, and in October 2014, another novel drug - delamanid - was included in the recommendations. Bedaquiline, developed by Janssen Pharmaceuticals (part of Johnson & Johnson (J&J)), was first approved by the United States Food and Drug Administration (US FDA) in December 2012, and delamanid, developed by Otsuka Pharmaceutical, was first approved by the European Medicines Agency (EMA) in March 2014 (13). In August 2019, pretomanid became the third novel drug to gain stringent regulatory approval for DR-TB and was recommended for programmatic use by the WHO in 2022 (14). TBA took a new approach by developing pretomanid as part of a regimen with bedaquiline and linezolid – two relatively new drugs without prior resistance to TB – rather than as a standalone drug. This regimen approach offered the important advantage that evidence on how pretomanid could be used with other drugs was available immediately upon regulatory approval, averting the need for additional trials to answer this key question – one factor that contributed to faster uptake compared to bedaquiline and delaminid. (13) (See Figures 1 and 2 for a comparison of uptake between the three new TB drugs).

1 In the remainder of this report, we use the acronym BPaL/M to indicate that the regimen may be used with or without moxifloxacin (M). WHO recommends moxifloxacin be dropped from the regimen when there is evidence of fluoroquinolone resistance. See https://www.who.int/publications/i/item/B09123. The regimen was first developed and approved in 2019 as BPaL (that is, without moxifloxacin), with WHO's updated 2022 guidelines adding moxifloxacin. To simplify, we use BPaL/M throughout this report except in cases where the addition or subtraction of moxifloxacin is of substantive importance, such as when calculating regimen prices.

2 WHO uses five categories to classify cases of drug resistant TB: isoniazid-resistant TB; rifampicin-resistant (RR) TB; Muti-drug resistant (MDR) TB, resistance to rifampicin and isoniazid; pre-extensively drug-resistant TB (pre-XDR-TB), defined as TB that is resistant to rifampicin and any fluoroquinolone (a class of second-line anti-TB drug); and XDR-TB, defined as TB that is resistant to rifampicin, plus any fluoroquinolone, plus at least one of either bedaquiline or linezolid (12).

Figure 1. Uptake of three novel TB drugs: Years after first SRA approval



Sources: (1–5). (Figure and data provided by TB Alliance)

WHO currently recommends treating almost all forms of drug-resistant TB with BPaL/M. Previously, the typical treatment required taking a combination of up to seven antibiotics for 18 months or longer, including injectables for some patients, making it a complicated, time-consuming, expensive treatment process (15). BPaL/M dramatically cuts down treatment duration to just six months, reducing the number of drugs required to three (or four), with fewer side effects, and as an all-oral treatment had the potential to put a much lighter footprint on the healthcare system and reduced associated costs. It improved cure rates from about 20% (even lower in certain countries) for pre-XDR TB to 90% (15). Ongoing studies are also evaluating pretomanid-containing regimens for drug-sensitive (DS) TB (15–26).

BPaL was developed by the TBA, a non-profit organization operating as a PDP founded in 2000. While PDPs vary in how they operate, they are generally non-profit organizations with independent legal identities, funded mainly by public and philanthropic sources, designed to advance R&D for health technologies targeting unmet health needs and prioritizing health outcomes rather than market returns (27). TBA's mission is "the discovery, development and delivery of better, faster-acting and affordable tuberculosis drugs that are available to those who need them." (28). TBA works with various stakeholders, including pharmaceutical companies, patient organizations, governments, research institutes, non-governmental organizations, donors, and academia (28). Although there is a growing body of literature on PDPs, it has largely focused on R&D, with less emphasis on strategies for ensuring access to the products they develop (29).

This study describes the wide range of interventions adopted to accelerate access to BPaL/M, analyses the role of TBA, and identifies potential lessons for how to ensure rapid access to other products emerging from PDPs and other non-profit R&D initiatives. It contributes to the literature on PDPs, particularly by focusing on access strategies. It also contributes to the literature on BPaL/M, complementing evidence on safety, efficacy, acceptability, and cost-effectiveness by analyzing how rapid uptake and access was achieved globally.

2. METHODOLOGY

This study was commissioned and funded by TBA with in-kind contributions from the Global Health Centre, to examine and analyze how uptake was achieved for the BPaL/M regimens in general, and the role played by TBA in particular. In addition, it aimed to draw broader lessons on opportunities and challenges for delivering products emerging from non-profit R&D. The dataset for this case study consists of data from publicly available information, including the academic and gray literature, internal documents from TBA, and semi-structured interviews with key informants.

DATA COLLECTION

Background research was carried out by the research team, including a review of published documents and internal documents provided by TBA. Semi-structured interviews were conducted by three researchers with 21 participants from 16 different organizations primarily between July - September 2024. The TBA provided an initial list of 14 potential interviewees, who were contacted via email to request their participation in the research project. Of these, 12 agreed to participate in semi-structured interviews for the case study. We then recruited an additional nine participants through snowball and purposive sampling. Interviewees were purposefully selected to represent different parts of the ecosystem of stakeholders involved in the uptake of BPaL/M, including funders (n=4), guideline developers (n=1), technical assistance providers (n=4), researchers (n=1), national TB programs (n=1), community members and civil society (n=3), TBA and other PDPs (n=6), and manufacturers (n=1). Interviews lasted between 45-90 minutes and took place online via video conference platforms. One interview was conducted via email. Interview guides were tailored to each type of interviewee, and questions asked pertained to the strategies adopted and specific roles that each stakeholder played in facilitating access to and uptake of the BPaL/M regimen. Interviews were conducted in English. With the informed consent of each interviewee, interviews were recorded and transcribed with Otter.ai software, and transcripts and quotes were lightly edited for clarity or to preserve anonymity. Due to the sensitivity of the information being shared, all quotes were anonymized to protect the participants' privacy. Interview transcripts were only seen by the three researchers and were not shared with TBA. We include quotes from interviews in this manuscript for illustrative purposes, but do not attribute them to a specific interviewee to further protect their anonymity. TBA employees were interviewed, shared internal documents, and provided valuable comments on earlier drafts of this report, which helped to ensure its factual accuracy and completeness; nevertheless, the analysis and final conclusions remain the product and responsibility of the authors.

ETHICS STATEMENT

Ethics approval for the study was obtained from the Geneva Graduate Institute's Ethics Review Committee on 2 June 2024. All methods were performed in accordance with the relevant guidelines and regulations of the Declaration of Helsinki. Informed consent for participation was obtained from all study participants. Written informed consent for the publication of quotes used within the manuscript was also obtained from all relevant study participants.

DATA ANALYSIS

Interview data was analyzed thematically, according to three thematic areas of activity identified inductively by the research team: 1) Regulatory and normative guidance, 2) Market shaping for affordability and availability, and 3) Country-level implementation support, with a cross-thematic focus on the role of TBA. All three members of the research team analyzed the interview transcripts according to these themes. All interviewees had an opportunity to review a draft of their quotes used in the manuscript and provide clarifying remarks on them.

LIMITATIONS

This study has three main limitations. First, due to time and resource constraints, interviews were carried out within a short time period, and it was therefore not feasible to interview all relevant stakeholders. We sought to mitigate gaps in the data by ensuring we included a wide range of interviewees in terms of organizational background and role; nevertheless, interviews with a broader set of national stakeholders in particular would provide a richer, more complete dataset. Second, the initial list of interviewees was provided by TBA and may not represent the full breadth of perspectives. We sought to mitigate potential bias by encouraging frank responses to questions by ensuring anonymity of the interviewees, and by identifying and interviewing additional key informants beyond the initial list. Relatedly, a key objective of the study was to understand the role played by TBA in facilitating access to BPaL/M, and we believe the study provides a reasonably complete picture of the actions TBA took to support access to BPaL/M and the role it played vis-à-vis other key actors. However, it does not purport to provide a full account of all interventions undertaken by all actors that contributed, which would require a far more extensive study. Third, this study focuses on the BPaL/M regimen and did not examine how access was handled for other newer regimens for DR-TB (e.g. delamanid-based regimens). Nor does it analyze the uptake of new treatment options for drug-sensitive (DS) TB or other products developed by PDPs, which we considered beyond the scope of this research. Future research that addresses these limitations would enrich our understanding of the strengths and weaknesses of various approaches to improving access to newer TB treatment in particular, and how to ensure access to the products of non-profit R&D more broadly.

3. RESULTS

Ensuring that the right medicine reaches the right individual at the right time – what we refer to for brevity as simply "access" – is a highly-complex and challenging undertaking, requiring many actors and actions across time and space (30). This section describes and explains the wide range of interventions that we found contributed to rapidly expanding access to BPaL/M. We also report here on interviewees' perceptions of TBA's role and strategies, including both positive and critical comments. For ease of comprehension, we grouped interventions into three thematic categories that emerged from the data:

A. REGULATORY AND NORMATIVE GUIDANCE

Regulatory approval is necessary for the use of any medicine, and normative guidance from WHO is pivotal for many countries to change national policies to adopt improved treatment options and for international funders to provide financial support for doing so. In the context of TB, many countries receiving funds from the Global Fund to Fight AIDS, TB and Malaria (GFATM) procure their TB medicines and diagnostic tools through the Global Drug Facility (GDF), established by the Stop TB Partnership in 2001. The GFATM mandates that any medicines or diagnostics it finances must either be prequalified by the WHO, be approved by a Stringent Regulatory Agency (SRA)[3], such as the United States Food and Drug Authority (US FDA) or the European Medicines Agency (EMA), or approved by the GFATM's Expert Review Panel (ERP). The GDF adheres to the same standards. Thus, the regulatory strategy and process for updating WHO guidelines were both critical for enabling patient access; we describe in the following sections the actions taken.

i. Regulatory approval

TBA obtained approval for pretomanid from the US FDA in August 2019 as part of a combination regimen with bedaquiline and linezolid for use in limited populations, for treating adults (above 14 years old) with certain forms of highly drug-resistant pulmonary tuberculosis (31). In 2007, pretomanid had received orphan drug and fast-track designations from the US FDA, which granted some benefits for its development, such as an expedited review process and registration fee waiver (32). It was approved under the FDA's Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD), which was intended "to advance development and approval of antibacterial and antifungal drugs to treat serious or life-threatening infections in a limited population of patients with unmet need", and may be supported by "a streamlined clinical development program", which "may involve smaller, shorter or fewer clinical trials" (32).[4]

3 WHO has changed the way it classifies regulatory authorities. The term/classification "Stringent Regulatory Authorities (SRAs)" has transitioned to "WHO-listed authorities (WLA)" in the context of WHO's regulatory system strengthening activities. A WLA is defined as "a regulatory authority (RA) or a regional regulatory system (RRS) that complies with all the relevant indicators and requirements specified by WHO for regulatory capability as defined by an established benchmarking and performance evaluation process" (WHO, 2024; WHO, 2024). We continue to use the term SRA in this paper, since that was the terminology in place at the time pretomanid was submitted for approval.

4 TBA also received a Priority Review Voucher (PRV) as part of the approval process by the US FDA in acknowledgment of the significant unmet medical need in the field of drug-resistant TB.

TBA prioritized the USFDA as the first regulatory authority from which it sought approval, on hopes that the USFDA being an SRA would give confidence to a wide range of stakeholders worldwide that the new regimen was safe and effective. SRA approval would also mean the regimen would immediately be eligible for funding from the GFATM and other international donors and procurement agencies, saving valuable time. Regular communication with USFDA's regulatory experts provided input on the kinds of data and trial design that would be required to meet its standards.

Further, medicines typically also need to be registered with national regulatory authorities for distribution in any given country. In some countries and situations, it is possible to obtain a waiver of national regulatory approval, especially for medicines procured through donor linked procurement mechanisms such as GDF, but not in all. In discussion with their commercialization partners, TBA ensured fast-tracked filings with countries where such waivers were difficult or not possible, as well as in countries that procure drugs with their national budgets (that is, not with international donor funds). In parallel, filings were prioritized for other TB high-burden countries.

In July 2020, the drug was approved by the Drug Controller General of India (DCGI) for conditional access, becoming the second country to approve pretomanid, and the first high-burden country (33). In the same month/year, it received a conditional marketing authorization from the European Medicines Agency (EMA), and was granted a standard marketing authorization in November 2023 (34).

In addition, regulatory approval of generic versions of pretomanid were also necessary to enable patient access. TBA licensed pretomanid to five manufacturers to date and their licensing agreements required manufacturers to have approval from an SRA or WHO PQ and to prioritize filing with national regulatory authorities in TB high-burden countries. In November 2020, Mylan (now Viatris), the first manufacturer to obtain a license from TBA to commercialize pretomanid, received abridged prequalification (PQ) from the WHO, based on the approval from the US FDA (35). Further details on licensing to generic manufacturers is presented below in Section 3.a. Overall, TBA's regulatory strategy sought to instill confidence in the safety and efficacy of the BPaL/M regimens, and to ensure the timely, widespread availability of quality-assured pretomanid in TB affected countries. As of December 2024, pretomanid had been approved as part of the BPaL regimens by 33 regulatory agencies for use in 62 countries.[5]

ii. Normative guidance

Prior to and in parallel with seeking SRA approval, TBA also prioritized engaging with WHO regarding providing data for their normative guidance. Such engagement was informal - unlike US FDA – as there were no formal processes for product developers to seek, or for WHO to provide, information on the kinds of evidence required by WHO's expert guidelines committees.

Shortly after pretomanid was approved by the US FDA, and following a WHO guideline development group (GDG) meeting, the WHO issued a rapid communication in December 2019 flagging to countries that it expected to recommend pretomanid-containing regimens for XDR-TB treatment, in order to accelerate transitions at the country level (36). In May 2020, the WHO released consolidated guidelines on TB, including a new recommendation for using BPaL for XDR-TB under operational research conditions (37).

The first regulatory approval and first WHO recommendation were based on the results of the Nix-TB trial, a Phase 3 single-arm study on potential use of the regimen for XDR-

5 Information provided by TBA.

TB conducted by TBA at three sites in South Africa with 109 people, including people co-infected with HIV (15,38). The trial was initiated in January 2015, and people were enrolled between April 2015 and November 2017, with primary completion in January 2019 and final completion in August 2020 (15,38). After completing treatment, participants were monitored for two years for relapse. At six months after the completion of therapy (primary endpoint), the period in which most relapses occur, 90% were found to have a favorable outcome (15). These findings generated great excitement in the TB community, as described by one interviewee:

> *"What TB Alliance brought with Nix-TB was clearly something revolutionary... everyone understood the potential of this regimen."*

However, concerns were raised regarding the relatively small number of people enrolled and, therefore, the limited evidence provided by this trial, as well as the fact that it was not a randomized controlled trial (RCT) (39,40). As explained by the Nix-TB trial team, a key reason warranting the single-group study was that there was no standard regimen for the treatment of XDR TB at the time of initiation of the study, and the high mortality and low cure rate of existing XDR TB regimens raised concerns about the ethical acceptability of a comparator group. The trial design had been approved by the USFDA and South African authorities.

While the available clinical evidence had shown high treatment success rates, the WHO GDG in 2019 raised concerns about the "likelihood and severity of adverse events, limitations in the study design, and the overall very low certainty of the evidence." It concluded that the available data limited the generalizability of the study findings to all populations and all regions (41). Therefore, the WHO stipulated that BPaL could not be considered for routine programmatic use worldwide until additional evidence on efficacy and safety had been generated, recommending instead that it be used under operational research conditions (41).

> *"Evidence generated from a single-group study with no control arm from a single country is generally insufficient for the World Health Organization to develop recommendations on the use of a new regimen under programmatic conditions. This is what happened in 2020 when WHO issued a recommendation on the use of BPaL to be used under operational research conditions, following review of the evidence generated by the Nix-TB study"*

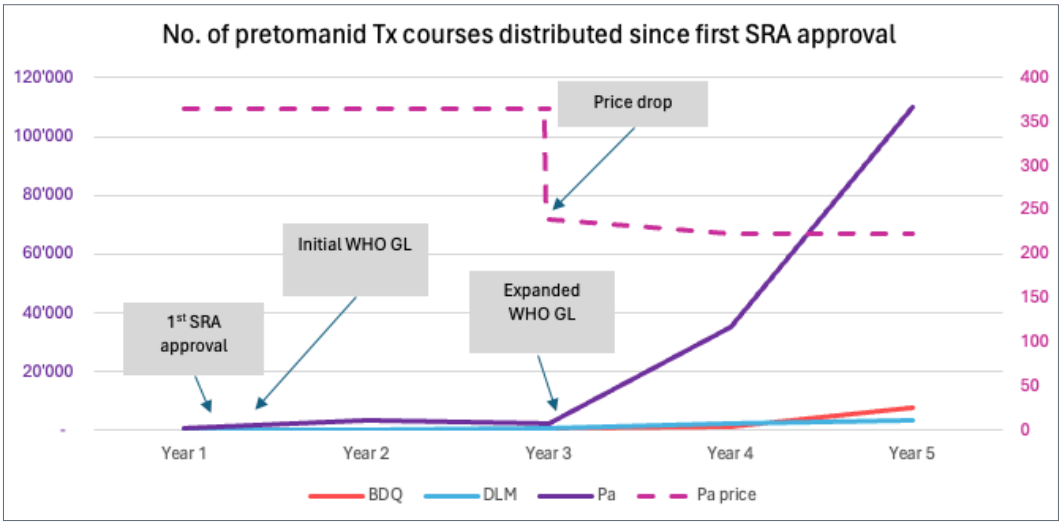
Recognizing potential to preserve efficacy of BPaL while improving safety, and to simplify dosing, TBA started a new RCT (15) –ZeNix – a Phase 3 randomized trial, conducted at 11 sites across Georgia, Moldova, Russia, and South Africa, enrolling 181 people. The study began in November 2017, with primary completion in February 2021 and study completion in February 2022 (24,42). The Nix-TB trial had demonstrated 90% efficacy of the BPaL regimen but also showed a high incidence of adverse events attributed to the high dose of linezolid. Therefore, the ZeNix trial had the primary objective of optimizing the linezolid dose and duration of treatment and a secondary objective of harmonizing dosing by evaluating once per day dosing of bedaquiline. This trial resulted in lower doses of linezolid and fewer adverse effects while maintaining the high efficacy shown by the Nix-TB study. However, the relatively low number of people enrolled and the lack of a standard-care control group were again flagged as limitations of the study (24).

In addition to the two TBA-led trials, another trial studying BPaL-based regimens was led by Médecins Sans Frontières/Doctors Without Borders (MSF) in three countries (Belarus, South Africa, and Uzbekistan). TBA collaborated as a partner in the trial, provided input on trial design, and ensured supply of pretomanid for use in the trial. The TB-PRACTECAL trial, a Phase 2/3 RCT, started in January 2017 and was completed in August 2022 and enrolled 552 people. The trial showed that BPaL and BPaLM regimens performed better than the standard of care, while being much shorter with a lower pill burden and fewer adverse events (26,43).

TBA and MSF shared data with WHO from the trials each organization had led, in preparation for the meeting of its GDG. Taking into account additional evidence from the ZeNix and TB-PRACTECAL trials, WHO updated its guidelines for treating DR-TB and issued a rapid communication greenlighting programmatic use of BPaL/M in almost all people with DR-TB. In December 2022, WHO incorporated this recommendation into the comprehensive revised guidelines issued (41,44). This recommendation has unleashed an upsurge of demand, as shown in Figure 2, underscoring the importance of WHO guidelines for access. Furthermore, following an application from the TBA, pretomanid was included in the WHO Essential Medicines List (EML) in 2023 (45). Countries often refer to the WHO EML when developing their own national EMLs. National EML listing often allows utilization of domestic funding and can accelerate uptake.

In parallel to the work at the international level, TBA worked with national TB programs (NTPs) and where needed, technical partners, to help update national treatment guidelines based on WHO guidelines and to add pretomanid to national essential medicines lists. Projects such as LIFT-TB (details later) supported these efforts. Currently, 24 of the 30 highest MDR-TB burden countries have implemented or decided to implement BPaL/M as of end 2024.[6] Furthermore, other clinical trials have continued to develop knowledge about the regimen. For example, in India, researchers conducted the modified BPaL trial (mBPaL), and found that it was possible to reduce the dose of linezolid during the 6 months of treatment with equal cure rates but fewer episodes of peripheral neuropathy (46).

Figure 2. Number of treatment courses distributed since first SRA approval



(Source: TB Alliance)

iii. Timelines for normative guidance

The TB community was very enthusiastic about the advances offered by BPaL/M, but several interviewees expressed concerns about the time between first SRA approval and WHO's conditional recommendation to use BPaL in 2019, and its full recommendation in 2022. This was a two-three year period of uncertainty for patients, healthcare providers, and national treatment programs eager for improved treatment options. In particular, some interviewees argued that the necessity for implementing BPaL first under operational research conditions could have been avoided and that the guideline development process could have been done more efficiently.

6 Information from TBA, February 2025.

As noted above, TBA filed for first regulatory approval from the US FDA because SRA approval would permit rapid use of donor funds to purchase the drugs and carry significant weight with other national regulatory authorities, formally or informally. Because pre XDR-TB cases were rare in the US, pretomanid was granted orphan drug status and other important support for the development process, including fast-track regulatory review and allowance for "smaller, shorter or fewer clinical trials" (32). This may have accelerated the timeline to first SRA approval, but did not generate evidence that WHO considered sufficient for global guidelines that would apply to TB high-burden countries.

With the benefit of hindsight, it seems that significantly shortening the timeline from a conditional (2019) to a full (2022) WHO recommendation could only have been achieved with an earlier generation of evidence through a multi-country RCT with a larger total sample size. Doing so would have required a different regulatory strategy, which in turn could have entailed a much longer timeline and a significantly higher level of funding.

In our view, one alternative strategy would have been to file for first approval from a TB high-burden country's national regulator (47), which could have led to a different trial design and generated enough evidence to obtain WHO recommendation for programmatic use from the start. However, none of these were an SRA (or WHO Listed Regulatory Authority (WLA), Level 4) (48), and many non-Level 4 regulators have limited experience reviewing applications for medicines that are new chemical entities. Seeking first regulatory approval from a TB high-burden country would therefore have restricted eligibility to procure medicines with international funding, which many high-burden countries rely upon for their TB programs. In other words, there were important tradeoffs regarding speed, degree of evidence and access to international funding between choosing to submit to an SRA vs a high TB-burden national regulatory authority for the first approval.

Interviewees flagged the need for clearer understanding between the product developer and WHO on its evidentiary requirements for recommending a new medicine for programmatic use for DR-TB. According to one interviewee:

> *"We know in TB that what the WHO recommends is as important, if not even more important, than what the FDA says. And I think that was a real shortcoming in their regulatory approval strategy, that they didn't kind of think about what the impact would be of going through the WHO's GRADE process and the fact that they can really only make a strong recommendation when there's randomized controlled data or a real abundance of programmatic data."*

Nevertheless, despite the existence of the GRADE standards, several interviewees argued that more specific guidance and clarity from WHO was still needed. This message seems to have been heard, as in December 2024 (after our interviews were conducted), WHO published guidance on the kinds of evidence needed for its TB treatment guidelines (49).

In addition, one interviewee pointed out that WHO has begun to seek data more proactively to inform its decision-making process. In 2021, WHO issued a public call for data that complemented the evidence base that led to the updated guidelines in 2022 (41), a practice that this interviewee argued should be continued:

> *"In my observation, WHO has been more proactive and started reviewing the data/evidence timely and more often, addressing a long-standing question on why it takes a long time to review evidence and provide recommendations. In the last few years, WHO has been active and asking everyone for publicly available information and encouraging submission of these rather than waiting for specific groups who are doing clinical trials and publishing in journals. I think that's a good practice. We need to encourage WHO to continue doing so."*

The conditional recommendation from WHO in 2019 seems to have come as a disappointment to TBA; but after 2019, TBA engaged more closely with WHO regarding the kinds of evidence needed to generate a broader recommendation for programmatic use. According to one observer:

> *"The TB Alliance worked very closely with WHO to understand what data they needed to make guidelines decisions about a new regimen like BPaL, and then did those studies to generate the evidence, so that when the WHO guidelines committees met, they could make a rapid decision on incorporating BPaL into their recommendations for the countries. And therefore, countries would then be free to use BPaL as part of their national program. Those two strategic decisions – thinking of limiting steps from the country perspective, and ensuring that, because WHO played such a central role in helping countries to make decisions about adoption of new regimens, that they worked closely with the WHO to generate the appropriate evidence – were really important, and it helped explain the success of the Access Program for the TB Alliance"*

B. MARKET-SHAPING FOR AFFORDABILITY AND AVAILABILITY

While BPaL/M's clinical benefits were considerable, the new regimen was unlikely to be adopted without addressing the question of cost and availability. In order to reduce prices and secure supply, TBA orchestrated various market-shaping activities at the global level and developed evidence to inform national-level decision-making. We present in the following sections the range of interventions undertaken, TBA's role, and critiques raised by interviewees.

i. Non-exclusive licensing for availability and affordability

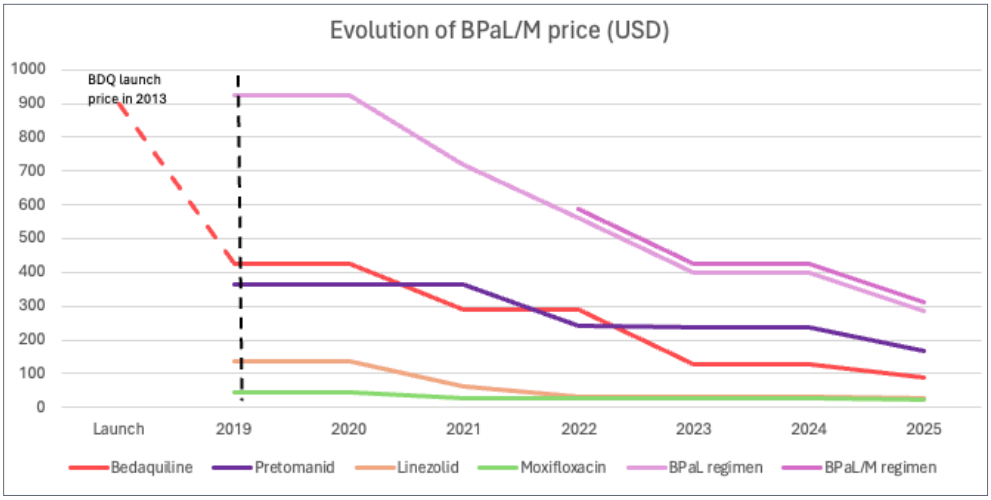
As a PDP, TBA did not have in-house manufacturing facilities and therefore engaged in licensing agreements for the manufacturing and commercialization of pretomanid for use in BPaL/M regimens. Aiming to ensure adequate supply and price competition, TBA opted not to engage in an exclusive licensing agreement and licensed the drug to multiple partners. So far, five manufacturers have the rights to manufacture and commercialize pretomanid: Viatris, Macleods, Lupin, Hongqi, and Remington.

In April 2019, TBA announced the first licensing agreement with US-based Mylan (now a part of Viatris). The license was non-exclusive for most LMICs, but it granted Mylan exclusive rights for commercialization in high-income countries (HICs) and select middle income countries (50). In October 2019, TBA granted India-based Macleods Pharmaceuticals a non-exclusive license to sell pretomanid in approximately 140 countries and territories (51). Over the next four years, TBA granted additional licenses to several manufacturing partners, including Shenyang Hongqi Pharmaceuticals in January 2020 to distribute the drug in China, Hong Kong, Macau and Taiwan (52), Lupin Limited in September 2021 for LMICs (53), and Remington Pharmaceutical Industries (Pvt.) Ltd. in August 2023 to distribute in Pakistan, with the opportunity to extend to other countries in the future (54). The purpose of licensing was not only global supply and price competition; working with manufacturers based in the high-burden countries of India, China, and Pakistan was also a strategy to facilitate product uptake and security of supply in those countries.

Following US FDA approval, a global access price of USD 364 for a six-month treatment course of pretomanid was announced as available for procurement covering 150 LMICs (55), (56). This was the lowest starting price for a new drug for DR-TB in LMICs – 60% lower than bedaquiline and 80% lower than delamanid. For comparison, when bedaquiline was launched, a treatment course was priced at USD 900, 3,000, and 30,000 for a six-month course in low-, middle- and high-income countries respectively (57), and delamanid was priced at USD 1,700 per six-month treatment course for GFATM-eligible countries procuring

through the GDF (2). Over time, the price for pretomanid dropped further by 38% to USD 224, and for the BPaL regimen from USD 1062 to USD 340, as volumes increased and competition entered the market (see Table 1; further discussion of price negotiations also below).

Figure 3. Evolution of the price of BPaL/M regimens (in USD)*



* Based on GDF's lowest prices for pretomanid 200mg (182 tablets), bedaquiline 100mg (200 tablets), linezolid 600mg (364 tablets in 2019-2021 and 182 tablets afterward due to dose reduction), and moxifloxacin 400mg (182 tablets).

** As BPaL/M was recommended in 2022, we included BPaL/M regimen prices from 2022 and listed prices for moxifloxacin for all years for reference.

*** The price for pretomanid is not included in the GDF's prices for 2019. It was extracted from the announcement of the inclusion of pretomanid in the catalog. This latter document also puts the BPaL regimen price at USD 1,040, using an average weighted price for linezolid.

Sources: (1–8)*

Developing multiple sources of supply took time. From 2019 to October 2024, Mylan (Viatris) was the only supplier with WHO PQ and therefore had a de facto monopoly on the donor-funded market. It took Macleods, the second licensee, about two years to initiate the PQ process, and it took WHO over three years to finally grant it in October 2024, introducing more competition into the market (58) (59). (Macleods had received GFATM ERP approval two years earlier, in December 2022, but according to one interviewee GDF did not purchase from them, such that Viatris's de facto monopoly continued until at least 2024.) Challenges regarding the PQ process were raised by some interviewees, particularly its slow process and high fees:

> *"WHO has started charging fees of $20,000 per product per year. Even if you pay these fees, you expect your approval to come in six months, but the timing has not changed much, even after levying this fee. The time is usually 18 months or 24 months for getting approval, which doesn't make sense. From a health point of view, 24 months, 18 months is too long a time to lose"*

A third manufacturer has submitted its application in Q2-2023, but as of mid- 2025 had not yet received PQ.

Uncertainties of supply were raised as a reason for countries not to adopt BPaL/M-based regimens sooner:

> *"The only reason [for not implementing BPaL/M] is if the supply line is unsure. (...) Looking at the pressure at the GDF, which they keep on talking about from time to time, the demand side is too strong, and the supply side is wavering. The concern is that if there are challenges in the supply of pretomanid, patients will suffer very badly"*

Furthermore, interviewees raised challenges around GDF's procurement process:.

> *"GDF may not be very efficient all the time in giving advance notice to manufacturers and some countries might come up with an emergency kind of a situation wanting the stocks yesterday. TB Alliance definitely helps because they have their separate outreach in many countries. But there is still a challenge regarding the demand forecast"*

Notably, TBA conducted a market projections exercise detailed below, and worked with Viatris to ensure readiness for pretomanid scale-up.

One interviewee summarized specific actions that stakeholders could take to prevent delays from the supply side, emphasizing better coordination between TBA, GDF, WHO and producers:

> *"TB meetings can be done better. GDF does their own meetings. They may not invite TB Alliance or other stakeholders. But guidelines work can happen better instead of doing it in silos or doing it abruptly, at least inform the industry ahead of time. So, three things – 1) forecasting, 2) doing meetings with a more serious purpose, with all stakeholders involved in the room, 3) changing guidelines: so at least they can inform ahead of time and inform all the stakeholders"*

Some interviewees also expressed concerns about the TBA's licensing strategy (60,61). For example, unlike the Medicines Patent Pool's licenses, which are all published in full, TBA's have remained confidential, hampering efforts to assess how well the terms and conditions promote fair access:

> *"There's still no clarity on issues like licensing terms and the royalty structure. So, there's also a transparency issue there. And that's not just an issue in principle, but also an issue regarding the power of GDF and other actors to negotiate lower prices and put out tenders that could be coming in at lower price points."*

Another interviewee raised concerns about the degree of competition in the market, but at the same time, the challenge of low volumes being potentially fragmented across multiple suppliers. The relatively low volumes of product for the DR-TB market have been a central challenge for ensuring security of supply and low prices, as it is difficult to achieve economies of scale, an issue also relevant for other neglected diseases and other small markets such as for pediatric formulations. When pretomanid was first approved for pre-XDR TB cases in 2019, there were only 12,000 total estimated patients worldwide on treatment with 9-18 month regimens (62). Once pretomanid was recommended for MDR-TB, the market was significantly larger at around 178,000 estimated patients treated worldwide (62). Compared to the HIV market, with nearly 20 million persons on lifelong treatment, volumes for XDR and MDR-TB at six months treatment were much smaller, and less attractive to producers. At very low volumes, it can be difficult to secure any manufacturers at all, especially if there is also pressure to keep prices low. Relying on one supplier may offer sufficient profit to keep them in the market for the long term, but multiple suppliers provide increased competition and security of supply – but may not enter or remain in the market if returns are low. Even more challenging is managing supply for pediatric patients, as pretomanid has not yet been approved for patients under 14 years old due in part to a safety signal in earlier animal testing that has required significant additional R&D work by TBA; this means national TB programs may procure BPaL for adults but replace pretomanid with small volumes of delamanid for children, further fragmenting the market.

Interviewees did not agree on what was the right balance between enhancing availability and affordability through competition among multiple suppliers, on the one hand, and fragmenting an already small market, on the other.

Finally, the TB market is characterized by a single large global purchaser that pools demand for TB drugs, the GDF. Its procurement decisions can significantly influence market entry and exit of competing firms. However, we did not find sufficient publicly available data to analyze GDF's market-shaping strategy vis-à-vis BPaL/M. Overall, we report here some of the concerns raised by interviewees, but did not have sufficient information to assess the determinants of pricing and security of supply for BPaL/M, and consider this issue beyond the scope of this paper.

ii. Price negotiation and volume guarantees for availability and affordability

In addition to licensing, TBA sought to improve availability and affordability of pretomanid by negotiating prices and volume guarantees. TBA negotiated the launch price of USD 364 with Viatris as a strategy to facilitate early adoption of BPaL, with the BPaL regimen priced at the time at USD 1,040 per treatment course (1).

Pretomanid had the lowest launch price of a novel TB drug and the price of the BPaL regimen was significantly lower than the price of some prior regimens to treat DR-TB (which had ranged from USD 2,000 to USD 8,000 for courses of at least 20 months (63). However, civil society groups raised concerns that it was still too expensive at over twice the price (USD 1,040) they had been advocating for (USD 500) (61,63). The ask to reduce the price of pretomanid was based on estimations that it could be produced and sold at a profit for less than USD 1.35 per day, or USD 246 for a 6-month (26-week) treatment course at annual volumes exceeding 108,000 treatments (64,65).

To further reduce the price, TBA helped negotiate a volume guarantee agreement between MedAccess and Viatris, announced in December 2022 immediately following WHO guidelines recommending BPaL/M for programmatic use for almost all DR-TB patients. The agreement established a ceiling price for pretomanid of USD 240 per six-month treatment course available to more than 140 countries and public sector procurers purchasing for those countries (66).

The price reduction helped to bring the price of BPaL/M closer to the target of USD 500/ treatment, which was achieved in 2023 for LMICs when the prices of the other drugs in the regimen were reduced. In August 2023, following the expiration of the primary patent for bedaquiline, J&J announced that they would drop the price for LMICs to USD 130 per six-month treatment course (67–69). By 2024, the total cost for the BPaL regimen had fallen to under $400 per six-month treatment course (68) (see Figure 3).

Furthermore, TBA engaged with international funders and procurers to ensure the availability of the BPaL/M regimen globally. Pretomanid was added to the list of drugs eligible for procurement through the GDF two months after receiving approval from the US FDA. It was the fastest drug to be included in the GDF's catalog after obtaining approval from an SRA (1). In July 2022, shortly after WHO's rapid communication on programmatic use, the Global Fund published an information note advising countries to consider transitioning to BPaL/M, following WHO recommendations (70).

The sum total of these interventions – eligibility for use of donor funds, licensing to low-cost quality-assured generic producers, price negotiation, volume guarantees, advocacy – all contributed to unprecedented scale-up of BPaL/M, with orders reaching over 150,000 courses in more than 100 countries by the end of 2024 (6), much faster than uptake observed for bedaquiline and delamanid 5 years since SRA approval (see Figure 2 above).

iii. Economic analysis to inform national-level policymaking

In addition to interventions on drug prices, TBA commissioned studies on cost-savings, budget impact and cost-effectiveness to facilitate national decision-making on the adoption of BPaL/M. As one interviewee explained:

> *"From the very beginning, [the TB Alliance] had a very practical view of what are the rate limiting steps, and what can we do to ensure that more countries are actually able to make decisions to incorporate this new regimen into their national TB program. For instance, there were questions around budget impact and costing, what was it going to cost the country to actually implement it. So, they did a series of studies around budget impact and total costs of care…to prepare the ground for introduction of BPaL/M, and also generated evidence through implementation studies and operations research. The TB Alliance did important work in all of those areas to help countries have the information they needed to implement these new regimens in an effective and in a rapid way."*

TBA commissioned KNCV Tuberculosis Foundation (KNCV) and John Hopkins University (JHU) to assess the budgetary impact of adopting the new regimen in Indonesia, Kyrgyzstan, and Nigeria. They found that the cost of treating patients with BPaL/M was between 57% and 78% lower than the conventional regimens adopted in those countries, and that a gradual adoption of BPaL/M would result in 5-year savings of up to 32% of the national budget to treat XDR-TB (71). TBA also commissioned the London School of Hygiene & Tropical Medicine (LSHTM) to conduct a further study in South Africa, Georgia, and the Philippines, which found that national TB programs could save 64%-70% by using BPaL/M instead of the standard of care, and avert an additional 46-56% of disability adjusted life-years (DALYs) (72).

Post launch, a study co-authored by the TBA, Stop TB Partnership, Global Fund, WHO and Survivors Against TB estimated that BPaLM would cost countries 40-90% less compared with current regimens due to the savings in medicines costs and health systems costs (including diagnostics and patient follow-ups), in addition to reducing costs incurred by patients (73). Additional studies corroborated these findings and determined that BPaL/M would be cost-saving and cost-effective for both patients and health systems in several countries compared to the existing standard of care (74–77). These studies provided further elements to support the rapid adoption of BPaL/M.

In addition, TBA developed an innovative tool to help countries and other stakeholders generate a country-specific customized cost analysis to ascertain cost and budget impact of BPaL/M. The "Savings from Leveraging & Adopting Shorter & Highly Effective TB Treatments" (SLASH-TB) tool was developed in collaboration with the Swiss Tropical and Public Health Institute. Typically, cost-effectiveness and budget impact calculations can take significant time and resources to complete. SLASH-TB is a relatively quick and free resource for countries. A recent study presented the results of four countries that used the tool (Pakistan, the Philippines, South Africa, and Ukraine), showing cost savings, increase in lives saved, treatment success and DALYs averted in each of the four countries (78).

Furthermore, TBA assessed the projected demand for DR-TB treatments in 13 high-burden countries in order to estimate the use of BPaL/M globally. The study can be used to guide global health stakeholders in planning and budgeting for DR-TB interventions. Projected usage could also help estimate cost of the individual components of DR-TB regimens over time. The study projected that BPaL/M would be used by the majority of DR-TB patients by 2024, reaching 78% by 2026 (79).

Together, these studies and tools effectively generated evidence that helped support the rapid adoption of BPaL/M.

C. COUNTRY-LEVEL IMPLEMENTATION SUPPORT AND KNOWLEDGE-SHARING

The third major area of activity was engaging countries through co-producing and sharing knowledge on how BPaL/M could be implemented on the ground, thereby also laying the foundation for advocacy. TBA's strategy was to work with a diverse set of countries that could provide a broad range of information on the types of implementation challenges that might arise, and also prioritized countries that could serve as examples to other similar countries.

i. Knowledge-building

A first priority was to build knowledge at country level on how BPaL could be implemented. Even prior to pretomanid receiving approval from the US FDA, TBA commissioned studies to confirm the value-proposition of BPaL and provide additional evidence to WHO for guidelines development. TBA contracted KNCV to conduct a study on acceptability and feasibility in three representative countries with varying burdens of MDR-TB and HIV, Indonesia, Kyrgyzstan, and Nigeria. The study concluded that there was a high likelihood (88%) that the treatment would be adopted once available, especially given its patient friendliness and potential to reduce workload and financial burden on the health care system. Overall acceptability of BPaL was high at 93%, and the majority of respondents were willing to start using BPaL as the new standard of care despite country-specific health system constraints. Nevertheless, concerns were raised about the monitoring of safety and long-term efficacy, as well as national regulatory requirements regarding the introduction of the regimen (22).

TBA also commissioned development of implementation plans in Indonesia, Kazakhstan, Kyrgyzstan, Uzbekistan and Papua New Guinea, which created early engagement with key countries and informed their subsequent scale-up.

Proactive involvement of country level and global stakeholders in generation of evidence for acceptability, feasibility, cost-effectiveness, potential savings and implementation plans enabled organic early buy-in from several high DR-TB burden countries, who became early adopters of the regimen upon WHO recommendation. As one interviewee described:

> *"The market studies that the TB Alliance did to prepare the ground for the introduction of BPaL/M, were important so that national TB programs would be confident that they could adopt BPaL/M and get the results that they needed.*

Following the initial WHO recommendation in May 2020 for using BPaL under operational research conditions and based on feedback from implementation planning exercises in 5 countries by TBA, in October 2020 TBA launched the project "Leveraging Innovation for Faster Treatment of Tuberculosis" (LIFT-TB) to conduct operational research in seven countries: Indonesia, Kyrgyzstan, Myanmar, Philippines, Ukraine, Uzbekistan, and Vietnam. Co-funded by TBA and the Korea International Cooperation Agency (KOICA), LIFT-TB was implemented in partnership with the International Tuberculosis Research Center (ITRC) and aimed to provide technical assistance and support operational research in participating countries. TBA also contracted international technical assistance providers such as KNCV and local partners to execute operational research (OR) in project countries, including engaging TB affected communities (80).

These OR projects helped to accelerate the adoption and scale-up of BPaL/M in LIFT-TB countries and generated field evidence that helped other countries develop confidence to adopt the regimens. One interviewee emphasized the importance of OR to generate local evidence and identify potential challenges for expanded implementation:

> *"Through this [LIFT-TB] project, the participating countries were able to collect local evidence on the adoption of the BPaL regimen and then identify their strengths and also challenges for the health system, not only in the lab but also on the clinical management side. Operational research definitely has benefits for the country, not only on the regimen itself, like investigating the efficacy and safety, but also to identify their strengths and weakness in the system, in both the clinical and laboratory side…operational research is helpful and beneficial for the country, and they make much more progress than countries that didn't do it before"*

One interviewee described the distinct roles that each stakeholder played:

> *"The TB Alliance focused on its role as a technical assistance provider, and then they worked with local partners who could actually develop these data so that national TB program managers would feel confident in adopting BPaL because they had data that showed that it could be used effectively in their environment. The TB Alliance made an important strategic choice to focus on the rate-limiting steps in adoption and then do the studies needed to generate evidence that would help program managers and policymakers to make decisions to incorporate BPaL into their national programs"*

Apart from LIFT-TB, studies also took place in other countries, sometimes directly with TBA but also sometimes independently. For example, TBA supported a pilot of BPaL in Pakistan, a key high burden country, and engaged directly in sub-national demand creation (81). Furthermore, in December 2020, South Africa launched its BPaL Clinical Access Program, which was similar to OR, and became the first country in Africa to provide 400 patients with access to the regimen. The program was funded by the United States Agency for International Development (USAID) and was run in partnership with the Wits Health Consortium (82). Notably, TB Alliance had conducted a cost-effectiveness study and supported developing an implementation plan for BPaL in South Africa, which helped provide evidence and a roadmap to the National Department of Health and National TB Programme, in addition to local clinical evidence generated through the Nix-TB and ZeNix trials conducted in the country. This body of work supported decision making in South Africa, helping it become the first country to begin implementing BPaL. In 2021 researchers at South Africa-based research organization THINK, Wits Health and TBA published a BPaL Implementation Guide, supported by Stop TB Partnership, that offered practical guidance on how to implement the new regimen based on direct experience (83).

In addition, in May 2021, Nigeria also commenced operational research on BPaL/M, which was implemented by the NTP. Furthermore, as mentioned above, in October 2021, India initiated a pragmatic trial for BPaL in a field setting with varying doses of linezolid (46).

After OR studies were complete, TBA continued supporting scale-up at sub-national levels – that is, at state/province or district level – in key countries, including Ukraine, the Philippines, Indonesia, Pakistan and Peru through a network of local, in-country partners. National guideline changes were necessary but not sufficient to prepare grassroots level clinicians and other healthcare workers to implement the new regimen, making more local-level engagement and peer-to-peer knowledge sharing (see below) valuable. As one interviewee explained:

> *"Educating about a regimen is pretty straightforward, but educating on managing adverse events and safety monitoring is critical. Because that's what people don't fully understand. When do I start? When do I stop? When do I interrupt? How long? What safety signals should I be watching out for?"*

As one interviewee explained, early adopter countries play an important role in providing evidence others can use:

> *"Some countries are a bit reluctant to implement a regimen recommended to be used under operational research, because they may believe that this is something which is not yet tested and proved, and they may prefer to wait for other countries to implement and generate more evidence, rather than introducing and scaling up the new treatment."*

ii. Knowledge sharing and advocacy

To share learnings from countries that conducted OR and other studies, TBA engaged in a range of knowledge sharing activities: publishing studies in open-access peer-reviewed journals, presenting findings at major TB conferences, hiring technical assistance providers, and creating forums for cross-border learning. These spaces also provided opportunities for advocacy with national decision-makers.

A notable development is a recent initiative to share learnings, best practices and foster collaboration among countries, launched in March 2024. The "Peer-to-Peer Learning for Innovative Cures" (PeerLINC) Knowledge Hub was launched in the Philippines, one of the earliest adopters of BPaL. The project is operated by TBA, hosted by the Tropical Disease Foundation in collaboration with the Department of Health of the Philippines, and funded by the Australian Government (84). PeerLINC provides practical training and technical assistance to countries through a peer-to-peer learning model, solving some of the identified problems with the standard technical assistance process, such as high costs and long timelines.

> *"International technical assistance providers are based in Europe and the US normally, [and] South based TA providers don't exist. These international TA providers, they've got very high cost estimates for doing training, capacity building and supporting guideline change in one country. So why not create an alternative, a South-based TA provider model?"*

PeerLINC trainings are provided in person in the Philippines, in the collaborating countries, or remotely through virtual meetings. Since its launch, PeerLINC has helped several countries advance in implementing the BPaL/M regimen, including Brazil, Peru, Nigeria, Rwanda, and the Democratic Republic of Congo (85). Interviewees emphasized the value of PeerLINC by connecting people who are actually working on the different aspects of the implementation:

> *"What makes this program so unique, special, and exciting is the fact that now you have a chance to build a peer-to-peer link between people who are running the program, who are actually making decisions that are going to affect the program in a manner that shares best practices. It gives them a chance to bounce off ideas, see how things work, and this shortens the amount of time you take to roll things out on the ground. So how do you do this? You don't just connect the government to the government, but you have a team of the communities who have worked on the ground, you have someone who is actually doing the implementation on a day-to-day basis on the ground, become a part of that team who can bring ground realities to the table"*

Knowledge-sharing activities could also provide important opportunities for advocacy. For example, TBA worked with WHO to conceptualize two important initiatives: a "Call to Action" by WHO for BPaL/M and the "BPaL/M Accelerator Platform". The Call to Action, launched on World TB Day in March 2023 by the WHO Director General and Director of the Global TB Programme, encouraged countries and stakeholders to rapidly implement BPaL/M. The

"Accelerator", introduced in January 2023, shortly after WHO recommended programmatic use, was created to promote technical exchange and knowledge sharing between program managers, WHO staff, clinicians, communities, technical and funding partners (86). Both initiatives were born out of discussions between TBA and WHO. The Accelerator is led and administered by WHO, with funding from TBA. Monthly virtual meetings of the Accelerator cover various topics surrounding the implementation of BPaL/M (e.g., clinical, regulatory, procurement) to assist countries in implementing the "Call to Action". According to one interviewee, besides being a space for exchange, the Accelerator has also been instrumental in stimulating countries that were lagging behind in the implementation of the new regimen:

> *"It is a platform for knowledge and experience sharing and can be used to stimulate those countries that have not yet embarked in BPaL/M implementation to gain the confidence to switch to new oral 6-month regimens, such as BPaL/M. Recently India has opted to include BPaL/M in their TB treatment guidelines and this is great news for all patients in that country. This forum has helped because it gives an opportunity to come to see where other countries are and get some peer-to-peer exchange"*

Following the Call to Action, the community-led "Fast Track the Cure" (FTTC) initiative was launched as an advocacy campaign by communities to bring their peers together to raise awareness about and facilitate access to BPaL/M, while also advocating for world leaders to adopt the regimen and make it available to whoever needs it within their countries. The initiative is supported by a growing consortium of four implementing partners (who were engaged in the initiative co-creation and implementation); 24 endorsing partners (who were in support of the initiative and amplified the work of implementing partners); and two sponsoring partners, TBA and Stop TB Partnership, who invested resources to support implementing partners (87).

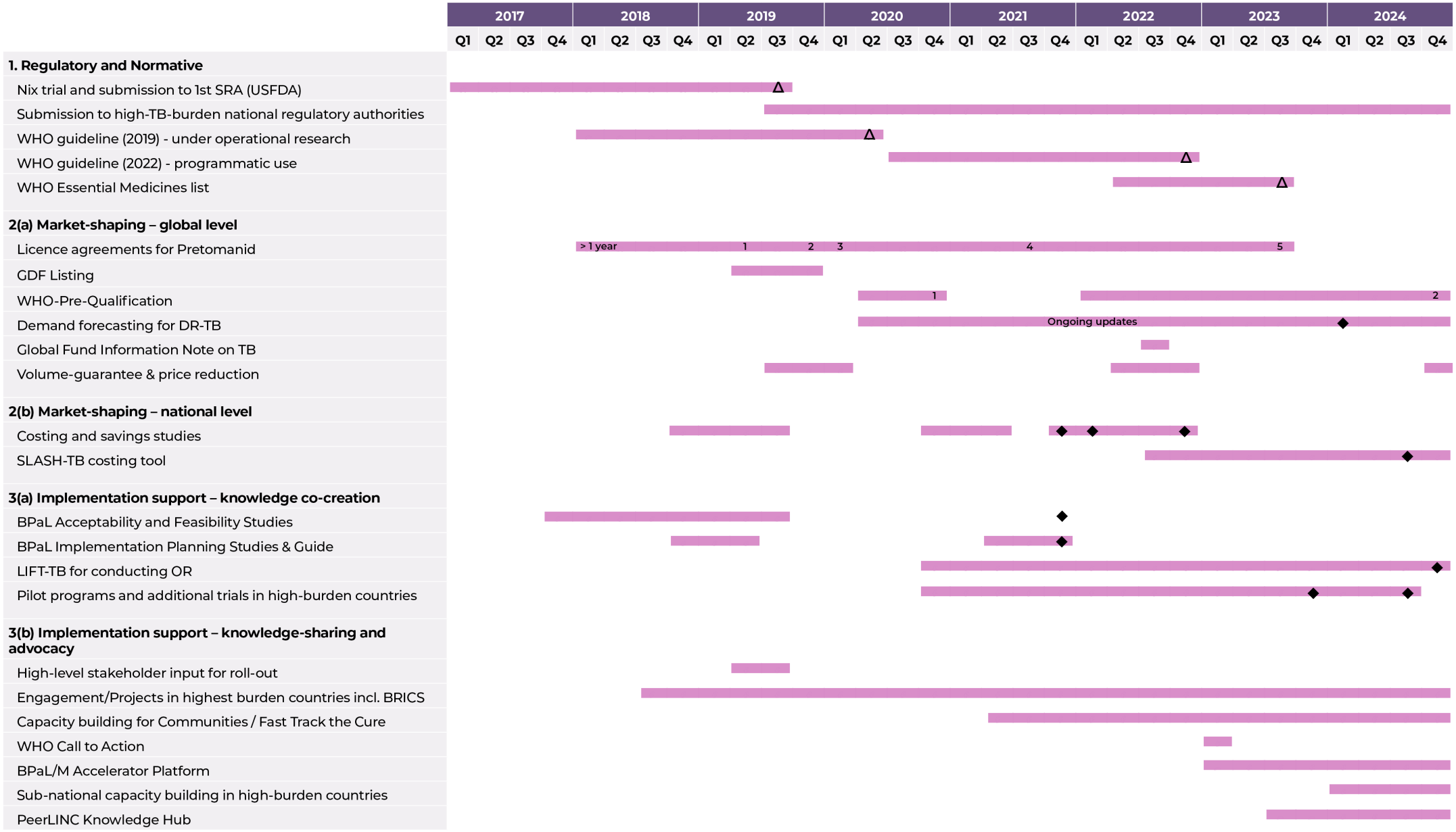
TBA also engaged with communities to monitor patient experiences, as communities could report back independently to their national programs on how the new regimen was working.

Before FTTC was launched, and while ORs were ongoing, TBA engaged with community-led organizations to create awareness, literacy and advocacy for the new DR-TB regimens among community stakeholders and patients. Such projects helped inform communities about new regimens as well as incorporate community perspectives early on during the roll-out of regimens.

Interviewees illustrated the value of community engagement through initiatives such as Fast-track the Cure or by involving communities in early awareness building, explaining:

> *"Having the local community and the countries in which they were operating be informed about TB and TB treatments, understand the characteristics of their new regimen, BPaL/M, and the advantages that it brought, and then incorporate community perspectives into the operational research work that government was doing in each of the countries, really helped to make sure that things were going to operate much more quickly and without bumps in the road... Because the community was already engaged, bringing these new treatment regimens to national TB programs went much more smoothly than it would have gone otherwise, in terms of acceptance and uptake, which are critically important. Taking community engagement seriously was another important dimension of what the TB Alliance did. They also worked with partner countries to disseminate the lessons of community engagement and make sure that as new countries came online, they learned from what others had done and didn't make the mistakes that some had made by ignoring the community."*

Figure 4. Timeline of Access Interventions Orchestrated by TBA



LEGEND		
1, 2, 3	Indicate different actors	Note: for all trials and ORs
◆	Publication	→ shaded till date of enrollment and for follow-up and analysis
Δ	WHO decisions	
*Conducted by country		

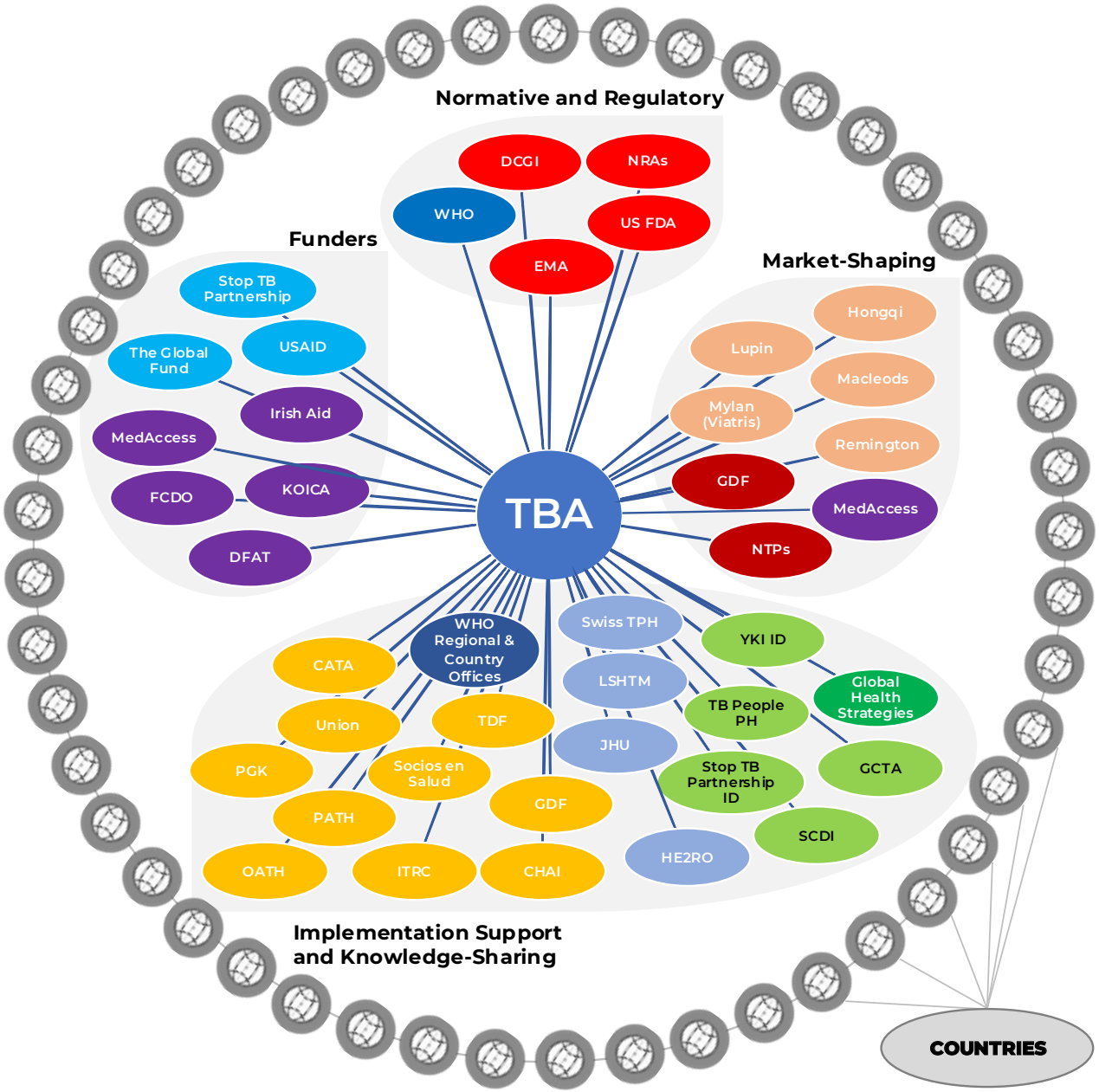
4. DISCUSSION

The previous sections described the interventions undertaken by TBA and other stakeholders to facilitate access, in this section we focus on the role TBA played.

A wide range of interventions working in parallel at global, national and sub-national levels, and involving many different actors, was necessary to accelerate access to BPaL/M. The interventions extended for over seven years, and did not progress sequentially but rather overlapped in time, as illustrated in Figure 4 (Timeline). This complex set of interventions reflect both a purposeful strategy and ad hoc reactivity as needs arose. How did this set of interventions come about, and what attributes enabled them?

TBA played a central role as the "orchestrator" of these actions, as illustrated in the network diagram in Figure 5. "Orchestration" refers to when actors "enlist public or private intermediary actors on a voluntary basis, by providing them ideational and material support to address target actors" to pursue their governance goals (7). It is a particularly relevant strategy for global actors, who often do not have hierarchical authority to command or decide what others do, but enlist the cooperation of other actors to achieve their goals.

Figure 5. TBA Orchestration of Access Interventions with Partners



ORGANIZATION TYPE
Advocacy
Community engagement; Advocacy
Donor; Advocacy
Evidence Generation
Implementing agency
Knowledge Dissemination, Advocacy
Manufacturer
Normative Guidance
Procurer
Regulator
TBA Donor

A. HOW DID TBA ORCHESTRATE ACCESS?

How did TBA orchestrate access? We identified five "ideational and material" attributes that enabled TBA to play this role effectively.

First was the ability to generate and share knowledge about pretomanid and BPaL/M. As the developer, TBA's in-depth knowledge of the product and regimen (e.g. data that had been generated about safety and efficacy) positioned it well to provide authoritative information quickly to regulators, WHO, NTP managers, clinicians and community members. In addition, TBA co-produced with countries further knowledge of how the product and regimen could be used through operational research, pilot projects, additional clinical trials, acceptability and feasibility studies, costing and cost-effectiveness studies, and market projections. Co-creation of this knowledge with NTPs, academics, clinicians, and other key stakeholders in the international TB community not only generated necessary knowledge, but also built familiarity among implementers with the new regimen. Investments in projects such as the BPaLM Accelerator Platform, SLASH-TB and PeerLINC were also critical to share this knowledge with key decision-makers at local, national and international levels.

Second was TBA's non-profit status, which strengthened its legitimacy to orchestrate other actors. It is difficult to imagine a for-profit firm engaging in the range of activities orchestrated by TBA, either because it would face insufficient incentive to do so or because stakeholders would not accept it. One interviewee commented that Viatris did not promote BPaL/M very assertively (perhaps because TB medicines are not highly profitable), although in theory it had the economic incentive and market power to do so. Even in high-income markets where it had exclusive rights, there have been reports of insufficient availability. A study conducted in 43 European countries showed that pretomanid was only available in four countries (88). In contrast, TBA's non-profit status allowed it to engage as a public health actor with other not-for-profit actors such as community groups, NTPs, regulators and WHO.

A third attribute was TBA's ability to mobilize material resources for access interventions, either by funding activities directly or by raising new funds. While TBA's donors had expected the organization to focus primarily on R&D, it had received flexible core funding that allowed it to finance at least some smaller-scale access activities early on. For other especially larger-scale access activities, TBA raised new funds – for example, from the Republic of Korea for LIFT-TB and from Australia for PeerLINC. For some interventions, TBA did not provide full funding but cooperated with other actors, such as GFATM, WHO or MSF, who could bring their own financial resources to bear on the shared objective of expanding access to BPaL/M.

Indeed, the fourth attribute we identified as critical for enabling success is TBA's relationships with the wide range of actors which were needed to effectively promote BPaL uptake. Many of these relationships originated in the product development process, such as with the regulators, WHO and manufacturers. Others became a focus later, as attention shifted to access, such as with the NTPs in high-burden countries, GFATM, new donors, in-country technical assistance contractors, community groups and advocacy organizations.

Finally, the fifth attribute was the intrinsic motivation to see the product reach people with DR-TB, which was a key indicator of how well TBA was achieving its non-profit organizational mission. TBA's mission motivated an energetic, creative and diverse set of interventions that successfully promoted rapid uptake of BPaL/M. While TBA was originally created to develop TB medicines, there was a risk that developed products would not reach patients without concerted attention to access. As one interviewee described:

> *"TBA decided that their remit should include ensuring that access actually became a reality. If you discover and develop new medicines, but they just sit on the shelf, they don't actually do anybody any good. So, they quite rightly interpreted their mandate to ensure access to these new medicines. It's clear when you look at the difference between the introduction of delamanid and bedaquiline, and pretomanid as part of the BPaL/M regimen, the TB Alliance's decision to work on the access issue was a smart decision because they cut the time to programmatic use of pretomanid compared to bedaquiline in half. If they hadn't done the work they did on access with partners around the world, that lag time would have been just as long for BPaL/M as it had been for bedaquiline."*

The motivation to see their product reach people was a critical enabler of a broad range of access interventions, but this motivation could also raise questions about potential conflicts of interest, as we discuss in the following section.

B. SHOULD NON-PROFIT PRODUCT DEVELOPERS ORCHESTRATE?: MANAGING POTENTIAL CONFLICTS OF INTEREST

We have identified above five attributes that enabled TBA to "conduct the orchestra," and several interviewees argued that TBA was a natural fit for this role:

> *"The convening of different groups of people is something that fits very well into the mindset and the model of the product development partnership. They have been very successful at doing that and bringing those groups of people together, recognizing that a whole lot of different skills are needed, most of which, quite properly, don't belong inside the PDP, but the convening of them is something that fits very well there. And that kind of convening isn't something that the big procurers or WHO, or any of the other organizations put a lot of thought and effort into. They're very busy doing their own thing. The PDP, then, is in a position to be an intermediary between the industrial partners and the procurement and policy organizations in a way that very few people are able to do."*

One interviewee explained the advantages PDPs have in playing this role:

> *"I don't see how other organizations can do it well, because you've got the R&D organization that's vastly familiar with the data, knows too much about the programs and can advocate for the programs in ways that most other organizations just can't. To just hand it off to somebody else doesn't make any sense to me. Certainly, you'll leverage other existing organizations that can help with procurement, Global Fund and GDF and the like. So, I believe in end-to-end research, development, and delivery. A PDP should be good at all those things. You have to understand the delivery side to do a good job on your development side. And if you're not looking at end-to-end, we'll end up with products that nobody wants"*

These are strong arguments for non-profit product developers such as PDPs to play the orchestrator role. The main counterargument is whether they have a conflict of interest (CoI) in doing so, and if so, how this could be managed. For-profit firms lobbying decision-makers to adopt public policies in favor of their commercial interests pose a clear conflict of interest to policymaking processes. As a non-profit organization, TBA's mission was not to maximize profits from sales of pretomanid. However, it did have an organizational interest in demonstrating success and health impact, with the rapid adoption of BPaL/M a central way of doing so. Views differed on whether such organizational interests comprised

a conflict, and if so, how to manage it. One interviewee argued that the product developer should provide information but not be involved in policy decisions:

> *"TBA, as a developer, can provide all the information that is necessary to make sure that the National TB Program can make the correct decision based on treatment outcomes…Then they need to let the department make its own decision on what it wants done"*

Another interviewee raised concerns that if TBA provided technical assistance this might only cover its own regimen, when such assistance should include support for all regimens for DR-TB. (TBA noted that PeerLINC also covers regimens beyond BPaL.) Another argued that all organizations have interests, and the challenge is how to manage and align them toward a shared goal:

> *"Every organization involved in drug development has interests, whether it's the WHO, a national government, the National TB program, an NGO like the TB Alliance, or for that matter, even community-based organizations like advocacy groups. It's not just commercial organizations that have interests, but public sector organizations have interests as well. The important thing is to have a mechanism by which people can declare those interests and you can figure out how to work together on some common objective."*

One strategy for managing potential conflicts of interest was to delineate clear roles and responsibilities, particularly identifying when the product developer should not be unduly influencing decisions, such as for regulatory decisions and guideline development. Interviewees described the relationship between TBA and WHO, which included meeting with WHO and participating as an observer during WHO guideline committee meetings:

> *"Principal investigators of studies being reviewed by the WHO Guidelines Development Group are invited to join the group in an observer role. Clearly, they have no possibility to contribute in any way to the discussion and decision on the recommendation, but they are instrumental to provide answers and clarification when requested, as they have the best understanding and knowledge of their studies. That was the case for TB Alliance who was there to provide answers and clarification when requested"*

We found that TBA's projects, such as LIFT-TB, supported local evidence-generation and informed policy development; none of the interviewees expressed concerns that TBA had unduly influenced policy decisions of NTPs or WHO.

Some interviewees viewed TBA's interest in seeing rapid uptake of BPaL/M as aligned with the public interest in switching to a treatment option that had clear advantages over the status quo. According to one interviewee:

> *"It took a very long time for bedaquiline to be introduced in countries, really too many years. Collectively, the whole community did not do well at that time and we should not be repeating the same story with new products. Bedaquiline was the first new drug after the introduction of the first-line anti-TB drugs, nearly 40 years earlier, and access was a major issue. I think with BPaL/M we are doing much better, although adoption of a new regimen remains a major undertaking for many countries. The TB Alliance has been behind this because they have a major interest to promote their own regimen, the regimen they developed, but there is no other interest apart from that"*

In summary, while there is the potential for conflict of interest when a product developer plays the orchestrator role, it is possible to manage such conflicts by clearly defining and limiting the product developer's role for key policy decisions such as regulatory, WHO guidelines and national adoption decisions. Where the product developer is involved in

evidence generation or technical assistance, transparency regarding its role and partnering with other organizations (as TBA did) can mitigate potential COIs. On the flipside, when a non-profit product developer's mission is aligned with public health objectives, the organizational interest in seeing its product used widely can be a valuable motivator and enable it to orchestrate effectively.

Finding ways to manage potential COIs is critical, as in some cases there may not be other actors beyond the PDP with the motivation or other attributes necessary to orchestrate access. One interviewee commented:

> *"I don't see someone stepping up and taking on the onus and responsibility of actually making sure that we do what it takes to have an absolutely unbiased view of what the patient requires. How can the countries help? How can we help the countries? No one's doing that. In the absence of that, if someone who's developing the drugs has a separate team which is actually trying to do this, and not doing this by themselves, they're actually working with people on the ground, I don't think there's anything wrong with that."*

5. CONCLUSIONS

Understanding how rapid access to BPaL/M was achieved requires examining not only what was done, but also by whom and how. We found that a diverse range of interventions and actors was necessary across global, national and local levels, with TBA playing a central orchestrating role across this complex ecosystem. Here we offer conclusions from the case for accelerating access to the products of non-profit R&D more broadly, first looking at each of the three categories of interventions then considering the attributes that enabled orchestration.

Regulatory and Normative Guidance: TBA's strategy to submit first to the US FDA offered the advantages of widespread credibility of the regimen's safety and efficacy, which was particularly important since it took a relatively new approach by developing a regimen rather than testing a single drug alone. It also ensured rapid eligibility for purchase with donor funds. In addition, TBA prioritized regulatory submissions to high-burden countries that did not rely on donor funding, a strategic way to accelerate access in those countries. However, the WHO guidelines committee's 2019 decision requiring more evidence before it would eventually recommend the regimen for programmatic use in 2022 highlights important differences between the evidence required by the US regulator, where DR-TB is rare, and that required by WHO for potential application in high-burden countries. In future, designing pivotal trials to provide the kind of evidence required for WHO to recommend programmatic use could mitigate the need to conduct further studies after first regulatory approval, saving valuable time. WHO's recently-published guidance on the kinds of evidence needed for its TB treatment guidelines, released as this study was coming to a close in December 2024, is an encouraging and important step towards facilitating such trial designs (49). Formalizing the current practice of informal exchanges between WHO and product developers could facilitate mutual understanding on the kinds of evidence needed.

In addition, in the medium term, wider adoption among WHO Level 4 Listed Regulatory Authorities of procedures that allow regulators to assess a product for use by populations other than their own may be needed; for example, EMA's Article 58 allows the EMA to collaborate with national regulators of disease endemic countries to issue a scientific opinion on a medicine that will be used outside the European Union. An important rationale for this procedure is to assess a medicine's risks and benefits in the context within which it will be widely used, which may differ substantially from the EU.[7] In the longer-term, investments in strengthening national regulatory capacity in high-TB-burden countries are merited. Furthermore, improvements in the WHO PQ process and timelines could also reduce the relative need for SRA approval for international procurement.

Market-shaping for affordability and availability: TBA recognized that BPaL's therapeutic advantages alone – considerable as they were – would be necessary but not sufficient to persuade decision-makers to change regimens. TBA sought to maximize affordability by getting drug prices down as far as possible through a combination of licensing to multiple

7 Further information on Article 58, also known as EU-M4all, is available here: https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/medicines-use-outside-european-union.

generic producers with a track record of achieving WHO PQ, publishing demand forecasts, negotiating a volume guarantee with MedAccess, negotiating further price reductions with the first supplier Viatris, and engaging with the GFATM and GDF as key actors for procurement. In addition, TBA generated evidence to inform national decision-makers through a wide range of economic studies, from budget impact to cost-effectiveness studies, from commissioning experts to estimate health systems savings to creating a costing tool for countries to do so themselves. When new medicines offer efficiencies in the health system, it can be impactful to make these savings visible to decision-makers through credible quantification. Accelerating access requires thinking beyond the clinical benefits of the product, to addressing the economic concerns of decision-makers at both global and national levels.

Country-Level Implementation Support and Knowledge Sharing: TBA began building understanding of how to implement BPaL/M in national TB programs by conducting acceptability, feasibility and implementation planning studies even prior to USFDA approval. Participating in clinical trials, operational research and pilot projects increased familiarity with the regimen among implementers in early adopting countries, and in so doing, built the foundation for rapid uptake after WHO recommended programmatic use in 2022. In addition, it was valuable to ensure other countries could tap into this knowledge base quickly and easily by supporting the creation of knowledge-exchange forums, such as the WHO BPaL Accelerator and PeerLINC. For other products of non-profit R&D, early and sustained country engagement seems critical to build knowledge on implementation. Access at country level can be accelerated through a strategy that coherently links knowledge-building with transnational knowledge-sharing and advocacy, leading to rapid uptake of new regimens.

Orchestration for products of non-profit R&D

No single organization can be responsible for all the different steps necessary to realize access, but the case of BPaL/M illustrates the critical role of an orchestrator able to steer the efforts of many actors across a complex ecosystem towards a shared goal. As illustrated in Figure 5, TBA had relationships with and provided resources (financial, informational, relational) to many diverse actors whose contributions were required to realize rapid patient access to BPaL/M. As one interviewee explained:

> *"Other organizations are willing to assist and help the TB Alliance – to a certain extent, WHO helped, Global Fund helped, Stop TB partnership helped. So, organizations are very helpful. But somebody had to orchestrate, and the TB Alliance took that responsibility"*

PDPs can play the orchestrator role for access, as they have often already done for R&D. We identified five attributes that enabled TBA to play the central orchestrator role effectively: knowledge of the regimen, non-profit status, ability to provide and/or mobilize funding, collaborative relationships with a wide range of stakeholders, and inherent motivation linked to mission. By definition, non-profit product developers are likely to have at least two of the five attributes (i.e. knowledge and non-profit status), but not all may have the other three (i.e. funding, relationships, access as part of core mission) needed to orchestrate access. This raises the key question of whether and how to address these gaps, either by providing funding, building relationships, amending or clarifying the mission or identifying other actors who can partner to bring these attributes to the effort.

Enduring motivation is necessary to do the hard work of mobilizing financial, human and organizational resources to continue putting in place intervention after intervention until medicines have reached those who need them. If non-profit R&D actors are to orchestrate access effectively, they need clear decisions and solid political support from their governing boards endorsing access as part of their organizational missions.

For PDPs that do see access as core to their mission, it is clear that significant resources are needed to successfully orchestrate access. While a full costing of access efforts is beyond the scope of this study, it may provide useful intuition regarding the magnitude of costs to flag that the single largest cost for BPaL/M access was the USD 11 million LIFT-TB project. Furthermore, addressing some of the identified areas for improvement in the BPaL/M case also implies the need for more resources: e.g. running larger, multi-country pivotal clinical trials earlier to generate sufficient evidence for both regulatory approval and WHO guidelines; or including specific populations such as children or pregnant women earlier in clinical trials.

With financing of PDPs shifting away from flexible core funding to become increasingly earmarked for specific (mainly R&D) projects, it may become more difficult for PDPs to act quickly and early to implement access interventions – unless funders provide resources to do so. However, PDPs have historically been financed primarily through official development assistance (ODA) and philanthropic foundations, but ODA from traditional donor governments is now under severe strain. The growing number of products successfully developed by non-profit R&D initiatives may sit unused on a shelf, unless significant resources can be mobilized for access interventions. Funders who have invested in successful non-profit R&D may be especially motivated to see the job through and ensure sufficient resources for access to them. But in the medium to longer-term, other sources of funding are likely to be required. One option is to generate funding from alternative sources, such as the US Priority Review Voucher (PRV), a program that grants the developer of neglected disease (and other) products a voucher for priority regulatory review that can be sold to a commercial firm. TBA obtained a PRV for pretomanid, and other PDPs have also obtained PRVs, which may provide flexible resources for R&D and access activities. Another option is for endemic countries to finance a greater proportion of access interventions, not only within their own borders but also to support the global-level orchestration of activities that facilitates national-level access. Ensuring policymakers have a clear picture of the full range of access interventions that require financing may help in some small way to mobilize it.

Limits to case applicability and directions for future research

The rapid uptake of BPaL/M makes it a highly instructive case, but specific aspects may also limit the generalizability of these findings. First, BPaL/M represented a major improvement in therapeutic and health system value over the status quo. It may be more difficult to achieve such a rapid uptake for products offering more incremental improvements. Careful health technology assessments will become even more important to make the case for adopting new products. Second, as TB is a global priority disease, there have been many international actors with the mission to support treatment efforts. This is not the case for most neglected tropical diseases, for which new products are most likely to emerge from non-profit R&D; this raises the question of how existing actors can optimally organize themselves to address the many steps needed to achieve access and who can play the role of effective orchestrator. Finally, the literature on non-profit R&D has focused on the innovation process itself, but further research on how access to its end products has been addressed would complement these findings.

Despite these limits, the BPaL/M case is a remarkable success story, as one interviewee simply stated:

> *"The introduction of BPaL/M is – we have not seen something like that before – the way countries have rapidly implemented this recommendation!"*

The case offers many broadly applicable findings, and points the way towards ensuring that the growing arsenal of products emerging from non-profit R&D can quickly reach those whose lives are on the line and cannot afford to wait.

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ANNEX 1 – LIST OF INTERVIEWEES

NAME	AFFILIATION(S)
Abdul Ghafoor	National Technical Advisor MDR, National TB Control Program, Pakistan
Anonymous	TB access advocate Former Global Tuberculosis Community Advisory Board (TB CAB) member
Aastha Gupta	Director, Market Access, TBA
David Hermann	Deputy Director, Global Health, Bill and Melinda Gates Foundation
Deanne Goldberg	Program Manager, TB Access, Clinton Health Access Initiative, South Africa
Dr Klara Henderson	New Products and Access Senior Adviser, Department of Foreign Affairs and Trade (DFAT), Australia
Jaap Broekmans	Adjunct Professor, Epidemiology, at the Bloomberg School of Public Health Chair of the WHO Global Task Force on TB Impact Measurement Member of TBA's Access Advisory Committee
Jeffrey Sturchio	Chairman and former CEO at Rabin Martin Member of TBA's Access Advisory Committee
Ji-young (written comments)	Global Disease Eradication Fund (GDEF) team, Korea International Cooperation Agency (KOICA)
Jong Seok Lee	Head, Division of Microbiology Research, International Tuberculosis Research Center (ITRC)
Mae Shieh	Head of Business Development, Drugs for Neglected Diseases initiative (DNDi)
Matteo Zignol	Unit Head, Global Tuberculosis Programme, World Health Organization (WHO) Member of TBA's Access Advisory Committee
Mel Spigelman	CEO, TBA
Mohammed Yassin	Senior Advisor, Tuberculosis, The Global Fund
Prashant Sisodia	Vice President, Viatris
Sandeep Juneja	Senior Vice President, Market Access, TBA
Sang Nae (Ray) Cho	Project Leader, International Tuberculosis Research Center (ITRC)

NAME	AFFILIATION(S)
Saurabh Rane	DR-TB Survivor Member of TBA's Access Advisory Committee
Sergiy Kondratyuk	Project Manager, International Treatment Preparedness Coalition (ITPC)
Stephanie, Jin-Kyung Jung	Head, Division of Global Health, International Tuberculosis Research Center (ITRC)
Tom McLean	Senior Advisor, Access and Strategy, Innovative Vector Control Consortium (IVCC)

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