

BLUEPRINT FOR A

Market-Driven Value-Based Advance Commitment

FOR TUBERCULOSIS

KALIPSO CHALKIDOU
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Acronyms

| | | | |
|--------|---|-------|--|
| AMC | advance market commitment | NCD | noncommunicable disease |
| BMGF | Bill & Melinda Gates Foundation | NPV | net present value |
| BRICS | Brazil, Russia, India, China, and South Africa | PDP | product development partnership |
| CIVETS | Colombia, Indonesia, Vietnam, Egypt, Turkey, and South Africa | PRV | priority review voucher |
| DALY | disability-adjusted life year | QALY | quality-adjusted life year |
| GDF | Global Drug Facility | R&D | research and development |
| HIC | high-income country | SMEs | small and medium-size enterprises |
| HTA | health technology assessment | SoC | standard of care |
| IP | intellectual property | TB | tuberculosis |
| LIC | low-income country | TBDA | TB Drug Accelerator programme |
| LMIC | low- and middle-income country | TPP | target product profile |
| MDB | multilateral development bank | TRIPS | Agreement on Trade-Related Aspects of Intellectual Property Rights |
| MDR | multi-drug-resistant | UDR | universal drug regimen |
| MIC | middle-income country | UHC | universal health coverage |
| MNC | multinational company | VBP | value-based price |
| MPP | Medicines Patent Pool | WHO | World Health Organization |
| MVAC | market-driven, value-based advance commitment | | |

Glossary

Advance market commitment (AMC): A binding advance commitment, offered by governments and donors, for purchase of a health technology meeting specific pre-agreed parameters.

At-launch HTA: An updated health technology assessment (HTA) conducted at the time of product launch, used to adjust pricing and volumes based on product performance against the pre-agreed target product profile (TPP).

Ex ante HTA: HTA conducted before the launch of a new treatment based on TPP characteristics.

Ex post HTA: HTA conducted after product launch, used to verify the product's clinical efficacy and confirm appropriate value-based pricing.

Governance arrangements: A range of explicit or implicit structures, institutions, organisations, or agreements that enable the governance functions to be executed.

Governance functions: Processes that must be managed or decisions that must be taken for the overall model to work.

Governance model: A cohesive and complete set of governance arrangements that will ultimately guide execution of the entire model.

Health technology assessment (HTA): A “multidisciplinary process that reviews the medical, economic, organisational, social and ethical issues related to the use of a health technology in a systematic manner,” whose “main purpose is to provide policymakers with evidence-based information, so they can formulate health policies that are safe, effective, patient-focused and cost-effective. It is also used by national authorities to help [them make] decisions on which technology should be reimbursed at national level.” [4, emphasis added]

Intellectual property (IP) risk: Risk of patent infringement or compulsory licensing.

Market demand risk: Risk of insufficient demand for volume/price to justify research and development (R&D).

Market-driven, value-based advance commitment (MVAC): An AMC that is driven by middle-income country demand, is informed by countries' ability to pay, and allows pharmaceutical companies to reap higher revenues from a more effective product.

Multi-entry risk: Risk that multiple R&D actors may produce the same product for the same target market.

Payment risk: Risk of non-payment or late payment.

Performance/impact risk: Risk that new drugs may underperform once deployed.

Price risk: Risk that prices demanded by R&D actors may be unaffordable.

Product risk: Risk that new products may fail to address local needs.

Proof of concept: Drug development up to Phase IIB.

Scientific risk: Risk that R&D may not lead to a viable product.

Target product profile (TPP): The target objective of a drug development programme described in terms of the regulatory label sought. For the full TPP specification that we use in this report, based on the World Health Organization version and incorporating input from the Bill & Melinda Gates Foundation, see Appendix 1.

Value-based pricing: The idea that payers should be willing to pay a price that represents the value to their respective healthcare systems produced by a given treatment.

Executive Summary

Background

Innovation—delivering new drugs, diagnostics, and devices—is a critical tool in the global fight against disease and premature death. Yet despite the potential for innovation to improve health around the world, the pharmaceutical industry’s investments in research and development (R&D) generally neglect diseases of the poor in favour of more lucrative high-income markets. Responding to this R&D gap, donor “push” investments have helped advance an innovation agenda to serve low- and middle-income countries. Though these investments have helped accelerate market entry of several important innovations, other donor-push products have fizzled upon market entry due to unaffordable or non-cost-effective pricing, disappointing efficacy, lack of political will, or lower-than-anticipated country demand. And with many large middle-income countries (MICs) poised to soon transition from donor aid, the sustainability of the current donor-led model is in question.

Tuberculosis (TB), an infectious disease primarily affecting the poor and vulnerable, ranks among the top 10 global causes of death. Current TB treatment cycles are long and toxic, causing some patients to discontinue treatment, develop acquired drug resistance, and risk spreading a drug-resistant pathogen to others. Drug-resistant strains are more difficult to treat, traditionally requiring long-duration toxic regimens and high-cost hospitalization (though recent innovations offer a shorter, more tolerable, and more affordable treatment).[1] Despite years of global investment in TB control, modelling suggests that global goals for TB cannot be achieved without major technological breakthroughs.[2] One particularly desirable

innovation would be a short-course universal drug regimen (UDR)—equally capable of treating drug-sensitive and drug-resistant strains, with a two-month or shorter treatment duration. Donors, particularly the Bill & Melinda Gates Foundation (BMGF), have funded substantial early-stage R&D to source new treatment compounds that could contribute to a UDR, but substantial additional investments in late-stage trials would be required to bring such a UDR to market.

The global market for TB therapies reached roughly \$1 billion in 2018 and is projected to grow by more than one-third by 2025—suggesting a potentially large and profitable market for better TB treatment.[3] Yet despite the clear health need and potential return, private-sector actors have mostly shied away from the TB market. Industry perceives MICs—which make up the vast majority of the TB treatment market—as risky markets for an innovative product. Historically, many MICs have either aggressively negotiated down innovative drug prices, declined to purchase innovative therapies until they go off patent, imposed price controls, or exploited flexibilities in the World Trade Organization’s Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) for compulsory licensing of on-patent drugs.

For MIC markets alone to generate private-sector R&D investment, innovator companies will need assurance that MIC purchasers are willing to pay a value premium for innovation—potentially far higher than the cost of older, less effective genericized competitors, but low enough to ensure local value and affordability. Notably, recent policy announcements by MIC governments signal their increasing willingness to engage with and contribute to global health initiatives,

including the TB R&D agenda. This suggests that a window of opportunity is opening to engage MICs in the development of a path-breaking health technology to address the TB scourge.

Introducing the Market-Driven, Value-Based Advance Commitment

The market-driven, value-based advance commitment (MVAC) builds on the advance market commitment (AMC) mechanism previously used in global health with several important innovations and improvements. Most crucially, the MVAC is driven by MIC demand rather than donor contributions; is informed by countries' ability to pay (see Box ES-1) rather than a single, "cost-plus" price; and allows pharmaceutical companies to reap higher revenues from a more effective product. In this report, we apply our new model—the MVAC—to a target product profile (TPP), published by the World Health Organization (WHO) in 2016 and endorsed by BMGF, for a pan-TB regimen.[11] The TPP describes a UDR to tackle both drug-sensitive and drug-resistant strains, with a treatment cycle of less than two months.

The MVAC rests on four essential design pillars:

- **Health technology assessment.** Health technology assessment (HTA), already a well-established process in MICs including Brazil, China, India, and South Africa, is a mechanism by which payers evaluate the value of a new product through the application of globally accepted methods. The MVAC will use HTA—based on country-specific evidence and ability to pay—to inform countries' purchase commitments.
- **Commitment guarantees.** To drive engagement and investment in R&D by the pharmaceutical industry, it is critical that industry perceive MIC commitments as highly credible. Commitment guarantees—underwritten by a financial intermediary—will help ensure that MICs credibly signal their demand and ability to pay.
- **Industrial policy alignment.** Based on an initial landscaping analysis, we know that developing local industry (including home-grown research capacity and pharmaceutical industries) is a priority for many MICs.

Box ES-1. Ability to Pay

In this report we use the term *ability to pay* to reflect healthcare systems' (not individual patients') ability to pay for lifesaving products based on the budgets those countries have allocated or plan to allocate to healthcare (and/or TB in particular) and given countries' historical decisions to pay for health outcomes. Our methodology calibrates prices against available resources while accounting for the savings that a healthcare system could directly realise from introducing a TB cure, hence ensuring that the price proposed is affordable to the healthcare system given local circumstances. Importantly, we

do not assume that these prices would be affordable to individual patients; rather, our calculations assume that governments will fulfill their responsibility and commitments to provide equitable, cost-effective TB care without user fees at the point of use. Differential pricing reflects the fact that affordability varies from country to country depending on each country's wealth level, healthcare budget, and population's ability to benefit from the technology. The specifics of our approach are detailed in Chapter 3).

- **Governance structure.** An MVAC governance structure credible to both MIC payers and industry is required to drive and operationalise the MVAC. This requires it to be authoritative, open, and sufficiently flexible to place MIC governments in the driving seat.

The MVAC model is intended to serve as a bridge between the dysfunctional status quo and a more sustainable and effective R&D ecosystem—one which more closely emulates the positive characteristics of high-income country (HIC) markets for healthcare products. Many of its core elements (including the need to underwrite commitments and the development of a joint TPP) will become less relevant as markets mature and trust is built between payers and industry. The governance structure—a secretariat to pool HTA resources, set and signal joint priorities, and conduct country-specific value assessments—may endure but evolve as national payers build up their own institutional, human resource, and data collection and analysis capacities.

Health Technology Assessment: Estimating the Value-Based Market for a New TB Treatment Regimen

HTA is defined as a “a multidisciplinary process that reviews the medical, economic, organisational, social and ethical issues related to the use of a health technology in a systematic manner,” whose “main purpose is to provide policymakers with evidence-based information, so they can formulate health policies that are safe, effective, patient-focused and cost-effective.” It is also “used by national authorities to help [them make] decisions on which technology should be reimbursed at national level” [4, emphasis added]. HTA is well established in many HICs; a wide range of MICs—including India (see Box ES-2), China, Indonesia, Thailand, South Africa, the Philippines, and most of Latin America and the Caribbean (including Mexico, Brazil, Chile, and Colombia)—have also established HTA bodies linked to their national health insurance and pharmaceutical

Box ES-2. India’s HTA Launch

India recently launched an HTA agency at the Ministry of Health and Family Welfare—HTAIn—to inform ceiling rates for reimbursement via a clearly defined process and set of methods. One of its earliest assessments evaluated lenses for cataract operations based on “clinical efficacy, cost-effectiveness, accessibility, availability, and feasibility.” The assessment concluded that “[small-incision cataract surgery (SICS)] with rigid lenses is the most appropriate intervention to treat cataract patients in India in [the] current scenario,” and recommended that the benefits package cover both phacoemulsification surgery and SICS at a cost of 9,606 Indian rupees (INR) and 7,405 INR, respectively.

procurement agencies. In the context of the MVAC, early (or ex ante) HTA, conducted before the launch of the new treatment (based on the TPP characteristics), can then be applied to estimate the maximum justifiable size of a guaranteed purchase commitment given treatment alternatives, expected patient numbers, and local ability to pay.

We engaged a team of world-class epidemiological and economic modellers to undertake HTA and estimate the value-based market for a new TB drug treatment in line with the TPP in three countries—India, Russia, and South Africa.¹ The modelling approach is rooted in *value-based pricing*—the idea that payers should be willing to pay a price that represents the value produced by a new TB drug regimen to their respective healthcare systems (see Box ES-3). The model evaluates the UDR from a healthcare perspective, considering two sources of value: (1) additional health gains of the UDR

1. Modelling work completed by Anna Vassall, Gabriela Gomez, Nim Pathy, and Lotte Steuten; report forthcoming.

Box ES-3. Value-Based Pricing

Throughout this report we use the term *value-based pricing* from the perspective of the payer/buyer—that is, a healthcare system or insurance provider. We always assume zero out-of-pocket costs for individual patients and their families. We adopt the recommended approach set out in a UK Office for Fair Trading report in 2007, whereby pricing is informed by an assessment of comparative clinical and cost effectiveness through HTA and is meant to “ensure the price of drugs reflect[s] their clinical and therapeutic value to patients and the broader

[National Health Service].” Similar approaches have been operational for several years in the UK National Health Service and several other universal and equitable healthcare systems, including those of Australia, Canada, and more recently, Brazil and Thailand. This HTA-informed approach has also been endorsed by the WHO Regional Office for South East-Asia (e.g., see paragraph 11 here) and the Pan American Health Organization. For further discussion of the term *value-based pricing* from the payer’s perspective, see here.

compared with alternative therapies, valued at country ability to pay per quality-adjusted or disability-adjusted life year (QALY or DALY) based on supply-side constraints or opportunity costs, and (2) health system savings (e.g., averted hospitalizations and a reduced need for drug-sensitivity testing).

The full report includes extensive sensitivity testing, but we report our main (baseline) results based on a set of highly conservative assumptions, including launch of new and superior TB technologies before the TPP-based new drug treatment comes to market (Table ES-1). Based on these assumptions, the model estimates a total market in India, Russia, and South Africa of around \$6.3 billion for the first 10 years after launch (Table ES-2).

The estimated value-based market for India, Russia, and South Africa will generate margins significantly larger than the expected cost of late-stage R&D. It could be possible, therefore, to pull a product to market with volume and/or price commitments that represent only a portion of total market demand.

Calculating and Securing the Advance Purchase Commitment

Drawing from the ex ante HTA results, participating countries must set a reasonable and sufficient purchase commitment to incentivise industry investments. The HTA results provide an upper-bound estimate for the size of that commitment; the lower bound of the commitment size must be expected to provide a risk-adjusted return for the successful innovator company. Given the large overall value proposition, there are many different commitment models that could deliver shared value to all parties.

We suggest a relatively simple and powerful model—a predictable revenue commitment pool, tied to product performance against the TPP—that could serve as a starting point for negotiations. As a first step, one or more high-burden countries would need to take a leadership role as “first movers”—for example, India and South Africa. Ex ante HTA for those two countries would reveal the total value-based market, the relative value of the TPP-based new drug treatment by country, and the relative value of the new drug treatment

Table ES-1. PICO Statement for TPP-Based Drug Treatment and National Strategic Plans

| PICO element | India | Russia | South Africa |
|--|---|---|--|
| Population (in terms of current burden and resistance) | High rate of TB, TB/HIV, and multi-drug-resistant (MDR) TB ^a Mainly resistance to first-line drugs | High rate of TB and MDR TB High levels of resistance to second-line drugs | High rate of TB, TB/HIV, and MDR TB Mainly resistance to first-line drugs |
| Intervention | UDR as defined by the TPP | | |
| Comparator | Standard of care at the time of UDR introduction: <ul style="list-style-type: none"> • New shortened regimen introduced in 2025 for drug-sensitive and MDR TB^b • New vaccine | | |
| Outcomes | <ul style="list-style-type: none"> • Additional DALYs averted • Net monetary benefit • Health sector cost savings | | |
| Context (national strategic plan) | Private-sector engagement Patient support (nutritional supplement) | Scale-up of GeneXpert MTB/RIF in 2018 Standardisation of WHO MDR revised regimen | WHO symptom screening for all Standardisation of WHO MDR revised regimen |

a. MDR TB (i.e., TB resistant to at least both isoniazid and rifampicin) leads to substantially longer treatments and costs to the health service and patients, as compared with drug-sensitive TB.

b. The standard of care was defined as new shortened regimens for first-line treatment (four months) in 2030 and for MDR (nine months, new drugs with no pre-existent resistance) in 2025. These regimens are similar to the BPaMZ and BPaL currently being trialled by the TB Alliance. In addition, we assume there will be a new vaccine coming to the market in 2027. This vaccine has clinical characteristics similar to the recently trialled M72/AS01E.

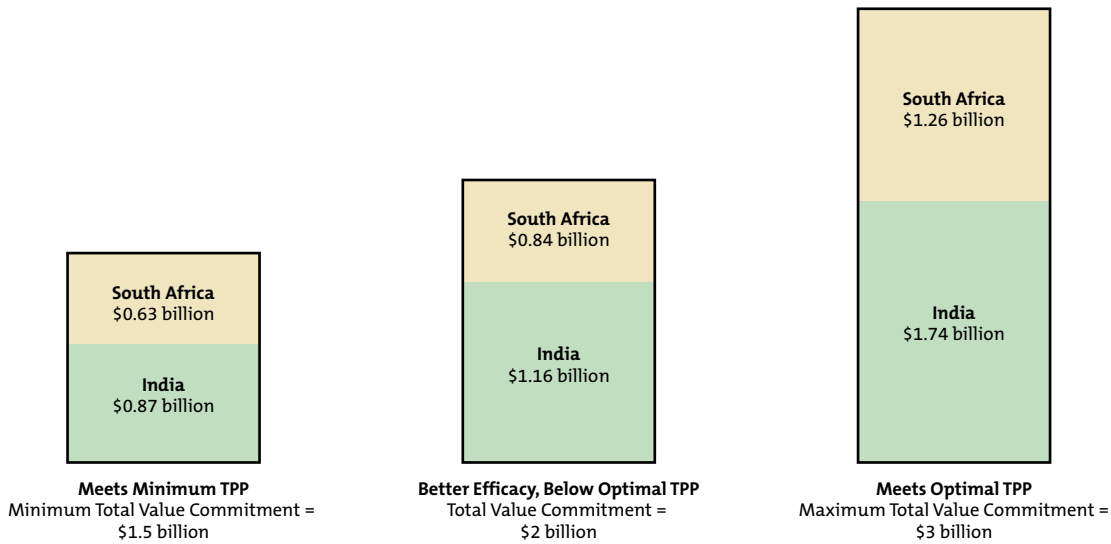
Table ES-2. Key Results from Early-Stage (ex ante) HTA

| | 100% value-based revenue (USD billions, 2017) | Maximum price per regimen (USD 2017) | Number of regimens 2030 to 2039 (millions) |
|---------------------|--|---|---|
| India | 3.24 | 501 | 6,467 |
| Russia | 0.6 | 2,498 | 240 |
| South Africa | 2.37 | 864 | 2,743 |
| Total | 6.30 | NA | 9,450 |

for each country vis-à-vis specific attributes of the TPP. Using the ex ante HTA results as a starting point, the first mover countries would set and divide up a total “commitment pool”—essentially, an advance purchase commitment (price x volume) tied to product performance. A minimum commitment pool would be offered for a product meeting a minimal TPP; a maximum commitment pool would be offered for a product meeting the entirety of the TPP. There are proposals as to the minimum acceptable TPP, but the minimum

acceptable TPP needs to be reviewed and endorsed by the technical committee and ultimately the countries. The two countries would assume “shares” of the total commitment pool based on the relative value propositions in their respective health systems (Figure ES-1). Potentially, additional countries could join the commitment pool at a later date—leaving the total revenue guarantee unchanged but reducing each country’s specific commitment.

Figure ES-1. Indicative Schematic for Defining and Dividing a Value-Based Commitment



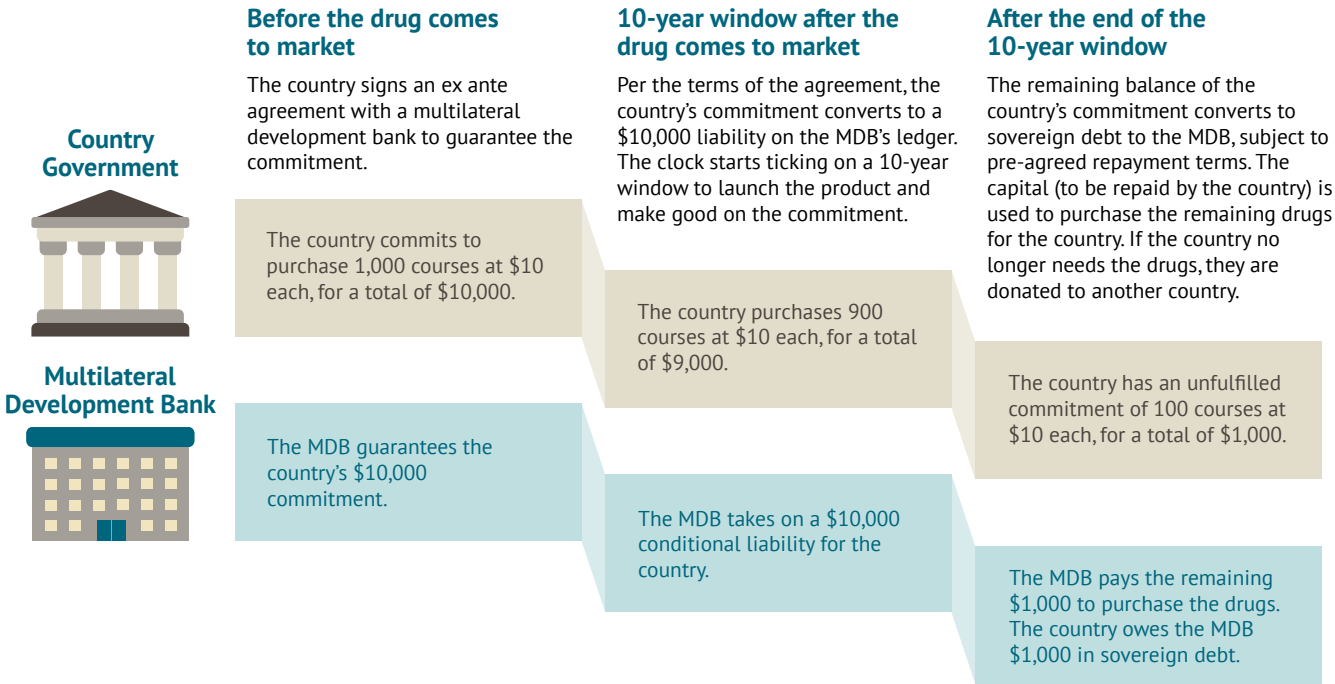
At the time of product launch, a form of at-launch HTA would be undertaken. Countries would rerun the early-HTA model with up-to-date product performance data, based on the clinical trial results with appropriate modelling. The value-based price in each country would be adjusted for performance. Countries would be responsible for fulfilling their prior volume commitments by purchasing a sufficient quantity of the product at the performance-adjusted value-based price. After fulfilling their commitments, countries would receive access to the product for the remainder of their demand at a discounted price (30 percent of the value-based price in the illustrative example) for a specified period. Ex post HTA (say two to five years later) using post-launch evidence collection could be used to assess whether the product is meeting the at-launch performance expectations; performance either exceeding or failing to achieve anticipated levels could prompt pricing adjustments for future purchases from a pre-agreed time point.

A more complicated (but potentially advantageous) approach would involve conducting a full HTA at

launch by inputting up-to-date data reflecting the current situation in 2030. This approach creates additional complexity but offers a better precedent for value-based pricing by incorporating accurate parameters at the time of launch. Country-guaranteed revenue commitments would still be calculated based on baseline assumptions, with volume adjustments to reflect any price change, to ensure that the agreed revenue commitments were unchanged. This would provide the necessary predictability to countries, industry, and the financial intermediary for overall guaranteed revenue. Whether such an alternative process is feasible will depend on whether there is a shared understanding between the parties that the HTA processes will have the necessary robustness and credibility.

To guarantee countries' purchase commitments, countries would leverage their own sovereign creditworthiness—intermediated through a AAA-rated intermediary guarantor such as a multilateral development bank (MDB)—to underwrite the advance commitments (Figure ES-2). As a first step—well before the drug comes to market—each country government would sign a

Figure ES-2. Simplified Straw Man of Model to Underwrite Country Commitments



contractual agreement with such an MDB laying out the terms of the commitment and clearly defining the country's obligations after the drug becomes available. After the drug comes to market, the country's commitment would convert to a conditional liability on the MDB ledger; the country would have 10 years (illustratively) to fulfil the entirety of its purchase commitment by purchasing drugs directly from the originator company or a local licensee authorized by the originator. If a commitment balance remains at the end of the 10-year window—that is, if a country were to partially or fully renege on its purchase commitment—the remaining balance would convert to a loan by the MDB, subject to repayment by the commitment-making country under pre-agreed terms. The remaining drug purchase commitment would be honoured by the MDB on behalf of the country, and the drugs would be supplied for the country to use as it finds appropriate.

Based on a needs assessment and preliminary conversations with relevant stakeholders, the World Bank and the Asian Development Bank emerge as promising candidates to serve as MDB partners.

The MVAC model mitigates and distributes risk, reducing total risk to a more acceptable level for all parties. Along several dimensions, the MVAC is fully de-risked:

- The commitment guarantees offer clarity on market demand for a product that meets TPP performance expectations.
- The commitment ensures that countries can access the new products at affordable prices.
- The TPP ensures that products will meet local demand.
- The entire structure is premised on respect for the originator's intellectual property.

Along other dimensions, risk is reduced and redistributed efficiently across parties:

- Suppliers continue to face the scientific risk that products will fail in late-stage trials; however, their overall development risk is substantially reduced with financial subsidies from global donors from early-stage pipeline development through proof of concept.
- Market entry of competitor products remains possible but unlikely, given the stringent TPP requirements (e.g., the requirement for a three-product combination); a more likely scenario would involve market entry of a vaccine (reducing the pool of people to be treated).
- We have assumed that at-launch HTA leads only to price adjustments from the full TPP price based on product performance. However, an alternative approach would include a full at-launch HTA, using a full set of up-to-date parameters, to calculate the value-based price at the time of launch. Ex post HTA, conducted after the product is launched, could again lead to price adjustment and further redistribute some performance/impact risk between countries and suppliers. *In either case, the revenue commitment would not change.* Instead, price adjustments would be offset by changes to the volume commitment, ensuring that countries, industry, and the guarantee provider all continue to benefit from a predictable revenue commitment.
- The MDB would reduce and absorb payment risk by transforming a stated commitment into a sovereign debt obligation.

Industrial Policy

The proposed MVAC model raises several issues related to participating countries' industrial policy objectives. Development of the biopharmaceutical industry is a priority for the governments of India, China, and Russia. Russia is particularly protectionist in its policies, which results in a high need for localisation by multinational companies (MNCs). In India, South Africa, and China, although localisation is not required, there may be an expectation that MNCs would generate productive clinical development partnerships and local manufacturing arrangements.

The MVAC will need to accommodate countries' preferential purchasing policies for local manufacturers, plus any specific requirements for local research. The successful innovator company could be expected to meet country industrial policy requirements by, for example, licensing production to local manufacturers. Given the high overall expected volumes, technology transfer models and license agreements between MNC developers and local manufacturing companies could also be a useful route to secure long-term supply.

It will be important, however, to avoid pushing up costs through the duplication of facilities. Having production facilities or clinical research facilities in each country is unlikely to be efficient. Compromise will be needed. High costs will lead to the need for a larger revenue commitment for the MVAC drug developers meeting the TPP. This is not a sensible use of MICs' scarce health budget resources.

Governance

The MVAC is a vehicle for multinational cooperation; ultimately, its structure and operations must be owned and governed by participating country governments in partnership with relevant trusted global experts and institutional stakeholders. Yet for the model to

work in practice, country governments must delegate key authorities to a permanent technical body that can manage day-to-day governance functions (Figure ES-3).

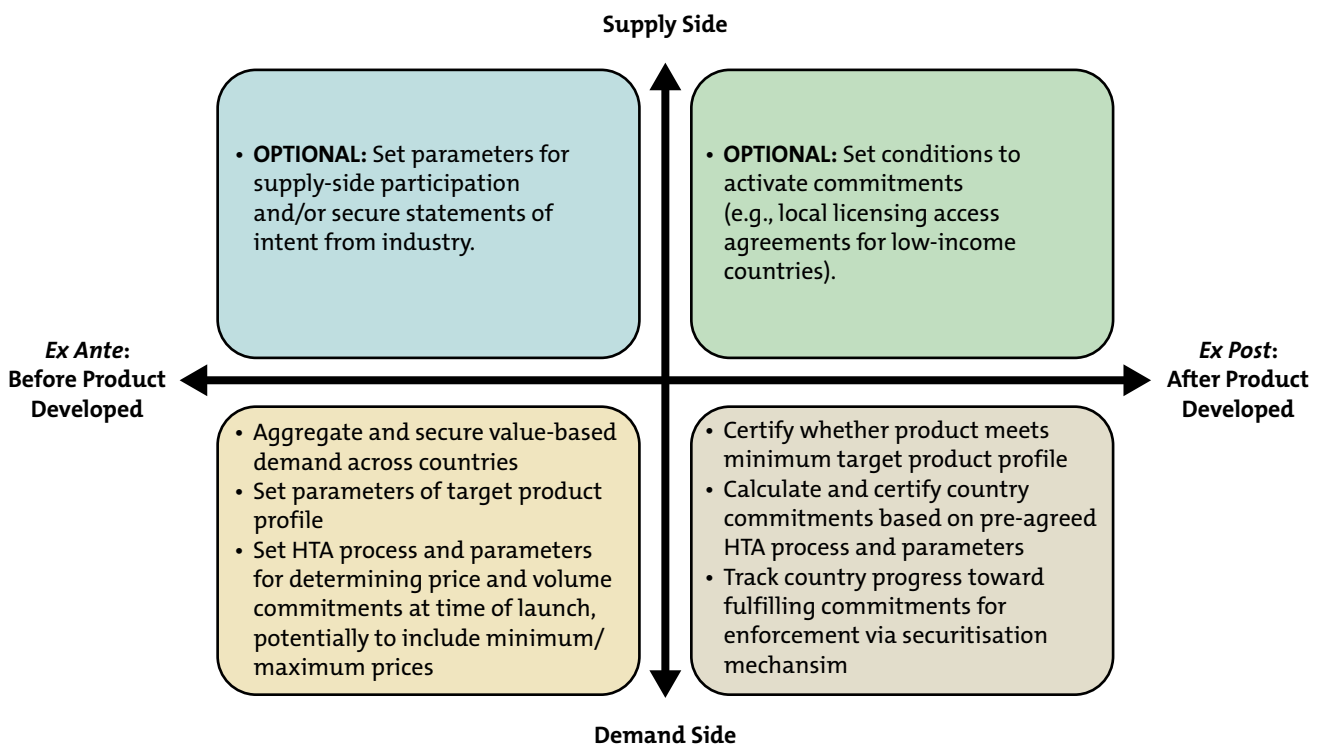
To serve its core functions—and successfully manage a complex and politically sensitive negotiation process—the MVAC governance model would benefit from the following characteristics:

- Openness and credibility to the BRICS countries (Brazil, Russia, India, China, and South Africa), the CIVETS countries (Colombia, Indonesia, Vietnam, Egypt, Turkey, and South Africa), and other MICs
- Credibility to industry
- Relevance to and/or expertise in TB
- Flexibility
- Ability to minimise transaction costs
- Ability to attract (or offer) long-term operational resources

Based on a needs assessment, we identified a World Bank trust fund as the best fit for MVAC operational needs. The World Bank is a credible multilateral institution—both for potential industry partners and for MICs—which already participates in institutional governance and could oversee a dedicated trust fund. The trust fund model is widely used to steward development resources and is well trusted by the donors who might subsidise the secretariat’s operational costs. Trust funds offer predictable multiyear funding—potentially using a single up-front investment to finance the MVAC secretariat over the entirety of its long-term life cycle.

The trust fund would be governed by an *MVAC board*, primarily comprising participating country governments; it may also include representation from external technical and funding partners plus independent technical advisors. The board would be responsible for setting the secretariat mandate and broad policy direction, as well as overseeing secretariat operations. To ensure that decision points are insulated from conflicts of interest—and thus credible to market actors

Figure ES-3. Mapping of Essential and Supplementary Governance Functions



looking to invest in TB R&D—the board would be supported by an independent technical advisory group.

In the first year, there would be a need to establish, test, and gradually expand a *transitional secretariat*, with costs of about \$2 million–\$3 million over a period of 12–18 months. This would build on the thinking and analysis delivered so far and would include (1) further modelling through modelling consortia; (2) contract drafting; (3) socialization and outreach to countries, industry, and MDBs; and (4) recruiting the core team at the secretariat.

Once fully functional, the secretariat would migrate in full to a *permanent home*, ideally within a World Bank trust fund. During high-intensity periods, we expect that the secretariat would need approximately 15–20 full-time staff members, including technical, legal, and country-specific staff, and it would commission and administer research grants from third parties.

Gathering and Reflecting Community Feedback

The Center for Global Development and Office of Health Economics released a consultation draft of the MVAC blueprint in March 2019 for public review and comment. Through mid-2019, we invited constructive feedback and dialogue to further hone the proposal and ensure it is responsive to the interests and concerns of all stakeholders. During this period, we worked proactively to engage with stakeholders in target countries, in international institutions, and within the pharmaceutical industry. This final report amends the draft in response to the comments we received (see Appendix 6 for details).

Chapter 1.

A Failing R&D Model for Tuberculosis

How Global Research and Development Excludes the World's Poorest

Innovation—delivering new drugs, diagnostics, and devices—is a critical tool in the global fight against disease and premature death. Yet despite the potential for innovation to prevent disease and improve health around the world, industry’s research and development (R&D) investments disproportionately serve high-income markets, where the burden of disease is predominantly concentrated in noncommunicable diseases (NCDs) such as cardiovascular disease, cancer, and diabetes. High-income country (HIC) markets are characterised by high profit margins (particularly in the United States)[3] and ever-growing demand from patients for new, innovative treatments. These markets are sufficiently large and profitable to incentivise R&D.

Low- and middle-income countries (LMICs) carry a burden of disease that sometimes overlaps with that of HICs—for example, several major NCDs, plus infectious diseases such as hepatitis C and HIV. However, LMIC patients often lack access to the innovative products for these conditions that are available in HICs. Access is constrained partly by pricing, but also by system inefficiencies, limited budgets, and weak regulation. Nonetheless, LMIC patients and payers can opt for many effective, relatively low-priced generic products to meet part of this need (at least for NCDs), although inefficient procurement often leads to unnecessarily

inflated prices even for off-patent products.[5] For the poorest countries, voluntary licensing arrangements by multinational companies (MNCs) to low-cost generic producers, coupled with pooled procurement through global institutions such as Gavi, The Vaccine Alliance (usually known simply as Gavi), and the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), have also greatly expanded access to innovative vaccines, treatments, and diagnostics targeting infectious diseases. In addition, there is the potential for differential (“tiered”) pricing of products that remain under patent and outside the scope of large global health institutions. This is a “win-win” solution in theory for countries and manufacturers, but the potential is often unrealised.

At the other end of the spectrum, diseases afflicting almost exclusively the world’s poorest, for which treatments are not widely available in HICs, have received targeted R&D investment funded by the global health donor community. This has typically come in the form of “push” investment—grants or loans provided by donors for early-stage pharmaceutical R&D. Yet 75 percent of those suffering from extreme poverty in the world are now living in middle-income countries (MICs)[6]—many of which will “transition” away from global health assistance over the next decade.[7] To the extent that such a transition leads to a reduction in push funding, R&D investment for diseases of the poor in MICs is likely to decline—slowing the pace and/or reducing the likelihood of breakthrough innovation.[8]

Tuberculosis: Addressing the Innovation Gap

Tuberculosis (TB)—an infectious disease primarily affecting the poor and vulnerable—ranks among the top 10 global causes of death. Although there is no effective vaccine, TB is curable with inexpensive and effective drugs; on average, the current first-line treatment regimen is reported to generate an 85 percent cure rate in drug-susceptible TB. However, the treatment cycle is long and toxic, causing some patients to discontinue treatment, develop acquired drug resistance, and risk spreading a drug-resistant pathogen to others. The treatment cycle for drug-resistant cases is even longer (6–12 months), more expensive (over \$1,000 per person), and less effective (with a 55 percent success rate historically, though the new BPaL regimen demonstrated an 89 percent success rate for extensively drug-resistant TB in an initial trial).[9] This is particularly concerning in high-burden countries such as South Africa and India, where demand for second-line TB treatment is expected to grow by 6.8 percent and 6.7 percent per year, respectively, over the next 10 years. As a result—and despite years of global investment in TB control—modelling suggests that global goals for TB treatment cannot be achieved without major technological breakthroughs.[3]

In 2016, to help guide global R&D investments and following an expert consultation, the World Health Organization (WHO) published a target product profile (TPP) for a pan-TB regimen.[11] The TPP describes a *universal drug regimen* (UDR) to tackle both drug-sensitive and drug-resistant strains, with a treatment cycle of less than two months. In addition, it specifies a drug combination of up to three distinct molecules, with no toxicity or drug interaction. For the full TPP specification that we use in this report, based on the WHO version and with input from the Bill & Melinda Gates Foundation (BMGF), see Appendix 1. Target Product Profile.

With push funding from BMGF, several candidate molecules are already at Phase I or beyond; there are also 20 programmes in early development (discovery and pre-clinical) which may yield additional candidates. According to the estimates we have been given by BMGF and its partners, development of a new product to meet the TPP would cost roughly \$1.6 billion—accounting for (1) the cost of capital and (2) an attrition rate that reflects the expected degree of scientific risk. However, this would drop to \$0.6 billion with a continuing commitment by BMGF to support development with push funding up to the end of Phase IIB.

A Risky Market? Barriers to Private-Sector R&D Investment

On paper, the numbers suggest a large and potentially profitable market for the proposed UDR. The global market for TB therapies reached roughly \$1 billion in 2018 and is projected to grow by more than one-third by 2025.[3] Almost three-quarters of this growth will be driven by increased expenditure on second-line therapies [3]—reflecting the ballooning burden of drug resistance. Given the projected risk-adjusted late-stage development cost of \$0.6 billion, sales could—in theory—cover industry outlays for R&D if a new therapy were able to displace much of this market, and if the substantial push funding that underpins this estimate of \$0.6 billion were put in place. Yet even in these circumstances, with the burden overwhelmingly concentrated in MICs (just nine MICs account for almost 70 percent of all TB cases) [10], innovator pharmaceutical companies are reluctant to invest, perceiving high commercial risk and limited upside potential.

The concentration of TB in MICs (North America and Europe combined represent just 13 percent of global sales) creates several distinct sources of risk for innovator pharmaceutical companies. The first source relates to donor transition from the highest-burden countries. Historically, TB treatments have been largely donor funded, with TB regimens purchased in

bulk through large-scale mechanisms for pooled procurement (e.g., the Global Drug Facility). Donors have also invested heavily in R&D for TB, helping accelerate the introduction of new treatments and diagnostics. But with most MICs already having transitioned from global health assistance or set to do so soon, donor investment may soon dry up, leading to both a more unreliable and fragmented TB market and a reduction in donor funding of R&D. Pharmaceutical companies are increasingly forced to deal directly with MIC governments and payers, rather than a global purchasing entity, where they must confront local purchasing preferences to pay low prices and to buy from local industry. This dynamic increases the risk and complexity of entry into the TB market.

Second, most MICs are undergoing rapid epidemiological transition paired with rising citizen expectations for universal health coverage (UHC). Citizens are demanding cancer treatment, dialysis, and other

expensive care—placing competing demands on growing but still scarce health budgets. Since TB is concentrated among poor and marginalized populations—groups with less power and visibility—there is a real risk that MICs will underprioritize TB within UHC benefit packages and overall health expenditure, constricting the market for an innovative TB therapy. Innovative pharmaceutical companies do not necessarily trust that TB will be prioritized by MICs into the future.

Finally, MICs are not yet sending strong and reliable signals about their ability to pay for health innovation. Historically, many MICs have either aggressively negotiated innovative drug prices down, declined to purchase innovative therapies until they go off patent, imposed price controls, or exploited flexibilities in the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) for compulsory licensing of on-patent drugs (see Box 1).

Box 1. TRIPS Flexibilities and Innovation

When lifesaving products are already on the market but protected by patents, the use (or threat) of TRIPS flexibilities, particularly compulsory licensing, has been a legitimate and often useful tool for country governments to expand their citizens' access to such products. But compulsory licensing cannot secure access to a product that does not yet exist—and industry typically views the potential for compulsory licensing as a threat to potential profits, which may dissuade investment in desperately needed innovations targeting LMICs.

Our approach, which we describe in detail in the forthcoming sections, moves price negotiations between industry and participating countries further upstream. Rather than waiting for a lifesaving product to (hopefully) come to market and then

attempting to secure an affordable price—which may include either the threat of or application of compulsory licensing—country governments and industry will agree to a locally affordable but still profitable price *before the drug is developed*, simultaneously ensuring that industry will make the requisite investments to bring the product to market and that the product will be accessible to all who need it once launched. As a result, participating countries will not need to use TRIPS flexibilities for this particular product and will agree to respect the originator's intellectual property (IP) rights, so long as the IP holder offers the product at the pre-agreed affordable price. Ability to use TRIPS flexibilities will remain in place for nonparticipating countries, and for all products not covered by an explicit MVAC agreement.

These risks are tolerable to innovator pharmaceutical companies for products with a large market in HICs which can give a return on R&D investment, but may be prohibitive when profitability is exclusively tied to MIC sales. For MIC markets alone to generate private-sector R&D investment, innovator companies will need assurance that MIC purchasers are willing to pay a value premium for innovation—potentially far higher than the cost of less effective generic competitors, but low enough to ensure local value and affordability.

A Political Window of Opportunity

In 2018, the United Nations hosted its first-ever high-level meeting on TB, a signal of global momentum to tackle this global challenge. Through policy announcements, MICs are also signalling their willingness to engage with and contribute to global health initiatives, including the TB research and development agenda. [12] For example,

- TB has featured prominently in discussions and communiqués at the annual summits of the BRICS countries (Brazil, Russia, India, China, and South Africa);[13,14,15]

- in 2017, Russia hosted the WHO Global Ministerial Conference on Ending TB;[16]
- India's Prime Minister Narendra Modi has announced a plan to end TB in India by 2025, and India has added \$740 million to its national TB programme, roughly quintupling its investment to fight TB; [17,18]
- the BRICS's respective ministers of health announced a TB cooperation plan in 2014;[19] and
- the BRICS have launched a joint TB Research Network, which has met annually since 2016.[20]

These recent events and commitments (Box 2) signal an opportunity to develop and test a new business model for investing in improved treatment of TB, which we detail in this report and which has significant implications for the way technologies and pharmaceutical markets for different diseases operate in emerging markets in the future.

Box 2. Commitments to End Tuberculosis

“Prime Minister Narendra Modi on Tuesday launched a campaign to eradicate TB from India by 2025, five years ahead of a globally-set deadline. After inaugurating the Delhi End-TB Summit here, the Prime Minister launched the TB-free India Campaign to take the activities under the National Strategic Plan for TB Elimination forward in a mission mode for ending the epidemic by 2025.”

—*Times of India*, March 13, 2018

“The [BRICS] Ministers approved the development of a cooperation plan that includes a common approach to universal access to first line tuberculosis medicines for all people with TB in BRICS countries, as well as in low- and middle-income countries. ... Ministers also agreed to cooperate on scientific research and innovations on diagnostics and treatment, including drug resistance and service delivery of TB. They identified sharing technologies, identifying manufacturing capacities and TB financing as key priorities.”

— Stop TB Partnership, December 5, 2014

Chapter 2.

A New Business Model for Global Health Innovation: The Market-Driven, Value-Based Advance Commitment (MVAC) for TB

Chapter 1 described how the global R&D system is failing to produce desperately needed innovation to address the global TB burden. In this chapter we introduce a potential solution—the market-driven, value-based advance commitment (MVAC), a new business model for global health innovation—and discuss how it can be applied to help bring a universal TB treatment regimen to market.

The MVAC is in part inspired by the advance market commitment (AMC) mechanism previously used in global health, but with several important innovations and improvements. Most crucially, the MVAC is driven by middle-income country (MIC) demand rather than donor contributions; is informed by countries' own ability to pay rather than a single, "cost-plus" price; and allows pharmaceutical companies to reap higher revenues from a more effective product.

This chapter proceeds as follows:

- First, we describe how the MVAC builds on the AMC approach, including a discussion of key differences and innovations.
- Second, we provide a high-level overview of the MVAC structure—built on four design pillars—that will be built out in greater detail throughout this report.

- Third, we describe the conceptual basis of the MVAC as a "bridging mechanism" between the dysfunctional R&D status quo and a more sustainable, effective, and efficient structure that can better serve the needs of MIC systems.
- Finally, we argue in favour of the MVAC over late-stage push funding.

From the AMC to the MVAC: Key Points of Evolution

The idea of an AMC first gained momentum in 2005 with the publication of a Center for Global Development working group report, *Making Markets for Vaccines: Ideas to Action*[22]. The AMC was conceived as a binding advance commitment, offered by high-income country (HIC) governments and other global donors, for purchase of a health technology meeting specific pre-agreed parameters. The AMC was intended for markets perceived as "risky"—that is, markets where private-sector actors would be unwilling to invest in upfront R&D without a guaranteed post-launch revenue stream.

In 2007, Italy, the United Kingdom, Canada, Russia, and Norway, in collaboration with the Bill & Melinda Gates Foundation, committed \$1.5 billion to launch an AMC

for pneumococcal vaccines. Gavi, the World Bank, and the AMC donor committee organised and oversaw the initiative. Participating manufacturers made a 10-year commitment to supply a share of the required 200 million doses annually at a price no higher than \$3.50 per dose,² intended to reflect their manufacturing and distribution costs. In return, each manufacturer received a share of the AMC funds (allocated in proportion to its respective supply commitments) at an initial premium price of \$7 per dose, intended to provide a return on R&D costs (i.e., there was a premium above the \$3.50 cost price). The pneumococcal vaccine AMC targeted a product that was already in the late stages of clinical development; as anticipated, two eligible products (from GSK and Pfizer, respectively) entered the market in 2010 and received shares of the AMC commitment pool. An evaluation of the initiative found that the AMC had helped accelerate investments in manufacturing capacity for the vaccine but had not influenced R&D investments or the innovation timeline. Nonetheless, the evaluation suggested that the AMC had achieved a rapid uptake of the vaccine in low- and middle-income countries (LMICs); the vaccine is projected to avert 3 million deaths of children younger than five by 2030.[23]

The MVAC builds on the core insight of the AMC model and applies it to the target product profile (TPP) for a universal TB drug regimen: the idea that credible advance commitments can solve a market failure for R&D and accelerate the introduction of new health technologies that serve the world’s poor. Informed by the pneumococcal disease experience and evaluation, however, the MVAC makes several important modifications, including additional design characteristics to help measure, aggregate, monetize, and underwrite future MIC demand for better TB treatment. Key differentiating factors, outlined in Table 1, include these:

- Stimulating earlier-stage R&D, thereby encouraging more competition

2. Paid for by Gavi with a cofinancing contribution from the recipient country governments, although in practice donors have met all of the \$3.50 cost and there have been no cofinancing contributors.

- Using value assessment of expected health and related gain, rather than “cost-plus,” as the basis for setting guaranteed prices and volumes
- MICs rather than global donors driving the process, creating a transition to a “normal” market for innovative drugs and vaccines in these countries
- Guarantees issued by financial intermediaries, on behalf of MICs, rather than by global donors

There are, of course, important similarities, including these:

- Early registration of manufacturer interest to create awareness of progress
- Effective governance arrangements in place to provide assurance to all stakeholders

The MVAC: Four Design Pillars

The MVAC is an advance purchase commitment built on four essential design pillars: health technology assessment (HTA) to assess value from the country perspective, third-party guarantees to underwrite the country purchase commitments, industrial policy alignment to strengthen the case for investment, and an appropriate governance structure to coordinate the effort. The design considerations for these components are briefly detailed below, while the actual design will be further explained in the forthcoming chapters.

Health technology assessment (Chapter 3): HTA, already a well-established process in a number of MICs including Brazil, China, India, and South Africa, is a mechanism by which payers evaluate the value of a new product through the application of globally accepted methods. The MVAC will use HTA—based on country-specific evidence and ability to pay—to inform countries’ purchase commitments. In the context of the MVAC, HTA can improve the confidence of national payers that the product they are committing to buy is appropriately priced and affordable given its incremental value for their setting and their country’s budgetary constraints.

Table 1. Leveraging the Lessons Learned from Previous AMC's to New Models

| Key factor | AMC pilot for pneumococcal vaccines | MVAC for TB |
|--|---|--|
| Time frame for meeting the TPP | Short, as products were in <i>late stage</i> of development | Long, as potential candidates are in <i>pre-clinical/early stage</i> of development |
| TPP | Product specifications defined by WHO experts including minimal characteristics to get reward | Product specifications defined by country payers, drawing on expert advice. Expert group to decide (as part of the governance) the minimum characteristics to get some reward. There are proposals around the minimum TPP, but these need to be reviewed and endorsed by the technical committee and ultimately by the countries. |
| Price | Initial AMC price (paid by donors to recover manufacturing investment) of \$7, subsequently reduced to a tail price of \$3.50, set at an estimate of the marginal cost of production. The \$3.50 became the minimum price. | Price based on health technology assessment (HTA) value assessment of the TPP and on local ability to pay of BRICS. Different prices in different countries. Prices adjusted to reflect percentage of TPP met in practice by the products. |
| Competition | <ul style="list-style-type: none"> • Non-exclusive scheme to cover first- and second-generation products • Initial contract not to take all of the commitment • Companies could compete on price and quality • Effectively, however, rewarded two companies | <ul style="list-style-type: none"> • Non-exclusive scheme to cover first- and second-generation products • Companies can in principle compete on price and quality; however, complexity of meeting TPP means combinations are likely and competition unlikely. |
| Countries it is designed for | Designed to engage donor countries | All except HICs, with a focus on large MICs, but in particular countries transitioning away from aid; TB burden concentrated in large MICs and low-income countries |
| Governance | <ul style="list-style-type: none"> • WHO experts defined the TPP • Gavi served as secretariat and supported eligible countries to purchase the product • The World Bank guaranteed the AMC fund • UNICEF managed the supply agreements | <ul style="list-style-type: none"> • Global secretariat (to be determined) and decision-making function on key scheme elements • Advisory/expert committee (with MICs, global TB and HTA experts, donors, other stakeholders) to provide recommendations on the extent to which the new product meets the TPP |
| Role of companies (developers and/or manufacturers) | <ul style="list-style-type: none"> • Enter the AMC Registered Manufacturers Agreement • Scale up manufacturing capacity to meet Gavi-eligible countries' demand for 10 years | <ul style="list-style-type: none"> • Register interest at an early stage • Develop and submit regulatory and HTA dossiers for the new product • Commit to developing manufacturing capacity for the agreed period of time and price • Show willingness to engage in a commercial agreement involving post-launch evidence collection |
| Who bears the risk? | Manufacturer bore R&D and manufacturing risk, donor bore volume risk | Multilateral development banks (MDBs) underwrite, companies bear R&D risk, countries bear volume risk (i.e., commit to buying a certain value of the product) |
| Role of donors | <ul style="list-style-type: none"> • AMC definition and governance (WHO, Gavi, UNICEF) • Price top-up to reward innovation (global donors) | <ul style="list-style-type: none"> • Facilitate scheme establishment • Help mobilize political support for the proposal • Potentially help cover costs for MVAC secretariat; subsidise or cover commitment fees for MDB guarantees; provide research grant funding for BRICS research bodies |
| Role of LMIC countries | Originally expected to contribute with a co-pay as a share of the tail price but in practice this has been met by global donors | <ul style="list-style-type: none"> • Actively involved in the definition of the scheme • Committing to pay a predefined price for a predefined volume based on their budget constraints and value offered by the prospective intervention(s) |
| Role of financing intermediaries | Donors guaranteed funding to Gavi. No intermediary. | Potential role for an MDB to provide loan financing to assist in guaranteeing the recipient commitments |

Commitment guarantees (Chapter 4): To drive engagement and investment in R&D by the pharmaceutical industry, it is critical that the industry perceive MIC commitments as highly credible. Commitment guarantees—underwritten by a financial intermediary—will help ensure that MICs credibly signal their demand and ability to pay. Key considerations include the total size of the purchase commitment, informed by HTA results; the expected return on investment by the manufacturer (which will need to be reconciled with MICs’ ability to pay); the choice of financial intermediary; and the transaction costs associated with the guarantee structure.

Industrial policy alignment (Chapter 5): Based on an initial landscaping analysis, we know that developing local industry (including home-grown research capacity and pharmaceutical industries) is a priority for many MICs. To get the support of these MICs for prices that enable the recovery of global R&D costs, multinational companies would need to adjust to varying expectations about localisation requirements.

Governance structure (Chapter 6): An MVAC governance structure credible to both MICs payers and industry is required to drive and operationalise the MVAC. This requires it to be authoritative, open, and sufficiently flexible to place MIC governments in the driving seat.

Key features of a successful governance model include relevance to and expertise in TB, ability to leverage established bureaucracies or operational systems to minimise transaction costs without compromising programmatic quality, and a strategic commitment to and technical capacity to address value for money and affordability concerns.

A Bridging Model to a Sustainable R&D Ecosystem

The MVAC model is intended to serve as a bridge between the dysfunctional status quo for MIC products and a more sustainable and effective R&D ecosystem—one which more closely emulates the positive characteristics of HIC markets for healthcare products. Many of its core elements (including the need to underwrite commitments and the development of a joint TPP) will become less relevant as markets mature and trust is built between payers and industry. The governance structure—a secretariat to pool HTA resources, set and signal joint priorities, and conduct country-specific value assessments—may endure but evolve as national payers build up their own institutional, human resource, and data capacities. Table 2 describes how the MVAC helps accelerate and shape a constructive evolution in MIC markets across three time periods: (1)

Box 3. Ability to Pay

In this report we use the term *ability to pay* to reflect healthcare systems’ (not individual patients’) ability to pay for lifesaving products based on the budgets those countries have allocated or plan to allocate to healthcare (and/or TB in particular) and given countries’ historical decisions to pay for health outcomes. Our methodology calibrates prices against available resources while accounting for the savings that a healthcare system could directly realise from introducing a TB cure, hence ensuring that the price proposed is affordable to the *healthcare system*

given local circumstances. Importantly, we do not assume that these prices would be affordable to individual patients; rather, our calculations assume that governments will fulfill their responsibility and commitments to provide equitable, cost-effective TB care without user fees at the point of use. Differential pricing reflects the fact that affordability varies from country to country depending on each country’s wealth level, healthcare budget, and population’s ability to benefit from the technology. The specifics of our approach are detailed in Chapter 3.

Table 2. The Bridging Model for Investments in Pharmaceutical Innovation for MICs and Low-Income Countries

| Description | Status Quo: Donors pay disproportionately for innovations for MICs and low-income countries (LICs) | MVAC: Donors pay for early-stage push investments and countries pull universal drug regimen to market using credible and underwritten revenue commitment | Future: Countries have established HTA bodies that can assist in pulling new innovations to market without the intervention of donors |
|---|--|---|--|
| Industry R&D investment | Limited for MICs and LICs [6] | Piloting a mechanism to deliver R&D for products for MICs | MICs signal own priorities, and investors and innovators respond |
| TPP | TPP developed for small subset of priority diseases by WHO and donors | TPP developed collaboratively with country payers | Investors invest where credible demand is signalled by countries, potentially to include joint priorities decided and signalled by a multinational coordinating body |
| HTA and pricing | Limited, but growing, use of and development of capacity for HTA; default preference is generic pricing <i>(Note: Ineffective markets drive up generic prices for consumers, while some very high on-patent prices target only the wealthy)</i> | Country HTA bodies used to measure and signal a justifiable value-based price with support from central secretariat. | Country HTA bodies are well established and systematically inform purchasing decisions; affordability and value drives price/volume negotiations, which result in higher and more sustainable returns on investment for investors and affordable prices to local purchasers. |
| MIC commitment to pay for innovation | Not (clearly) signalled | Increasingly signalled through policy choices, given health priorities and budget constraints | Signalled through established HTA body coupled with track record of evidence-based coverage and purchasing decisions |
| Role of MDBs | None | Underwriting revenue commitment | Limited |
| Who bears the scientific and the commercial risk | Scientific: Early stage—donors through push investments and product development partnerships; late stage—industry (if it is willing to invest) Commercial—industry (if it is willing to invest) | Scientific: Early stage—donors; late stage—industry Commercial—shared between industry and payers, but underwritten by MDB | Scientific—industry Commercial—industry, provided payers have established “normal” markets, but some role for payer guarantees may continue |
| Role of the secretariat | None—does not exist | Aggregates and secures country demand; manages HTA and pricing negotiations; sets TPP parameters and certifies TPP compliance; tracks fulfilment of country commitments; helps build HTA capacity in MICs | Helps aggregate and signal demand; assists countries in signalling interest in new innovations; helps build HTA capacity in LICs |
| Who pays when | Donors pay for push <i>now</i> Downstream: donors purchase innovative products; out-of-pocket spending on overpriced generics; little innovation diffusion despite significant spending | Donors pay for push <i>now</i> , countries pull and pay <i>later</i> if treatment reaches market | Countries pay <i>later</i> if/when treatments come to market |
| Push/pull split | Significant donor-funded early-stage push Limited pull | Continued significant push from donors Strong pull from MIC markets | MICs expand investments in basic scientific research (as a global public good, as in HICs, e.g., the US National Institutes of Health). No targeted MIC or donor push investments for specific products. Pull brings products to market |
| MIC industrial production | Limited for innovative products | MVAC complies with and boosts industrial policies of participating countries | Increased industrial production and R&D cooperation in MICs; MICs’ innovative base is strengthened |

the status quo, (2) the bridging MVAC model, and (3) a sustainable MIC market for innovation.

The MVAC versus a \$1+ Billion Push

The MVAC is a bridging mechanism designed to mimic the pharmaceutical market in HICs. In HICs, industry bears the standard innovation risk and invests in R&D, anticipating an overall reward for innovation that exceeds the cost of development, sometimes significantly. Through our bespoke model, rather than simply paying industry the amount it costs to develop a universal drug regimen (UDR), MVAC accelerates the establishment of a sustainable global R&D paradigm that works for MICs and their citizens as well as for industry. Below are key reasons why the MVAC model for TB is superior to a large push investment as a bridging mechanism, though the MVAC model is not suitable for perpetual replication.

First, while the TB market has received significant push investment, aid transitions are likely to reduce the future availability of both push and pull funding from global donors. The MVAC complements targeted donor push funding and helps introduce MIC-led pull funding as the predominant driver of innovation in MICs.

Second, MVAC uses HTA to estimate the size of a value-based market, helping secure country participation and a sufficiently large guaranteed market to justify private investment in the required R&D costs (estimated at between \$0.6 billion and \$1.6 billion per product in addition to already committed and expected future push funding). A credible argument is needed to convince MICs to pay the \$1+ billion price tag without tangible evidence of value conferred to their national healthcare systems by the innovation. Further, the MVAC approach allows flexibility in adjusting the value-based market size to reflect the performance of the final UDR against the TPP. Without an HTA model and the accompanying process, such adjustment would not be possible.

Third, the MVAC will help build capacity in evidence-informed product selection and price negotiation in MICs, an area where weak governance has

been identified as a major cause of an underperforming market, with resulting obstacles to access, leading patients to incur significant out-of-pocket costs to obtain the drugs they need.

Fourth, a cost-plus pricing approach, based on often-quoted US dollar figures for R&D costs, including an estimated return on investment, is not a sustainable or desirable approach. Nor is a substantial increase in push funding by global donors realistic, sustainable, or desirable. Both risk inefficiencies by rewarding inputs rather than outputs. An HTA-based value-driven approach instead assesses value to the system and rewards innovators along a scale commensurate with locally experienced benefits.

Finally, a repeat of the AMC—albeit with pooled MIC and donor procurement—is unlikely to drive industry and investors into the market. The pneumococcal vaccine AMC has had limited price competition and no new entrants. In addition, industry understandably remains averse to pooled procurement arrangements where a single price is applied across countries, despite different wealth levels and healthcare spending.

As the MVAC gets underway, the world will not need to wait until 2030 to see whether it “worked.” The MVAC is instead designed as a dynamic model that supports development of MIC markets as they evolve. Already, expanded HTA capacity at the country level is informing purchasing decisions in China, India, Indonesia, the Philippines, many countries in Latin America, and elsewhere, supported by a WHO resolution on HTA-informed purchasing decisions. Drawing on this political commitment, the secretariat can scope out other disease and technology opportunities, evolving into a demand aggregation and signalling centre while also helping expand technical and institutional capacity for HTA across MICs.

Ultimately, the MVAC approach will help transition industry and national payers toward an R&D ecosystem where MIC market demand can drive private-sector innovation to address local needs and priorities, all within local affordability and resource constraints.

Box 4. MVAC Interface with Other Incentives or Mechanisms

MVAC complements other initiatives aimed at fast-tracking TB innovation and access. For example, all low-income countries (LICs) would be entitled to cost-plus pricing for the UDR at launch, potentially managed through mechanisms such as the Global Drug Facility (GDF), Medicines Patent Pool (MPP), or other voluntary licensing schemes. Our proposed model also requires participating manufacturers to make their products available at cost-plus prices to participating MICs after the pre-agreed revenue commitment has been fulfilled, again implying a potential role for the GDF and MPP. Further, our MVAC proposal would not compete with the Life Prize for resources, as funding for the Life Prize is likely to come from philanthropists and donors rather than MIC governments. Further, a product developed through the Life Prize could meet the MVAC terms; the suppliers could donate their proceeds to LICs on behalf of MICs (which can then count them as aid) or return them to the payer governments.

One concern raised is that MVAC favours a “Big Pharma” model whereby big players buy promising products from small and medium-size enterprises (SMEs) to commercialise them, as opposed to the Life Prize approach, which in principle can support SMEs all the way to commercialisation. We could explore combining the MVAC with the Life Prize, offering a midway milestone reward to encourage SMEs to stay in the race instead of licensing their products out to Big Pharma. However, such an approach would require upfront funding from donors (foundations and HICs); the Life Prize requires a similar front-loaded donor investment and has not yet raised sufficient funds to trigger the prize model. Instead, the MVAC relies on MIC funding, paid out only if and when a new product comes to market. As a result, the risk is passed to manufacturers who put up the capital for R&D (in this case with push funding for Phase I and Phase IIA). Further, there is limited evidence of successful commercialisation efforts led from beginning to end by SMEs, including in LMICs; it is also not necessarily true that SMEs would offer lower prices than large companies for equivalent innovations.

Applying MVAC Principles to Other Innovations, Including Later-Stage Products

The MVAC itself is targeted toward upstream products, and this report considers its application to a TB universal regimen. In theory, the MVAC model could be applied to products with similar characteristics, such as products with a major health impact and a large potential market in emerging economies but an insufficient market in HICs alone to justify private-sector R&D investment. Limiting factors here are the transaction

and opportunity costs associated with negotiating and underwriting countries’ formal commitments; these expenses introduce a degree of friction in the model that makes it unsuitable for perpetual replication.

Nonetheless, as described in the previous section, the MVAC itself is intended to help introduce key principles and practices that will gradually build a sustainable R&D ecosystem. To that end, several elements of the MVAC can and should be used to help create viable, functional markets for other innovations, including products at later stages in the development pipeline—including new TB drugs or vaccines expected to come

to market in the next 5 to 10 years but also, more broadly, the entire universe of new health innovations that might be purchased by LMICs. These MVAC elements include the following:

- **Use of HTA to assess value and define a maximum price point.** Countries should routinely use HTA to assess the extent to which innovative products will add value in their specific health systems, allowing them to define a maximum price point at which the product would be cost-effective in their respective contexts. These HTA results can help countries negotiate a lower, more affordable price with originator companies, or inform a decision to conserve scarce public health funds for more cost-effective uses.
- **Proactive use of HTA as a market signal.** Beyond reactive use of HTA to make prudent resource allocation decisions at the time of product introduction, countries can expand proactive use of HTA as a market signal for industry. For example, countries could undertake horizon scanning to identify products at a late stage in the pipeline that might be locally relevant; they could then conduct proactive HTA on the expected characteristics of those products to help illustrate the

potential size of their markets and incentivise the rapid introduction of new products—including, if required by local law, licensing arrangements with a local manufacturer.

- **International collaboration.** Potentially leveraging the MVAC secretariat, country governments could pool their proactive HTA analyses to create a larger-volume market signal for upcoming products. The secretariat could also become a hub for international collaboration on priority setting and HTA capacity building.

Looking Forward

The remainder of this report offers one chapter for each of the four components of the MVAC model. Chapter 3 uses HTA to evaluate the potential price and revenues for a UDR; Chapter 4 details how country commitments will be calculated and guaranteed; Chapter 5 describes how the MVAC will be aligned with industrial policy; and Chapter 6 outlines the proposed governance arrangements for the MVAC secretariat. The report concludes with practical next steps to operationalise the model.

Chapter 3.

Health Technology Assessment: Estimating the Value-Based Market for a Universal Drug Regimen

What Is Health Technology Assessment and Why Is It Important for the MVAC?

Health technology assessment (HTA) is defined as “a multidisciplinary process that reviews the medical, economic, organisational, social and ethical issues related to the use of a health technology in a systematic manner” and whose “main purpose is to provide policymakers with evidence-based information, so they can formulate health policies that are safe, effective, patient-focused and cost-effective. It is also *used by national authorities to help [them make] decisions on which technology should be reimbursed at national level.*”^[4, emphasis added]

In the context of the market-driven, value-based advance commitment (MVAC), HTA is a mechanism that can improve the confidence of national payers that the product they are committing to buy is appropriately priced and affordable, given its incremental value and the country’s budgetary constraints. Early (or *ex ante*) HTA, conducted before the launch of the new treatment (based on the characteristics described in the target product profile, or TPP), requires stakeholders to agree on assessment processes and key features of the assessment model. HTA can then be applied to underpin an estimate of the maximum justifiable size of a guaranteed purchase commitment given treatment alternatives, expected patient numbers, and local ability to pay. It can also inform the design of post-launch

studies to prove the regimen’s value in routine clinical practice. Figure 1 further elaborates on the role of HTA in helping drive innovation.

HTA is already well developed in high-income countries (HICs), with Australia, Canada, France, Germany, the UK, Norway, and most recently, Japan, requiring HTA to inform pricing and/or reimbursement decisions for major new technologies.³ In addition, some HICs already collaborate [24] to carry out joint horizon scanning and evidence assessments, helping inform product selection and price negotiations at the country level. For example, Belgium, the Netherlands, Luxembourg, Austria, and Ireland are experimenting with joint HTA through the BeNeLuxA initiative, informing local coverage decisions. Unlike arrangements supported by donors in low- and middle-income countries (LMICs), where a single price per product may be offered to all participating countries (e.g., the Pan American Health Organization’s Revolving Fund for vaccines), these HIC partnerships allow differential pricing based on each country’s budget allowance and local value.

Many middle-income countries (MICs)—including India (see Box 5), China, Indonesia, Thailand, South Africa, the Philippines, and much of Latin America (including Mexico, Brazil, Chile, and Colombia)—have

3. For an overview of HTA in HICs see the ISPOR Global Health Care Systems Road Map, available here: <https://tools.ispor.org/htaroadmaps/>.

Figure 1. The HTA/Value-Based Pricing Process: Why It Matters for Driving Innovation in Low- and Middle-Income Countries



also established HTA bodies linked to their national health insurance and pharmaceutical procurement agencies. Payers in these countries should be familiar with the MVAC approach to value assessment and supportive of deploying their own national agencies within the assessment process. Further, by offering to strengthen in-country HTA capacity, the MVAC builds

on the current momentum for evidence-informed coverage decisions, helping drive the local institutionalization of evidence-based decision making that may accelerate uptake of cost-effective innovations across LMICs. For a worldwide summary of HTA initiatives, see Appendix 2.

Box 5. India’s HTA Launch

India recently launched an HTA agency at the Ministry of Health and Family Welfare—HTAIn—to inform ceiling rates for reimbursement via a clearly defined process and set of methods. One of its earliest assessments evaluated lenses for cataract operations based on “clinical efficacy, cost-effectiveness, accessibility, availability, and feasibility.” The assessment concluded that “[small-incision

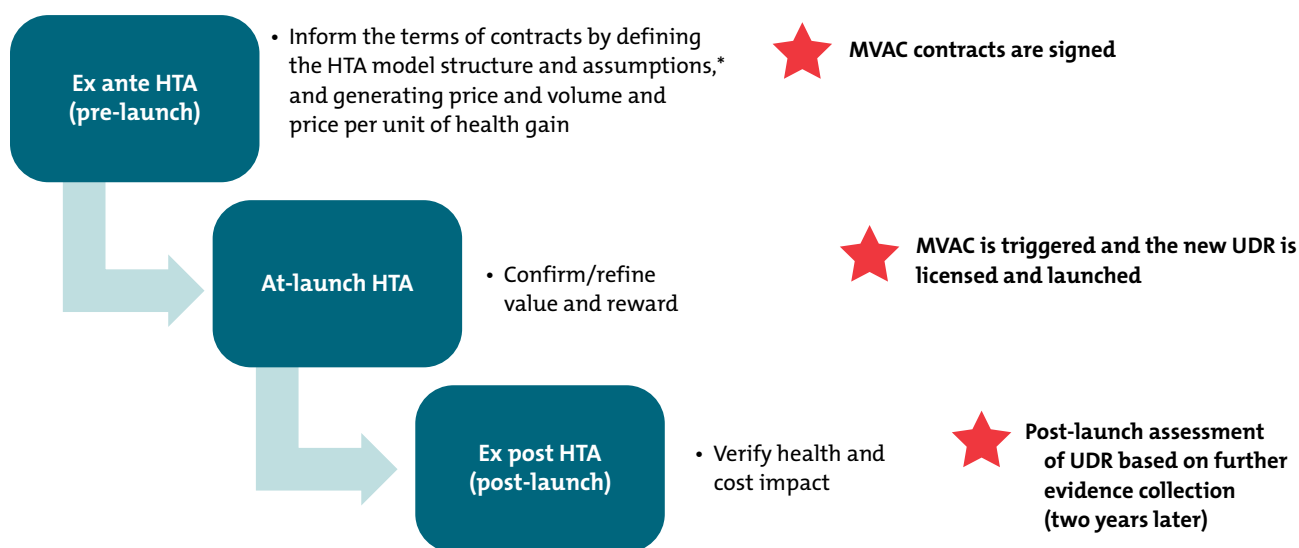
cataract surgery (SICS)] with rigid lenses is the most appropriate intervention to treat cataract patients in India in [the] current scenario,” and recommended that the benefits package cover both phacoemulsification surgery and SICS at a cost of 9,606 Indian rupees (INR) and 7,405 INR, respectively.

In the MVAC model, early (or ex ante) HTA would first measure the value that the new UDR treatment would add in the participating countries—thereby estimating the size of the market for a UDR, including value-based prices and volumes for each country. The prices and volumes would incorporate two drivers of value:

1. Additional health gains of the UDR compared with alternative therapies, valued at country ability to pay per quality-adjusted life year (QALY) or disability-adjusted life year (DALY) based on supply-side constraints and opportunity costs
2. Health system savings (e.g., averted hospitalizations, reduced need for drug-sensitivity testing)

The MVAC secretariat (see Chapter 6) would facilitate negotiations that would translate country-level value assessments into minimum and maximum advance purchase commitments (floor and ceiling prices and volumes) for each country. Following launch of the UDR, at-launch HTA would be used to adjust pricing and volumes based on product performance against the pre-agreed TPP. Depending on the specific design of the commitment (discussed in Chapter 4), the at-launch HTA may hold a set of other parameters constant to limit complexity and reduce uncertainty. Potentially, ex post HTA could be used to verify the product's clinical performance and confirm appropriate value-based pricing (Figure 2).

Figure 2. Three Key Points at Which HTA Could Be Performed



*Model assumptions which might change from pre-launch to at-launch HTA are:

- (i) Technical (related to new regimen efficacy): the extent to which the new regimen meets the TPP elements
- (ii) Environmental: technology comparator/s (the standard of care) and its price (particularly if a new regimen (pre MVAC) is made available at manufacturing cost; the way TB services are delivered and managed in a specific country; TB incidence. Effect is the same—less incremental health gain per patient than anticipated and also less volume. So, price and quantity would be lower “at launch” than expected ex ante.

Early-Stage Economic Model— Overview and Aims

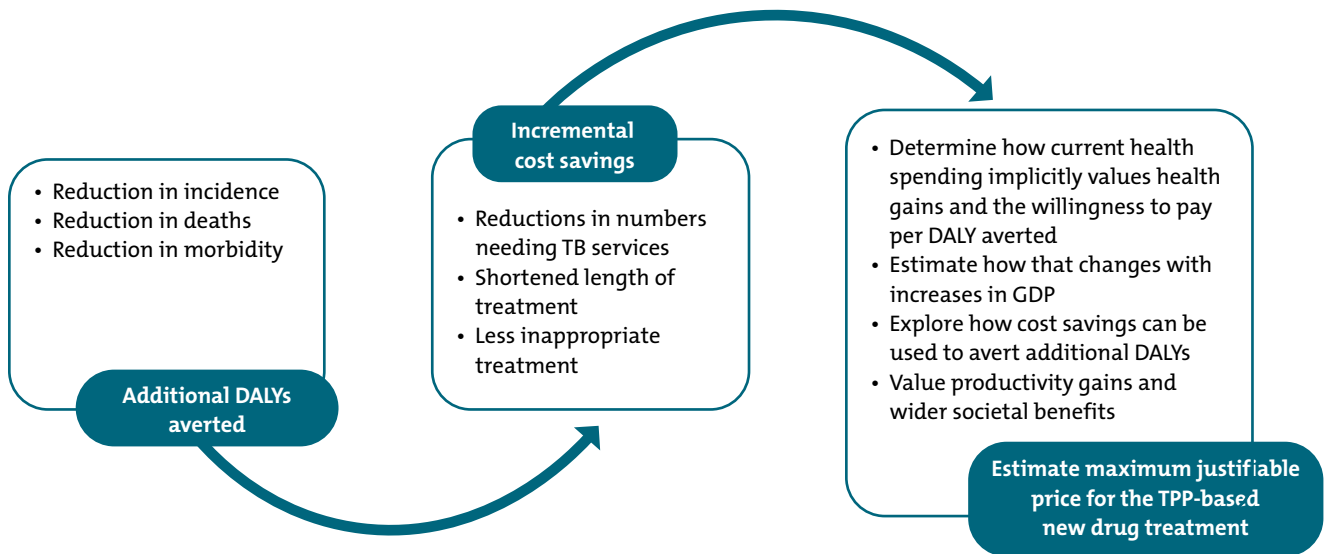
We engaged a team of world-class epidemiological and economic modellers to estimate the value-based market for a TPP-based new TB drug treatment in three countries—India, Russia, and South Africa. We selected these countries from among the BRICS (Brazil, Russia, India, China, and South Africa) based on their high TB burden, data availability, and accessible previous modelling. The modelling approach used is rooted in value-based pricing—the idea that payers should be willing to pay a price that represents the value produced by the UDR to their respective healthcare systems. The team’s full report is to be published in early 2020.⁴

4. The full results will be published in early 2020. For analytical report or methods, contact Anna Vassall (Anna.Vassall@lshtm.ac.uk) Gabriela Gomez Gabriela (Gomez@lshtm.ac.uk)

We assess the UDR value using conventional cost-effectiveness analysis from a **healthcare perspective** (Figure 3). First, we estimate health gain (incremental DALYs averted) from the TPP-based new drug treatment as compared with the standard of care (SoC) at introduction. Second, we examine ways in which the introduction of the TPP-based new drug treatment will change the health system costs associated with TB diagnosis and treatment; for example, we expect that the new drug treatment’s shorter treatment duration and reduced need for drug susceptibility testing will generate significant health system savings and change care pathways (see Box 7 for a discussion as to how the TPP-based new treatment would change diagnostic needs).

Finally, we use these costs and effects to estimate the value of the TPP-based drug treatment to public payers. We first convert health gains into (monetary)

Figure 3. Overall Approach for the Analysis



Box 6. Value-Based Pricing

Throughout this report we use the term *value-based pricing* from the perspective of the payer/buyer—that is, a healthcare system or insurance provider. We always assume zero out-of-pocket costs for individual patients and their families. We adopt the recommended approach set out in a UK Office for Fair Trading report in 2007, whereby pricing is informed by an assessment of comparative clinical and cost effectiveness through HTA and is meant to “ensure the price of drugs reflect[s] their clinical and therapeutic value to patients and the broader

[National Health Service].” Similar approaches have been operational for several years in the UK National Health Service and several other universal and equitable healthcare systems, including those of Australia, Canada, and more recently, Brazil and Thailand. This HTA-informed approach has also been endorsed by the WHO Regional Office for South East-Asia (e.g., see paragraph 11 here) and the Pan American Health Organization. For further discussion of the term *value-based pricing* from the payer’s perspective, see here.

health benefit by determining the *ability to pay for a DALY averted*. We estimate the available health budget in the year at which the TPP-based drug treatment becomes available, and then derive the ability to pay by estimating an opportunity cost threshold, using several different approaches. In principle, the threshold represents the least efficient intervention within the health budget, that is, the value forgone if those resources were reallocated to fund the TPP-based drug treatment.

Our estimates of the value of the TPP-based drug treatment in 2030, when it is expected to be launched, are highly uncertain. Many factors that influence the value of the new regimen will change considerably in the next decade in ways that are hard to predict, including *the launch of other TB technologies, the evolution of the TB epidemic, national healthcare strategies to tackle TB, and the future growth of health budgets*. Sensitivity analyses are used to explore different types of uncertainty, and scenario analyses are used to explore the impact of (1) existing and (2) *future comparator technologies*. Our exploration of uncertainty is intended to draw out sources of risk and inform contracts which appropriately distribute risk between different stakeholders.

The economic model, described above, estimates the maximum justifiable price (from now on called the “value-based” price) for a TPP-based drug treatment, the number of patients to be treated, and the associated revenue/expenditure stream (representing the size of the market) over 10 years post-launch (2030 to 2039) in India, Russia, and South Africa. We note that the health gains of the new universal drug regimen (UDR) are estimated based on the “optimal TPP,” that is, a regimen that meets in full the characteristics described in the WHO definition (provided in Appendix 1). This is why the price is defined as the “maximum justifiable.” A “minimum TPP” is not directly presented in the baseline results of the model but explored through sensitivity analysis. There are proposals around the content of a minimum TPP, but ultimately the concept needs to be reviewed and endorsed by the technical committee and the countries. To reduce risk for commitment-making countries, our primary or baseline estimates—reported in this section—rely on a series of conservative assumptions around future technology availability and the evolution of the healthcare systems in the selected countries, all of which effectively reduce the projected market size for the new drug regimen.

Box 7. Diagnostics and Care Pathways for a Universal TB Regimen

Several methods are currently used to diagnose TB and detect whether the disease is susceptible to first- or second-line treatments—all with important limitations. Challenges include low sensitivity (e.g., sputum smear), low specificity (e.g., chest X-ray), or both (symptom screening); high cost (GeneXpert and culture); inability to detect drug resistance (sputum smear and others); long delays (culture); and high lab/biosafety requirements (culture and line probe assay).[24] Almost all diagnostic approaches require complicated care pathways and multiple visits to a health provider, although GeneXpert enables diagnosis and rifampicin susceptibility testing within two hours. TB product development partnerships have therefore urged development of new diagnostic tools to help improve accurate diagnosis and TB case finding, including

- “an easy-to-use, low-cost, non-sputum-based rapid test that can be deployed in active case finding strategies or used in primary health-care facilities;
- rapid drug resistance tests that can determine response to critical drugs to direct patients to appropriate treatments and safeguard medicines against the build-up of antimicrobial resistance; [and]
- an incipient TB test to identify individuals at high risk of progression from latent TB infection to active disease and enable targeted preventative treatment.” [25]

Part of the promise of a universal TB regimen is the potential to bypass drug-sensitivity testing, at least in the short term—thereby generating substantial health system savings, getting patients on appropriate treatment much more quickly, reducing onward transmission, and limiting the likelihood of loss to follow-up. A product meeting the TPP would have no pre-existing drug resistance; therefore, all patients who tested positive for TB could be promptly enrolled on a single treatment regimen. (Countries would need to conduct careful surveillance to monitor and detect the emergence of resistance to the new regimen, but there would likely be a “window of opportunity” without a need for drug-sensitivity testing before substantial resistance emerged in the population.)

The development of a product meeting the TPP would therefore transform TB diagnostic needs and care pathways, negating the need for drug-sensitivity testing while amplifying the potential opportunities offered by cheap, accurate, and precise point-of-care testing, since positive patients could be immediately enrolled on treatment. Potentially, the MVAC commitment for a TB universal regimen could even be accompanied by a smaller commitment for a complementary diagnostic—one that would open up new care pathways, better reach vulnerable communities, and find the “missing millions” of TB cases each year.

Early-Stage Economic Model—Methods

Defining the Baseline Scenarios

Table 3 defines the model’s population, intervention, comparator, and outcomes (as part of the PICO statement) for each of the three countries.

Importantly, our choice of comparator is drawn from the most optimistic scenario, assuming successful introduction of several new technologies to tackle TB. This choice of comparator results in a relatively smaller estimated market, as better comparator treatments (compared with the current SoC) and a vaccine would reduce the marginal benefit of the TPP-based drug treatment and, in the long run, decrease the size of the patient population in need of treatment.

In addition, the incremental effect of the TPP-based drug treatment will depend on the state of country-specific TB programmes and/or healthcare systems at the time of its introduction (estimated for 2030). The modelling team explored several scenarios and used the most likely outcome for each country given current trends in national policy. In India, we considered a scenario (the “national strategic plan scenario”) with an increase in private-sector engagement (achieved via incentives to private providers to improve notification and treatment completion rates) and patient social and nutritional support. In South Africa, we use a scenario with scale-up of WHO symptom screening for all clinic attendees and a standardisation of MDR regimens based on WHO revised guidelines. In Russia, we modelled standardisation of MDR regimens and scale-up of GeneXpert MTB/RIF for diagnosis of TB and for rifampicin resistance.

Table 3. PICO Statement for TPP-Based Drug Treatment and National Strategic Plans

| PICO element | India | Russia | South Africa |
|---|---|---|--|
| Population (in terms of current burden and resistance) | High rate of TB, TB/HIV, and multi-drug-resistant (MDR) TB ^a Mainly resistance to first-line drugs | High rate of TB and MDR TB High levels of resistance to second-line drugs | High rate of TB, TB/HIV, and MDR TB Mainly resistance to first-line drugs |
| Intervention | UDR as defined by the TPP | | |
| Comparator | SoC at the time of TPP-based drug treatment introduction: <ul style="list-style-type: none"> • New shortened regimen introduced in 2025 for drug-sensitive and MDR TB^b • New vaccine | | |
| Outcomes | <ul style="list-style-type: none"> • Additional DALYs averted • Health sector cost savings • Net monetary benefit | | |
| Context (national strategic plan) | Private-sector engagement Patient support (nutritional supplement) | Scale-up of GeneXpert MTB/RIF in 2018 Standardisation of WHO MDR revised regimen | WHO symptom screening for all Standardisation of WHO MDR revised regimen |

a. MDR TB (i.e., TB resistant to at least both isoniazid and rifampicin), which leads to substantially longer treatments and costs to the health service and patients, as compared with drug-sensitive TB.

b. The SoC was defined as new shortened regimens for first-line treatment (four months) in 2030 and for MDR (nine months, new drugs with no pre-existent resistance) in 2025. These regimens are similar to the BPAmZ and BPAL currently trialled by the TB Alliance. In addition, we assume there will be a new vaccine coming to the market in 2027. This vaccine has clinical characteristics similar to the recently trialled M72/AS01E.

The SoC in 2030 was defined as a new shortened regimen for first-line treatment (four months) and an improved regimen for MDR (nine months, new drugs with no pre-existent resistance) in 2025. These regimens are similar to the ones used for BPamZ⁵ and BPAL,⁶ currently in the TB Alliance drug development pipeline. In addition, we assume there will be a new vaccine coming to the market in 2024. The impact of a new vaccine was modelled based on the expected percentage reduction in TB cases in upper-middle-income countries at 60 percent efficacy, 10-year protection, in adults.[26] Appendix 7 provides more details on the input data and assumptions used in the model to define the selected (optimistic) SoC at the time of the UDR launch.

In all three countries a key output of the HTA modelling is the estimation of potential health system savings each country can capture following the introduction of the TPP-based drug treatment. In Russia, those savings are mainly due to avoiding or reducing hospitalization of TB patients.

Estimating the Value of DALYs Averted—the Opportunity Cost Threshold

Three approaches were used to estimate the “opportunity cost” value of a DALY averted, by estimating the least efficient investment (or the marginal productivity of expenditures within the public health sector budget) that the UDR would replace in 2030.

5. <https://www.tballiance.org/portfolio/regimen/bpamz>.

6. <https://www.tballiance.org/portfolio/regimen/bpal>.

We present here the approach used in the primary estimates, which bases the value of DALYs averted on the opportunity cost at the health sector level and assumes that TB budgets are flexible within the overall health-care spend. These thresholds estimate the least efficient investment (or the marginal productivity of that expenditure, within the public health sector budget) that the TPP-based drug treatment would replace in 2030. We use work by Ochalek et al.[28] that estimates the elasticity of health outcomes to changes in health sector budgets. We then estimate the size of the health sector budget considering GDP growth and increased public-sector revenue and use these elasticities to estimate the marginal productivity of the health sector, in each country, in 2030.

Early-stage Economic Model—Primary Results

We combine maximum justifiable prices with numbers of patients treated between 2030 and 2039 to estimate revenues. We present revenues undiscounted from 2030 to 2039.

Our early-stage HTA modelling estimates that the market size in India, Russia, and South Africa can total around \$6.3 billion for the first 10 years after launch, using the conservative assumptions described in the previous section (Table 4). The value-based calculations include only health gains and savings within the health system, excluding productivity gains and non-health impacts on patients. Across different scenarios, revenue estimates range between \$3.24 billion and \$7.19 billion for India, between \$0.69 billion and

Table 4. Key Results from Early-Stage HTA Model

| | 100% value-based revenue (USD billions) | Maximum price per regimen (USD) | Number of regimens 2030 to 2039 (millions) |
|---------------------|---|---------------------------------|--|
| India | 3.24 | 501 | 6,467 |
| Russia | 0.60 | 2,498 | 240 |
| South Africa | 2.37 | 864 | 2,743 |
| Total | 6.30 | | 9,450 |

Note: Total revenues are not discounted. We note that in the economic model presented here, health gains and costs were discounted at 3 percent to obtain the maximum justifiable price (or “value-based” price), in line with HTA methods guidelines.

\$2.62 billion for Russia, and between \$2.37 billion and \$5.46 billion for South Africa. These projected revenues are potentially transformative as compared with current expenditure on TB treatments and tests (estimated at around \$750 million per year).

It is important to note the quality of data used to model cost and health gains. There are substantial data limitations for Russia, while more robust evidence is available in India and South Africa.

Sensitivity Analysis around the TPP-Based Drug Treatment

In the previous section, we estimated the value-based market for a new drug regimen meeting the full TPP. In the full (forthcoming) modelling report we also explore the sensitivity of the maximum price to changes in product characteristics, for example the value of a product that meets part but not the entirety of the TPP. Here we report highlights of that analysis.

Overall, we found that the main value driver of the TPP-based drug treatment is its shortened duration. We modelled the effect of a six-month variant of the TPP-based drug treatment (compared with the optimal two-month duration). In India, for example, such a variant would lose up to 80 percent of its maximum regimen price. In South Africa, a six-month new drug regimen would be less valuable than the comparator SoC (including a four-month regimen for first-line treatment and a six-month regimen for second-line treatment). In Russia, the longer treatment duration would reduce the value of the new drug regimen by at least 40 percent. In Russia and India, we also found that the need for drug-sensitivity testing and the ineligibility of patients with extensively drug-resistant TB for the new treatment would result in larger value reductions than a need for lab monitoring. In South Africa, the presence of GeneXpert at scale would reduce the cost impact of drug-sensitivity testing.

Results from this sensitivity analysis can inform selection of the minimum and optimal TPP, and the corresponding purchase commitments.

Size of the Commitment Required to Incentivise Private Investment—Net Present Value Scenarios

The global pipeline for new TB treatments has improved substantially in the last five years and is summarised in Appendix 3. Based on industry estimates provided to the Bill & Melinda Gates Foundation (BMGF), the total cost of R&D for a successful TB drug is around \$1.6 billion. However, if current push funding by BMGF is maintained through proof of concept (Phase IIB), late-stage R&D costs to develop a successful regimen may be as low as \$600 million, taking account of failures.

Estimates of the costs of drug development are highly dependent on several assumptions, including company out-of-pocket costs for each development stage, success rates at each stage of the process, and the cost of capital. A range of cost estimates for drug development (up to the point of product launch) have been published, notably by DiMasi et al. and by Prasad and Malinkody.[34,35] The former estimated \$2.7 billion (in 2017 US dollars) with a 10 percent cost of capital, and focused on products for which large companies finance and undertake all development stages; this model is not typical for drugs currently being developed, which usually involve a mix of small- and large-company activity. It is likely therefore to be an overestimate. The latter estimated \$794 million (in 2017 US dollars) with a 9 percent cost of capital, based on the R&D costs incurred by (usually small start-up) companies bringing a single (successful) product to market; that is, it excludes R&D costs incurred by companies who failed to bring a product to market. It is likely therefore also to be an underestimate. One of us has also published estimates of \$1.9 billion (in 2011 US dollars) and (for a new antibiotic) \$1.6 billion (in 2017 US dollars). [19,20]

The estimated R&D costs to meet the MVAC TPP will need to be revisited when taking the MVAC to the next stage. They will in part depend upon the extent of early-stage push funding that donors will make available. However, based on current estimates, we estimate that the value-based market for India, South Africa,

Table 5. Estimated Net Present Value

| | Scenario 1 | Scenario 2 | Scenario 3 | Scenario 4 |
|----------------------------------|------------|------------|------------|------------|
| Cost of R&D | \$600m | \$600m | \$1.6bn | \$1.6bn |
| Cost of capital per annum | 8.50% | 8.50% | 8.50% | 8.50% |
| Priority review vouchers* | - | \$300m | - | \$300m |
| Gross sales | \$1.8bn | \$1.8bn | \$6bn | \$6bn |
| Gross margin | 50% | 50% | 50% | 50% |
| NPV** | -\$217m | \$40m | -\$271m | -\$13m |

All prices in 2019 US dollars.

* Assuming a value of \$100 million for each PRV and that three are made available to the companies with a compound that is part of the regimen, sold one, two, and three years after launch.

** NPV calculations are as of 2030, the expected date of product launch.

and Russia significantly exceeds the expected cost of late-stage R&D. It could be possible, therefore, to pull a product to market with volume and/or price commitments that represent only a portion of the total expected market demand.

Table 5 presents illustrative estimated net present value (NPV) based on (1) covering only late-stage R&D costs and (2) covering all expected R&D costs. For the late-stage costs, we show the results at 30 percent of the potential value-based revenue commitment (i.e., \$1.8 billion) from across India, Russia, and South Africa. This excludes China, where there is also a substantial market for a product meeting the MVAC TPP. For the total R&D costs, we show a commitment for the full \$6 billion market. For both, we also show NPV with and without inclusion of a priority review voucher (PRV) that could be acquired at launch.⁷

7. “The priority review voucher (PRV) program, currently administered by the US Food and Drug Administration (FDA), was passed into United States law in 2007 as a pull mechanism to help promote R&D for new medicines targeting [neglected tropical diseases], malaria, and tuberculosis. Under this law, companies that receive FDA approval for a novel drug or vaccine targeting one of 16 tropical diseases are awarded a transferable voucher. This voucher can be sold to a second organization or can be redeemed to grant

The results suggest that industry NPV is sensitive to the amount of R&D, the value of PRVs, and the guaranteed revenues. With income from PRVs and only late-stage R&D to fund, a commitment of 30 percent of the market of India, South Africa, and Russia can produce a positive NPV. With full R&D funding to be met by the companies, NPV is slightly negative (effectively breakeven), even with the full market guarantee of \$6 billion and income from PRV sales.

We emphasise that these calculations are only illustrative, requiring imprecise assumptions about gross margins; post-launch research expenditure; and manufacturing, administrative, and distribution costs. They can nevertheless be used to inform a dialogue about balancing commercial incentive with sustainable access to an innovative TB therapy.

the bearer priority six-month review for a future medicine of their choosing. As average standard review periods can range between 10–16 months, the voucher could potentially allow drugs to reach the market up to eight months earlier. Economic models have predicted that this faster time to market could be worth between US\$50 million to US\$300 million” (21).

Chapter 4.

Calculating and Securing the Advance Purchase Commitment

In the previous chapter, we used *ex ante* health technology assessment (HTA) to estimate the potential value of the global TB market. Even under very conservative assumptions, our results show that three countries alone—India, South Africa, and Russia—could capture over \$6 billion of value in terms of health gains for their citizens and health system savings from access to a TB universal drug regimen (UDR). If these countries purchased a hypothetical regimen at prices and volumes commensurate with local value, pharmaceutical company innovators would easily recoup investments in late-stage R&D—plus a healthy profit margin. Yet as we discussed in Chapter 1, industry remains sceptical that low- and middle-income country (LMIC) markets alone will yield sufficient revenue to justify upfront investment, noting uncertainties around ability to pay, intellectual property (IP) protection, industrial policy, and budgetary prioritization of health and of TB within health. The status quo represents a lose-lose-lose scenario: industry is scared off from developing products for a potentially profitable market; LMICs miss an opportunity to shape global R&D investments; and TB patients must make do with long, unpleasant, and increasingly ineffective treatment regimens, leading to both suffering and premature death.

In this chapter, we consider a model to bridge the gap between industry and LMICs, addressing the sources of mistrust and misalignment that prevent emergence

of a mutually beneficial transaction—and consequently prevent development of a new, lifesaving product. Through our proposed model, countries will make secured advance purchase commitments for a product meeting the prespecified target product profile (TPP). As a result, industry will be offered an avenue to sell into middle-income countries (MICs) with market visibility, revenue guarantees, and respect of company IP rights; countries, in turn, will receive guaranteed access to innovative drugs targeted to local disease and priorities, at locally affordable prices. Patients get access to treatment that will transform their lives. The value proposition is sufficiently large that all parties will benefit from the arrangement—a win-win-win for all involved.

This chapter proceeds as follows:

- First, we describe the challenges in transforming Chapter 3's HTA results into country-specific commitments and lay out principles to guide and manage the negotiation process.
- Second, we discuss how a value commitment can be set and adapted over time.
- Third, we describe a mechanism, intermediated by a multilateral development bank (MDB), to secure countries' voluntary advance purchase commitments using their own sovereign creditworthiness.

- Fourth, we consider how to “crowd in” additional countries, suggesting a relatively simple incentive-compatible model—a set *value* commitment that varies with product performance— helping to sidestep common free-rider and first-mover problems, producing value for all parties to the transaction.
- Finally, we analyse how this set of arrangements redistributes and mitigates risk, overcoming the market failures that have heretofore hampered innovation.

From HTA to a Value-Based Commitment: Challenges and Principles

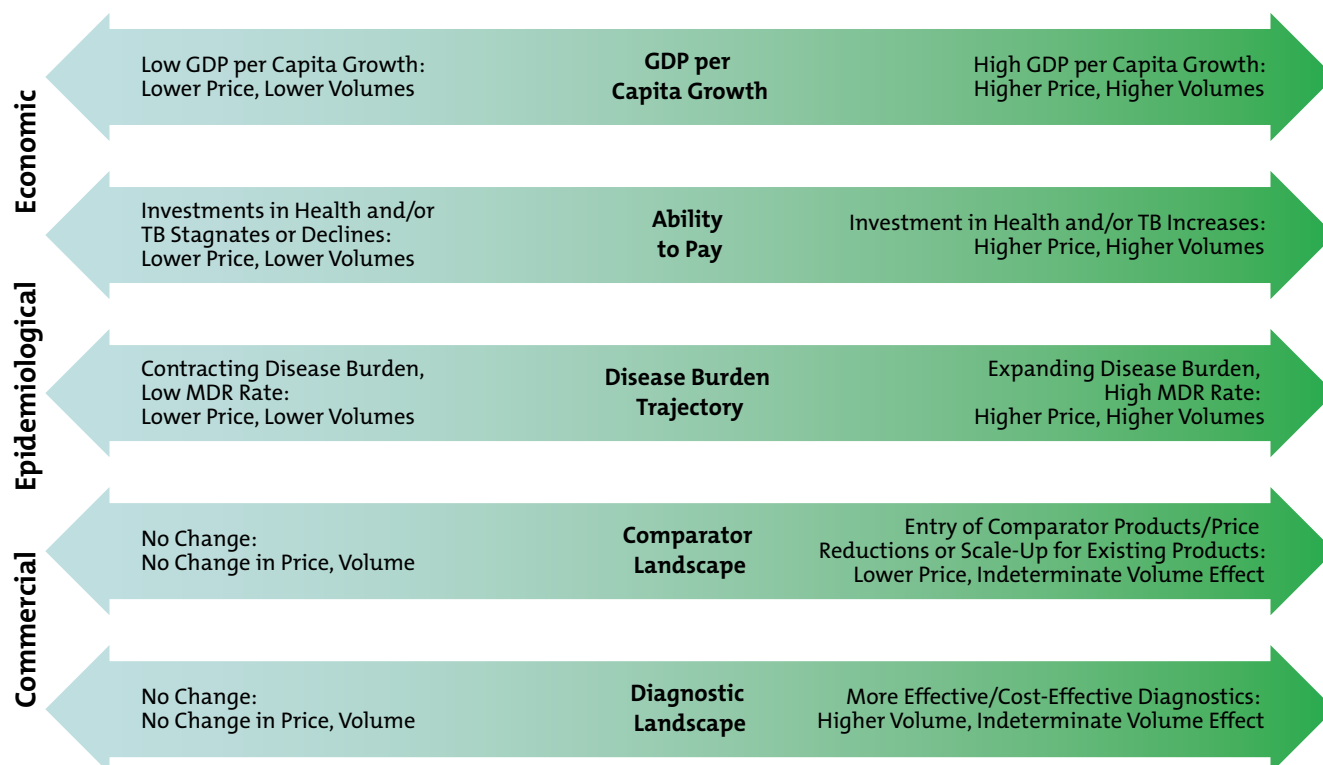
As a first step, participating countries must set a reasonable and sufficient purchase commitment to incentivise industry investments. The HTA results based on the TPP and opportunity cost provide an upper-bound estimate for the size of that commitment; theoretically,

countries would be expected to “break even” (i.e., net benefit to countries would in this case be zero) in value terms if they were to pay those maximum justifiable prices at the given volumes.⁸ There are several challenges to be tackled before the results of the ex ante HTA can be translated into fixed purchase commitments:

- **Uncertainty and complexity.** As described in Chapter 3, early HTA results necessarily rely on many assumptions and are therefore vulnerable to uncertainty about how the market will evolve between now and the time of product entry. Sources of uncertainty include questions about the performance of the product, exogenous factors such as GDP growth and other factors that will influence health expenditure, programmatic choices around the investment in TB

8. We can note that, strictly speaking, the opportunity cost we have used is relevant within the context of the health budget and applies only to health expenditure. Treating TB may bring other benefits (for example in productivity gains) that are much greater than those from any displaced health expenditure. We are also assuming, conservatively, that the availability of a breakthrough TB treatment does not lead to an increase in the health budget over and above the trend growth we have assumed.

Figure 4. Value-Based Price and Volume; Axes of Exogenous Long-Term Uncertainty



services prior to the arrival of the TPP product, the TB disease burden trajectory, market entry of comparator products, and diagnostic advances (Figure 4). Fixed price and volume commitments—directly derived from the early HTA results—would transfer a high proportion of that risk directly to the commitment-making countries without conferring offsetting benefits that justify that risk absorption. At the other extreme, overly flexible commitments—essentially guaranteeing use of a standard HTA process at launch but opening all other parameters to variation—would mean country commitments that directly correspond to actual conditions at the time of purchase. This would insulate countries from all exogenous risk factors—but given the high level of uncertainty, and industry fears about opportunistic behaviour, such a process is likely to be seen by industry as shifting all of the commercial risk back to companies and rendering the early HTA process of no practical value. Full flexibility at launch would therefore be insufficient to change industry incentives, and overly complicated and contentious to contractually guarantee and execute in practice.

- **Shared surplus.** Country governments might wish to negotiate or otherwise set a “discount” from opportunity cost-based (break-even) price points, allowing payers to capture a larger portion of the economic value (the health gain and cost savings) generated by the innovator product.
- **Transaction costs.** The market-driven, value-based advance commitment (MVAC) model uses a financial intermediary—likely an MDB—to guarantee countries’ advance purchase commitments. The financial intermediary is likely to charge a commitment fee for its services; the size of the fee would be directly proportional to the total size of the guaranteed purchase commitment. Reducing the size of the guaranteed purchase commitment may thus be advantageous as a strategy to minimise transaction costs.

- **Subsidy and commercial risk mitigation.** As the MVAC is designed to mitigate companies’ commercial risk, intending to provide a guarantee of a profitable return for a good product, and push funding is available to reduce R&D financial risk (giving companies a pipeline of early-stage compounds, pushed to Phase IIA with direct donor support), it may be considered reasonable to limit industry’s upside profit margin—though industry must be assured of sufficient expected revenues to justify the R&D investment.
- **Second-entrant competition.** Given the scientific and commercial complexity of meeting the TPP within the next 10–15 years, a second entrant is unlikely. However, because it is important for the MVAC to be prepared in the unlikely but possible case of a second and subsequent entries, we suggest the following principles:
 - A second or subsequent follow-on product may enter the market. Any product that meets the minimum TPP will qualify to be part of the MVAC commitment.
 - As with the first entrant, the guaranteed price for the product will be determined based on the ex ante HTA, including the extent to which the TPP will have been met (always between the minimum and the maximum TPP).
 - The products can then compete for market share from the participating MVAC countries; that is, countries have a fixed total revenue commitment but can choose to allocate that commitment to either of the qualified products.
 - Although the guaranteed price for each product in each country will be determined by the ex ante HTA, based on their respective performance against the TPP, any qualified company can offer a lower price (below the MVAC guaranteed price for that product) to increase market share.

- Different products may have different efficacy profiles; for instance, one product could be better for multi-drug-resistant and another better for drug-sensitive TB (though we have not considered differential pricing by indication in this analysis). Thus different participating MVAC countries may prefer different products when presented with a choice.
- *The contract value is inviolable* once the prices have been set in relation to the TPP, so lower prices will lead to a *higher overall volume commitment*. Therefore, the guarantor MDB (see below) must be able to observe and audit actual transaction prices. Countries could consider a confidential rebate mechanism to enable auditability while maintaining price confidentiality.

We illustrate how second-entrant competition might work in two scenarios in Appendix 4.

We expect, as with other important design elements of MVAC, that this will be further refined by the MVAC secretariat in discussions with manufacturers, scientists, and payers as MVAC progresses to implementation.

- ***Splitting the value of a combination treatment across originator companies.*** For a combination treatment, the TPP price would need to be allocated between the component parts of the combination. We expect this to be solved through commercial agreements between the different companies (as is typical for HIV treatment combinations) versus a calculation or formula overseen by the secretariat. However, the secretariat may play a role in facilitating discussions between companies to ensure issues are resolved quickly to accelerate development and launch of products.

These inherent challenges make the direct translation of an HTA assessment into a purchase commitment difficult if not impossible. To manage this complex question, we suggest a few principles to guide negotiations,

helping create a viable purchase commitment while also setting important precedents for the healthy long-term development of MIC pharmaceutical markets:

- ***Upper bounding not to exceed ex ante value.*** Countries should not, under any circumstances, make purchase commitments that exceed a product's expected local value based on the ex ante HTA assessment.
- ***Lower bounding required to deliver a return on investment.*** Subject to the upper-bound constraint, total commitments must be set at a sufficiently high level to ensure a risk-adjusted return for the successful innovator company. Countries should pay a price premium for innovation that is not directly tied to the marginal cost of producing the product. In effect, we need to establish a "reserve price," or more strictly, a "reserve revenue," for the MVAC.
- ***Minimum TPP (and corresponding revenue commitment) must offer value to countries.*** The minimum TPP to trigger the MVAC commitment must be set at a level that offers meaningful clinical and economic benefits. This can be subject to ex ante HTA to derive a price in each country. We anticipate that an ex ante HTA model will also be used to assign a price to different levels of performance against the TPP (between the minimum and the full TPP) in each country.
- ***Rewarding value.*** Companies should be rewarded for developing a more efficacious product; the purchase commitment should scale in a way that is commensurate with the value produced by a more effective product compared with the existing standard of care (however defined).
- ***Minimising the collective action problem.*** To the extent possible, the commitment model should work to minimise the collective action problem by providing clear incentives for countries to be first movers, with long-term incentives to "crowd in" additional countries.

- **Differential, value-derived pricing.** Country-specific pricing should be connected to country-specific value; this necessarily implies differential pricing across countries.
- **Simplicity and predictability.** To the extent possible, commitments should be simple and predictable, allowing payers to plan for their own fiscal liability and industry to make informed investment decisions.
- **Risk compensation.** Parties (in this case country payers) that assume additional risk should be compensated with a larger share of overall value.

How a Value Commitment Can Be Set and Adapted over Time: A “Commitment Pool” Tied to Product Performance against the TPP

Given the large overall value proposition, there are many different commitment models that could deliver shared value to all parties. Here we suggest a relatively simple and powerful model—a predictable revenue commitment pool, tied to TPP performance—which could serve as a starting point for negotiations.

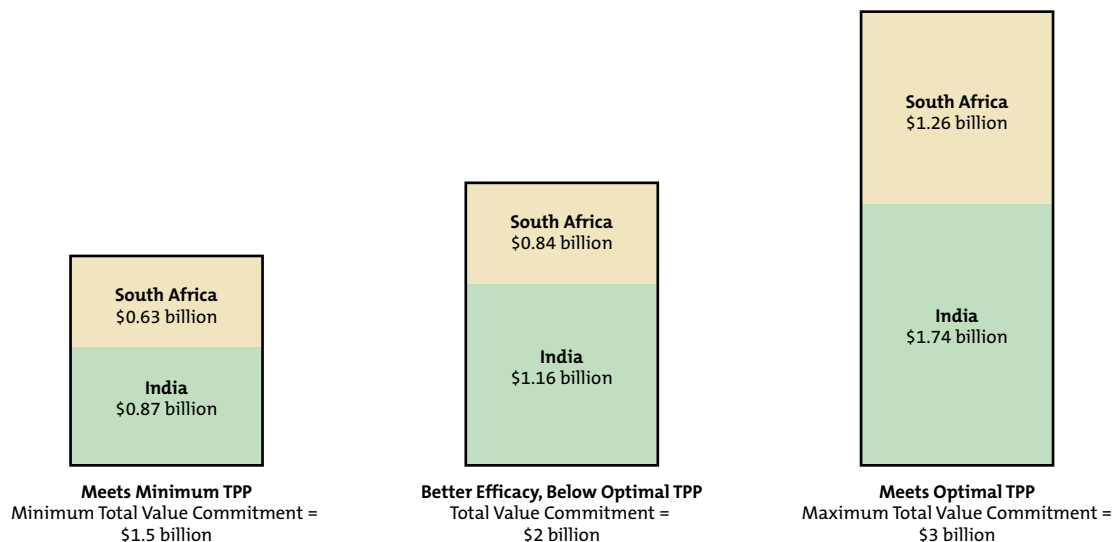
Step 1. First movers assess value. As a first step, one or more high-burden countries would need to take a leadership role as “first movers”—for example, India and South Africa. Ex ante HTA for those two countries would give several important pieces of information:

1. **The total value-based market.** HTA would provide an upper bound for value-based commitments. As we showed in the previous section, the total value-based market for India and South Africa could exceed industry’s “reserve price” for pharmaceutical investment.
2. **Relative value by country.** HTA would show how the total value proposition of a UDR varies across countries.
3. **Relative value by product profile.** HTA would show how the total value proposition of a UDR varies vis-à-vis specific product characteristics. For example, it might show that the value of the UDR is closely tied to regimen duration.

Step 2. First movers define and divide a value-based commitment pool. Using the HTA results as a starting point, the first-mover countries would set and divide up a total “commitment pool”—essentially, an advance purchase commitment (price x volume) tied to product performance. The total commitment pool would need to be sufficiently high to incentivise industry investment. In the next section, we consider issues involved in calculating the total size and form of the commitment pool. For now, for the sake of illustration, Figure 5 offers an indicative schematic for how countries could divide up the total commitment pool, using arbitrary numbers.

Imagine that a product meeting the minimum TPP would be entitled to a minimum total value commitment (e.g., \$1.5 billion) and a product meeting the optimal TPP would be entitled to a maximum total value commitment (e.g., \$3 billion). Between those two extremes, the total value commitment would vary based on different product characteristics and levels of performance. The schematic here is based on illustrative numbers, but in practice the scale should reflect real HTA-derived value differences between different iterations of the product. Country-specific commitment “shares” would also be derived from HTA results. For example, our preliminary HTA results suggest a total value-based market of \$3.24 billion for India and \$2.37 billion for South Africa—a 1.37:1 ratio. For the sake of simplicity, Figure 5 assumes that the ratio (1.37:1) holds constant across different levels of product performance; in reality, different permutations of product characteristics will create differential value for different countries, and the ratio between commitments should reflect relative value between countries. In this example, for the minimum TPP, India would be liable for a \$0.87 billion purchase commitment and South Africa for \$0.63 billion; for the maximum TPP, India would pay \$1.74 billion and South Africa \$1.26 billion.

Figure 5. Indicative Schematic for Defining and Dividing a Value-Based Commitment



Setting and Adjusting the Commitment Pool: A Recommended Model

In the previous section, we explained our rationale for setting a fixed-value commitment that would vary based on product performance. Yet this approach still leaves several unanswered (and intertwined) questions that will need to be resolved during negotiations:

- How large should the total commitment pool be?
 - Should the commitment pool represent the entirety of the expected market? Or is it sufficient to guarantee just a portion thereof?
 - Within the general principles laid out earlier in this section, what is the total value commitment for a product meeting the minimum TPP? What is the total value commitment for a product meeting the optimum TPP?
- Value is calculated as price x volume. If the total value commitment for each country is indeed below the total value-based market, does the reduction occur via a *smaller volume commitment*, a *reduced price*, or some combination of the two?

- Each country's share of the value commitment is calculated via ex ante HTA. Are these shares "locked" based on prospective modelling, or are they recalculated at the time of launch to reflect changing circumstances?

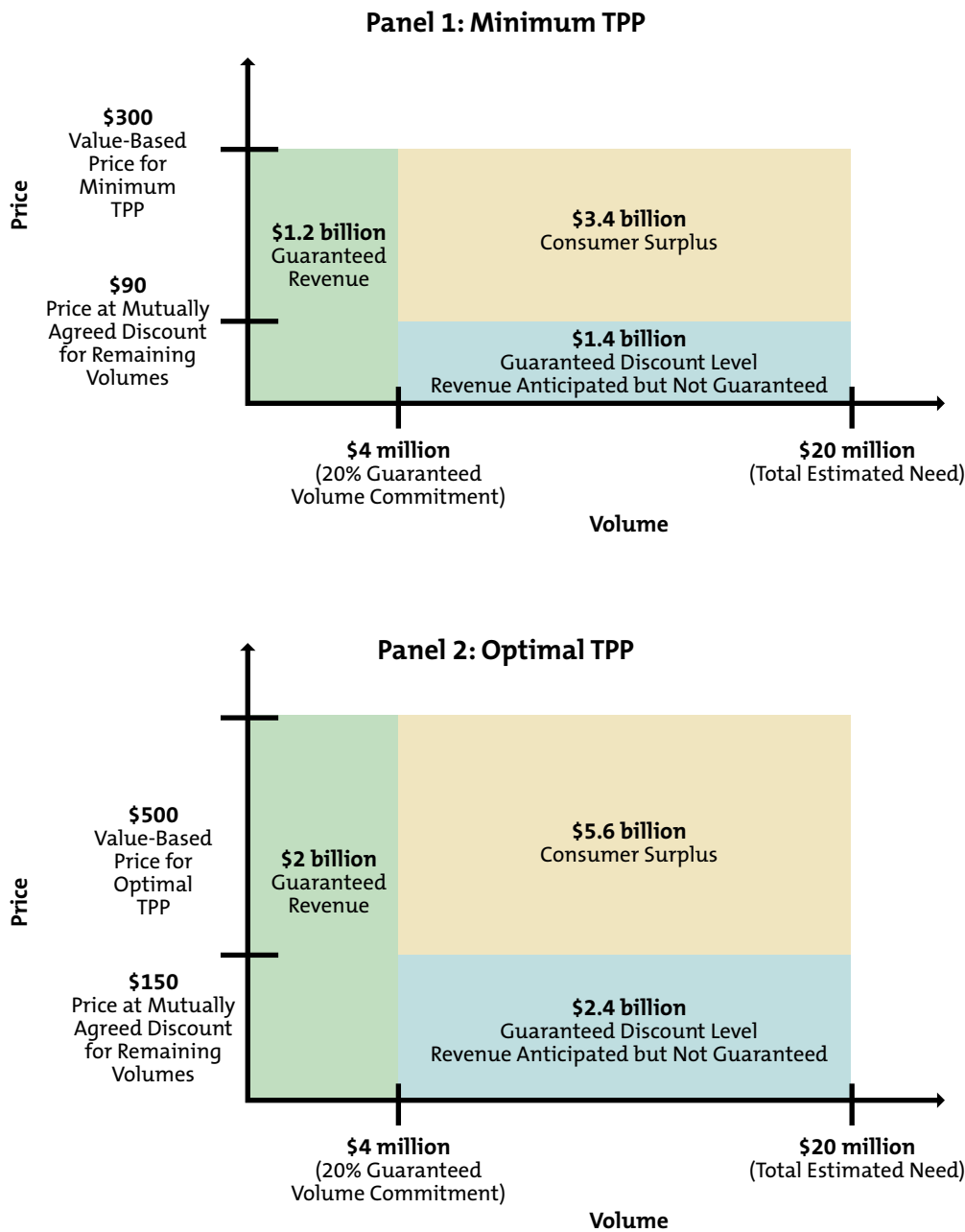
In this section we suggest one plausible model that we believe effectively balances these interests while creating important precedents for the use of HTA and value-based pricing. For illustration, imagine a simplified scenario wherein all countries have the same value-based price, though in reality there will be country-specific value-based prices, given the different country characteristics. For the optimum TPP, imagine that ex ante HTA shows a total \$10 billion market in participating countries (at value-based prices) over 10 years (\$500 per course x 20 million courses); for the minimum TPP, the value-based market is \$6 billion (\$300 per course x 20 million courses).

These countries agree to guarantee (say) 20 percent of the total projected value-based market at the value-based price; collectively, they thus commit to a total (fixed) commitment pool of \$2 billion for a product meeting the optimum TPP (\$500 per course x 4 million courses) and \$1.2 billion for a product meeting the

minimum TPP (\$300 per course x 4 million courses); see Figure 6. To access the purchase commitment, the successful innovator must agree that any volumes beyond the guaranteed commitment pool—up to a pre-agreed

maximum or for a pre-agreed time period—will either receive a heavily discounted price (e.g., a 70 percent discount as illustrated in Figure 6) or be made available to local licensees for a predefined royalty rate.

Figure 6. Model to Define Commitment

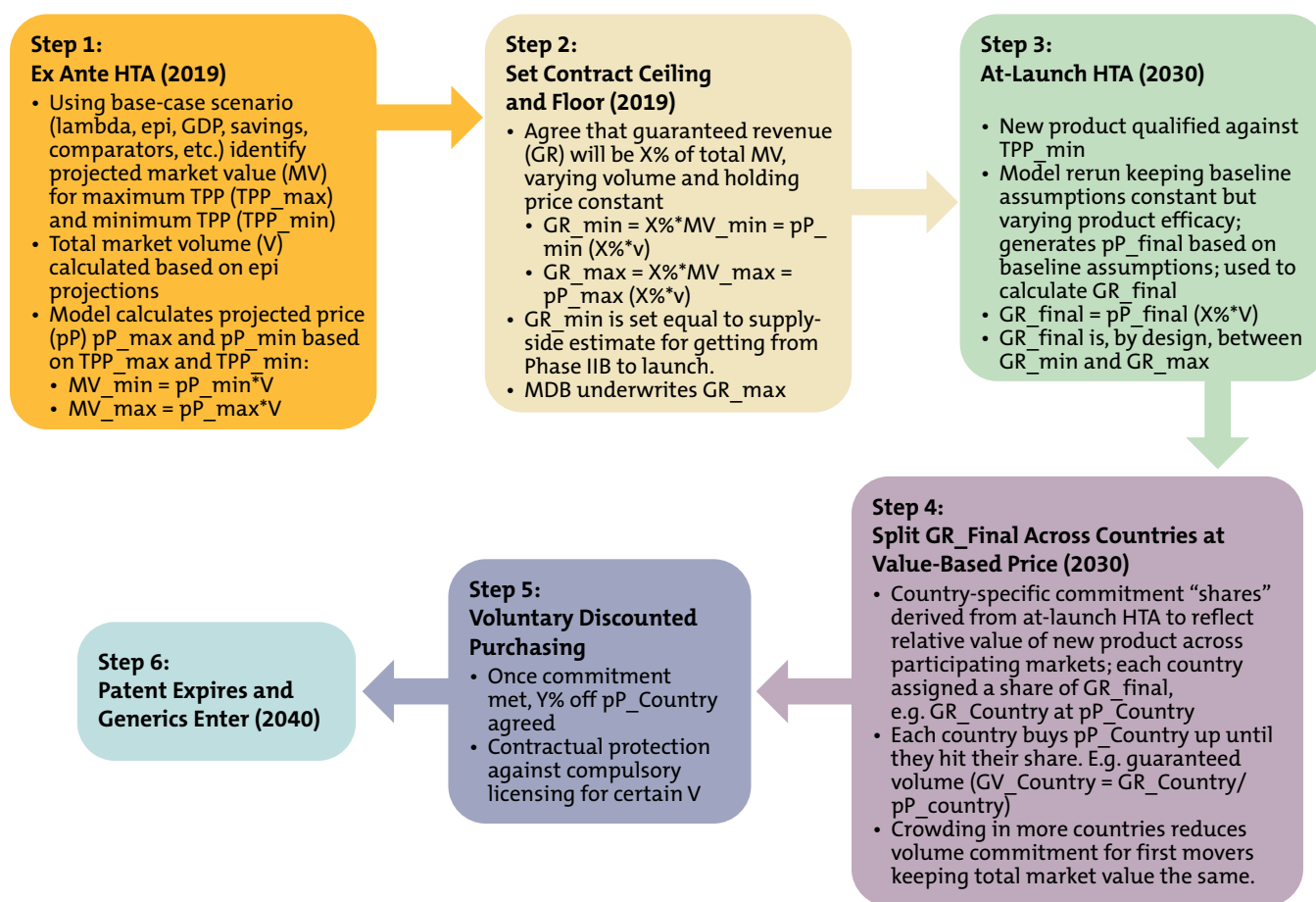


In this illustrative example, industry would be guaranteed \$2 billion in revenue and could reasonably expect another \$2.4 billion from participating countries if it met the optimal TPP; participating countries would capture \$5.6 billion in economic surplus if they purchased sufficient quantities to treat their entire population in need. If its product met the minimum TPP, industry would be guaranteed \$1.2 billion and could reasonably expect another \$1.4 billion in revenue. Participating countries would capture \$3.4 billion in value.

Figure 7 sets out a simplified version of how this approach could work. Ex ante HTA would estimate

the future size of the market and inform the guaranteed value commitment (i.e., the price x volume and therefore the revenue commitment) for products at different levels of performance. At the time of product launch, countries would rerun the ex ante HTA model with up-to-date product performance data, based on the clinical trial results with appropriate modelling. Note that the ex ante model is adjusted only for the up-to-date estimate of the effectiveness of the product in relation to the TPP. Countries would be responsible for fulfilling their prior value commitments by purchasing a sufficient quantity of the product at the performance-adjusted value-based price. After fulfilling

Figure 7. Process for Calculating and Fulfilling Advance Purchase Commitments



their commitments, countries would receive access to the product for the remainder of their demand at a discounted price (we have set this at 30 percent of the value-based price in the illustrative example). Ex post HTA could be used to ensure the product is meeting performance expectations; performance either exceeding or failing to achieve anticipated levels could prompt pricing adjustments for future purchases. The extent to which there were any subsequent price adjustments based on ex post HTA would be a matter to be agreed when the MVAC is established.

A more complicated (but potentially advantageous) approach would revise Steps 4 and 5 in Figure 7. In this revised approach, country revenue commitments (GR_Country) would still be calculated based on baseline assumptions (Step 1) and realised product performance (Step 3); this would provide predictability to both countries, to industry, and to the financial intermediary for overall guaranteed revenue. However, countries using a standardised methodology and the original model, and supported by the secretariat (see Chapter 6) would also conduct a full HTA at launch, inputting up-to-date data reflecting the current situation in 2030. This process would yield an updated value-based price (VBP) for each country. Countries would fulfil GR_Country by purchasing a sufficient product volume at the updated VBP (VBP_Country) instead of the 2019-projected price (pP_Country); the pre-agreed discount (Step 5) would also be applied to the updated VBP_Country instead of the projected pP_Country. This approach creates additional complexity but offers a better precedent for value-based pricing by incorporating accurate parameters at the time of launch. It would also offer an opportunity to engage country payers and HTA agencies through a thorough at-launch HTA process similar to the one high-income countries are likely to apply as a starting point for their negotiations with manufacturers.

As we stated earlier, using a standard HTA process at launch—which would open all parameters to variation, not just performance against the TPP—would allow country commitments to directly correspond to actual conditions at the time of purchase. However,

industry fears opportunistic behaviour and is likely to view such a process as shifting all commercial risk back to its own sector, thus rendering the ex ante HTA process of no practical value. The modified approach set out above reassures companies that revenue commitments will remain unchanged. In other words, the ex ante model is rerun with only the performance of the product against the TPP varying. This determines the price x volume (revenue) commitment. The full at-launch HTA could change the price but not the revenue commitment. Volumes would adjust to reflect this. Whether such a process is feasible will depend on whether there is a shared understanding between the parties that the HTA processes will have the necessary robustness and credibility. If agreement is lacking, then use of ex ante HTA with at-launch adjustment only for performance against the TPP would remain the approach.

Overall, the MVAC model has several advantages:

- Importantly, it establishes the precedent and principle of value-based pricing; each country pays the entire value-based price for a portion of its total projected demand, and a discounted value-based price for additional volume. Each country pays a country-specific price.
- The revenue commitments de-risk the market for industry, while leaving the scientific and development risk with companies. The substantial discounts for additional volume, once the commitment is met, create a large consumer surplus for country payers.
- The model is simultaneously flexible and predictable; it caps countries' financial exposure and guarantees a minimum level of industry revenue, but it enables countries to adjust pricing based on product performance.
- By limiting the “guarantee” to just a portion of the overall market, it also helps reduce transaction costs due to underwriting fees (discussed in the next section).

Underwriting the Commitment

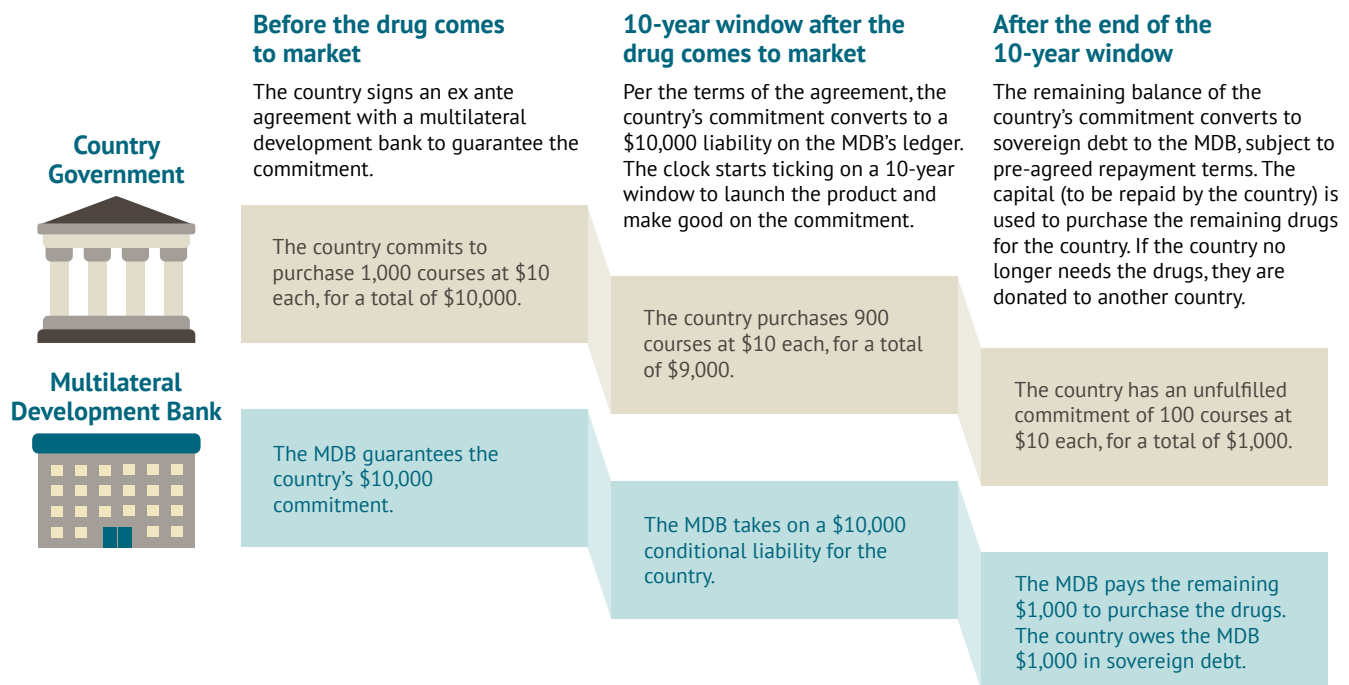
MIC statements about intended purchase commitments send an important market signal about their priorities and ability to pay for an innovative product. Nonetheless, industry is unlikely to make significant R&D investments without a firmer purchase guarantee until there is an established pattern of such announcements' leading to contract commitments. Political leadership and priorities can change dramatically over a 10- to 15-year time horizon, with verbal commitments from previous governments easily disregarded or overturned. Industry will need assurance that today's purchase commitments will be honoured 10 to 15 years in the future—withstanding political, economic, and social winds of change.

Here, we propose a model wherein countries leverage their own sovereign creditworthiness—intermediated through a AAA-rated intermediary guarantor such as an MDB—to underwrite their purchase commitments. Figure 8 presents a simplified straw man

for how the guarantee would be structured (indicative numbers only, using India as an example; in practice, the commitment amount and structure would vary as described in the previous section). As a first step—well before the drug comes to market—each country government would sign a contractual agreement with the MDB. The contractual agreement would lay out the terms of the commitment, clearly defining the country's obligations after the drug becomes available.

After the drug comes to market, the country's commitment would convert to a conditional liability on the MDB ledger; no money would change hands. From that point forward, the country would have 10 years (illustratively) to fulfil the entirety of its purchase commitment. The country would purchase drugs directly from the originator company or a local licensee; in turn, the value of its purchases would be deducted from the country's conditional liability. Countries that fulfil the purchase commitments would thus erase the entirety of their conditional liability, subsequently ending their contractual relationship with the MDB.

Figure 8. Simplified Straw Man of Model to Underwrite Country Commitments



If a commitment balance remains at the end of the 10-year window—that is, if a country were to partially or fully renege on its purchase commitment—the remaining balance would convert to a loan by the MDB, subject to repayment by the commitment-making country under pre-agreed terms. The capital would be used to fulfil the remainder of the purchase commitment, ensuring that the originator company receives the entirety of the guaranteed return; the drugs could either be used in the commitment-making country or (if the commitment-making country is unable to absorb or effectively use the product) donated for use in low-income countries (LICs).

This specific guarantee model has several advantages. The model relies on MICs' own creditworthiness; the development bank will accept the arrangement only if it has confidence that the MIC will make good on sovereign debt payments. In this role, the development bank is acting as a financial intermediary—not a donor. The model is also transactionally simple; if voluntary commitments are met, no money ever changes hands except between countries and the successful company. Countries can continue to manage contracting, appropriation, and payment through their own standard budgetary and appropriation processes—but industry can rely on the MDB guarantee as a backstop for full payment.

In addition, commitment-making countries can use their contracts with the MDB to set out specific conditions for their participation. Commitment-making countries could ensure the contracts align with local industrial policy (see Chapter 5), for example by conditioning their commitment on local licensing (while respecting IP rights) or use of local clinical trial networks. The contract could specify pricing conditions after the commitment is exhausted, potentially including further pricing reductions for later purchases (as described earlier in this chapter). It could also require the originator companies to offer the drugs at cost for use in LICs—an in-kind contribution to global health that could be recognised as a contribution to the Global

Fund, credited perhaps to the MICs entering the MVAC early (e.g., India).

Potential MDB Partners

The underwriting model relies on the existence of MDBs with a set of specific capabilities and characteristics. These include the following:

- **High credit rating.** To drive private-sector investment, industry would need to perceive the MDB-issued guarantee as highly credible and reliable.
- **Sufficient capitalization.** Guaranteed commitments could easily total \$2 billion to \$3 billion. The MDB would need sufficient capital to cover these expenditures in the case of country default.
- **Low opportunity cost of capital.** The MDB would essentially need to “hold” a large sum of capital for potential (but unlikely) deployment 20 or more years in the future. A high opportunity cost of capital might prohibit use of funds for this purpose.
- **Appropriate instruments.** The MDB would need to have appropriate financial instruments that could be deployed or adapted to meet MVAC needs.
- **Country eligibility and regional purview.** Many development banks serve only a subset of countries. Regional development banks may be unable to serve all participating MVAC countries.
- **Exposure limits.** Some development banks cap total lending to any given country. The MDB would need sufficient lending space for all participating countries.
- **Low commitment fees.** MDBs' “commitment fees” are typically charged at the time of issue and subsequently on an annual basis. Commitment fees are typically 100 basis points per year or less; nonetheless, even small fees could quickly accumulate given a large overall commitment

and a long-term time horizon. Depending on total commitment size, time horizon, and how the commitment is structured, commitment fees could range from (say) \$22.5 million (a 0.15 percent annual commitment fee on a \$1.5 billion commitment for 10 years) to \$600 million (a 1 percent annual fee on a \$3 billion commitment for 20 years). Identifying guarantee structures with relatively low commitment fees will be important for the overall feasibility of the model.

Given these characteristics—and based on preliminary conversations with relevant stakeholders—the World Bank and the Asian Development Bank (ADB) emerge as promising candidates to serve as MDB partners (Table 6). Based on their respective comparative advantages—and the large overall commitment size—it may be desirable for different countries to underwrite their conditions using different development banks, essentially splitting the total commitment value across the two institutions. The ADB could serve countries within its regional scope (e.g., potentially, India, China, Indonesia, the Philippines, and Pakistan, among others), while the World Bank could serve countries ineligible for ADB lending (e.g., South Africa, Russia, and Brazil, among others). The World Bank Treasury has confirmed the theoretical viability of such a commitment model within its operating framework. The World

Bank may also be an appropriate host institution for the MVAC secretariat (see Chapter 6)—we assume that the regional remit of the ADB makes it ineligible as a candidate.

A Mechanism to Crowd in Additional Countries

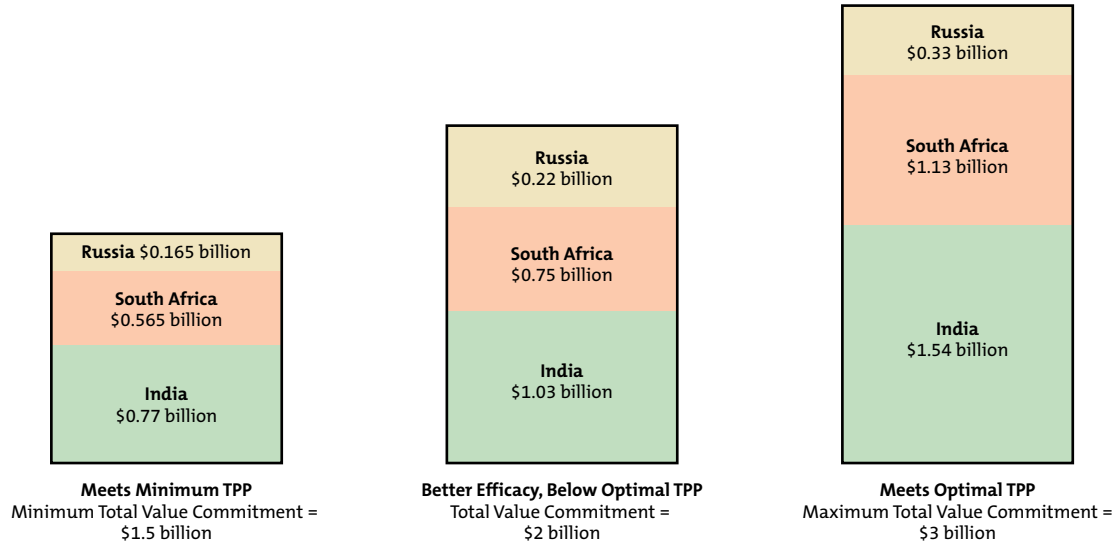
Once the MVAC is underway, additional countries may see benefit for their populations in joining the commitment pool; participation in the pool guarantees affordable access to a path-breaking technology, whereas nonparticipating countries could face lengthy delays in negotiating prices and supply volumes. The MVAC could create a mechanism that enables and incentivises other countries to join the pool, expanding the beneficiary population and helping push prices lower across all parties.

For example, imagine that Russia wishes to join a few years after the MVAC is launched. HTA results (see Chapter 3) show that Russia’s value-based market totals \$0.69 billion, compared with \$3.24 billion for India and \$2.37 billion for South Africa. The three countries now agree to a three-way split of the purchase commitment; once again, the relative commitment shares would be based on relative value, so a ratio of 1.37 (India) to 1.00 (South Africa) to 0.29 (Russia); see Figure 9.

Table 6. Assessing Potential MDB Partners

| | World Bank | Asian Development Bank |
|----------------------|---|--|
| Opportunities | <ul style="list-style-type: none"> • AAA credit rating • Global scope • High capitalization • Large health practice | <ul style="list-style-type: none"> • AAA credit rating • No firm exposure limits • Decreasing need for concessional financing among its members; interested in alternative models to add value • High capitalization • Commitment fees potentially as low as 0.15 basis points for a standby credit facility (requires further exploration) |
| Challenges | <ul style="list-style-type: none"> • Firm exposure limits; may not be able to offer additional lending to India specifically • Potential conflict of interest if secretariat is also housed in the World Bank | <ul style="list-style-type: none"> • Cannot serve countries outside its regional scope |

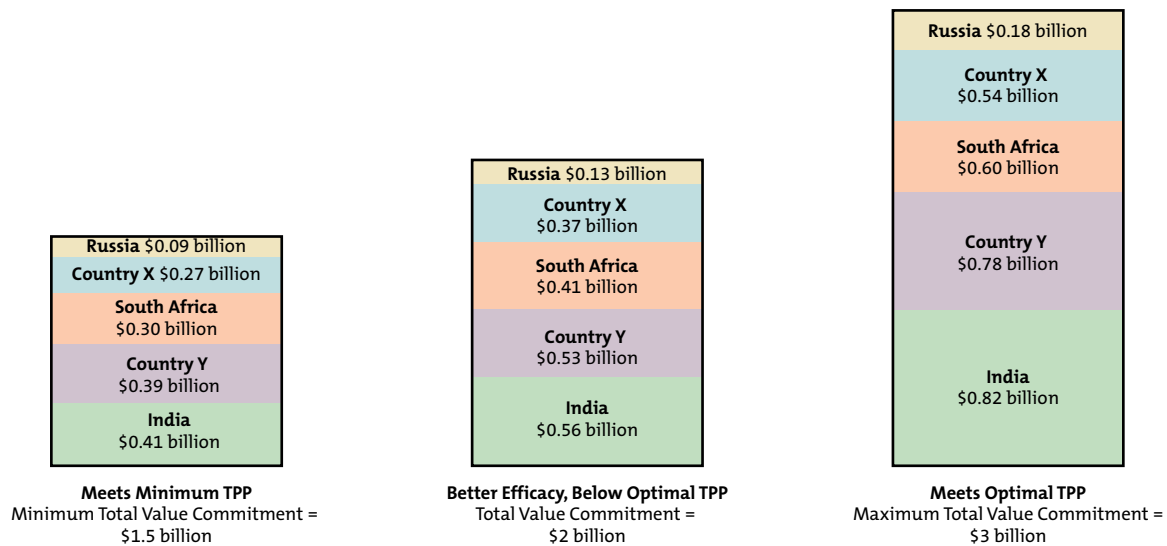
Figure 9. Expanding the Value-Based Commitment Pools to Include an Additional Country



This process could repeat multiple times; entry would be open to all middle-income countries up until market entry of the successful product. Potentially, countries could receive an additional incentive/reward for entering the pool early, or late entrants could owe an additional fee. After several additional entries, the pool might look something like Figure 10 (indicative numbers only).

The commitment pool model we describe here has several benefits. First, it maintains a strong incentive for industry to develop the best possible product; a more efficacious product will lead to higher guaranteed returns. Second, there is a powerful mechanism to crowd in additional countries, reducing each country's purchase liability without affecting guaranteed industry returns. Finally, the model is simple and

Figure 10. The Value-Based Commitment Pools after Several Additional Entries



predictable for both countries and industry; countries have a clear limit on their financial exposure, while industry is guaranteed a minimum return for a product meeting the TPP.

When additional countries enter the pool, the volume commitment of each existing country is reduced, but the price for the guaranteed segment remains unchanged. The level of discount for volumes beyond the purchase guarantee becomes more important. We assumed in our earlier discussion an illustrative discount of 70 percent, but this will need to be subject to negotiation.

A Distributed and Mitigated Risk Model

Under the status quo, several types of risk are concentrated among suppliers and countries (Figure 11). The risks are sufficiently high to prevent a desirable product—the TB universal regimen—from coming to market.

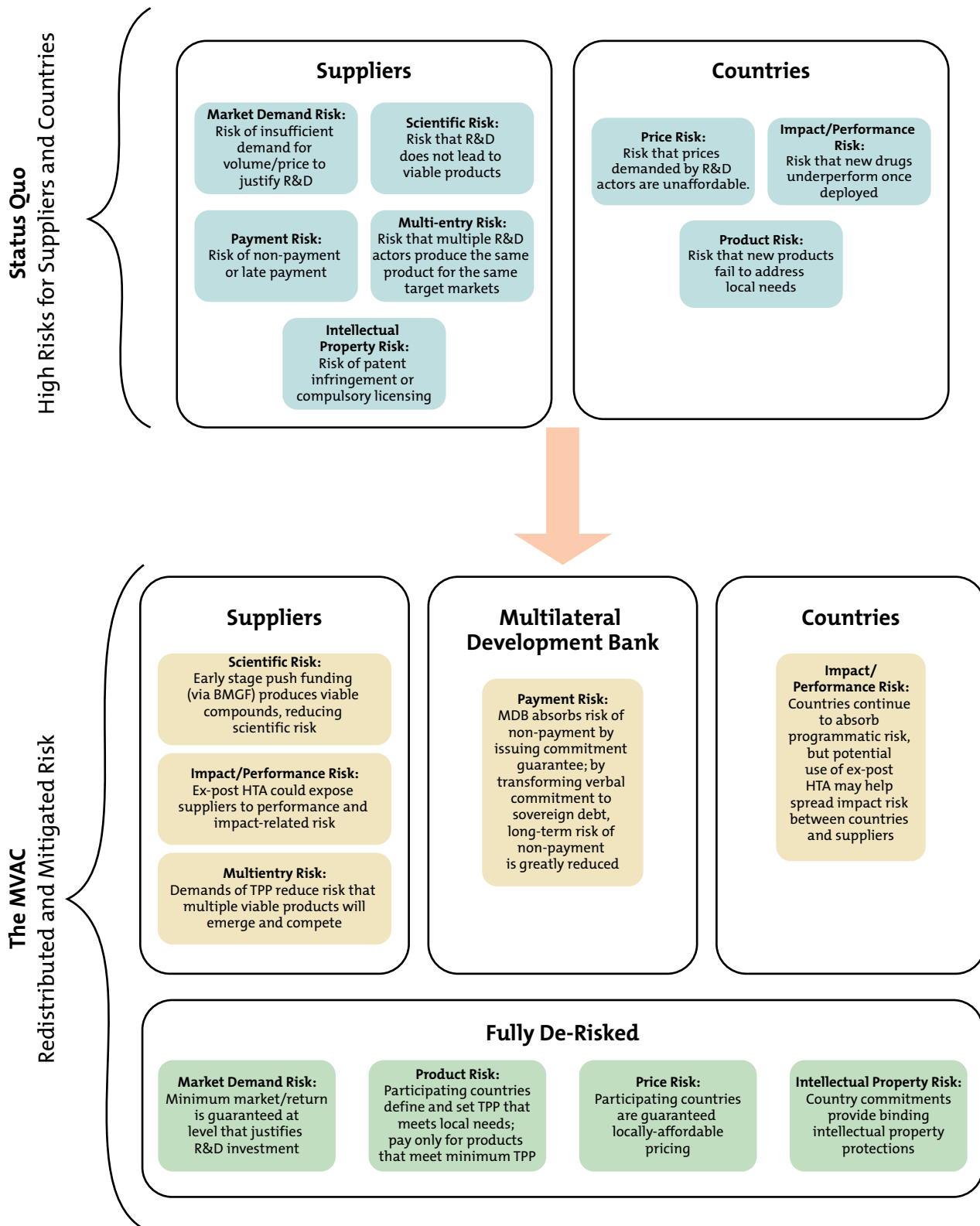
The MVAC model mitigates and distributes risk, reducing total risk to a more acceptable level for all parties. Along several dimensions, the MVAC is fully de-risked:

- The commitment guarantees offer clarity on market demand for a product that meets TPP performance expectations.
- The commitment ensures that countries can access the new products at affordable prices.
- The TPP ensures that products will meet local demand.
- The entire structure is premised on respect for the originator's IP.

Along other dimensions, risk is reduced and redistributed efficiently across parties:

- Suppliers continue to face the scientific risk that products will fail in late-stage trials; however, their risk is substantially reduced with financial subsidies for early-stage pipeline development to proof of concept.
- Market entry of competitor products remains possible but unlikely, given the stringent TPP requirements, including the nature of the UDR as a three-product combination; a more likely scenario would involve market entry of a vaccine (reducing the pool of people to be treated).
- We have assumed that at-launch HTA leads only to price adjustments from the full TPP price based on product performance. However, at-launch HTA could be used to vary more parameters to change price, while keeping the revenue commitments based on the performance-against-TPP adjustment. Ex post HTA, after the product is launched, could further redistribute some performance/impact risk between countries and suppliers. Prices could again be revised, albeit while maintaining the revenue commitments. Volumes would adjust as a consequence of any price change.
- The MDB would reduce and absorb payment risk by transforming a verbal commitment to a sovereign debt obligation.

Figure 11. Risk Transformation under the MVAC Model



Chapter 5.

Industrial Policy

BRICS Industry Policy in Relation to Biopharmaceutical Innovation and Manufacture

The proposed market-driven, value-based advance commitment (MVAC) model raises several issues related to participating countries' industrial policy. The MVAC will need to accommodate countries' purchasing policies giving preferential treatment to local manufacturers (as opposed to multinational companies, or MNCs), plus any specific requirements for local research or manufacturing. Overall, most BRICS countries (Brazil, Russia, India, China, and South Africa) have industrial strategies to support domestic companies, including those in the pharmaceutical sector. We describe the key issues below, largely based on a landscape analysis commissioned by the Bill & Melinda Gates Foundation from McKinsey & Company.

Localisation requirements in Russia are significant and are likely to become more stringent going forward. Since 2014, Russia has offered a 15 percent price preference for locally produced products; suppliers with an insufficient level of localisation must therefore bid at least 15 percent below the price of any local player to win government tenders. This is a critical barrier for MNCs that seek access to the Russian market as there is a clear pricing advantage to firms that have local manufacturing facilities. Many MNCs use a local manufacturer to package drugs, enabling preferential pricing and market access. Some MNCs are beginning to produce drugs in Russia for export to other Commonwealth of Independent States and eastern European countries. Additionally, in-country clinical trials are a prerequisite for drug reimbursement by Russian

government payers. The state has used compulsory licensing for some specific disease areas to increase access for patients (e.g., to anti-HIV therapies). There is a small but growing R&D presence in Russia, with a few local companies with R&D labs in Moscow and St. Petersburg. The state has been supportive of this trend, but we are not aware of specific policy initiatives to promote private-sector biomedical research.

In China, MNCs benefit from partnerships with local manufacturers, as they enjoy access and distribution advantages. (Chinese distributors have entrenched distribution networks and relationships that are almost impossible for MNCs to replicate, given the complexity of the Chinese market.) At the provincial level, localising production can also help secure preferential placement within regional formularies. Intellectual property (IP) rights are not strongly enforced in China, and violators are often not prosecuted, though there is no government use of compulsory licensing. For some new advanced therapies, the Chinese state prioritizes having local supply (e.g., in December 2017 the government instituted a regulation that all cell therapies need to be manufactured locally). Developing the domestic Chinese pharmaceutical industry is a priority for the Chinese government and is included in the 12th and 13th five-year plans. Chinese R&D for innovative therapies is growing, with institutions such as the Shanghai Institute of Materia Medica and the Beijing Institute of Technology producing globally recognised research.

Though local manufacturing is not mandatory in South Africa, showing an effort to develop local supply is a requirement for participation in government tenders. This will become increasingly important as the

fledgling National Health Insurance scheme expands coverage. The country is also experiencing drug registration delays, with registration taking approximately five years—though registration of drugs to address an unmet need or treat life-threatening illnesses has historically benefited from a fast-track process. To ensure drug and vaccine supply, the South African government has promoted public-private partnerships (e.g., the Biovac Institute’s partnerships with MNCs for vaccines). Other than these public-private partnerships, the South African government has not yet taken significant policy action to promote biopharmaceutical innovation or manufacture. Most efforts have been related to import substitution and to lowering the cost of health products.

No localisation requirements are currently in place in India, although indigenous manufacturing is a growing priority for the government. India is among the top pharmaceutical producers in the world (ranked 3rd in volume and 16th by value, with more than 10,000 manufacturers and more than 500 FDA-approved manufacturing facilities). Although India’s IP climate is improving, it is still unpredictable and can be unfavourable for innovative drugs, given recent trends in compulsory licensing and delays in patent approval. This environment has driven some companies to opt for voluntary licensing (e.g., Gilead for its drug Sovaldi).

Many MNCs have manufacturing plants in Brazil, although they are primarily “fill and finish,” or packaging, plants. Although localisation is not required for market access and joint ventures, the government has promoted agreements between MNCs and local manufacturers (so-called product development partnerships, or PDPs) to facilitate local production via technology transfers and royalty arrangements. This

approach was successful for vaccines in the 1980s and led to more PDPs for drugs and biologics by 2009. However, due to the added manufacturing complexity of drugs and the high volume of contracts signed, there have been some delays and cancellations. Local industry players dominate due to their low-cost structures, low prices, and brand recognition, making it difficult for MNCs to compete. Brazil has used the threat of compulsory licensing to pressure companies to lower prices of patented medicines, including the HIV/AIDS drug Kaletra; compulsory licensing was ultimately used in 2007 for Merck’s HIV/AIDS drug Stocrin when Merck and the government could not agree on a price. This practice is now less common.

How Can MVAC Align with National Industrial Policy?

Industrial policy alignment would mean that the MVAC design accommodates country-level industrial policy goals and local purchasing preferences. The successful innovator company could be expected to meet country industrial policy requirements by, for example, licensing production to local manufacturers. Given the high overall expected volumes, technology transfer models and license agreements between MNC developers and local manufacturing companies could be a useful route to secure long-term supply. It will be important, however, to avoid pushing up costs through the duplication of facilities. Having production facilities or clinical research facilities in each country is unlikely to be efficient. Compromise will be needed. High costs will lead to the need for a larger revenue commitment for the MVAC drug developers meeting the target product profile. This is not a sensible use of middle-income countries’ scarce health budget resources.

Chapter 6.

Governance

The market-driven, value-based advance commitment (MVAC) is a vehicle for multinational cooperation; ultimately, its structure and operations must be owned and governed by participating country governments in partnership with relevant trusted global experts and institutional stakeholders. Yet for the model to work in practice, country governments must delegate key authorities to a permanent technical body that can manage day-to-day functions. In this chapter, we outline and map the governance arrangements required to drive forward the MVAC model from concept to operational reality. Based on a comprehensive needs assessment and comparative options analysis, we propose a secretariat housed within a World Bank trust fund, governed by participating countries in partnership with trusted technical and development partners.

Defining Terms and Scope

The term *governance* is widely used in global health, but it does not have a single, agreed-upon definition. For the purposes of this report—and the MVAC, more generally—we put aside the broader definitional debate and set our own functional vocabulary. In this chapter,

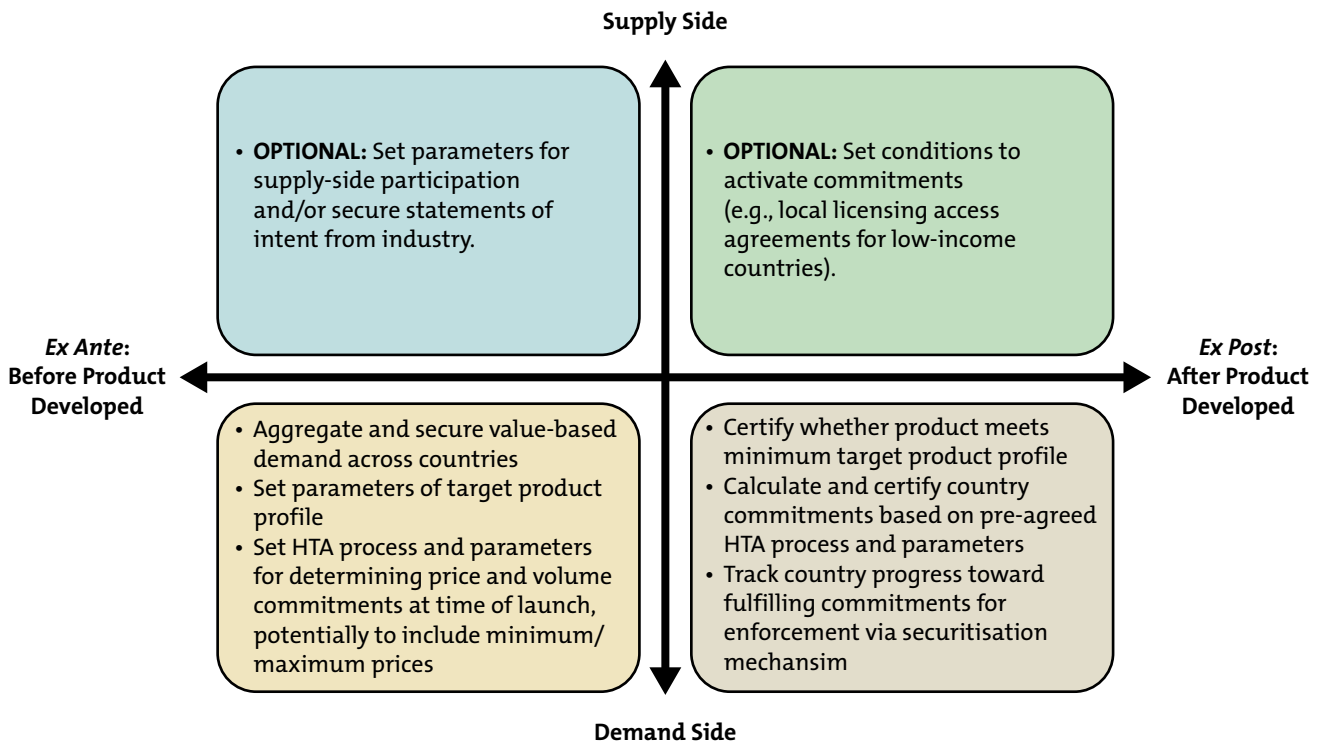
- *governance functions* refers to processes that must be managed or decisions that must be taken for the overall model to work;
- *governance arrangements*, in turn, refers to a range of explicit or implicit structures, institutions, organisations, or agreements that enable the governance functions to be executed; and

- the *governance model* we propose for the MVAC refers to a cohesive and complete set of governance arrangements that will ultimately guide execution of the entire model.

Many different governance functions are required to refine and operationalise the proposed model; for simplicity, they can be mapped along two axes: supply side versus demand side, and ex ante (before the product is developed) versus ex post (after the product is developed); these axes are depicted in Figure 12. The MVAC is primarily a demand-driven instrument; as a result, its *essential* governance functions are exclusively found on the demand side. Demand-side governance arrangements are initially needed to aggregate and secure value-based country commitments, set parameters of the target product profile (TPP), and set health technology assessment (HTA) processes and parameters for determining price and volume commitments at the time of launch—essentially creating the “market” that can be guaranteed or secured and can subsequently drive industry investments in R&D. Following development of a therapy matching the TPP, demand-side governance structures must certify that the product meets the minimum TPP, calculate and certify country commitments based on pre-agreed HTA processes and parameters, and track country progress toward fulfilling purchase commitments.

Beyond the essential demand-side governance functions, some variants of the MVAC structure could benefit from additional, or supplementary, supply-side governance arrangements. As a general principle, before a product is developed, a true “pull model” does not need supply-side governance. The incentive

Figure 12. Mapping of Essential and Supplementary Governance Functions



provided by the “pull” is, in theory, sufficient. The aggregation of and guarantee of demand is intended to mimic the market forces that typically stimulate private-sector investment in R&D, with companies competing for the “pull” rewards. As a “light touch” option, however, we recognise it may be desirable for the MVAC secretariat to engage directly with potential suppliers at the outset—for example, to negotiate parameters for supply-side participation or secure statements of intent from interested companies. The expected continued existence of “push” incentives from global donors increases the case for early engagement by the MVAC secretariat.

Once the drug comes to market, suppliers may be bound by certain “conditionalities” to activate the purchase commitment. Any conditions on supplier participation must be set at the outset, creating a clear and consistent set of market incentives. Potential

conditions for supplier participation may include the following:

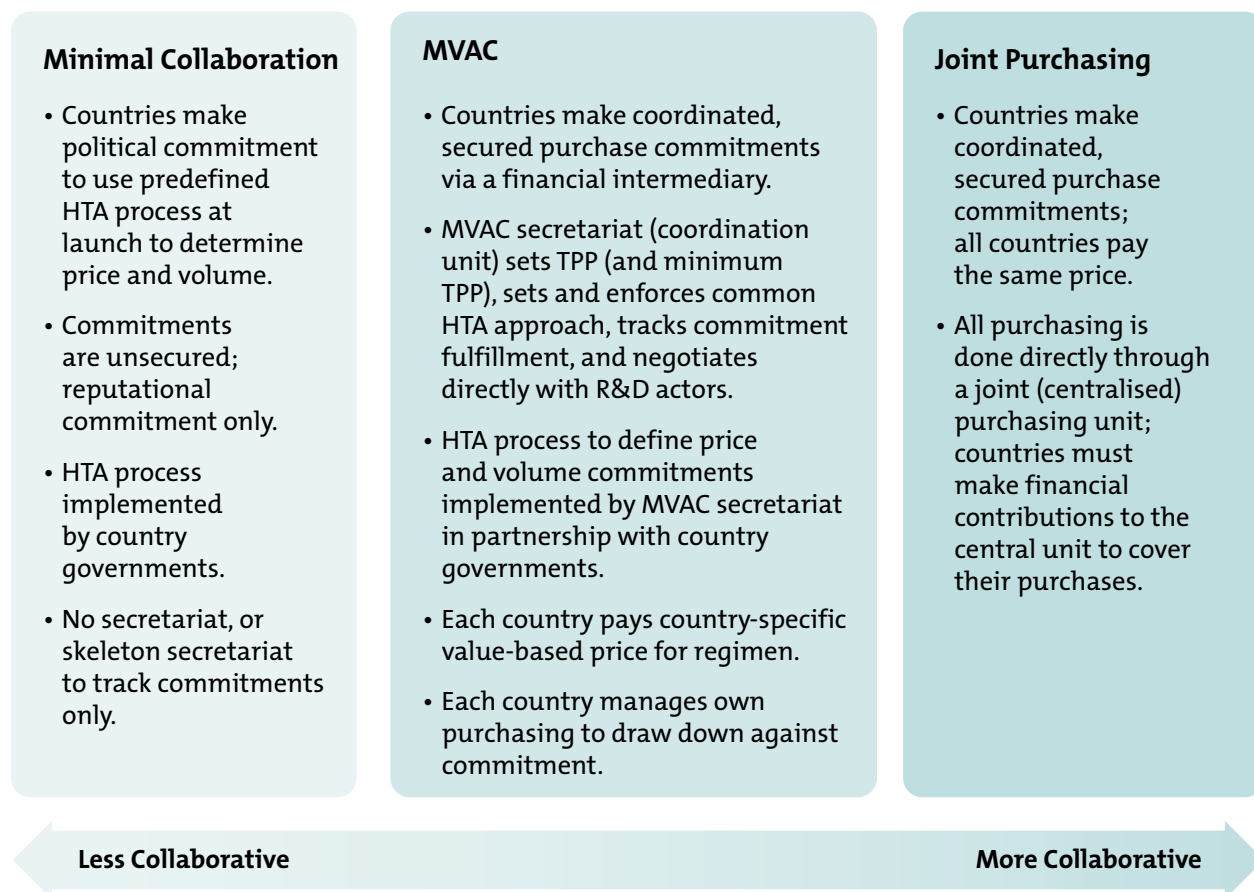
- Supplier commitment to supply the entire MVAC-guaranteed volume at the agreed prices, either directly or via licensed intermediaries
- Access agreements for low-income countries (LICs), perhaps linked to global donor purchase agreements
- Sustained or further reduced pricing for participating countries once the purchase commitment is exhausted (for a specific total volume or a specific period of time)
- Alignment with industrial policy priorities, potentially including licensing to local manufacturers, technology transfer, or partnerships with local clinical trial networks (see Chapter 5)

- Agreement that a portion of payment (if any) will be tied to ex post HTA
- Acceptance of contingency arrangements for
 - adverse events,
 - development of drug resistance, or
 - introduction of new or superior therapies

The proposed governance model is also notable for the functions it *excludes*—that is, the functions that remain vested with participating country governments outside

the proposed secretariat. Most important, national governments will continue to directly manage their own purchasing (drawing down against the agreed commitments) through standard local procurement systems, in compliance with all national regulations as well as with the terms of the MVAC agreement. Countries will also maintain direct control and management over their own budgets; there will be no need to transfer funds to the MVAC secretariat, except (potentially) to help cover operational costs. In total, our model proposes a moderate level of collaborative but not pooled purchasing (Figure 13).

Figure 13. Moderate Level of Collaborative Purchasing Managed by the MVAC

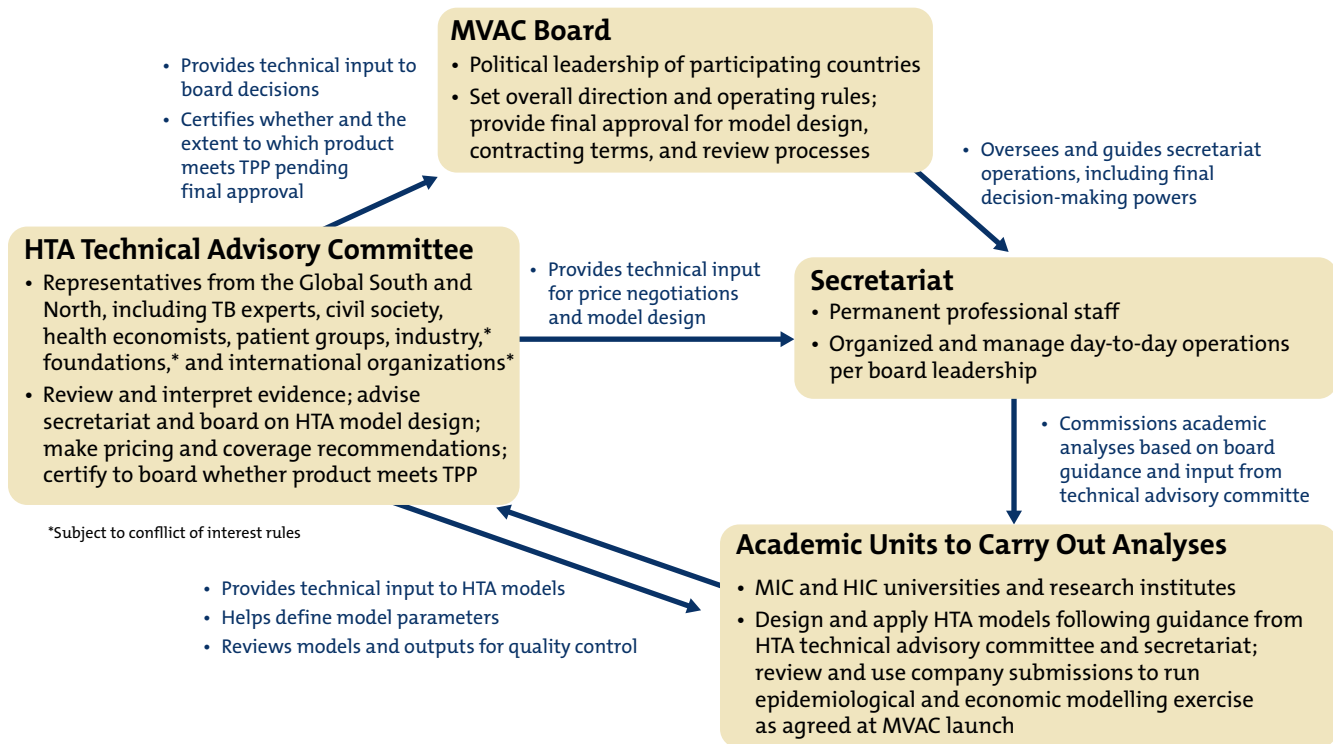


Scoping the MVAC Governance Model: Needs Assessment

To serve its core functions—and successfully manage a complex and politically sensitive negotiation process—the MVAC governance model would benefit from the following essential characteristics:

- **Openness and credibility to the BRICS countries (Brazil, Russia, India, China, and South Africa), the CIVETS countries (Colombia, Indonesia, Vietnam, Egypt, Turkey, and South Africa), and other middle-income countries (MICs).** The success of this entire model is contingent upon successful engagement of MICs with high TB disease burdens, including countries which (1) have successfully transitioned away from Global Fund support (e.g., China, Russia), (2) are in the process of doing so (e.g., South Africa and Indonesia), or (3) are still largely eligible but are committing increasing domestic resources through cofinancing requirements (e.g., India and Nigeria). A successful governance model will allow these countries to lead or at least share both responsibility and power, and gain prestige. This implies that the model must also have enough operational and strategic flexibility to engage with nongovernmental, product development partnership, and private-sector players in high-income countries and MICs.
- **Credibility to industry.** The MVAC model is designed to respond to a market failure: the lack of trust from industry that MICs will pay value-based prices for innovative products, hampering investments in R&D. Secured country commitments (see Chapter 4) are the primary vehicle through which the MVAC mitigates this “counterparty risk”; nonetheless, credibility of governance arrangements remains an important lever to stimulate industry participation. For example, the governance structures will hold ultimate responsibility for certifying whether a product meets the minimum TPP; industry may remain wary of investment if it believes the decision-making process would be vulnerable to conflicts of interest or unpredictable political forces.
- **Relevance to or expertise in TB.** Determining the appropriate product profile and managing the aggregation of demand will require substantial expertise in TB as a disease. This could be accomplished in two ways: (1) by leveraging existing expertise at existing institutions, or (2) by creating a new mechanism that can attract or leverage outside expertise.
- **Flexibility.** By design, the activity/intensity level of the MVAC would vary substantially over time. Early on, there would be a flurry of activity as the secretariat scrambles to recruit countries, agree to a TPP, and “kick off” the MVAC process. Immediately thereafter, the MVAC would enter a period of dormancy, with perhaps just a skeleton staff needed to maintain operations, interface with industry, monitor R&D, and recruit additional countries. Several years later, when a candidate drug emerges from late-stage trials, the MVAC secretariat would need to rapidly ramp up once again. The governance structures thus require significant flexibility to expand and contract across the project cycle.
- **Minimal transaction costs.** To direct as many resources as possible toward R&D and the subsequent purchase of innovative TB therapies, the governance arrangements should be designed to minimise unnecessary transaction costs. This could potentially be achieved by taking advantage of well-established bureaucracies/operational systems, or by establishing new, light-touch organisations. However, efficiencies in operational costs should not be achieved at the expense of cutting programmatic corners.

Figure 14. Proposed MVAC Governance Structure



- **Ability to attract (or offer) long-term operational resources.** We estimate that secretariat costs over a 15-year time horizon would total about \$40 million. Though this is a relatively modest sum by global health standards (and compared with the anticipated value of the commitment), it may nonetheless be difficult to secure predictable, long-term financing. The MVAC would benefit from a host institution that either (1) has dedicated, predictable income streams to fund secretariat operations or (2) can attract and manage a dedicated long-term trust fund, disbursed over many years.

Though the precise governance arrangements will need to be further scoped out and negotiated among key stakeholders, in the next sections we offer one potential arrangement to drive the MVAC process (Figure 14).

Governing Board and Independent HTA Technical Advisory Committee

An MVAC board would primarily comprise the political leadership of participating countries; it might also include representation from external technical and funding partners plus independent technical advisors. The board would be responsible for setting the MVAC's overall direction and operating rules, plus providing final approval on model design, contracting terms, and review processes. The board would also oversee secretariat operations.

However, there are some decision points where board members would have a natural conflict of interest. These include the following:

- **Design and approval of HTA models and results.** Because price and volume commitments would be tied to HTA results, board members would have a fiduciary interest in promoting HTA models that understate the local benefits of a new product.

- **Definition of the minimum TPP.** Because the minimum TPP will trigger the commitment, countries might have an incentive to set it very close to the full TPP.
- **Approval of a product as meeting the minimum TPP.** Because approval of a product activates the time-limited purchase commitment, board members may have an interest in rejecting a suitable product.

To ensure that these decision points are insulated from conflicts of interest—and thus credible to market actors looking to invest in TB R&D—the board would be supported by an independent HTA technical advisory committee. Comprising independent TB and HTA experts, the independent HTA technical advisory committee would be responsible for approving HTA models, approving the results of country-level HTA, defining the minimum TPP that needs to be met by a new regimen to initiate the HTA review, and certifying that a product meets (at least) the minimum TPP and should thus qualify for MVAC value-based purchase commitments. The board would maintain final approval rights over the modelling approach and certification, subject to pre-specified rules that define when and under what conditions a board decision can deviate from the technical advisory committee’s recommendations.

The Secretariat

As depicted in Figure 14, the board would devolve day-to-day operational responsibilities to a permanent secretariat. Based on our needs assessment for a credible and effective governance structure (above), we identified and evaluated three potential options for housing the MVAC secretariat. The following section (summarised in Table 7) presents an options analysis for the three potential hosts, including description, advantages, and disadvantages. The analysis suggests that a World Bank trust fund (option 1) offers the best fit for MVAC operational needs. Accordingly, it is our recommended structure for the secretariat.

Option 1: Recommended—World Bank Trust Fund

Description: “Trust funds are vehicles used to manage funds contributed by development partners for specific development activities and administered by the World Bank.”[29] Though they are housed within World Bank fiscal and administrative systems, trust funds are governed based on an agreement between donors and the World Bank, and can thus include direct oversight by external parties.

Advantages: The World Bank is a credible multilateral institution—both for potential industry partners and for MICs which already participate in institutional governance and could oversee a dedicated trust fund. The trust fund model is widely used to steward development resources and well trusted by the donors who might subsidise the secretariat’s operational costs. Trust funds offer predictable multiyear funding—potentially using a single upfront investment to finance the MVAC secretariat over the entirety of its long-term life cycle.

Disadvantages: Though the World Bank finances many health programmes, it has no specific expertise in either TB or health procurement. There are potential conflicts of interest if the secretariat and underwriting mechanism are housed within the same institution.

Option 2: Existing Donor-Led Secretariat

Description: The new purchase commitment would be embedded as a unit or programme within an existing donor-led global health institution or secretariat. This would essentially follow the model of the advance market commitment for pneumococcal disease, which was hosted by Gavi. Candidate host organisations for the model include these:

- **The Global Fund to Fight AIDS, Tuberculosis and Malaria.** The Global Fund has a long history in the fight against TB and substantial in-house expertise. Its financial resources are also relatively

Table 7. Options for MVAC Secretariat Host Institutions

| Option | Strengths | Weaknesses |
|---|---|--|
| RECOMMENDED: World Bank | <ul style="list-style-type: none"> • Credible to MICs; MICs already participate in governance. Dedicated trust fund could be governed by MICs • Credible to industry • Significant capitalization and fiscal resources • Easy to coordinate with underwriting function if housed within same institution • Flexibility to expand/contract given differing needs over MVAC duration | <ul style="list-style-type: none"> • No specific TB or health procurement expertise • Potential conflicts of interest if secretariat and underwriting mechanism are housed within the same institution |
| Existing secretariat-based institution (e.g., Global Fund, UNITAID, GDF) | <ul style="list-style-type: none"> • Experience and expertise in TB • Existing infrastructure and expertise in procurement • Fiscal resources to help secure commitments (e.g., Global Fund catalytic funding; TB allocations for LICs) • Track record of raising money from donors; credibility with donor institutions • Credibility and track record with pharma companies | <ul style="list-style-type: none"> • Perceived as donor-driven mechanisms; may not be credible to MICs or sufficiently flexible to be included in governing bodies • Existing bureaucracies may have operational constraints that prevent flexibility • Existing bureaucracies are disease-specific (mostly infectious diseases), which limits generalizability of the model |
| New secretariat-based institution | <ul style="list-style-type: none"> • “Clean slate” offers the opportunity to create purpose-built, agile mechanism, avoiding bureaucratic entanglement • Opportunity to co-found and co-lead a new mechanism may be more attractive to MICs than working with existing, donor-driven institutions • Creation of a secretariat offers an opportunity to insource the most relevant expertise | <ul style="list-style-type: none"> • Need to start from scratch in building operational capacity • No established funding base to support initiative, and no track record of attracting donor funds • May have less credibility engaging with pharma industry than an established organisation • May have limited ways to engage with countries not directly involved in governance arrangements |

large; in total, \$1.84 billion was allocated to TB programmes for the 2017–2019 cycle, [30] and an additional \$800 million was made available for “catalytic investments,” which include “strategic initiatives that are needed to support the success of country allocations but cannot be funded through country grants.”[31] The Global Fund could potentially use its existing resources to guarantee country commitments; it could also “commit” parts of country TB allocations to purchase of an innovative TB therapy. The Global Fund has also shown its willingness to support

market-shaping efforts in the past. However, many of the target countries have already graduated from Global Fund support or are positioned to do so shortly. In addition, anecdotal reports suggest that the Global Fund is now resistant to purchasing first-line TB drugs.

- **UNITAID.** UNITAID describes itself as a mechanism that “invests in new ways to prevent, diagnose and treat HIV/AIDS, tuberculosis and malaria more quickly, more cheaply and more effectively.” Its mission—to accelerate and

facilitate the development and market entry of innovative tools—is clearly aligned with the goal and structure of this model. However, UNITAID is relatively small (with an average spend of about \$250 million per year over the past 10 years).[32] It is also widely perceived as a French-led initiative, as France provides the majority of its funding; this might constrain its credibility and ability to engage with BRICS and other MICs, and its ability to secure other donor commitments, for example from the United States.

- **Global Drug Facility.** Hosted within the StopTB Partnership, the Global Drug Facility (GDF) is a pooled procurement mechanism for quality-assured TB drugs, servicing many Global Fund principal recipients. The GDF is specialised in TB and experienced in managing procurement and distribution of innovative formulas.

Advantages: Use of an existing donor-led secretariat would facilitate access to existing concentrations of TB, market-shaping and procurement-related expertise, and existing bureaucracies or operational structures; this could help minimise transaction costs and enable rapid setup. Current donors are already comfortable channelling funding through these organisations; their use could help to mitigate perceived fiscal and operational risk. Existing secretariats may have their own pre-existing funding pools that can be used to help guarantee country commitments.

Disadvantages: Although some mechanisms, such the Global Fund and UNITAID, include recipient countries within their governance structures, they are widely perceived as donor-driven mechanisms. Many of the target MICs are no longer eligible for their assistance or will be graduating shortly; as a consequence, they no longer engage directly with these mechanisms and may see themselves as no longer “needing” their assistance. Existing bureaucracies may have operational constraints that prevent flexibility and could prove problematic in managing this initiative.

Option 3: New Secretariat

Description: Following the model of previous global health funding mechanisms, MICs and donor governments or their representatives could jointly create and govern a new mechanism with a permanent secretariat. Representatives from MIC governments and donors would sit on the board of the organisation and set broad direction, but day-to-day operations would be managed by the secretariat.

Advantages: A “clean slate” offers the opportunity to create a purpose-built, agile mechanism, avoiding bureaucratic entanglement. Opportunity to co-found and co-lead a new mechanism may be more attractive to BRICS and other MICs than working with existing, donor-driven institutions, and may create a greater sense of ownership to mitigate the risk that they will renege on commitments. Creation of a secretariat offers an opportunity to insource the most relevant expertise.

Disadvantages: The need to start from scratch in building operational capacity. No established funding base to support initiative, and no track record of attracting donor funds. May have less credibility in engaging with the pharma industry than an established organisation. May have limited ways to engage with countries not directly involved in governance arrangements.

Secretariat Design and Operationalisation

In the first year, there would be a need to establish, test, and gradually expand a *transitional secretariat*, with costs of about \$2 million to \$3 million over a period of 12–18 months. This would build on the thinking and analysis delivered so far and would include (1) further modelling through modelling consortia; (2) the drafting of contracts; (3) socialization and outreach to countries, industry, and multilateral development banks; and (4) recruiting the core team at the secretariat.

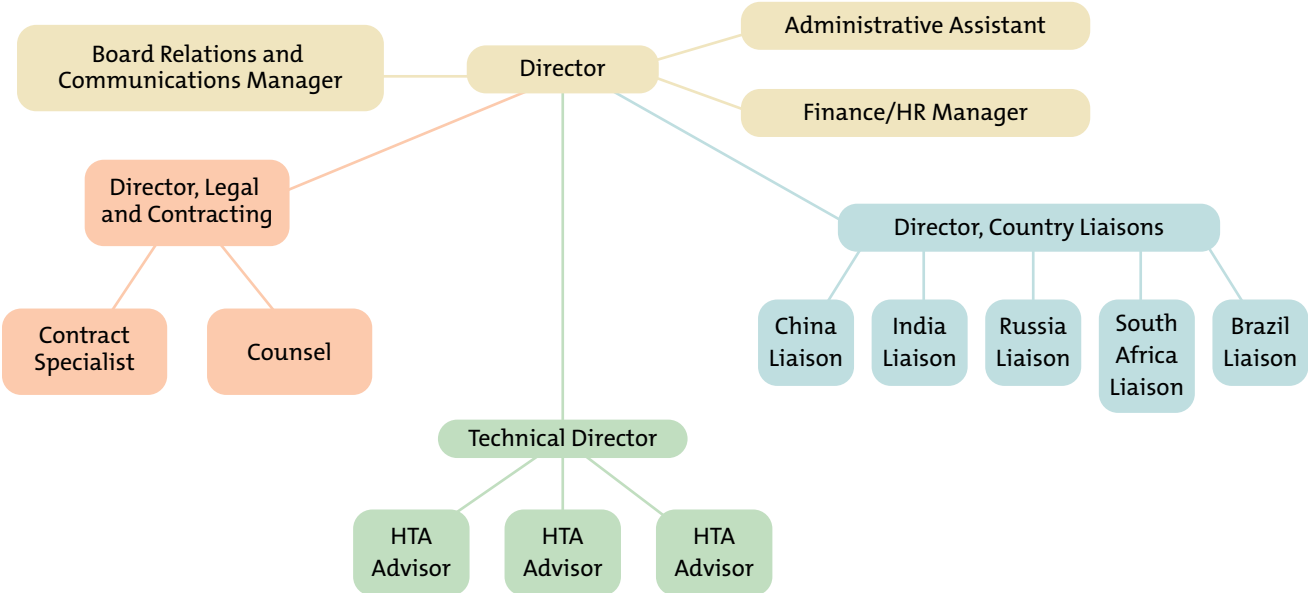
Once fully functional, the secretariat would migrate in full to a *permanent home*, which we recommend be within a World Bank trust fund. During high-intensity periods, we expect that the secretariat would need approximately 15–20 full-time staff members, including technical, legal, and country-specific staff, and it would commission and administer research grants from third parties. The secretariat would be organised along regional and functional lines (Figure 15).

- **A country liaison team** would host dedicated liaisons for each of the participating countries; the designated liaisons would be the primary contacts for in-country technical and political stakeholders. The country liaisons would be responsible for building relations with relevant in-country stakeholders (requiring frequent travel), for facilitating countries’ access to technical resources from elsewhere in the secretariat (HTA advisors, legal or contracting experts), and for knowledge management for all country-specific data and resources relevant to the MVAC.

- **A technical team** would host a dedicated group of HTA specialists. These specialists would partner with in-country HTA resources (e.g., universities, consultancies) to commission, build, validate, and implement HTA models for use by the MVAC, including ex ante and ex post HTA.
- **A legal and contracting team** would work with the underwriting partner to assess and review the terms of conditional liabilities and purchase commitments.
- **A front office team** would report directly to the director, handling finance, administration, human resources (HR), board relations, and communications.

During the low-intensity interim period, the secretariat would contract to a shell (e.g., a director, single legal advisor, and technical advisor). The shell secretariat could continue to recruit additional countries to join the mechanism even during low-intensity periods.

Figure 15. Proposed Secretariat Structure during High-Intensity Periods



Chapter 7.

Gathering and Reflecting Community Feedback

The Center for Global Development and the Office of Health Economics released a consultation draft of the market-driven, value-based advance commitment (MVAC) blueprint in March 2019 for public review and comment. Through mid-2019, we invited constructive feedback and dialogue to further hone the proposal and ensure it is responsive to the interests and concerns of all stakeholders. During this period, we worked proactively to engage with stakeholders in target countries, in international institutions, and within the pharmaceutical industry. This final report amends

the draft in response to the comments we received (see Appendix 6 for further detail).

The MVAC offers a real opportunity for innovative financing, led and supported by BRICS countries and other middle-income countries, to develop new TB drugs and change millions of lives across low- and middle-income countries. Continued engagement from the broader TB and global health community will be essential to moving the MVAC forward and ensuring it best serves all constituencies.

Appendix 1.






Target Product Profile

| Attribute | Target |
|--|--|
| Indication | Regimen is first-line treatment without drug-sensitivity testing requirement |
| Target population | All groups irrespective of HIV status |
| Efficiency | Not inferior to rifampicin-sensitive TB standard of care (SoC) in \leq 2-month regimen |
| Safety | <ul style="list-style-type: none"> • Incidence and severity of adverse events better than drug-sensitive SoC • No active clinical or lab monitoring for toxicity (except in special populations) • No ECG monitoring of QT interval |
| Drug-drug interactions and metabolism | <ul style="list-style-type: none"> • No dose adjustment with other meds • Ability to safely use regimen without active lab test monitoring |
| Barrier to emergence of drug resistance | <ul style="list-style-type: none"> • Mutation rates not $>$ 1/10; essentially no acquired resistance ($<$ 0.1%) • No pre-existing resistance |
| Formulation, dosage, route of administration | <ul style="list-style-type: none"> • Oral, once daily, no special weight banding • \leq 3 novel antibacterial compounds; 2 of 3 or all in fixed-dose combination |
| Stability/shelf life | Stable $>$ 3 years in climate zones 3 and 4 at 30°C and 75% relative humidity |

Source: Based on WHO (2016).[11]

Appendix 2.

Summary of Health Technology Assessment (HTA) Initiatives

| Emerging Markets | |
|--|--|
| <p>China</p>  | <p>“We have fully utilized HTA ... to balance [financial] sustainability and access to new cancer drugs ... up to 30% price reductions compared to nearby countries.”</p> <p><i>Director of Chinese Medical Insurance Bureau, Beijing, October 2018</i></p> |
| <p>India</p>  | <p>“The India Medical Technology Assessment Board [MTAB] for evaluation [of] appropriateness and cost effectiveness of the available and new Health Technologies in India ... standardized cost-effective interventions that will reduce the cost and variations in care, expenditure on medical equipment, ... overall cost of treatment, reduction in out of pocket expenditure of patients...”</p> <p><i>MTAB, Ministry of Health & Family Welfare, Government of India, January 2019</i></p> |
| <p>Indonesia</p>  | <p>“(5) Health Technology Assessment Committee provide[s] policy recommendation to the Minister on the feasibility of the health service as referred to in paragraph (4) to be included as benefit package of National Health Insurance.”</p> <p><i>Indonesia: Minister of Health’s Decree No. 71/2013, Article 34</i></p> |
| <p>Philippines</p>  | <p>“The Corporation shall not cover expenses for health services which the Corporation and the [Department of Health] consider cost-ineffective through health technology assessment ...”</p> <p><i>National Health Insurance Act of 2013, Section 11 – Excluded Personal Health Services</i></p> |
| <p>South Africa</p>  | <p>Service coverage (5.3): “Detailed treatment guidelines, based on available evidence about cost-effective interventions, will be used to guide the delivery of comprehensive health entitlements. Treatment guidelines will be based on evidence regarding the most cost-effective interventions.”</p> <p><i>Republic of South Africa National Treasury (HTA unit budgeted at 368 million South African rand in 2018 Treasury budget)</i></p> |

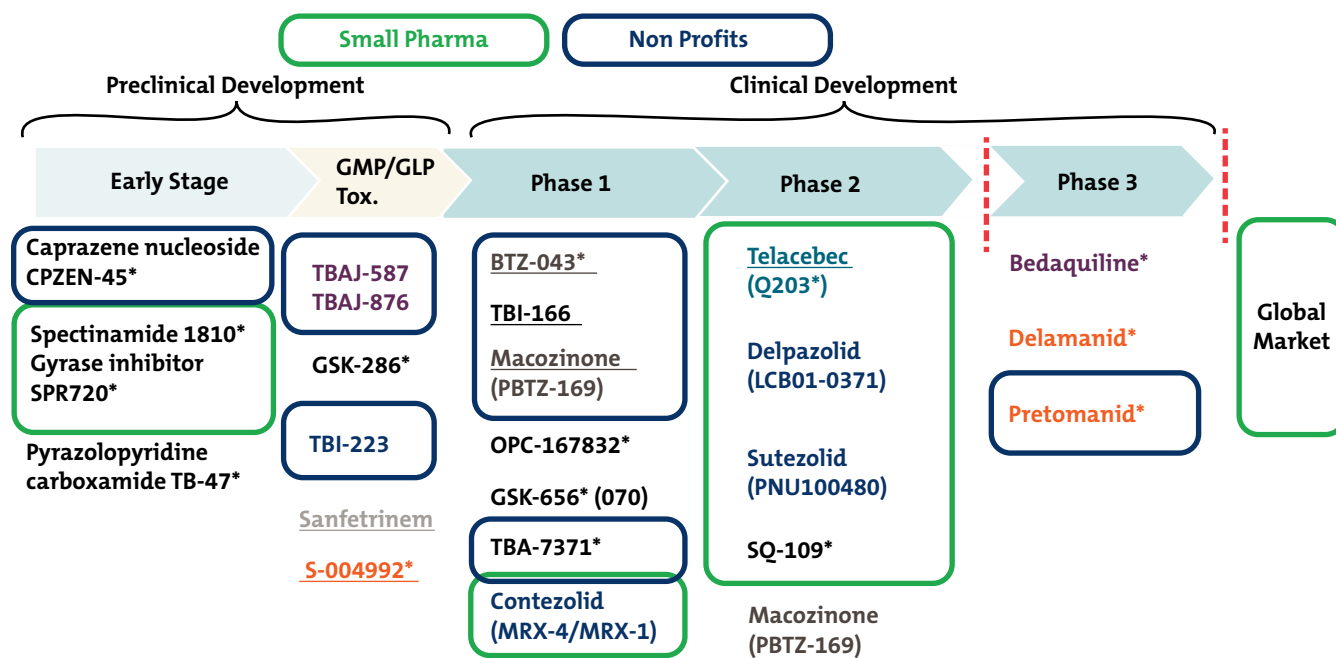
| Low- and Middle-Income Markets | |
|---|--|
| <p>Ghana</p>  | <p>“MOH [Ministry of Health] should develop a transition plan to ensure sustainable financing and operational management of the supply chain to transition to a government led supply chain system; MOH should establish a National Pricing Committee for Medicines; MOH should institutionalise Health Technology Assessment to provide technical advice to the NPC.”</p> <p><i>Ghanaian National Medicines Policy, November 2018</i></p> |
| <p>Kenya</p>  | <p>“ Define an evidence-based benefit package for Kenyans under Universal Health Coverage: (A list of services that should be prioritized and made available taking into account the cost effectiveness, impact on financial protection, and equity in access across the population).</p> <p>“ Define a framework for institutionalization of Health Technology Assessment (HTA).”</p> <p><i>Cabinet Secretary, Government Gazette, July 2018</i></p> |
| <p>Tanzania</p>  | <p>“The aim of the Tanzanian Health Technology Assessment Committee (THTAC) is to make evidence-informed recommendations to the [Ministry of Health, Community Development, Gender, Elderly and Children] based on the internationally recognized HTA framework. The committee will make recommendations about the public provision of health technologies that will contribute to maintaining and improving the health and well-being of Tanzanians, provide value for money and lead to the ultimate goal of Universal Health Care.”</p> <p><i>Tanzania Health Technology Assessment Committee report, 2018</i></p> <p>“The government will improve adequate knowledge in health technology assessment (HTA) for evidence-based selection of quality and safe technology as well as realizing value for money.”</p> <p><i>2017 National Health Policy, 5.14.3. Policy Statements</i></p> |
| High-Income Markets | |
| <p>European Union Commission</p>  | <p>“The outcome of HTA is used to inform decisions concerning the allocation of budgetary resources in the field of health, for example, in relation to establishing the pricing or reimbursement levels of health technologies. HTA can therefore assist Member States in creating and maintaining sustainable healthcare systems and to stimulate innovation that delivers better outcomes for patients.”</p> <p>Regulation of the European Parliament and of the Council on Health Technology Assessment and Amending Directive 2011/24/EU</p> |
| <p>BeNeLuxA + Ireland</p>  | <p>“The initiative aims to achieve its goals by ... increasing efficiency in the assessment, pricing, and reimbursement of pharmaceutical products by exchanging expertise and the mutual recognition of HTA ...”</p> <p>BeNeLuxA Initiative on Pharmaceutical Policy Terms of Reference, 2018</p> |

Appendix 3. Current R&D Pipeline for Tuberculosis

The global pipeline for new TB treatments has improved substantially in the last five years. As shown in Figure 16, there are currently seven programmes in Phase I, led by a mix of organisations including research organisations and product development partnerships, as well as large and small pharmaceutical companies.

A key role in this expansion of the global pipeline is the creation in 2012 of the TB Drug Accelerator programme (TBDA), which is a partnership between pharmaceutical companies and research organisations with support from the Bill & Melinda Gates Foundation (BMGF).

Figure 16. 2018 Global New TB Drug Pipeline



New chemical class* Known chemical classes for any indication are color coded: **fluoroquinolone**, **rifamycin**, **oxazolidinone**, **nitroimidazole**, **diarylquinoline**, **benzothiazinone**, **imidazopyridine amide**, **beta-lactam**.

*New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at <http://www.newtbdrugs.org/pipeline/clinical>.

Ongoing projects without a lead compound series identified: <http://www.newtbdrugs.org/pipeline/discovery>

Underline = new to Phase since March 2018

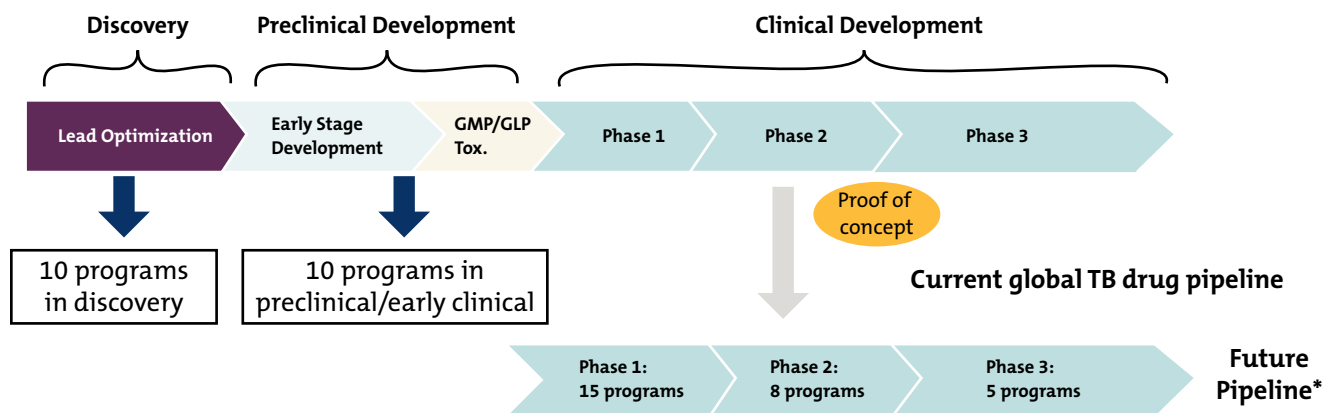
Working Group on New TB Drugs,
www.newtbdrugs.org,
Updated: October 2018

Launched in August 2012, TBDA is a ground-breaking partnership between eight pharmaceutical companies and seven research organisations with support from BMGF. One of the fundamental aims of the initiative is to support the discovery and development of new compounds which could form the basis of new short-ened regimens in the next 5 to 10 years.

Based on the current clinical programme (from Phase I to Phase III), it is expected that at least one new regimen will be introduced in around 7 years. The new regimen will not meet the TPP for a universal drug regimen (UDR) but should have a better profile than those currently available for multi-drug-resistant and extensively drug-resistant TB.

Based on the current rate of discovery and pre-clinical development (from lead optimisation to toxicity tests), a UDR may potentially be developed in the next 12 to 15 years. As shown in Figure 17, when considering the 20 programmes in early stages (including those supported by the TBDA) and the attrition rates from one phase to the next (as predicted by pharma companies in recent calculations), it is expected that 15 programmes will enter Phase I, eight will enter Phase II, and five will enter Phase III, to subsequently lead to one successful new regimen meeting or close to meeting the UDR target product profile.

Figure 17. Current Early Discovery and Pre-clinical Global TB Drug Pipeline versus Expected Clinical Development Pipeline



* Based on estimated on industry attrition rates.

GMP/GLP Tx.: Good manufacturing practices and good laboratory practice toxicology.

Source: Adaptation of <https://www.newtbdrugs.org/pipeline/clinical>.

Appendix 4.

Second-Entrant Competition

Although the likelihood of a second entrant is low because of the scientific and commercial challenges, it is important that the MVAC be able to manage second and subsequent entrants. Principles that could govern second entry are as follows:

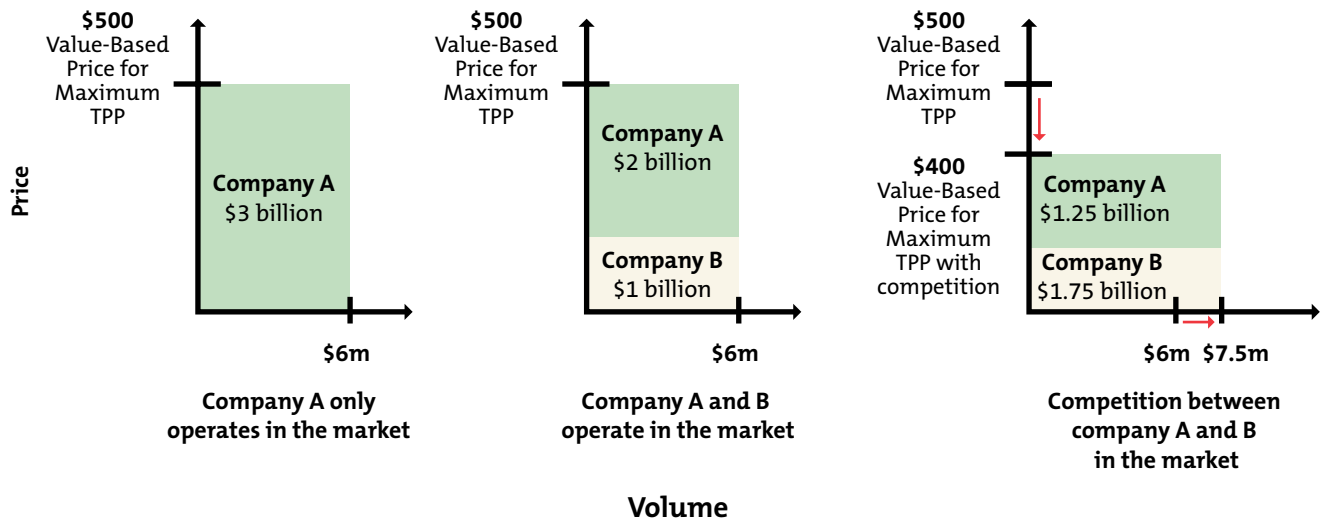
- A second or subsequent follow-on product may enter the market. Any product that *meets the minimum target product profile (TPP)* will qualify to be part of the MVAC commitment.
 - As with the first entrant, the guaranteed price for the product will be determined based on the ex ante HTA and the extent of the TPP met (if it is between the minimum and the maximum TPP).
 - The products can then compete for market share from the participating MVAC countries; that is, the MVAC country commitment is to a total value of purchase, and not to any individual product.
 - Although the price is set by the ex ante health technology assessment (HTA) and the TPP, any supplying company meeting the MVAC entry requirements can offer a lower price (below the MVAC guaranteed price for that product) to get more market share.
 - We might expect that countries will opt for the most effective (and therefore higher-priced) products, if they offer value for money (in terms of DALY gain per healthcare money spent), although one product may be better (say) at fighting multi-drug-resistant TB and the other product may have a better universal drug regimen profile. Thus different participating MVAC countries may prefer different products.
- It is important to note that *the contract value is inviolable* once the prices have been set in relation to the TPP. This means that *lower prices lead to a higher overall volume in the commitment*. It will be important therefore that price cuts not be hidden from the guarantor multilateral development bank. Transaction prices should be subject to audit.

We illustrate how second-entrant competition might work in two scenarios below. For simplicity, *we assume that there is only one country* which makes the full commitment. In reality there will be several participating countries, and the pricing levels and degree of competition associated with a second entry will vary by country.

In competitive entry scenario 1, set out in Figure 18, we assume that initially there is one entrant, Company A, which meets the full TPP. We assume for this analysis that the full TPP price is \$500, the volume commitment is 6 million treated patients, and therefore the contractual value commitment is \$3 billion. This is illustrated in the left part of the figure. We then consider two possible options when a second entrant, Company B, comes in which also meets the full TPP and so is entitled to a price of \$500.

- In Option 1, set out in the centre part of Figure 18, neither company cuts its full TPP product price of \$500. Company B gains market share, but by the end of the contract commitment sum Company A has achieved a two-thirds market share and Company B a one-third market share. 6 million patients are treated under the MVAC contract.

Figure 18. Competitive Entry Scenario 1



- In Option 2, set out on the right side of the figure, both companies cut their product prices from \$500 to \$400. As a consequence, the contract commitment of \$3 billion is met by increasing the volume of patients treated under the contract from 6 million to 7.5 million. Company A achieves a slightly lower market share, gaining \$1.75 billion, and Company B gets \$1.25 billion.

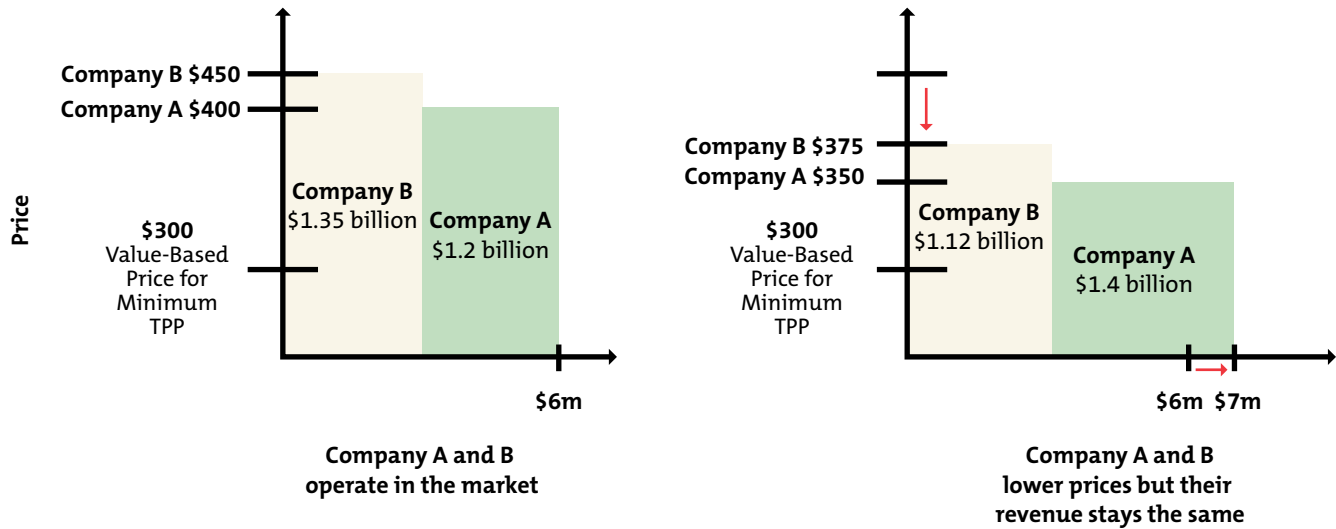
In competitive entry scenario 2, set out in Figure 19, we make the assumptions a little more complex. We assume that neither the first entrant, Company A, nor the second entrant, Company B, achieves the full TPP, but both are above the minimum TPP, which qualifies for a price of \$300. We have two options:

- In Option 1, in the left side of the figure, Company A prices at the maximum it is entitled to at \$400. Company B has a product that meets more of the TPP and prices at the maximum allowed of \$450. There are two ways in which the contract commitment can be met in the circumstances of two competing products which meet different levels of the TPP and so have different guaranteed prices. The first is to have a fixed volume commitment but with the revenue consequences depending on which product the country prefers. We illustrate this. The volume commitment

is 6 million treated patients, giving a maximum contract commitment of somewhere between \$2.4 billion if Company A takes all of the market and \$2.7 billion if Company B takes all of the market. We assume that they get 50 percent of the volume each, and so the revenue commitment becomes \$2.55 billion. A second alternative is for the revenue commitment to be set by the guaranteed price of the superior product. In this case, it would be Company B's product, and so the revenue commitment would be \$2.7 billion. In the situation in which Company A has significant market, the volume commitment would need to increase in order to ensure that the revenue commitment of \$2.7 billion is met. We do not illustrate this.

- In Option 2, in the right side of Figure 19, both companies cut prices below the TPP levels they are allowed. Company A prices at \$350 and Company B prices at \$375. Again, we have two ways in which the contract commitment can be met. The first is to have a fixed volume commitment but with the revenue consequences depending on which product the country prefers. We illustrate this. The volume commitment increases in order to meet the contract revenue commitment of

Figure 19. Competitive Entry Scenario 2



Volume

between \$2.4 billion and \$2.7 billion depending on the relative market shares of the two products (i.e., the commitment is set by reference to the maximum price allowed at the share of the TPP delivered, multiplied by the contracted volume of patients treated, of 6 million). If Company A were to win all of the market, the volume commitment would increase to $\$2.4 \text{ billion} / \$350 = 6.657$ million. If Company B were to win all of the market, then the volume commitment would increase from 6 million to $\$2.7 \text{ billion} / \$375 = 7.2$ million. In practice, we see that Company B wins a volume of 3 million, which gives it a revenue of \$1.12 billion. Company A is treating 4 million patients at \$350 each, which gives it a revenue of \$1.4 billion. If we take the volume shares, A has 57 percent and B has 43 percent. At the original 6 million patients, this gives a commitment of 57 percent x \$2.4 billion + 43 percent x \$2.7 billion = \$2.52 billion. The revenues are \$1.4 billion for A and \$1.12 billion for B, which totals \$2.52 billion; that is, the price cuts and market shares won increase the overall MVAC volume commitment from 6 million to 7 million to deliver the contract

sum of \$2.52 billion. The second alternative is for the revenue commitment to be set by the guaranteed price of the superior product. In this case, it would be Company B's product, and so the revenue commitment would be \$2.7 billion and the volume commitment would increase beyond 6 million to reflect both the price cutting from the maximum guaranteed price and the fact that Company A's product, which had a lower guaranteed price, had a significant market share.⁹

9. In scenario 2, as in scenario 1, we set out two ways of adjusting the guaranteed commitment:

1. Adjusting the revenue commitment to take account of the different market shares of the two products (based on the guaranteed price and volume of each product)
2. Setting the revenue commitment based on the guaranteed price and volume of the superior product (i.e., the product that meets more of the TPP)

There are two quite different things going on:

1. Price cuts below the guaranteed price lead to additional volumes as the revenue commitment is unchanged.
2. Changes happen in the revenue commitment. We can either link the revenue commitment to the product (as in the first way) so the revenue commitment varies depending on the market share of the product (reflecting the country's preferences), or it can be based on the superior product.

The two ways of adjusting the guaranteed commitment have advantages and disadvantages:

1. Adjusting the revenue commitment to take account of the different market shares of the two products better reflects the preferences of the country between the two products. However, it may encourage use of an inferior product to reduce the size of the revenue commitment.
2. Setting the revenue commitment based on the guaranteed price and volume of the superior product (i.e., the product that meets more of the TPP) increases the incentive for the country to use the better product and also increases the market available to a superior second entrant, making such an entry more likely. However, it complicates budget planning for the country if it is a late second entrant that is superior.

Note that in both cases, price cuts below the guaranteed price lead to increases in volume (i.e., the revenue commitment is determined by the guaranteed price).

These examples are illustrative, and discussions would need to take place as to how volume commitments would be adjusted among countries in response to different market share effects, but the two key principles are these:

1. Competitive entry should be encouraged and price competition will work to the advantage of MVAC participating countries, unlike what happened with the advance market commitment for pneumococcal conjugate vaccine (PCV).
2. However, the revenue commitment should be unchanged and set by the TPP prices and volumes. Thus price competition translates into more delivered volume rather than less revenue, hence increasing coverage in a situation where ex ante estimated demand is likely to be an underestimate.

Appendix 5.

Frequently Asked Questions

Why does this matter? According to the World Health Organization (WHO), the Sustainable Development Goal (SDG) for tuberculosis (TB) “cannot be achieved” without a “major technological breakthrough.”[10] Bill & Melinda Gates Foundation funding and product development partnerships have helped source new and promising compounds, but major new investments are needed to bring drugs to market. In the absence of intervention, pharmaceutical companies will not invest the requisite financial resources to fund late-stage clinical trials and bring a path-breaking drug (in the form of a universal drug regimen, or UDR) to market, and global TB goals will not be achieved.

What’s in it for industry? Industry receives a de-risked and guaranteed market for an innovative drug, protected from compulsory licensing and other threats to intellectual property (IP). In the long run, industry builds relationships, experience, and precedent for value-based pricing that would help expand sales in emerging markets.

What’s in it for countries? Participating countries get guaranteed access to innovative drugs, targeted to local needs, at locally affordable prices—driving multinational and domestic investments to address local disease and population priorities.

What is health technology assessment (HTA)? Where and how is it used? Is it realistic in low- and middle-income countries? The WHO defines HTA as the systematic evaluation of the properties, effect, and/or impacts of a health technology. HTA informs decision making about the use of new products by helping payers quantify trade-offs and draw informed comparisons between alternative potential uses of finite health

budgets. HTA offers a starting point for product listing and price negotiation and for policy decision making, but it is not an automated decision rule. Many of the largest middle-income countries (MICs)—including India, Brazil, China, Thailand, Vietnam, Indonesia, and South Africa—already use HTA to inform coverage and purchasing decisions within their health sectors (see more here).

How is this different from the advance market commitment for pneumococcal vaccines? The MVAC targets products in an earlier stage of clinical development, relies on commitments from country governments rather than donors, guarantees commitments through a financial intermediary (e.g., a development bank), is led and governed by country governments, and determines pricing based on a local value and affordability assessment in participating countries (i.e., is not cost-plus).

What happens to the IP? The innovator company retains IP rights. At the very least, participating countries are guaranteed pricing at MVAC levels in perpetuity (e.g., after their commitments are exhausted); potentially, participating countries could condition the guarantees on more aggressive price reductions once the commitment is fulfilled.

What exactly are countries committing to pay? Based on a minimum and optimal target product profile (TPP)—paired with some conservative assumptions about GDP growth—the MVAC approach would set a floor and a ceiling total expenditure level for country commitments. Within that range, the final price and volume would be calculated via a predefined process and using the HTA model once the drug comes to market, based on its performance, product characteristics, and

other pre-agreed parameters that influence its value to country health systems, including local affordability constraints.

What is guaranteed in the MVAC model? The MVAC offers guaranteed revenue to a product developer; the total guaranteed revenue will vary based only on product performance, within a preset range (floor and ceiling).

Are there ways to continue downward pressure on pricing through the MVAC structure? Yes. The total value-based market—if appropriately de-risked—is likely to significantly exceed industry’s “reserve price” to make the requisite investments and bring the product to market. As a result, the MVAC can cap the guaranteed revenue at only a portion of the overall value-based market. The MVAC could then “crowd in” other MICs into the same pool of a guaranteed market—lowering the revenue commitments for every participating country.

Would the MVAC involve pooled procurement? No. Although countries would collaborate to negotiate prices and agree to a common TPP, each participating country would procure the UDR directly from the originator or local licensee through its own national procurement procedures at a price which represents value for each country while complying with all relevant national regulations.

How does the MVAC compare with most favoured nation (MFN) clauses? MVAC relies on differential pricing based on locally determined value and affordability. Differential pricing (though not necessarily based on country budget realities and local value) is currently the norm for on-patent products across MICs. A trend toward MFN would distort markets, possibly resulting in selective launches in higher-income markets and hence impeding access. By linking markets, it would also undermine R&D which addresses poorer countries’ and MICs’ needs.

How do we ensure access for lower-income countries (LICs)? To benefit from the guaranteed country commitments, the successful company must offer the drug at cost for use in LICs—either to third parties or directly

to country governments. By helping ensure access for LICs, participating countries would be credited with indirect contributions to the Global Fund to Fight AIDS, Tuberculosis and Malaria. Global donor commitments would still be needed to enable LICs to purchase the new TB drugs at cost.

Does the MVAC involve tiered pricing? Yes. Each country would pay a country-specific price, calculated based on the value that the drug provides within its own health system. Tiered pricing is the norm for non-donor-provided health products within and across MICs.

How does the MVAC align with countries’ industrial policies? To comply with countries’ industrial policy requirements, the successful innovator would work with in-country manufacturers—through means potentially including licensing agreements, investments in clinical trial networks, and joint ventures—to help build industrial capacity.

Is the MVAC only for large multinational companies? What about companies based in developing countries? The MVAC is a flexible, demand-based pull mechanism. All companies—including those based in developing countries—can participate, as either innovators or licensees.

Is there precedent for countries to pay differential prices through a collaborative purchasing arrangement? Yes. In the EU, several country groupings—most recently Belgium, Ireland, Austria, Luxemburg, and the Netherlands—have come together to collaborate in their purchasing of high-priced pharmaceutical products. Countries share information on comparative effectiveness and budget impact but continue to purchase individually at country-specific, confidential prices.

Is there precedent for the development banks to serve as a guarantor/intermediary? Yes. Both the Asian Development Bank and the World Bank offer guarantees among their suites of financial products, using their AAA ratings to mitigate commercial risks. Representatives from development banks have expressed confidence that the proposed guarantee instrument is technically feasible.

Appendix 6.

How We Have Addressed Feedback on the Draft Report

The following table describes key points of feedback and how we have addressed the feedback within the revised report.

| Theme | Issue | Stakeholder | Response |
|---|---|--|---|
| Terminology | Define <i>value-based pricing</i> | Civil society | See Box 6 and this blog post |
| | <i>Willingness to pay</i> versus <i>ability to pay</i> | Civil society, product development partnerships, and R&D facilitators | <i>Willingness to pay</i> replaced with <i>ability to pay</i> in all instances within final report. <i>Ability to pay</i> is defined in Box 3. For further details, see this blog post |
| | Compulsory licensing | Civil society | See Box 1 and this blog post |
| Model inputs | Establishing reasonable R&D costs | Industry | See page 21 and Table 5 |
| | Openness to revising target product profile based on country inputs | Industry, civil society | See page 17 and Appendix 1 |
| | Need to ensure all comparators are explained including incremental-value products | Industry, civil society, product development partnerships | See Appendix 7 |
| Second entrant and competition | Second entrant | International organisations and donors | See Appendix 4 |
| | Pulling existing products already in Phase III to market | Product development partnerships and R&D facilitators | See page 21 and Appendix 3 |
| | TB vaccine (and why it can't be used alongside the universal drug regimen) | Product development partnerships and multilateral development banks | See Appendix 7 |
| Interlinks between MVAC and other incentive mechanisms such as Life Prize, Medicine Patent Pool | Civil society, product development partnerships, and R&D facilitators | See Box 4; for further details, see this blog post | |
| Transparency and consultation | Civil society | We have amended the final report to clarify that civil society organisations are central in all health technology assessment processes and the MVAC secretariat (see Figure 14). In addition, we have produced this socialization summary report as well as presentations, and blog posts here and here | |

Appendix 7.

Description of Comparators and Key Input Data and Assumptions

| Comparator technology | Example used for model assumptions | Population targeted | Price/cost per dose (US dollars) | Efficacy/clinical performance | Year of introduction | Source |
|--------------------------|------------------------------------|--------------------------------|----------------------------------|------------------------------------|----------------------|--------------------------|
| Shorter regimen | BPamZ | Drug-sensitive TB | 103.9/month | 4-month duration | 2025 | Knight et al. (2015)[38] |
| More efficacious regimen | BPaL | Multi-drug-resistant TB | 664.7/month | 9-month duration | 2025 | Knight et al. (2015)[38] |
| Vaccine | None | Adults with possible latent TB | 1.50–10 (tiered by income group) | 60% efficacy 10-year protection | 2024 | Knight et al. (2014)[27] |

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