

Keeping the Promise

Product Development
Partnerships' Role
in the New Age of
Health Research
and Product
Development



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Introduction

Product Development Partnerships (PDPs) develop new products for people suffering from diseases and health threats underserved by traditional markets by building partnerships between the public, private, academic, and philanthropic sectors. In the global health space, PDPs have developed and introduced treatments, vaccines, diagnostics, vector controls, devices, and various other forms of innovation that have led to significant progress against some of humanity's oldest and deadliest pandemics, including tuberculosis, malaria, HIV/AIDS, neglected tropical diseases (NTDs), and a host of other poverty-related neglected diseases. In disease areas where traditional market incentives have not been sufficient to encourage significant investment by the private sector, PDPs and their funders and partners are the primary drivers of innovation, developing health solutions that would otherwise likely not exist.

Since 2010 the coalition of PDPs featured in this report have developed and introduced 66 new health technologies, which have reached more than 2.4 billion people around the world, including women, children, and other vulnerable populations often ignored by developers of new health technologies. This success has been driven by a needs-based approach, developing products appropriate for the settings in which they are most needed, which are often low-resource environments. Further, by pooling resources and leveraging partnerships, PDPs are consistently able to develop products at a total cost below that of the private sector. Recent examples of such innovations include:

- TB Alliance achieved U.S., EU, and Indian regulatory approval for pretomanid between 2019–2020, the first ever drug approved for treatment of highly drug-resistant forms of tuberculosis (TB);
- Medicines for Malaria Venture (MMV), in partnership with GlaxoSmithKline (GSK), earned regulatory approval for tafenoquine (TQ), a single dose treatment to prevent relapse of *P. vivax* malaria. TQ was approved by both the U.S. Food and Drug Administration and the Australian Therapeutic Goods Administration in 2018; and
- Drugs for Neglected Disease initiative (DNDi) developed a new chemical entity, Fexidazole, as the first all-oral cure for sleeping sickness, which was approved by the European Medicines Agency in 2018.

This report will highlight these and many additional examples of impactful global health technologies developed by PDPs.

In addition to saving millions of lives, the work of PDPs has helped strengthen health systems and promoted global health security in endemic countries, contributed to progress toward the United Nations 2030 Sustainable Development Goals (SDGs), and increased global capacity to conduct research. PDP coalition members have conducted clinical-stage research at more than 550 sites in more than 80 countries, most of them low- and middle-

income countries (LMICs). With more than 375 potential new technologies in the pipelines of these PDPs, there is strong promise for a new wave of global health technologies to reach people around the world in the near future. Furthermore, new health technologies that strengthen primary health care responses and help to avoid hospitalizations, strengthen health systems' capacity and efficiency by their nature.

The PDP model has further shown its efficacy in the global response to COVID-19, which makes use of many of the attributes, human capital, and approaches core to PDPs, including innovative partnerships that share the risks and rewards of product development. More directly, PDPs themselves play a critical role in preventing and responding to urgent and emerging health threats, including COVID-19, antimicrobial resistance (AMR), and pandemic preparedness. Addressing these threats promotes global development and security.

Maximizing the impact of the next generation of PDP-driven health solutions hinges on coordinated support from the public, private, and academic sectors, as well as local communities, multilateral organizations, advocates, and more. Addressing issues like more robust, diverse, and flexible funding for PDPs across the full value chain—from epidemiology to discovery, to development, to access—can help fully realize the promise in the pipelines of PDPs. Political will and coordination to reduce barriers to access, harmonize regulatory standards, and commit to the rapid uptake of new health solutions will further broaden and accelerate the impact of PDP-developed products around the world.

With sufficient financial and political investment, PDPs can continue to develop and drive equitable global access to health technologies with the potential to save millions of additional lives, help lift people out of poverty, and improve global security over the coming decades.

66 NEW HEALTH TECHNOLOGIES
HAVE REACHED MORE THAN
2.4 BILLION PEOPLE AROUND THE WORLD



PDPs Emerge to Address Neglected Health Crises and Build Capacity for Current and Future Research in LMICs

The PDP Movement

Some of the world's deadliest and most globally prevalent diseases have historically seen little investment in the pursuit of new and improved tools to prevent, diagnose, and cure them. NTDs affect more than 1 billion people around the world each year, resulting in tremendous morbidity and mortality, severely burdening ill-equipped health systems, and costing developing economies billions annually.¹ Listed separately from the WHO's list of neglected diseases, but subject to the same market challenges, tuberculosis, malaria, and HIV/AIDS are often referred to as "the big three" and have disproportionate and destructive impacts on the world's most vulnerable populations. There were 1.4 million deaths from tuberculosis (TB) in 2019,² 228 million cases of malaria and 409,000 deaths in 2019—two-thirds of which were children under five³—and 38 million people living with HIV/AIDS in 2019.⁴

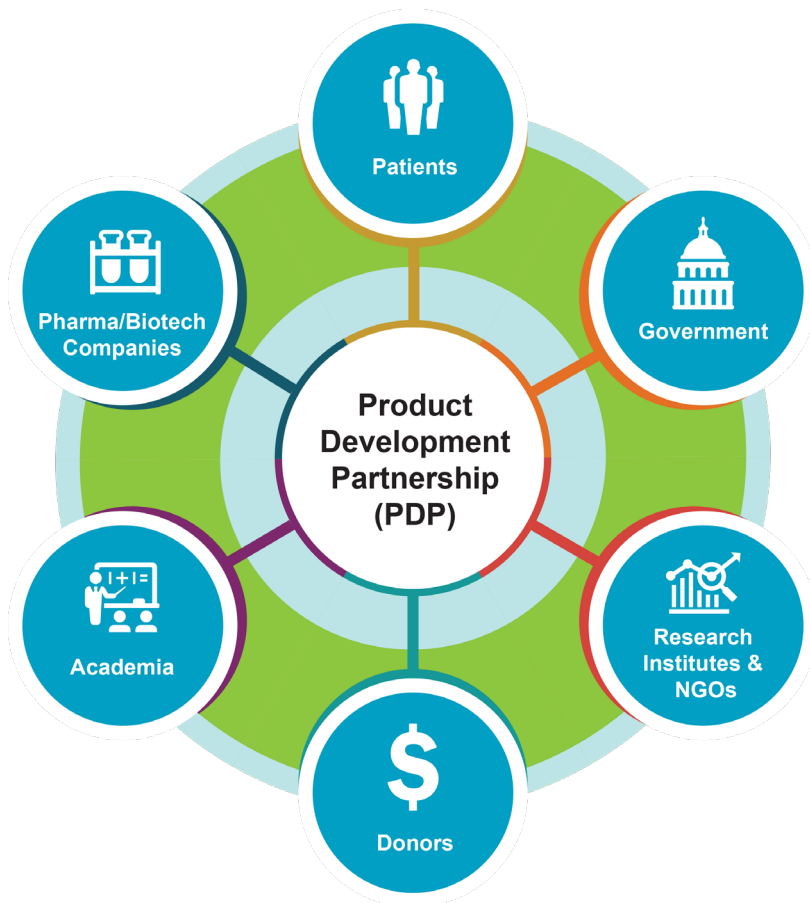
Because neglected diseases, TB, HIV/AIDS, and malaria disproportionately impact the poor, including women and children, there has historically been little financial incentive for private sector product developers to invest in developing the innovative solutions required to mount a sufficient and robust response to them. Without lucrative markets for new technologies, product development for neglected diseases remained stagnant for decades. As evidence, only 16 of 1,393 medicines developed between 1975 and 2000 were for specific diseases in least-developed countries (LDCs).⁵

In the late 1990s and early 2000s, a movement of stakeholders, including researchers, governments, philanthropists, activists, affected communities, global health organizations, and others, came together to forge new models to address these acute global health needs and the gap in market incentives precluding the development of new technologies in these fields. The response to this movement led to a wave of product development partnerships. At least 17 PDPs were founded from 1996–2003,⁶ many of which are members of the PDP coalition.

Needs-Based Approach Yields Unique Strengths

Product Development Partnerships develop new products for people who suffer from diseases and health threats underserved by traditional markets by building partnerships between the public, private, academic, and philanthropic sectors. Their science-based and needs-driven approach uniquely positions them to access resources, broker collaborations, and leverage a global network of public and private partners to efficiently and effectively advance product development. For example, TB Alliance oversees a preclinical regimen

development program, in partnership with Johns Hopkins University, which tests combinations of experimental stage TB drugs, combining drug candidates from multiple sponsors. Similarly, in 2019, MMV launched the Malaria Drug Development Catalyst—a legal and scientific framework that enables smooth collaboration between industry partners to accelerate the development of next-generation antimalarial drug combinations. Product developers allowing experimental stage products to be tested in combination with that of their “competitors” is quite rare, and precisely the type of collaboration PDPs are uniquely capable of brokering.



PDPs not only build partnerships across key strategic sectors, but enable collaboration among partners

To maximize impact, PDPs closely and continuously engage local communities, care providers, researchers, policy makers, advocates, and others to ensure they are designing products for use in the settings where they are most needed, which are often low-resource environments. This means prioritizing product attributes such as low cost of goods, manageable dosing schedules, easily administrable forms of treatments, stability in warm environments without need for refrigeration, sustainable low-footprint methods of production, resistance-breaking mechanisms, and long shelf lives.

For example, to ensure novel HIV prevention products are designed with the needs of these young women in mind, the IAVI conducts Social Behavioral Research with prioritized female at-risk cohorts to assess behavioral factors that facilitate the adoption and use of future long-acting HIV prevention technologies, alone or in combination with long-acting contraceptives.

Efficient Engines of Innovation

Most PDPs engage in virtual product development, retaining direct management, scientific overview, and strategic oversight of research programs, though much of the laboratory and clinical work is performed through partners, external research facilities, and contractors. While most PDPs are highly specialized in their areas of research, they are able to amass unprecedented collections of disease-specific product development knowledge and expertise. PDPs also implement a portfolio approach, utilizing expertise and best practices from the industry in portfolio management and product development to maximize chances of short- and long-term success. Further, PDPs derive funding from both public and private sources, not only governments and philanthropies, but in-kind contributions through collaborations with industry partners, as well as academic and research institutions.

This combination of abilities to operate leanly and flexibly, collaborate with and leverage resources from diverse global partners, and implement expert-level decision-making yields results that are a tremendous value for money. Further, by pooling donor investments, PDPs are able to spread risk across investors and multiple projects within their portfolios. Each donor benefits from the technical expertise of other collaborators, rendering investment in PDPs impactful and relatively safe. As independent entities, PDPs themselves also assume the ultimate risk, as they must deliver results to continue to earn support.

According to the Tufts Center for the Study of Drug Development estimates, the total cost of bringing a new drug to the market surpasses US\$1.3 billion—more if failure and post-approval research and introduction efforts are accounted for in the estimate.⁷ DNDi documented the full costs for its research and development of a new chemical entity at US\$70–225 million, with adaptations of existing drugs costing between US\$7–38 million. These full, actual costs exclude in-kind contributions from industry partners, where there are significant variations according to product, stage of development, and the terms of the partnership.

The PDP model also saves costs through its public funding model. Since PDPs are funded up front by public sources rather than borrowing capital, costs of capital do not apply. In contrast, in the industry model designed by Tufts, the “opportunity cost” of capital invested along the development cycle is a key cost component, accounting for more than half of total costs.

Ultimately, the PDP model minimizes costs by leveraging partnerships and reducing direct investment in overhead, while optimizing scientific capability to speed new product development.

Building Global Capacity for Scientific Research

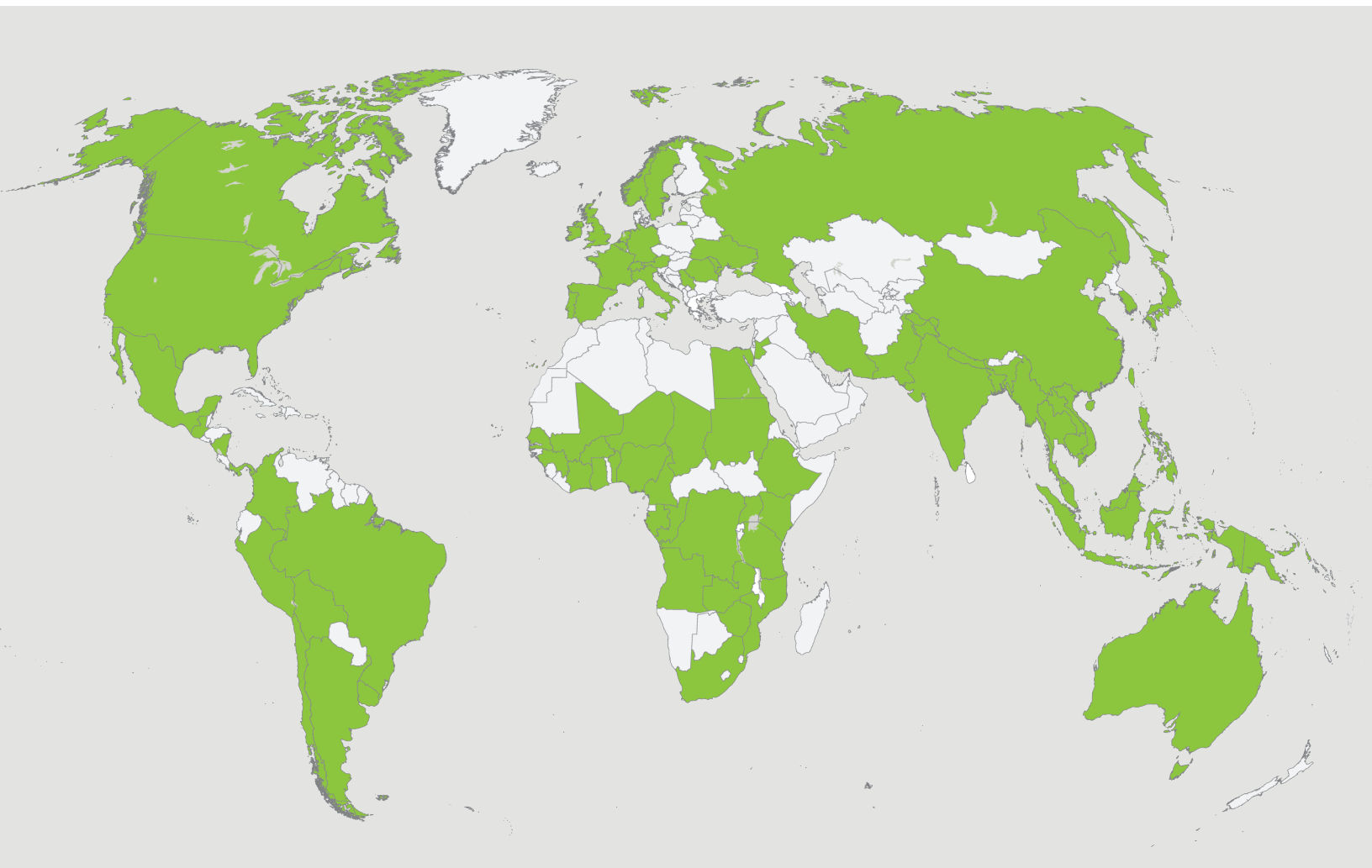
By pursuing their missions, PDPs help build capacity and skills for scientific and medical research and product development. PDP coalition members have performed clinical research at more than 550 sites in more than 80 countries, mostly in low- and middle-income countries (LMICs). Through partnerships, training, infrastructure improvements, and the development of the next generation of researchers, disease experts, and scientific

leaders, PDPs build sustainable platforms for research that will better prepare countries to address current and future health issues and research questions.

Countries like South Africa, Kenya, and Thailand have emerged as global leaders and centers of excellence in neglected disease research through continued participation in PDP-led research efforts. With growing local expertise, these countries are better equipped to define and carry out their own research agendas for various health challenges. Today, the infrastructure in many LMICs that is currently being used to operationalize local efforts to combat COVID-19 has been substantially developed through collaborative product development work with PDPs.

Furthermore, the very products that PDPs develop enhance the performance of health systems. For example, improved treatments avoid hospitalization, and rapid diagnostics enhance primary health care capacity to meet health needs and reduce costs.

COUNTRIES IN WHICH PDP PARTNERSHIPS HAVE HELPED BUILD CAPACITY FOR SCIENTIFIC RESEARCH



PDPs as Drivers of Global Development

The products that PDPs develop are essential to achieve universal health coverage (UHC) as defined by the World Health Organization (WHO) Constitution, and the United Nations' 2030 Sustainable Development Goals.

Successful development of and wide and equitable access to the products in PDPs' portfolios, such as improved vaccines, treatments, diagnostics, and vector controls for poverty-related diseases and TB, HIV/AIDS, and malaria, as well as improved tools for women's and children's health, are necessary preconditions for universal health coverage and the achievement of the following Sustainable Development Goals (SDGs):



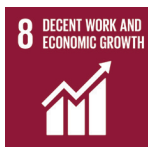
SDG #1: End poverty in all its forms everywhere



SDG #3: Ensure healthy lives and promote well-being for all at all ages



SDG #5: Achieve gender equality and empower all women and girls



SDG #8: Promote sustained, inclusive, and sustainable economic growth, full and productive employment, and decent work for all



SDG #10: Reduce inequality within and among countries



SDG #17: Strengthen the means of implementation and revitalize the global partnership for sustainable development

Neglected Tropical Diseases

(as defined by World Health Organization)

Buruli ulcer

Chagas disease

Dengue and Chikungunya

Dracunculiasis (guinea-worm disease)

Echinococcosis

Foodborne trematodiasis

Human African trypanosomiasis (sleeping sickness)

Leishmaniasis

Leprosy (Hansen disease)

Lymphatic filariasis

Mycetoma, chromoblastomycosis and other deep mycoses

Onchocerciasis (river blindness)

Rabies

Scabies and other ectoparasites

Schistosomiasis

Soil-transmitted helminthiasis

Snakebite

Envenoming

Taeniasis/Cysticercosis

Trachoma

Yaws (endemic treponematoses)

PDP coalition

PDP	Disease Area	Product Type
Drugs for Neglected Diseases initiative (DNDi)	Sleeping sickness (HAT), leishmaniasis, Chagas disease, filarial disease (river blindness), mycetoma, pediatric HIV, hepatitis C, COVID-19.	Drugs
European Vaccine Initiative (EVI)	Diseases of poverty and emerging infectious diseases	Vaccines
Foundation for Innovative New Diagnostics (FIND)	Buruli ulcer, Chagas disease, fever, sleeping sickness (HAT), leishmaniasis, malaria, tuberculosis, COVID-19	Diagnostics
Innovative Vector Control Consortium (IVCC)	Malaria and additional insect-borne disease	Insecticides
IAVI	HIV/AIDS, tuberculosis, COVID-19, emerging infectious diseases, neglected tropical diseases	Vaccines and antibodies
International Partnership for Microbicides (IPM)	Women's HIV prevention, sexual and reproductive health	Drugs and devices
International Vaccine Institute (IVI)	Cholera, typhoid, shigella, salmonella, schistosomiasis, group A strep, hepatitis A, HPV, tuberculosis, HIV, MERS, COVID-19, chikungunya	Vaccines
Medicines Development for Global Health (MDGH)	Neglected infectious diseases	Drugs and vaccines
Medicines for Malaria Venture (MMV)	Malaria	Drugs
PATH	Cancer, diabetes, diarrheal diseases, early childhood development, Ebola, epidemic preparedness, heart disease, HIV/AIDS, HPV, influenza, Japanese encephalitis, malaria, maternal and newborn care, meningitis, neglected tropical diseases, nutrition, pneumonia, polio, sexual and reproductive health, tuberculosis, water sanitation and hygiene	Devices, diagnostic, drugs, and vaccines
TB Alliance	Tuberculosis	Drugs
Tuberculosis Vaccine Initiative (TBVI)	Tuberculosis	Vaccines



Ensuring Continued Product Development and Health Impact

The needs-based, science-led, and patient-first approach of PDPs has led to the successful development and introduction of a diverse set of new health solutions around the world—66 new products since 2010 from this PDP coalition alone. When evaluating past performance, as well as ongoing and future challenges, several critical success factors emerge as needed to continue and expand the work and impact of PDPs, and to support the next wave of product development and introduction. This work will require strong commitments from many sets of actors.

As the world's experience with COVID-19 has reinforced, pandemics are not siloed. Diseases may have synergistic impacts, as in the cases of TB and HIV or COVID-19. Further, the impact of any endemic or pandemic disease can affect entire health systems, straining its resources and the ability to control others. For example, WHO estimates that the number of people developing TB could increase by more than 1 million per year between 2020–2025 due to COVID-19.⁸ A well-rounded response to the health threats PDPs are focused on confronting can enable a cascade of global health and development gains.

The global response to COVID-19 has also illustrated the true scope of what is needed to mount a speedy, equitable, and thorough response to a resilient and widespread disease. As with COVID-19, any realistic attempt to eradicate TB requires a tremendous global financial and political commitment to discover and develop new technological modalities and support their widespread and equitable introduction and uptake.

The factors below will be critical to realize a robust and effective response to neglected and emerging disease threats and ensure continued innovation from the PDPs who drive these advances.

Sustained, Substantial, and Flexible Investments

To continue to deliver innovation at a rapid pace and large scale, PDPs require sustained, diverse, and flexible funding to increase their impact on global health and development. With growing and maturing portfolios, PDPs need increased investment to bring technologies in development across the finish line and make them accessible to the most vulnerable groups and realize the promise of their pipelines.

To account for the relatively lengthy timelines of medical technology development and attrition rates, PDPs rely on stable long-term funding and investment across every stage of the research process—from discovery and epidemiology to clinical trials, support for regulatory processes, distribution and uptake—and sufficient latitude to shift funding across their pipelines to prioritize the most promising and impactful research programs.

Product development efforts carry high rates of attrition and considerable timelines, even for nonprofits. Among drug candidates that reach Phase I clinical trials—a significant milestone unto itself—fewer than 10% will ultimately achieve regulatory approval and reach the market.⁹

Those who invest in product development should consider that continued investment in new generations of product candidates is required to mitigate attrition and continually improve upon standards of care. This means that investment is required in every stage of the development pipeline to ensure new candidates are continually entering the pipeline. Even after a product is successfully developed, funding to support work to ensure widespread access to that product is needed. Successful product development and deployment may require investment over a decade or more, but will ultimately yield a high return on investment, as exemplified by the many breakthroughs detailed in this report.

While the discovery and development of a new medical technology takes several years, investors often don't have to wait for the approval of a safe and effective product to see returns on investment. PDPs develop valuable technologies, infrastructure, expertise, and networks that can create impact long before the product is developed. The utilization of PDP capabilities to accelerate the COVID-19 research and development (R&D) response is a point in case.

Overall, donors should be willing to invest early and with foresight rather than simply responding to crises or only at most urgent times of need. While a longer-term investment may be considered more difficult to justify politically, the COVID-19 pandemic is a stark reminder that waiting for a major outbreak before acting not only increases death and suffering but is also more expensive and potentially politically damaging.

PDPs need enough flexibility in the use of funding to be able to apply funding to the most promising and best performing programs within their portfolios. Such pivots are often required, especially earlier in the product development process. The provision of flexible funding can create more value for money, as the funding can be aligned to new scientific insights and geared toward the most promising approaches. Flexibility strengthens the ability to create products that address the right needs and are acceptable, affordable, and accessible. Furthermore, flexibility allows PDPs to pivot toward new emerging threats like new pandemics and AMR, when needed, achieving important dividends.

Consistent communication between PDPs and donors is key to build and maintain donor confidence in PDPs to be highly effective stewards of funds, and to ensure goals and timelines align.

INNOVATIVE FINANCE MECHANISMS (IFMs) AND INCREASED PRIVATE SECTOR ENGAGEMENT

New innovative financing mechanisms are needed to incentivize increased participation in global health product development by the private sector.

One of the most well-established IFMs to incentivize global health innovation is the Priority Review Voucher (PRV); more than 30 have been awarded.¹⁰ The PRV awards a voucher to an organization that earns FDA approval of a new treatment for a neglected or rare disease.

The voucher entitles the holder to priority review a drug of their choice, and the voucher may be used by its recipient or be sold. By using a PRV, a product developer can reach the market sooner with its innovative products. For-profit developers can use the voucher on a drug with greater market potential. This creates an incentive for them to earn PRVs by developing products for neglected diseases. PDPs that earn PRVs typically sell them to for-profit developers to help finance future research or access programs.

Alone, this is not sufficient to incentivize the level of increased engagement from the private sector needed to further support and galvanize global health innovation. The attrition rate of product development and the length of time between initial investment and potential payoff means the PRV is not a sufficiently compelling incentive for all potential product developers.

To fully support and incentivize investment in global health research and development, especially from the private sector, a larger, better-rounded portfolio of IFMs is required. A diverse menu of IFMs would offer different mechanisms designed to incentivize various kinds of work, throughout the full development chain. Additionally, a diversity of “push” mechanisms (lowering the cost of R&D) and “pull” mechanisms (establishing stronger demand for or return on investment) are needed to meet the diverse needs of product developers and stakeholders.

INCREASED ENGAGEMENT AND INVESTMENT FOR ENDEMIC COUNTRIES

To fully unlock the potential of PDPs, increased investments are needed from all parties and sectors, including BRICS and LMICs. Many of the deadliest and most damaging pandemics are concentrated in some of the world’s fastest growing economies. Domestic health care investments have long been understood as yielding a high return, and the financial and health benefits of new health technologies are immense.

In the case of neglected diseases, the current state of treatment, prevention, and diagnosis is often sufficiently antiquated and inadequate that the poor standard of care itself allows for an even more pronounced benefit from the introduction of modern tools. Investing in product development also builds local capacities and skills to address future research opportunities.

Despite the clear benefits of such investments, the overwhelming majority of countries around the world are not investing enough resources into global health product development. For example, at the United Nations High Level Meeting on Tuberculosis in 2018, member states committed to increasing their overall global investments in TB research and development to \$2 billion,¹¹ in order to close the TB research funding gap, estimated at \$1.3 billion annually.¹² Despite publicly making this commitment—and receiving praise for doing so—exceedingly few countries are actually meeting this target. Nations around the world with the economic capacity to invest in long-term R&D for health care product development need to considerably increase their commitment to global health product development.

Regulatory Harmonization

Regulatory harmonization is needed to accelerate the global availability of PDP-developed products.

Earning approval and registration of new products in markets around the world is challenging and complex; requirements and procedures vary greatly between countries. Further, many countries have distinct regulatory requirements, but very little capacity to conduct regulatory reviews, leading to lengthy or poorly understood processes.

National and regional health bodies need to work with regulators and multilateral organizations, including WHO, to accelerate and expand efforts to harmonize regulatory requirements to enable a coordinated review of products by multiple countries in faster and more streamlined processes. Relieving these barriers can also serve as a financial incentive for donors and product developers. Enabling lifesaving products to develop more rapidly and reach larger numbers of patients results in a quicker and larger return on investment, both financially and in health impact.

Examples of innovation and progress in harmonizing and evolving regulatory standards include:

- IAVI has worked with the East African Health Research Commission (EAHRC) to develop a policy guide to standardize the research ethics review process in six African countries to ensure trial safety and timely approval. Regulatory approval times were reduced by 30% for IAVI-sponsored protocols due to enhanced regulatory approval systems in Kenya, Uganda, and Zambia. This standardized review process is expected to have benefits for other clinical research in the region.
- TB Alliance has been instrumental in evolving regulatory standards and approaches relating to the development of combination therapies that include multiple new agents. By working with stringent regulatory authorities, TB Alliance has helped pave the way for the more rapid development and regulatory review of new combination therapies.
- IAVI has partnered with Africa Medicines Regulatory Harmonisation Initiative (AMRH), who improves access to quality, safe, and efficacious medicines by providing an enabling regulatory environment for pharmaceutical sector development in Africa. As a member of the AMRH partnership, IAVI is involved in discussions that will help shape how the African Medicines Agency (AMA) is structured, and how it will streamline regulatory requirements across Africa for the approval of clinical trial protocols, especially of biological products, i.e., vaccines and broadly neutralizing antibodies (bnAbs). Moreover, this regional standardization process will leverage existing regulatory expertise within the region for complex regulatory approvals for clinical trials and dossiers for product licensure to strengthen the regulatory authorities in other parts of Africa.

Expansion of Access-Related Work

Increased investment and cross-sector collaboration are needed to ensure the widespread adoption, delivery, and implementation of new health technologies.

The impacts of new technologies—health, economic, or otherwise—are not achieved until those products reach the people who need them. In the current environment, and with more products in—or soon to reach—the market, PDPs are becoming increasingly active, relied upon, and skilled to drive and facilitate widespread and equitable access to the technologies they develop. Thus, PDPs have learned to take an end-to-end approach to product development, partnering with local health systems and communities, multilateral organizations, donors, and advocates to ensure technologies reach the end-user.

This end-to-end commitment to access starts with an in-depth understanding of the environments in which products will be used, the practical and resource-related challenges to delivery and uptake, and the target product profiles that take these challenges into account. It culminates in driving innovative partnerships with manufacturers and working with local health systems to help enable the smooth, rapid, and responsible uptake and use of new technologies.

Successfully achieving global access to health solutions, especially in LMICs, requires dedicated investment and coordination across stakeholder groups. Thus, PDPs, health systems, multilateral organizations, donors, and advocates must further prioritize, coordinate, and invest to ensure products are affordable, available, and accessible.

For PDPs, that means engaging manufacturers, local communities, and experts to ensure they are developing the right products, engaging downstream partners during development and access processes, catalyzing market competition, and setting strict parameters around affordability. PDPs approach the challenges to access with the same unconventional thinking and commitment to innovation they bring to research and product development, and to marketing and delivering products.

For governments and national health programs, committing to facilitate access to new technologies means preparing for new product introduction in advance, issuing clear and prompt guidance, investing in training and familiarizing health service providers and local communities with upcoming and newly available products and policies, and implementing accurate forecasting and timely procurement processes.

Donors should support critical access work to ensure the products they have helped develop reach those in need and make a maximal public health impact, yielding the greatest possible return on investment. Multilateral organizations should support the rollout of new products, update guidelines in a timely manner, and endorse new products that offer clear health benefits. It is also critical that communities be empowered to demand access to affordable new technologies.

ENGAGING LOCAL COMMUNITIES

Local communities are crucial to successful product development and implementation. By engaging with and earning the trust of local communities, research is carried out more quickly, soundly, and efficiently. Communities engaged in the development of new products are also more willing to adopt and use products once approved and available. When properly engaged and respected, community-level partners can become a new product's most important advocates. Many PDPs operate community engagement programs connected to their research. Such programs partner with local communities and confer significant benefits, including:

- **Improved research and scientific literacy among local populations**
- **Greater sensitivity to issues that may delay or reduce participation in trials**
- **Mechanisms to mediate potential conflicts**
- **Increased awareness of diseases among communities and improved health-seeking for diagnosis and treatment**
- **Development of local advocates for medical product development and access to new products**
- **Inclusion of local leaders and already influential voices**
- **Primed and educated market for new products upon availability**

In the access phase, community health delivery programs are key PDP partners to increase access to health tools to the most vulnerable and most difficult-to-reach populations.



Photos by, left to right: John-Michael Maas;
John-Michael Maas; Taharqa Elnour

Beyond Neglected Diseases: PDPs' Critical Role in the Future of Health Care, Global Development, and Security

While the focus of PDPs remains on developing new health solutions for people underserved by traditional market incentives, their work is increasingly relevant to current and emerging health crises that threaten the entire world, not just LMICs. PDPs are equipped to help prevent and respond to health threats and are directly contributing to the efforts aimed to address many of them. Additionally, the success of PDPs yields benefits in global development and advances in product development and distribution strategies that align with recognized health and development targets and goals, and have a broad impact on many facets of global health.

PDP Contribution to Global COVID-19 Response

The COVID-19 pandemic has served as a wake-up call to the world. Regions unable to cope suffer from waves of death and disability and major impacts on local and regional economies. This is the power of pandemics. In addition to the direct impact of COVID-19 cases, its residual impacts threaten the hard-won progress made against malaria, tuberculosis, and many other neglected diseases over the past decade.

For example, based on modelling data, WHO estimated potential disruptions in access to core malaria control tools during the COVID-19 pandemic in 41 countries could have resulted in up to 769,000 malaria deaths in Sub-Saharan South Africa in 2020, twice the number of deaths reported in the region in 2018, representing a return to malaria mortality levels last seen in the year 2000. Of these, approximately 70% were forecast to have been among children under the age of five.¹³

Thankfully, despite the challenges, malaria-endemic countries and global health partners, including PDPs, mobilized, and over 90% of lifesaving malaria intervention campaigns scheduled for the year are on track across Africa, Asia, and the Americas.

The coordinated efforts to accelerate product development, surge of political will, rapid deployment of funding and other resources by governments, advanced market commitments, and other tools and characteristics of the global response to COVID-19 make use of established PDP approaches and illuminate the true potential of PDP-style research. In fact, many of the COVID-19 vaccines in development have built on vaccine technologies developed for HIV/AIDS.

The predominantly need-driven response being applied to COVID-19 is expected to result in vaccines and other new products developed in record time. The substantial progress PDPs have achieved against malaria, tuberculosis, HIV/AIDS, and other neglected diseases could be exponentially increased if similar political will, urgency, and resources were applied to PDP efforts.

In order to address COVID-19 and protect gains in poverty-related and neglected diseases, the following PDPs have moved swiftly to contribute to the global response to COVID-19.



Drugs for Neglected Diseases *initiative*

- Co-launched and hosts the COVID-19 Clinical Research Coalition, which seeks to accelerate research on the prevention and treatment of COVID-19, leverage coalition members' expertise to fast-track research, promote open sharing of data, and champion equitable and affordable access. The Coalition currently has 168 institutional members with more than 265 representatives from 59 countries.
- Coordinating the ANTICOV clinical trial consortium of 26 prominent African and global R&D organizations. The trial aims to identify treatments to treat mild and moderate cases of COVID-19 early and prevent spikes in hospitalization that could overwhelm fragile and already overburdened health systems in Africa. The clinical trial will be carried out at 20 sites in 13 African countries.
- Along with MMV, made available a Pandemic Response Box free of charge to researchers. This box contains 400 diverse drug-like molecules active against bacteria, viruses, or fungi, allowing them to be tested for potential use in the COVID-19 response.
- Advocating for public interest R&D and equitable access for COVID-19 R&D.



Because diagnosis matters

- Partnered with The Global Fund to Fight AIDS, Tuberculosis, and Malaria to co-convene the *Access to COVID-19 Tools (ACT) Accelerator* Diagnostics Pillar, designed to accelerate the development, production, and equitable access to COVID-19 tests, treatments, and vaccines. Highlights of this initiative include:
- Building a global pipeline tracker of critical diagnostic tests.
- Launched evaluations of prioritized tests—initial results currently available online.
- A multi-country evaluation platform to test diagnostics, online training of more than 18,000 health care workers across more than 100 countries (MOOCs), and mapping of COVID-19 supply chains.
- Issued a formal call to scale research and manufacturing of antigen rapid diagnostic tests.
- Member of COVID-19 Clinical Research Coalition, which seeks to accelerate research on the prevention and treatment of COVID-19.



- With many partners, is supporting the development of several COVID-19 vaccines via the TRANSVAC (funded by European Commission) infrastructure, which offers free scientific-technical and other services to accelerate the development of urgently needed vaccines for global health.



- Collaborating with Merck (known as MSD outside the United States and Canada) to develop an investigational vaccine against SARS-CoV-2 to be used for the prevention of COVID-19; a Phase I clinical trial was started across seven sites in the United States in November 2020.
- Collaborating with partners to accelerate the development of affordable and accessible antibodies for COVID-19 therapy. Neutralizing antibodies identified from convalescent donors provide strong protection against SARS-CoV-2 infection. These monoclonal antibodies are advancing to clinical studies in early 2021.



- Providing technical guidance on contact tracing to COVID-19 response staff in KwaZulu-Natal, South Africa.
- Facilitating discussions to engage, support, and educate adolescent girls and young women on addressing gender-based violence, maintaining HIV prevention efforts, and contraception use during lockdowns and pandemic conditions.



- Facilitating adoption of novel dual-active ingredient bed nets (through New Nets Project), which can help halve malaria deaths in Africa during COVID-19.¹⁴



- Working with INOVIO on clinical development of a COVID-19 vaccine. The vaccine candidate entered clinical trials in South Korea in June of 2020.
- Supporting clinical sample analysis of Genexine's COVID-19 vaccine candidate in South Korea.
- Working with the National Institute for Biological Standards and Control and the Korea Centers for Disease Control and Prevention to establish standard material to assess vaccine efficacy in an internationally agreed unit.
- Supporting clinical trial site preparedness in four African and Asian countries to potentially support future COVID-19 Phase III efficacy vaccine trials.
- Conducting preclinical studies for COVID-19 vaccines and therapeutics with Sumagen and Celltrion in South Korea.
- Supporting efficacy tests of COVID-19 vaccine candidates in collaboration with the Korea Mouse Phenotype Consortium in South Korea.



- Executives serve on Commonwealth of Australia's Industry and Science COVID-19 committee, chair the Doherty Vaccine Advisory committee, and serve as an executive member of the ASCOT trial, evaluating multiple experimental therapies for SARS-CoV-2 infection.
- Published content on inappropriate use of ivermectin for SARS-CoV-2 infection.



- Along with DNDi, made available a Pandemic Response Box free of charge to researchers. This box contains 400 diverse drug-like molecules active against bacteria, viruses, or fungi, allowing them to be tested for potential use in the COVID-19 response.
- Made available a second COVID Box, containing a standard set of compounds with known or predicted activity against COVID-19, shipped free of charge, to accelerate research into treatments for COVID-19 and other SARS coronaviruses.
- Co-leads of WHO Supply and Commodity Workstream for the malaria COVID-19 response, working with manufacturers, procurement partners, and international organizations to identify drug supply chain bottlenecks, safeguard malaria drug supplies, and help ensure the production of critically needed malaria medicines during COVID-19.
- Is partnering on clinical studies investigating already approved medicines as options for a COVID-19 therapy and is a member of COVID-19 Clinical Research Coalition, which seeks to accelerate research on the prevention and treatment of COVID-19.
- Is contributing its expertise to various high-level working groups convened by the WHO Global Malaria Programme, the Wellcome Trust, NIH, the Bill & Melinda Gates Foundation, and the Coalition for Epidemic Preparedness and Innovation (CEPI).



- Working with donors, vaccine developers, researchers, and countries to accelerate the development of COVID-19 vaccines, support and define vaccine supply and distribution, and ensure equitable access and delivery once a vaccine is available. Work in this area continues to evolve and has illustratively included the following:
 - The MDHT program in partnership with CVIA's Chemistry, Manufacturing and Controls (CMC) team have conducted several COVID-19 technical assistance projects related to manufacturing and supply.
 - As Gavi's COVAX Facility takes shape, PATH is providing policy and financing advice on different aspects of its design and implementation.
 - PATH has supported several manufacturers to develop applications to CEPI's COVID-19 calls for proposals.
 - Prioritizing working with countries on continued routine immunization so that critical disease prevention gains do not backslide due to COVID-19 and worsen the public health crisis.
 - PATH is applying its deep vaccine development, regulatory, and clinical experience and expertise to help accelerate the development of safe, effective, and scalable COVID-19 vaccines.
- Member of COVID-19 Clinical Research Coalition, which seeks to accelerate research on the prevention and treatment of COVID-19.
- PATH is engaging with countries to support readiness on the ground to introduce and deliver COVID-19 vaccines when they become available.



- In partnership with Harvard University, evaluating a library of compounds for the potential to be effective in the treatment of COVID-19.
 - Synthesizing specific inhibitors it believes will be active against SARS-CoV-2.
 - Member of COVID-19 Clinical Research Coalition, which seeks to accelerate research on the prevention and treatment of COVID-19.
 - Provided technical and/or fundraising support to several projects, evaluating the potential efficacy of currently approved and experimental TB vaccines against the severe COVID-19 disease.
 - Investigating the potential of new vaccine technologies and platforms developed under COVID-19 programs for potential use in TB vaccine research and development.
-

Antimicrobial Resistance

Antimicrobial resistance (AMR)—which occurs when microorganisms no longer respond to the drugs designed to treat them—is emerging as one of the critical health issues of our time. From a development perspective, drug-resistant infections have the potential to cause a level of economic damage similar to the 2008 financial crisis, causing low-income countries to lose more than 5% of their GDP and push up to 28 million people into poverty by 2050.¹⁵

New, novel therapies are required to overcome the growing number of drug-resistant infections. Additionally, improved therapies for NTDs that are simple, short, and easy to administer and take can help prevent the emergence of new drug resistance by reducing the frequency of patients defaulting on treatment mid-course.

PDPs are among the leaders in efforts to combat growing resistance to drugs that play pivotal roles in global health and global health security.

- Tuberculosis is estimated to cause a third of all AMR deaths globally.¹⁶ Advances like TB Alliance's newly approved regimen to treat XDR-TB and treatment-intolerant or nonresponsive multidrug-resistant pulmonary TB represent significant progress against AMR. Further, with additional late-stage novel treatment regimens for drug-resistant and drug-sensitive TB in its pipeline, TB Alliance is poised to expand the pool of drug-resistant patients who can access its new treatments and shorten and simplify therapy for drug-resistant TB, making it easier to comply with therapy, and thereby curbing the initial development of drug resistance.
- Historically, in South East Asia, antimalarial drug resistance has emerged to every effective medication. Today, several artemisinin combination therapies (ACTs), which are a first-line treatment for malaria, are also failing in this region, with resistance to

both artemisinin and partner drugs having been identified. Most recently, markers of partial artemisinin resistance have also been reported in Rwanda. Though at the time of writing ACTs continue to cure malaria in Africa, if resistance to artemisinin (or partner drugs) were to take hold on the continent, where the malaria burden is highest, it could lead to failure of the ACTs, which would pose a major threat to malaria control and elimination efforts. MMV and partners are prioritizing the development of new therapies by identifying molecules with novel mechanisms of action and activity against all known resistant parasite strains. The new molecules either kill the parasite quickly, stay in the blood long enough to ensure complete parasite clearance, and/or can protect against subsequent reinfection. These compounds could form part of a Single Exposure Radical Cure (SERC)—a single dose combination expected to ensure better compliance.

- IAVI is developing preventive vaccines and other immune-based approaches to combat drug-resistant infections including against HIV and TB. IAVI is also working to translate technologies used to discover and optimize bnAbs for HIV, and to discover and develop antibody-based therapies to treat bacterial infections from shigella, an enteric pathogen with rising drug resistance. These antibodies have therapeutic potential for overcoming antimicrobial resistance.
- The widespread emergence of pyrethroid resistance is a threat to the preservation of the great progress made against malaria by the use of Long Lasting Insecticidal Nets (LLINs). In response to the need to develop new technologies to ensure the continued effectiveness of nets in the fight against malaria, IVCC, with partners, developed Interceptor® G2—a dual active ingredient (AI) bed net, which was a major advance in combatting insecticide resistance. Dual AI bed nets help address the growing resistance to pyrethroids. Through their New Nets Project (NNP), IVCC continues to develop and test additional dual AI nets, which could potentially reach the market in the coming years to overcome insecticide resistance and help eradicate malaria.
- Together with the WHO, DNDi launched the Global Antibiotic Research and Development Partnership (GARDP) in 2016, a new organization based on the PDP model. GARDP is a not-for-profit R&D organization that addresses global public health needs by developing and delivering new or improved antibiotic treatments, while working to ensure their sustainable access.

Promoting the Health of Women and Girls

Poverty-related diseases and NTDs severely impact all, but they disproportionately affect women and girls. Therefore, initiatives to tackle NTDs, AIDS, TB, and malaria significantly benefit women's health, both directly and indirectly. The reasons poverty-related diseases and NTDs most severely impact women include:

- Biological and physiological factors leading to increased vulnerability to particular pathologies
- Sociocultural factors impacting exposure to pathogens and access to care
- NTDs causing disfigurement and disability have a disproportionately negative impact on employability and marriageability of affected women
- Women and girls are more likely to have to give up jobs or drop out of school to take care of a sick family member

PDPs develop products that address the health needs of women and girls both directly and indirectly, including the following:

- IPM's dapivirine ring is the first long-acting HIV prevention product and is designed to help address women's unmet need for new methods they can control, given the persistently high rates of HIV they face, especially in Sub-Saharan Africa.
- PATH and Sinapi biomedical, a South African medical device manufacturer, are advancing the Ellavi UBT—a low-cost, fully assembled uterine balloon tamponade (UBT) designed specifically for use in low-resource health facilities. UBTs are an effective, safe, and easy to use intervention to manage severe postpartum hemorrhaging, the leading cause of maternal death.¹⁷
- DNDi has identified that expanding access to pediatric formulations creates a new entry point for progress on maternal health and access to medical care for neglected women. Indeed, for several diseases such as Chagas disease and HIV, efforts are being scaled up for active screening of girls and women of childbearing age and prevention of mother-to-child transmission: the availability of treatments for babies born with the disease provides a new impetus to identify and better serve mothers left behind by these efforts.
- MMV is working with its extensive network to ensure that quality assured sulfadoxine pyrimethamine (SP), a potentially lifesaving intervention which protects pregnant women in Sub-Saharan Africa against malaria, is made available to all pregnant women. Efforts include diversifying and promoting local manufacturing in malaria-endemic countries.
- IAVI facilitates equitable participation of women in clinical studies to ensure the products that are being developed are safe, effective, accessible and acceptable, especially for women. IAVI has been able to lower barriers to female participation by ensuring gender- and family-friendly settings for counseling and health services at clinical sites. This approach, embedded in a strong community engagement program, has improved the safety, recruitment, enrollment, and retainment of

women in HIV prevention trials and epidemiological studies. Today, females make up an average of 50% of trial participants at IAVI partner sites. 107 community and health workers have been trained on gender integration in HIV vaccine research, and approximately 400,000 women and girls in Africa have received counseling services and health care referrals for treatment and care.

- Other products that improve diagnosis, prevention, and treatment of NTDs as well as AIDS, TB, and malaria are not designed specifically for women, but have significant impacts on the health of women and young girls, both indirectly and by reducing the indirect impact of these pandemics on women. The positive impact of improved health, stability, prosperity, and security yielded by PDP innovation reaches global levels, but starts most immediately within the family unit.

Other Fast-Emerging Threats and Twenty-First Century Health Challenges

PDPs are also making substantial progress against other looming global health threats and challenges facing the entire world, not just LMICs. In addition to advancing key technologies, approaches, and models utilized, PDPs can be instructive to health systems, product developers, and stakeholders outside the PDP environment.

PANDEMIC PREPAREDNESS

The COVID-19 pandemic has taught the world expensive lessons about the benefits of proactively identifying, responding to, and containing pandemics. PDPs are leading some of the world's most effective pandemic preparedness and response efforts, including the following:

- During the 2018 DRC Ebola outbreak, PATH partnered with the Ministry of Health (MOH) to streamline the collection of high-quality data to understand and process information, and make quick, data-led decisions. Using the existing National Health Information System based on District Health Information System 2, PATH created a dashboard for monitoring Ebola cases. Updated daily, this dashboard provided real-time information on important indicators such as the epidemic curve, case data, contact-tracing, treatment, and timelines. The Minister of Health and his team used this dashboard to stay informed at all times. PATH is also working alongside ministries of health to share, analyze, and leverage reliable data using integrated digital systems that span emergency operating systems, clinics, and laboratories during the current pandemic, standing up data visualization dashboards and mapping tools. Armed with real-time data, decision-makers can develop a targeted response and therefore slow the spread of a virus like COVID-19.
- In Vietnam in 2018, PATH and the CDC supported the MOH in establishing a reporting portal to collate AMR WHONET data files from 16 hospitals and provided technical assistance to hospitals to ensure completeness of the data. The portal underwent several iterations to incorporate feedback from users, international experts, and policy and decision-makers. The result is a revised version in 2020 that

integrates powerful visualization and data analysis functions that are user friendly and useful. PATH also worked with two hospitals to pilot initiatives to prevent multidrug-resistant infections and enhance the appropriate use of antibiotics.

- In 2019 MMV and DNDi launched the Pandemic Response Box, a collaborative open-access project that aims to accelerate the discovery of new treatments for life-threatening pandemic diseases by providing researchers free access to 400 diverse compounds. In the first 18 months of the project, 116 labs received the Pandemic Response Box, of which 13 are evaluating compounds for activity against COVID-19. MMV made available a second COVID Box containing a standard set of compounds with known or predicted activity against COVID-19, shipped free of charge, to accelerate research into treatments for COVID-19 and other SARS coronaviruses.
- Digital Square, a PATH-hosted initiative, is co-leading the new OpenHIE COVID-19 Task Force, which supports collation of information relating to data standards and data exchange relevant to the pandemic response. The goal of this task force is to ensure that rapidly deployed solutions can be integrated into national digital health architectures and contribute to long-term health system improvements.
- IAVI is developing vaccines for Lassa fever, Marburg hemorrhagic fever, and Ebola Sudan.

Further investment in pandemic preparedness could support additional initiatives around the world to enable countries to better prevent and respond to future health threats, minimizing their health and financial impacts.

DIGITAL MEDICINE

The rapid expansion of access to telecommunications technology has the potential to help close health gaps in low resource settings. Further, recent experiences with COVID-19 have revealed the need for and applicability of digital medicine and virtual health technologies. PDPs have gained substantial experience and expertise working in low-resource settings, making use of and developing digital technologies to, among other uses, track disease spread, conduct contact tracing, connect patients and care providers, and encourage compliance with treatment. PDPs are well suited to offer guidance in making use of existing digital health technologies, as well as to shape the types of innovations that are most urgently needed.

For example, DNDi is piloting a global SIM card service designed by FIND to send clinical trial data securely from several clinical sites, which enables the secure sharing of data where connectivity is unreliable. SIMplicity provides cost-effective and dependable mobile data capabilities for diagnostics and other connected healthcare devices, via global SIM cards.

INTRODUCTION TO AND EXPERIENCE IN LMIC MARKETS AND HEALTH SYSTEMS

Full eradication of diseases of poverty and significant reduction in communicable disease spread in low-resource settings will not alleviate the world's health burdens. As regions make health and economic gains, causes of mortality and morbidity shift. LMICs are future

markets for the health interventions commonly developed for and used in high-income countries today. Expertise in navigating the health, regulatory, and delivery systems of these markets will be integral to facilitate future growth of the pharmaceutical industry as well. By partnering with PDPs and adopting elements of their strategies, private sector product developers can gain experience and insight that can unlock future growth opportunities and allow those organizations to seize them.

COST OF HEALTH CARE AND UNIVERSAL HEALTH COVERAGE

With health care costs continuing to rise, maintaining and expanding the availability of affordable, essential medical technologies is precarious, yet critical to achieving universal health coverage and delivering the Sustainable Development Goals, notably SDG #3, to “ensure healthy lives and promote well-being for all at all ages.” This includes the target of ending the epidemics of HIV/AIDS, TB, and malaria.

The costs of diseases PDPs develop tools to combat are staggering—both in terms of expenditure to control them and lost potential for economic growth and development. Direct costs to governments include maintenance, supply, and staffing of health facilities; purchase of drugs and supplies; public health interventions (for example, in the case of malaria, insecticide spraying or distribution of insecticide-treated bed nets); lost days of work with resulting loss of income; and lost opportunities for joint economic ventures and tourism.

A 2017 report predicted the overall cost of TB from 2015–2030 could reach \$983 billion. Some African countries face losing 3% of GDP annually due to TB alone.¹⁸ Direct economic costs of malaria have been estimated to be at least US\$12 billion per year. The cost in lost economic growth is many times more than that.¹⁹

By developing cost-effective treatments for common diseases, health care costs can be better controlled. Beyond prevention, addressing health problems rapidly and effectively is the most cost-effective approach to health care; therefore investing in the products and pathways to do so is prudent. PDPs’ commitment to reducing the cost of new therapies through innovation and focusing on the most cost-effective interventions codifies this principle within their approach.

**TUBERCULOSIS ALONE IS ESTIMATED TO COST
THE GLOBAL ECONOMY NEARLY \$1 TRILLION
OVER THE NEXT 15 YEARS, 2/3 OF WHICH
WILL BE IN THE G20.**



Conclusion

PDPs have proven to be effective and efficient product developers. Since 2010, PDPs in this coalition have developed and introduced 66 new health technologies, which have led to significant progress against some of humanity's oldest and deadliest pandemics. PDP-developed products have reached more than 2.4 billion people around the world. PDPs minimize product development cost and develop products that yield significant financial and health benefits, making investment in PDPs a sound strategy for partners looking to improve global health, catalyze global development, and uplift vulnerable populations, including women and children.

Current PDP pipelines are stronger than ever. With more than 375 products in PDP coalition pipelines, roughly 25% of which are in late-stage development, PDPs are poised to introduce a new wave of global health technologies in the near future. Coordinated investment, political will, and cross-sector partnerships are critical to ensure that key new health tools are developed and made widely and equitably accessible for all.

While PDPs' focus remains primarily on diseases of poverty and NTDs, the approaches and skills of PDPs are broadly applicable to other health threats. PDPs are making use of their expertise, portfolios, and partner networks to forge progress in response to current and looming global health threats, including COVID-19 and AMR. PDPs also possess valuable experience developing and introducing pandemic preparedness and digital health tools, and navigating health care and regulatory systems in markets around the world.

COVID-19 may be the defining global health threat of our era. The global response to COVID-19 makes use of many of the attributes and approaches core to the PDP model, particularly the need-driven, partnership-based global approach. In many ways, the global response to COVID-19 reflects the potential of the PDP approach when bolstered by a historic allocation of resources and political will from a wide array of partners and investors.

The concrete successes of the PDP model underscore the need for global health stakeholders to increase their support for and investment in PDPs, as doing so efficiently and meaningfully accelerates humanitarian, economic, development, and security goals. Development and widespread use of the technologies developed by PDPs are a prerequisite to achieving development targets at every level, from national health and economic growth agendas to the internationally adopted 2030 Agenda for Sustainable Development.



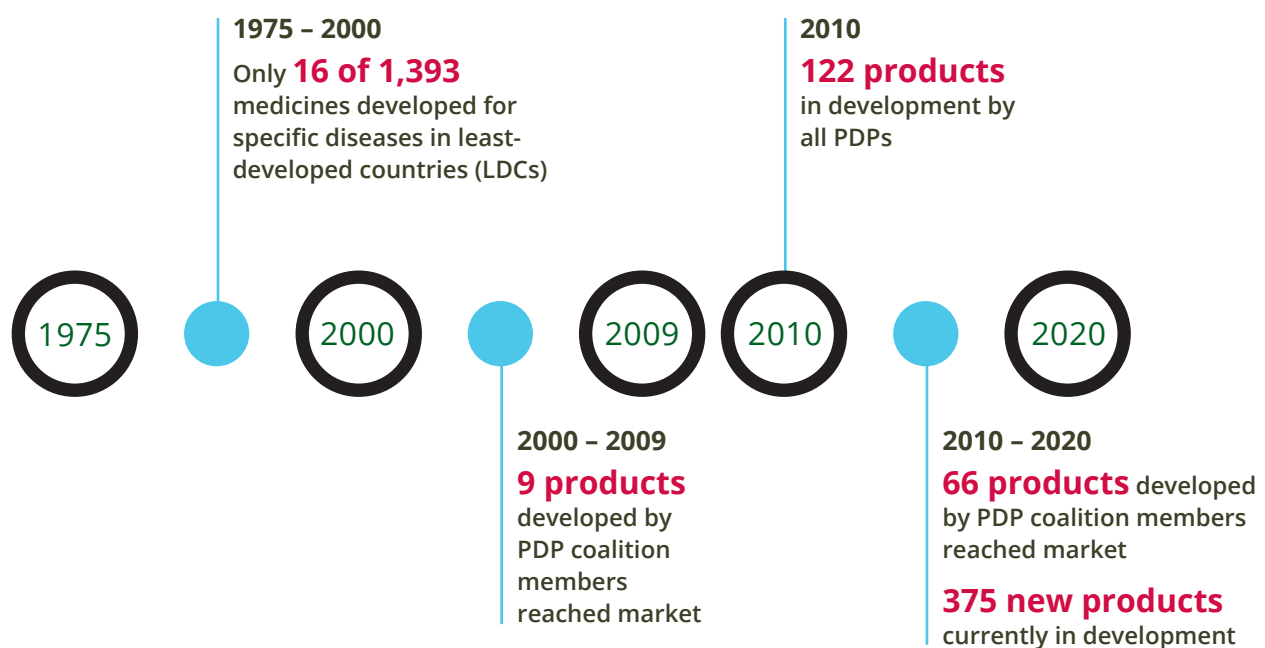
Case Studies: PDPs Achieve Significant Breakthroughs

After increased PDP formation around the turn of the century, PDPs began building their portfolios through innovative partnerships, their own scientific efforts, and the acquisition of promising technologies whose development had previously stalled. Within the past decade, the efforts to grow pipelines and advance product candidates have yielded tremendous impact. Since 2010, PDPs featured in this report have developed and introduced 66 new and repurposed health technologies that have led to advances in combating diseases such as malaria, tuberculosis, cholera, river blindness, meningitis, and others. These products have reached more than 2.4 billion people around the world, including especially vulnerable populations, such as women and children.

In 2010 there were 122 candidates in the development pipelines of all PDPs collectively.²⁰ Today, there are more than 375 potential new technologies in the pipelines of these twelve PDPs alone. Roughly 25% of these research programs are currently in late-stage development (usually defined as Phase II clinical trials or beyond).

Past product development successes and robust and mature portfolios suggest that with appropriate support from donors, regulators, and communities, PDPs will be able to deliver a new wave of game-changing global health innovations in the near future.

The following case studies detail some of the recent signature global health innovations and impacts led by PDPs.



TB Alliance

New TB Drug Approved to Treat the Deadliest Forms of TB

Tuberculosis (TB) is the leading infectious disease cause of death worldwide. In 2019, 10 million people fell ill from active TB and 1.4 million died.²¹ There is growing resistance to available drugs, which means the disease is becoming more deadly and difficult to treat. Multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) are difficult to cure and have high mortality rates even with treatment. Therapies for XDR-TB have long required people to take drugs for 18 months or longer, and the World Health Organization (WHO) reports a global XDR-TB treatment success rate of 39 percent.²² There are close to half a million cases of drug-resistant TB annually, with XDR-TB comprising about 6% of those cases.²³ More than 130 countries have reported cases of XDR-TB.²⁴

In August 2019, the U.S. FDA approved pretomanid for use as part of the “BPaL regimen” for the treatment of highly drug-resistant forms of TB, including XDR-TB. Pretomanid has subsequently been recommended by the WHO,²⁵ authorized by the European Commission, and approved by the Drug Controller General of India.

Pretomanid is the second drug approved for drug-resistant TB by the U.S. FDA in more than 40 years, and the first approved as part of a full treatment regimen. It is the first to be developed and registered by a not-for-profit organization. Prior to BPaL, XDR-TB patients were traditionally treated with combinations of up to eight antibiotics, including daily injections for 18 months or longer, with poor success rates. BPaL is approved as a three-drug, 6-month, all-oral regimen for people with highly resistant forms of TB. In clinical trial settings, it cured 90% of patients, which is comparable to outcomes with optimal therapy in drug-sensitive TB.²⁶

BPaL generally reduces the cost per successful treatment by 65–80%, and a McKinsey investment case study estimated that the rapid introduction of BPaL could translate to a savings for health systems of US\$0.7–1.1 billion from now until 2023.²⁷

TB Alliance initially in-licensed pretomanid in 2002, leading it through a full clinical development program; the FDA submission ultimately detailed data from a total of 19 clinical trials. Throughout its development, TB Alliance has collaborated with and received significant support from numerous governments, academia, philanthropic institutions, the private sector, civil society organizations, and other partners. This network of partners is representative of the unique PDP capabilities to build diverse and effective coalitions to drive global health innovation.

PRODUCT:

Pretomanid

PRODUCT TYPE:

Drug

DISEASE:

**Tuberculosis
(extensively
drug-resistant
tuberculosis)**

Coordination with private and public sector partners has continued since United States approval through global commercialization partnerships with Mylan, Macleods, and Hongqi pharmaceuticals to advance regulatory applications around the world. Pretomanid was also added to the catalog of medicines of Stop TB Partnership's Global Drug Facility, making it available to more than 130 countries, representing the vast majority of the global TB burden. These efforts ensured pretomanid was available around the world as quickly as possible after approval and that generic competition was in place immediately to help drive affordability and a stable supply.

With pretomanid, TB Alliance pioneered the concept of regimen development for TB—instead of developing a single drug to be added to existing treatments, pretomanid was developed only as part of a specific set of drugs comprising a fixed regimen. This approach can markedly accelerate clinical development, protect new drugs from developing resistance, and ensure that there is rigorous clinical evidence for the use of a specific combination. The regimen development model has since become the gold standard for TB research and is applicable to developing new therapies for other diseases that require treatment with multiple agents. The work related to regimen development has helped push the evolution of regulatory science to approve regimen-based clinical trials and accurately interpret their results.

“With this breakthrough, we can readily envision a future in which the treatment of what we now call drug resistant TB should be no more complicated, costly, lengthy or less safe or effective than that which is now available for what is presently termed drug sensitive TB.”

**—DR. MEL SPIGELMAN,
PRESIDENT & CEO, TB ALLIANCE**



TB Alliance's 6-month, all oral XDR-TB therapy reduces the length and number of pills compared to the previous standard of care.

Photo by: Michele Spatari

DNDi**Development of First All-Oral Cure for All Stages of Sleeping Sickness Brings Easy-to-Use Medicine to Those in Need**

Sleeping sickness occurs primarily in the poorest, most remote rural areas in Africa, affecting people who are arguably among the most neglected and most excluded from medical innovation.

The disease is usually fatal without treatment. Transmitted by the bite of a tsetse fly, it causes neuropsychiatric symptoms, including aggression, psychosis, the debilitating disruption of sleep patterns that give the neglected disease its name and, finally, coma. While sleeping sickness is now on the cusp of elimination, history shows that it can surge again if control measures are withdrawn, as happened in the 1960s and 1970s.

Until 2009, the best treatment for sleeping sickness, eflornithine, was extremely complex to distribute and administer in regions affected by the disease. All too often, doctors would have no choice but to use melarsoprol, a highly toxic, arsenic-based drug that killed 1 in 20 patients.²⁸

In 2009, results from DNDi clinical trials showed that a simpler and shorter nifurtimox-eflornithine combination therapy (NECT) was safe and effective to treat sleeping sickness.

Despite the considerable improvements brought about by NECT, the challenge of making treatment accessible in remote rural areas remained acute. The treatment is cumbersome—difficult to ship, store, and administer—and patients needed to be hospitalized to receive intravenous infusions and undergo a lumbar puncture to determine the stage of the disease, since NECT is only indicated for stage-2 sleeping sickness.

DNDi's long-term strategy for sleeping sickness has focused on the development of entirely new and innovative oral treatments with the power to dramatically simplify treatment and support global sustainable elimination efforts.

Through an extensive compound mining exercise, DNDi screened more than 700 compounds from 15 different sources in academia and industry, in collaboration with the Swiss Tropical and Public Health Institute. These efforts led to the rediscovery of fexinidazole, which had been developed but abandoned for strategic reasons by Hoechst (now Sanofi) in the 1980s. In 2009, DNDi and Sanofi partnered to develop fexinidazole for sleeping sickness, with DNDi responsible for preclinical, clinical, and pharmaceutical development, and Sanofi responsible for industrial development, registration, and production.

PRODUCT:**Fexinidazole****PRODUCT TYPE:****Drug****DISEASE:****Sleeping sickness
(human African
trypanosomiasis)**

“This first-ever all oral treatment for sleeping sickness, Fexinidazole, radically improves patient care, unburdens health systems, and opens the path to sustainable elimination of this disease. Moreover, it demonstrates the capacity of PDPs to bring brand new chemical compounds from the laboratory bench all the way through to the patients’ bedside.”

**—DR BERNARD PÉCOUL,
EXECUTIVE DIRECTOR OF DNDi**

After several years of preclinical and Phase I trials, DNDi began a Phase II/III pivotal clinical study in the Democratic Republic of Congo (DRC) and the Central African Republic (CAR) in 2012.

The HAT Platform, bringing 120 members from over 20 institutions and set up with DNDi's support since 2005, played an important role in supporting the challenging conduct of clinical trials in remote and conflict areas, providing extensive training in diagnostic and treatment procedures, pharmacovigilance, Good Clinical Practice (GCP), and medical waste management. This coordination and repeated training were essential for undertaking the clinical trial in a difficult context.

Through screening activities to identify patients eligible for clinical trials, DNDi also contributed significantly to national disease control efforts—supporting mobile teams that screened over 1,780,000 people from 2016 to 2018. All patients diagnosed with sleeping sickness received treatment, either with the standard of care (NECT) or with fexinidazole as participants in clinical trials. These screening efforts contributed to a better understanding of sleeping sickness prevalence and helped pave the way forward for sustainable elimination.

For many of the clinics involved, the trials represented partners' very first experience conducting a clinical trial. Close collaboration with national sleeping sickness control programs and the HAT Platform helped overcome the significant challenges to conducting clinical research in very remote settings in accordance with international ethical and scientific quality standards. More than 200 researchers, monitors, and practitioners were trained in GCP, universal standard precautions, laboratory diagnoses, patient examination techniques, laboratory procedures, treatment algorithms, pharmacovigilance, and waste management.

The three fexinidazole clinical trials, which enrolled 749 patients at 10 clinical sites in DRC and CAR, demonstrated the high efficacy and safety of fexinidazole for treatment of both stages of the disease in both adults and children.

Fexinidazole is the first all-oral treatment for both stages of T.b. gambiense sleeping sickness, the most common form of the disease. Taken as simple pills for 10 days, fexinidazole presents significant advantages over NECT because it eliminates the need for systematic hospitalization, thus reducing the number of painful lumbar punctures, while strengthening the primary care systems' ability to accelerate treatment.



Fexinidazole is the result of a ten-year partnership between DNDi, Sanofi, National Sleeping Sickness Control Programmes, and clinical partners.

Photo by: Xavier Vahed, DNDi

MMV

Partnering with Pharma to Prevent Malaria Relapse with a Single-Dose Treatment

PRODUCT:

Tafenoquine

PRODUCT TYPE:

Drugs

DISEASE:

Malaria

Plasmodium vivax causes between 5.9 and 7.1 million clinical infections every year worldwide.²⁹ More than half of these infections occur in the Americas, while about one-third are in South East Asia.³⁰ *P. vivax* is particularly debilitating because this species of parasite can lie dormant in the liver, reactivating to trigger multiple episodes of malaria weeks, months, or even years after the initial mosquito bite. These relapses not only cause further illness for the individual, but also perpetuate the cycle of onward transmission of parasites back into the mosquito. Owing to this relapsing nature, *P. vivax* malaria poses a substantial economic burden on families and nations and represents a significant challenge for countries pressing toward malaria elimination, particularly those where *P. vivax* is responsible for more than 70% of malaria cases.³¹

Until recently, primaquine (PQ) was the only available treatment for preventing relapses of *P. vivax* malaria. However, ensuring patient compliance to its 7- to 14-day treatment regimen, given that symptoms resolve after the first few days, is difficult, and low compliance can compromise therapeutic efficacy. A medicine with a reduced dosing schedule to improve compliance was therefore urgently needed.

In 2018, tafenoquine (TQ; *Kozenis/Krintafel*),³² developed through a Medicines for Malaria Venture (MMV) and GlaxoSmithKline (GSK) partnership, became the first new treatment for the prevention of relapse of *P. vivax* malaria in more than 60 years—and the first-ever single-dose treatment for this indication. TQ was approved by both the U.S. Food and Drug Administration and the Australian Therapeutic Goods Administration in 2018, marking a major regulatory milestone for *P. vivax* elimination efforts.

Increasing access to this essential medicine has continued to be a priority for MMV and GSK, with marketing authorization granted in Brazil in 2019 and Thailand in early 2020, and regulatory submissions made in five other *P. vivax*-endemic countries between 2018 and 2020.³³ As a single-dose cure, tafenoquine overcomes the compliance challenges of primaquine.

Both PQ and TQ, however, can lead to the destruction of red blood cells (hemolysis) in patients with a specific enzyme deficiency (known as glucose-6-phosphate dehydrogenase or G6PD deficiency). To enable TQ and PQ to be administered only to patients with adequate G6PD enzyme levels, the sister organization and fellow PDP, PATH, has been working to develop a point-of-care G6PD diagnostic test. The test is now also enabling countries to expand access to appropriate relapse prevention through their national health systems and support national efforts to eliminate *P. vivax*.

“Globally, the human and economic cost of relapsing malaria is high. Each malaria episode keeps a child from school or an adult from work, and in susceptible individuals the disease can potentially be fatal. Moreover, as gains are made against the other key malaria parasite, *P. falciparum*, we’re seeing the proportion of cases of *P. vivax* increase. As a single dose medicine, we hope that tafenoquine will increase patient adherence and help endemic countries move closer to malaria elimination. We are proud to have worked side-by-side with GSK for more than a decade to reach this point. Our focus is now on working to ensure the medicine reaches the vulnerable patients that need it most.”

—DR DAVID REDDY, CEO, MMV



A person receives treatment for malaria.

Photo by: Elizabeth Poll

PATH**First Vaccine Developed Specifically for Africa Virtually Eliminated Meningitis across Majority of African Meningitis Belt****PRODUCT:****MenAfriVac®****PRODUCT TYPE:****Vaccine****DISEASE:****Group A meningitis**

Meningitis is a serious infection of the thin lining surrounding the brain and spinal cord. It has many causes, though bacterial cases are extremely serious and often fatal without treatment. In Africa, more than 80% of meningitis epidemics have historically been caused by *Neisseria meningitidis* group A bacteria,³⁴ a form of the disease that mostly attacks infants, children, and young adults. Without treatment, 50% of those infected can die within days. Those who survive the infection often suffer severe, lifelong disabilities such as deafness or paralysis.³⁵

Following the particularly devastating group A meningitis epidemic of 1996–1997 (which sickened more than 250,000 people and killed more than 25,000),³⁶ African leaders called for a low-cost vaccine that would permanently end group A meningitis epidemics in Africa.

In 2001, PATH and WHO formed the Meningitis Vaccine Project (MVP) to develop a low-cost vaccine that would prevent group A meningitis outbreaks in Africa. No multinational vaccine manufacturer was willing to make a group A meningitis conjugate vaccine at a price African governments could afford; however, Serum Institute of India Private Ltd (SIPL) agreed to produce the vaccine for less than US\$0.50 per dose—the price set by African health ministers.

Together, PATH and partners created a new group A meningitis vaccine in record time, navigating rigorous regulatory and technical rules, organizing numerous clinical studies to test the safety and effectiveness of the vaccine, and building local capacity to conduct research and ultimately support product delivery.

MenAfriVac® was the first vaccine to be developed for meningitis specifically for Africa. In addition to its relatively low cost, MenAfriVac® promotes herd immunity by reducing the bacteria carried in the nose and throat and interrupting the chain of transmission. MenAfriVac® also provides relatively long-term protection, which prevents group A meningitis epidemics before they start, and it can be delivered outside of the cold chain, providing access to even the most remote communities.

MenAfriVac® was prequalified by WHO in 2010. Its introduction in 2010 via mass vaccination campaigns has had an immediate and dramatic impact in breaking the cycle of group A meningitis epidemics. At the end of 2019, MenAfriVac® had been delivered to approximately 340 million people in 24 of 26 “meningitis belt” countries, virtually eliminating meningitis A wherever MenAfriVac® has been used.

Group A meningitis isn't the only form of the disease that plagues Africa; groups C, W, X, and Y also circulate and can cause outbreaks and epidemics. With funding from the United Kingdom's Foreign, Commonwealth, and Development Office (FCDO), PATH is once again partnering with SIIPL, this time to develop an affordable meningococcal conjugate vaccine against serogroups A, C, W, X, and Y. The vaccine candidate is undergoing Phase III clinical studies in Mali and The Gambia—a crucial step on the pathway to licensure, and to potentially eliminating all forms of epidemic meningitis in the meningitis belt.

“Meningitis is one of the most feared diseases in Sub-Saharan Africa. For decades, people lived epidemic to epidemic—until the Meningitis Vaccine Project developed and introduced MenAfriVac®, which changed the course of meningitis in Africa. The groundbreaking vaccine has prevented hundreds of thousands of cases of meningitis A and saved tens of thousands of lives. MenAfriVac® demonstrates the remarkable power of vaccines as public health tools, and what can be accomplished when a need becomes idea becomes action, a global need is met with global action.”

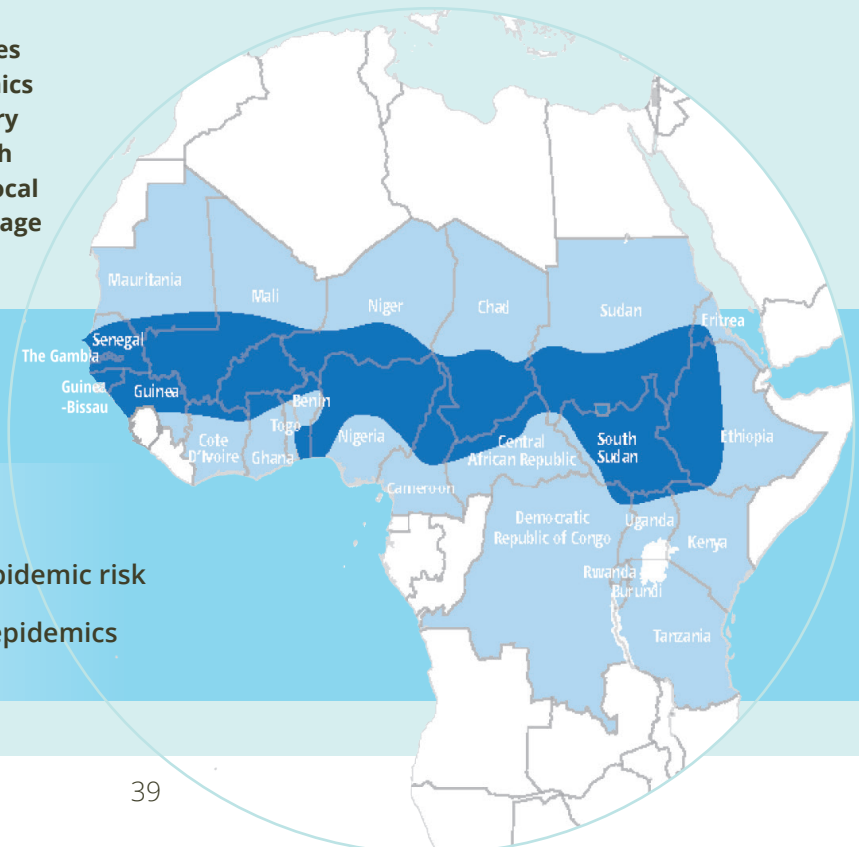
—NIKOLAJ GILBERT, PRESIDENT & CEO, PATH

MENINGITIS BELT

Africa's Sub-Saharan meningitis belt stretches from Senegal in the west to Ethiopia in the east. It faces meningococcal meningitis epidemics during the dry season from January to June. These epidemics can reach massive proportions, burdening local health systems and inflicting damage long after the disease passes.

MENINGITIS DISEASE EPIDEMICS

- Meningitis Belt—areas at high epidemic risk
- Countries at risk for meningitis epidemics



MDGH:**Innovative Financing Enables Development of Moxidectin, Yielding Returns for Social Impact Investors**

Approved by the U.S. Food and Drug Administration (FDA) in 2018,³⁷ moxidectin is predicted to accelerate elimination of onchocerciasis (better known as “river blindness”) as a global health burden—a disease affecting more than 20 million a year³⁸—as well as add an important new treatment option for approximately 1.5 billion people affected by lymphatic filariasis, soil transmitted helminths, strongyloides, and scabies.³⁹

Medicines Development for Global Health (MDGH), an Australian-based, not-for-profit biotechnology company, licensed moxidectin for all human indications from the World Health Organization in 2014. Before MDGH's involvement, the development of moxidectin had been advanced by a partnership between UNICEF, UNDP, World Bank, the WHO Special Programme for Research and Training in Tropical Diseases (TDR), and Wyeth/Pfizer. Once Pfizer withdrew from the relationship in 2011, moxidectin as a potential global health medicine was carried by TDR alone.

MDGH chose to submit to the FDA to ensure the first review was by a stringent regulatory authority and to leverage the FDA's priority review voucher (PRV) incentive to raise capital of US\$13 million to support the development and registration of moxidectin. This social impact investment from the Global Health Investment Fund (GHIF) was the first capital raised to leverage the potential return of the PRV.

MDGH subsequently signed legally binding supply, pricing, and quality obligations for moxidectin with GHIF. MDGH also designed and completed the drug development program, including re-establishing manufacture, clinical trials, preparation, and submission of the dossier to the FDA for a successful approval. In a striking example of the lean and efficient capabilities of PDPs, MDGH completed this effort with just a six-person team.

MDGH was the sole sponsor of the development program to ensure that the scrutiny and requirements of the FDA would be satisfied. A partnership with TDR was key to this success, and an army of collaborators and scientists all over the world contributed to the program.

The U.S. FDA approved moxidectin on June 13, 2018, and awarded MDGH a priority review voucher. Moxidectin is the first onchocerciasis treatment approved by the U.S. FDA in 20 years and brings new prospects for the elimination of onchocerciasis.

PRODUCT:**Moxidectin****PRODUCT TYPE:****Drug****DISEASE:****Onchocerciasis
(better known as
“river blindness”)**

Further, as MDGH is a not-for-profit, proceeds from the sale of the priority review voucher (sold to a for-profit pharmaceutical company) were recommitted to the NTD field, supporting access to moxidectin through subsidies and funding further R&D on moxidectin and other products. MDGH continues to work through the WHO process to facilitate implementation, including pediatric and field studies in Africa.

This progress demonstrates how social impact investing can yield both financial and humanitarian returns on investment, especially when carried out by a capable, mission-driven partner.

“Moxidectin is an outstanding compound with potential to be one of the most important global health medicines. Yet it suffered the typically tortuous development history of an NTD medicine. MDGH built on the work of the team from TDR and a broad community of researchers, medical researchers, patients, and regulators to achieve the highest bar of regulatory approval. This was achieved with a lean team, without an industry partner, and with a novel social impact investment model. Critically, it is now about working with the community to make it available and achieve moxidectin’s potential.”

—MARK SULLIVAN, FOUNDER AND MANAGING DIRECTOR, MDGH

SPOTLIGHT ON: PRVs

Following U.S. FDA approval of a new treatment for a neglected or rare disease, the sponsor may receive a voucher. The voucher entitles the holder to priority review a drug of their choice, and the voucher may be used by its recipient or be sold. The value of this voucher comes from its ability to lengthen the amount of time a new product is on the market under patent by allowing that product to reach the market sooner. The voucher saves approximately four months from the review cycle. For example, a small company might win a voucher for developing a drug for a neglected disease and sell the voucher to a large company for use on a commercial disease.

FIND:

Self-Administered Tests for Hepatitis C Could Ease and Broaden the Reach of Testing

FIND and DNDi partnered with the Malaysia Ministry of Health on the Hepatitis C Elimination through Access to Diagnostics (HEAD-Start) project to improve the diagnosis of Hepatitis C (HCV) by making it more affordable and more widely available to those in need, with a focus on serving people co-infected with HIV. This project was supported by UNITAID and the Dutch government.

At the outset of this initiative, very few tools available for HCV screening and diagnosis were affordable or appropriate for use at the point of care in low-resource settings. Moreover, these tools were of limited use in certain populations, especially for patients who were co-infected with HIV. Malaysia was using a complicated screening algorithm that was performed in centralized hospitals and took up to six months for results to reach patients.

Through the HEAD-Start Malaysia study, FIND helped introduce screening using HCV rapid diagnostic tests (RDTs) at primary health centers. This increased access for HCV screening and reduced the time to first result to 15 minutes, enabling the Malaysian Ministry of Health to adopt a decentralized approach to national testing and treatment, bolstering their elimination efforts.

Currently, FIND and Clinical Research Malaysia (CRM) are working together to make HCV even easier and more expansive by studying both oral and blood HCV self-tests. This study is ongoing and examining the feasibility and acceptability of HCV self-testing among the general population and men who have sex with men (MSM). The study is seeking to gather data to enable WHO prequalification and CE marking, a MSM designation indicating conformity with health, safety, and environmental protection standards for products sold within the European Economic Area.

Both of these groups are of particular interest. In the era of COVID-19, HCV self-testing could be a way to increase access to HCV testing while minimizing the general population's

PRODUCT:

MHCV self-tests

PRODUCT TYPE:

Diagnostics

DISEASE:

Hepatitis C

exposure to the health systems. In addition to benefiting those individuals, this reduces the burden on the health system in a time when systems are particularly strained.

Emerging evidence suggests that MSMs are a high-risk group for HCV, but in the Malaysian context it is very difficult to enable that group to come forward for testing and services. Exploring HCV self-testing among MSMs could expand access to this key population in a way that minimizes the risk of social harm.

Partners in this effort include Orasure, PMC, Wits University, NCDC Georgia, University of Washington, and CRM.



HCV self-tests are easier to use, increase privacy, and reduce exposure to overburdened health systems.

Photo by: B. Otieno, FIND, 2020

IVI:**Affordable Oral Cholera Vaccine Goes Beyond Outbreak Response; Enables Mass-Scale Prevention by Solving Manufacturing Equation****PRODUCTS:****Euvichol®;
Euvichol-Plus®****PRODUCT TYPE:****Vaccines****DISEASE:****Cholera**

Cholera is a poverty-associated diarrheal disease that primarily affects vulnerable populations in low-income countries, causing disease in more than 2.5 million people every year and killing nearly 100,000.⁴⁰ Although an oral cholera vaccine (OCV) has been globally available since 2001, its high unit cost prevented wide use in endemic, resource-poor countries. With low demand, a lack of commercial incentive hampered production of cholera vaccines for the public sector market.

To fill this gap, the International Vaccine Institute (IVI) set out to facilitate the development and production of affordable, WHO-prequalified OCVs and bring them to market for global public use. Ultimately, the creation of a global stockpile of OCVs led to an adequate supply to address outbreaks and enabled widespread preventative campaigns to stop outbreaks before they start.

In 2009, following IVI's first success with the development of the reformulated low-cost Shanchol™ vaccine, IVI committed to further increasing a global supply by partnering with another manufacturer, EuBiologics, a South Korean bioventure company who at the time had no experience in vaccine production. IVI provided hands-on training in fermentation, downstream processing, and quality control to manufacture another OCV. By the following year, a laboratory-scale technology transfer was complete, and by 2014, advanced clinical studies confirmed that Euvichol® was safe and induced an immune response.

It took fewer than seven years and approximately US\$19.7 million from the start of IVI's partnership with EuBiologics to achieve WHO prequalification of Euvichol® and Euvichol-Plus®—the same vaccine in innovative packaging enabling it to be sold for a slightly lower unit cost.

Achieving WHO prequalification requires vaccines to undergo a standardized procedure to ensure they are safe and effective for use in vaccination campaigns. Prequalification also provides all the necessary information to vaccine procurement and delivery agencies like Gavi, the Vaccine Alliance, and UNICEF to help develop effective vaccination programs.

Overall, IVI's Cholera Vaccine Program, a philanthropic-funded, public-private partnership, reversed the vicious cycle of high-cost/low-demand that often constricts vaccine research and production for neglected diseases. IVI's partnership with EuBiologics increased supply and demand, reduced the price, and ultimately made protection against cholera more accessible to the people who need it most.

As of November 2019, over 42 million doses of Euvichol® and Euvichol-Plus® have been released globally, and IVI continues to work with EuBiologics to lower costs and increase production capacity by exploring further vaccine improvements.

“The creation of a global public stockpile of OCV continues to save countless lives and helped map a pathway to a world free of this devastating disease, an undertaking made possible by close partnerships between the public and private sectors.”

—DR. JEROME KIM, DIRECTOR GENERAL, IVI



IVI Director General Jerome Kim delivers an oral cholera vaccine to a child in Ethiopia during a preventive campaign against endemic cholera in 2015.

Photo by: IVI

IAVI:

Applying Cutting-Edge Technologies in HIV Vaccine Research to Develop Novel Treatment and Prevention Modalities, Including for COVID-19

The PDP model can be exceptionally nimble. One example of this has been the ability of PDPs, typically dedicated to a single or defined group of diseases, to pivot their expertise and capabilities to contribute to new health challenges, such as the global response to COVID-19. IAVI exemplifies this flexibility as it has translated work on HIV vaccine development to identifying and developing broadly neutralizing antibodies (bnAbs) to combat HIV, COVID-19, and other diseases, spearheading novel partnerships and business models to ensure that these can become globally accessible.

In its effort to translate technologies to COVID-19 research and development, IAVI is collaborating with Merck and Co., Inc., to develop and ensure broad availability of an

investigational vaccine against SARS-CoV-2, the virus that causes COVID-19, to be used for prevention of the disease. The IAVI-Merck COVID-19 vaccine program leverages IAVI's expertise in recombinant vesicular stomatitis virus (rVSV) vector technology that it has developed through its rVSV-based HIV vaccine candidate and its viral hemorrhagic fever vaccine candidates.

On the antibody front, historic investments from donors, including members of the PDP Funders Group, led to the discovery and isolation of bnAbs, which present promising strategies for preventing and potentially treating HIV infection. IAVI is using novel technologies to identify, characterize, and optimize antibodies for potency and breadth, as well as working with partners, including the U.S. National Institutes of Health (NIH) and the Serum Institute in India, to prepare for production at a larger scale, and applying more sustainable, state-of-the-art, and low-cost manufacturing technologies, targeting the most desirable product profile to ensure affordability and foster ease of implementation and acceptance. A first set of these bnAbs are being evaluated in clinical trials, and next-generation versions are expected to progress to clinical development in late 2021.

PRODUCTS:

Broadly neutralizing antibodies (bnAbs); monoclonal antibodies; vaccines

PRODUCT TYPE:

Therapeutics, preventive therapy

DISEASES:

HIV/AIDS, COVID-19, snakebite, enteric bacterial infections

“Antibodies are poised to play a significant role in preventing and treating infectious and neglected diseases, which often disproportionately affect those living in poverty. The crisis with COVID-19 is a once-in-a-century opportunity to develop new solutions to overcome the profound inequities in access to monoclonal antibodies and enable these promising solutions to be globally used to protect people from many diseases now and in the future.”

—DR. MARK FEINBERG, PRESIDENT AND CEO, IAVI

Such advances in identifying and developing antibodies are now also being used to develop prevention tools and treatments beyond HIV/AIDS collaborations enabled by IAVI's PDP model, which brings partners and funders together in unique ways to spur biomedical innovation.

For example, IAVI, The Liverpool School of Tropical Medicine, and other partners, with funding from the United Kingdom's Foreign Commonwealth and Development Office (previously DFID), are applying these techniques to develop novel antibody-based snakebite therapy. More recently, IAVI work supported by Wellcome focuses on using antibodies to treat bacterial infections from shigella.

With monoclonal antibodies (mAbs) becoming rapidly one of the most powerful tools in modern medicine, but yet less applied for combatting infectious diseases, IAVI partnered with Wellcome to publish in 2020 a Global Access to Antibodies report. This examination of the gaps and opportunities for end-to-end development and equitable global access to mAbs is an urgent call to action for leaders across the globe to realize a roadmap for global access, especially for people in LMICs, to innovative antibody-based solutions for COVID-19, HIV, and other infectious and noncommunicable diseases that affect people in LMIC countries disproportionately.

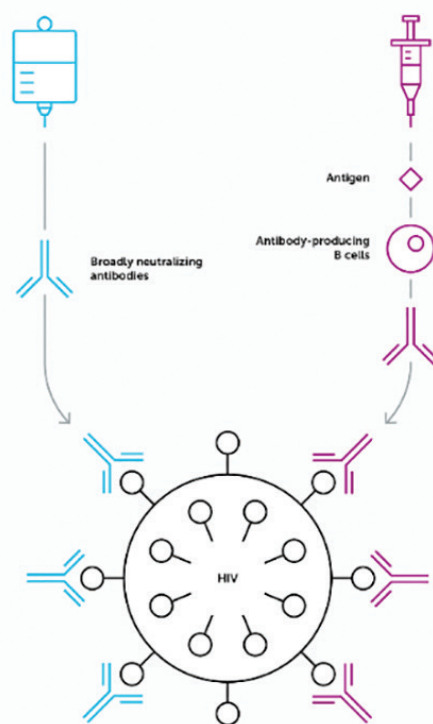
Understanding antibody-based protection versus active immunization

ANTIBODY-BASED PROTECTION

- Direct administration of bnAbs
- Able to neutralize most types of HIV
- Instant protection that lasts months
- Potential for self-administration

ACTIVE IMMUNIZATION

- Traditional approach to eliciting immunity
- Stimulates the body to make antibodies and elicits other immune responses
- Often requires 2-3 immunizations to stimulate protective immunity
- Can provide long-lasting protection



Adapted from Nolo Moima, Sunday Times, and Carina Kriel, NICD.

IPM:**Dapivirine Ring Would Offer Women in Sub-Saharan Africa First Long-Acting HIV Prevention Option****PRODUCT:****Dapivirine ring****PRODUCT TYPE:****Device****DISEASE:****HIV/AIDS**

Every day, nearly 1,400 women in Sub-Saharan Africa acquire HIV.⁴¹ Existing HIV prevention tools like condoms and the daily oral antiretroviral (ARV) pill known as PrEP (or pre-exposure prophylaxis) are highly effective, but not all women are able to use them. In a milestone development for women's HIV prevention, the dapivirine vaginal ring, developed by the nonprofit International Partnership for Microbicides (IPM), recently received a positive opinion from the European Medicines Agency and prequalification from the WHO, paving the way for national regulatory approvals.

The monthly ring is the first long-acting HIV prevention product and is designed to help address women's unmet need for new methods given the persistently high rates of HIV they face, especially in Sub-Saharan Africa. Made of a flexible silicone, the ring slowly releases an ARV called dapivirine locally in the vagina with minimal systemic absorption elsewhere in the body, which could help minimize side effects. Women would insert the ring themselves and replace it each month.

The dapivirine ring reduced women's HIV risk by 35% in one Phase III⁴² trial and 27% in a second Phase III trial,⁴³ with no safety concerns. Subsequent open-label extension (OLE) studies saw higher product use and suggested greater HIV risk reduction.⁴⁴ The ring has shown a strong safety profile in all clinical trials to date.

The development of the dapivirine ring is a result of IPM's global partnerships with researchers; trial communities in Africa, Europe, and the United States; civil society; governments; industry; and donors spanning 16 years of research. IPM is building on those collaborations to shorten the time to potential product introduction, including with Johnson & Johnson, which granted IPM the rights to dapivirine, the USAID-funded OPTIONS and PROMISE projects, and a range of stakeholders across sectors. With strong political will and funding, it may be possible to begin making the dapivirine ring available in some communities in Africa in 2021.

Next steps in the effort include WHO guidelines on the ring's use, regulatory reviews by African national regulatory authorities and the U.S. FDA, and continued market research and implementation planning.

IPM will also be collecting additional research on the ring's efficacy among young women, who are among the highest risk for HIV. IPM is also collaborating with the Microbicide Trials Network (MTN) on studies of the monthly ring's safety and use among other key populations, including adolescent girls, pregnant women, and breastfeeding women, results from which will inform next steps on potentially expanding the indication for the ring to those groups in the future. Follow-on products include a longer-acting three-month dapivirine ring and three-month multipurpose technology that could simultaneously reduce the risk of HIV and unintended pregnancy.

“Empowering women with new HIV prevention options is critical not only to controlling the HIV/AIDS epidemic but also to protecting women’s sexual and reproductive health. We are grateful to our many partners across sectors who helped make a long-acting woman-controlled product a reality. We look forward to building on these and new partnerships to get the dapivirine ring into the hands of women where the need is urgent.”

—ZEDA ROSENBERG, CEO AND FOUNDER, IPM

IPM’s dapivirine ring is the first long-acting HIV prevention product and is designed to help address women’s unmet needs.

Photo by: Andrew Loxley



IVCC:**Dual-Active Ingredient Bed Nets Combat Insecticide Resistance and Help Preserve Hard-Fought Progress against Malaria**

World Malaria Report estimates that in 2018, 228 million cases of malaria occurred worldwide (3 million fewer cases than in 2017) resulting in 409,000 deaths (15,000 fewer than in 2017), 94% of which occurred in Africa (384,000).⁴⁵ While this represents a remarkable improvement in comparison with 2010, with malaria deaths falling by 29% in Africa, the downward trends of incidence and mortality have stalled since 2016. This failure to progress in the past four years has caused WHO to describe malaria as being at a crossroads, calling for increased funding, development, and implementation of new tools to combat malaria.

In the context of these challenges, the role of vector control, and the public health problem and commodity access issues challenging its continuing effectiveness, may be summarized as:

- Universal coverage of vector control in malaria endemic countries is a global and national priority because of its fundamental importance for malaria control and elimination.
- The gains in malaria control achieved over the past decade, largely because of vector control, are threatened by the emergence and spread of pyrethroid resistance, which poses significant risks to the future efficacy and impact of these tools.

In collaboration with BASF and the London School of Hygiene & Tropical Medicine, and with funding from organizations including the Bill & Melinda Gates Foundation and UKaid, the Innovative Vector Control Consortium (IVCC) helped support the development of the Interceptor® G2, which was prequalified by WHO in 2018. IVCC played an instrumental role in bringing this product to the prequalification stage, supporting field trials and shepherding the technical progress of the project through its External Scientific Advisory Committee (ESAC).

Interceptor® G2 is a dual-active ingredient bed net (ITN) that combines alphacypermethrin, a pyrethroid class insecticide used in bed nets across malaria endemic countries, with chlorfenapyr, a repurposed insecticide from agriculture. Chlorfenapyr has a different mode of action from other WHO-recommended public health insecticides. The mixture of these two active ingredients coated on an ITN makes for an effective net that helps overcome the growing and intensifying resistance to pyrethroids.

In one experimental hut study, the chlorfenapyr-alphacypermethrin combination killed 71% of resistant mosquitoes (65% after 20 washes), compared to a standard alpha-cypermethrin net that killed only 20% of the same resistant mosquitoes.

PRODUCTS:

**Interceptor® G2;
Royal Guard®**

PRODUCT TYPE:

**Insecticide treated
bed nets (more
commonly known
as “bed nets”)**

DISEASE:

Malaria

A second dual-active ingredient bed net, Royal Guard®, received WHO prequalification in 2019. Royal Guard® combines a pyrethroid (alphacypermethrin) with pyriproxifen (an insect growth regulator). The combination of pyrethroid and insect growth regulator active ingredients in DCT's Royal Guard® is intended to knockdown, kill, and reduce the numbers of offspring of any surviving mosquitoes, which would result in an overall reduction in the vector population.

However, access to these new ITNs is restricted by insufficient evidence to support World Health Organization (WHO) policy recommendations, high prices, lack of evidence of cost-effectiveness compared to pyrethroid-only ITNs, and consequent poor demand in an uncertain market. Consequently, with funding from UNITAD and the Global Fund, IVCC is leading the New Nets Project, which addresses each of these issues to achieve the following goal:

Continued reduction in malaria incidence, morbidity, and mortality by the establishment of a sustainable market for a broader set of ITN tools, which perform in areas of pyrethroid resistance, and have the potential to support insecticide-resistance management.

As part of the New Nets Project, IVCC is supporting the introduction of Interceptor G2® and Royal Guard® into 10 endemic countries (i.e., Benin, Burkina Faso, Côte d'Ivoire, Ghana, Liberia, Malawi, Mali, Mozambique, Nigeria, and Rwanda). A volume guarantee negotiated by MedAccess and the Gates Foundation provided countries with reduced net prices. Through a combination of a randomized controlled trial, and evidence generated from pilot net deployments, the New Nets Project will produce efficacy evidence for WHO, along with effectiveness and operational learnings that will help to optimize future deployments of dual-active ingredient bed nets.

“The progress made against malaria since 2000 is threatened by the growing intensity and distribution of resistance to pyrethroids, previously the only insecticide class available to treat bed nets. By combining pyrethroids with new classes of chemistry, new ITNs have the potential to protect and save many more lives.”

**—CHRISTEN FORNADEL,
TECHNICAL COORDINATOR, NEW
NETS PROJECT**

ITNs save lives and are fundamental to malaria control and elimination efforts.

Photo by: IVCC



EVI:**Maintaining a Robust Vaccine Portfolio to Combat Diseases of Poverty**

Vaccination is one of the most successful and cost-effective health interventions; however, developing vaccines is a notoriously lengthy, costly and difficult process. To ensure ultimate success, the development of urgently needed vaccines requires the existence of a robust and diverse pipeline of vaccine candidates at different stages of the development process. The European Vaccine Initiative (EVI) plays an important role in this process as it feeds the vaccine development pipeline for different diseases with novel and innovative vaccine candidates and supports their progression through the development path.

To date, EVI has supported the development of more than 40 different vaccine formulations from pre-clinical to early and mid-stage clinical development for a variety of diseases/ pathogens, including malaria, leishmaniasis, diarrheal diseases, and emerging infectious diseases. These new vaccines, once available, will not only reduce mortality and morbidity but will have an enormous socioeconomic impact, especially in LMICs, which are hardest hit by these diseases and where the benefits of vaccination are expected to be greatest.

Among the projects in its diverse portfolio, EVI is currently evaluating ChAd63-KH as a vaccine for visceral leishmaniasis (VL; kala azar) and post kala azar dermal leishmaniasis (PKDL), a skin disease that follows treatment for VL. Leishmaniasis are poverty-related neglected diseases with a major impact on global health. They affect the poorest of the poor in nearly 100 countries with over 1 billion people living in areas endemic for leishmaniasis, resulting in more than 1 million new cases every year. Some forms of leishmaniasis are chronic and non-life-threatening, but VL forms are life-threatening. Collectively, approximately 2.4 million disability-adjusted life years (DALY) are lost to the leishmaniasis. No vaccines are currently licensed for any form of human leishmaniasis.

The stigma and isolation resulting from having multiple PKDL lesions on the face, limbs, and trunk significantly reduce quality of life, particularly for children and women. In addition, PKDL is widely considered a threat to the elimination of VL, with recent modeling of VL epidemiology indicating that a vaccine to prevent PKDL would help sustain elimination targets.

PRODUCT:**ChAd63-KH
(vaccine)****PRODUCT TYPE:****Vaccine****DISEASE:****Leishmaniasis**

The ongoing ChAd63-KH development program—funded by European and Developing Countries Clinical Trial Partnership (EDCTP) and the Wellcome Trust—is being carried out in partnership with the University of York and Sudan's Institute of Endemic Diseases (IEND), with additional regional capacity building for vaccine research being conducted across East Africa. This promising vaccine candidate is currently in late-stage (Phase IIB) development.

“Vaccines have a unique ability to prevent and control infectious diseases, including some of the world’s most devastating yet neglected conditions. EVI is proud to work with the University of York and other partners in developing a vaccine against one of these conditions, namely leishmaniasis. By developing vaccines that can either treat or prevent post kala azar dermal leishmaniasis we can reduce the impact of this disease, whilst at the same time reducing the spread of fatal visceral leishmaniasis in the community.”

—DR. OLE OLESEN, EXECUTIVE DIRECTOR, EVI

The first PKDL patient being administered the experimental ChAd63-KH vaccine at the Professor El-Hassan's Centre for Tropical Medicine, Dooka, Gedaref State, Sudan.

Photo by: ANON



TBVI:**Pursuing a Vaccine to Prevent the World's Deadliest Infectious Disease**

Tuberculosis is the world's deadliest infectious disease, killing 1.4 million each year.⁴⁶ Yet, the only vaccine against TB in use today, Bacille Calmette-Guerin (BCG), is a live attenuated strain from a *Mycobacterium bovis* strain isolated from cattle and discovered nearly 100 years ago. BCG is administered at birth, and despite its effectiveness in reducing the incidence of forms of TB in children, it is inconsistent in preventing pulmonary TB, the most common form of the disease in adolescents and adults, and the form most responsible for transmission of TB.

In 1993, WHO declared TB a global emergency, prompting several funders to invest in R&D efforts to develop new TB vaccines to address this global epidemic. Much of this investment was in PDPs. Today's global TB vaccine pipeline contains several promising vaccine candidates. With adequate institutional, technical, and funding support, the first new TB vaccines could be available as early as 2026 to 2028.

Since the early 2000s, Tuberculosis Vaccine Initiative (TBVI) has supported several collaborative research projects for the development of promising TB vaccine candidates. Among the most advanced and most promising new candidates is the MTBVAC TB vaccine.

MTBVAC is a live rationally attenuated derivative of the *M. tuberculosis* isolate MT103, which belongs to Lineage 4 (Euro-American), one of the most widespread lineages of *M. tuberculosis*. MTBVAC has been the first and only live attenuated *M. tuberculosis* vaccine approved to enter into clinical trials. A first-in-human MTBVAC clinical trial was

conducted successfully in healthy adults in Lausanne (Switzerland). Subsequent clinical trials in TB endemic regions (South Africa, Mozambique) are currently ongoing, and a Phase III trial to test the projected efficacy of the MTBVAC vaccine is scheduled to start in 2021.

MTBVAC is a true example of successful international collaboration in the PDP area. R&D progress on the MTBVAC candidate has been made possible due to support from and collaboration between universities and research institutions (University of Zaragoza, Institut Pasteur Paris, and the broader TBVI research organization community), private industry (Spanish vaccine company, Biofabri), public funders (European

PRODUCT:**MTBVAC****PRODUCT TYPE:****Vaccine****DISEASE:****Tuberculosis**

“TBVI, over the last 10-plus years has used the PDP model to accelerate the most promising TB vaccine candidates through the pipeline—such as MTBVAC—and aims to continue to innovate and diversify both the global tuberculosis vaccine pipeline and TB vaccine platforms via the same PDP approach.”

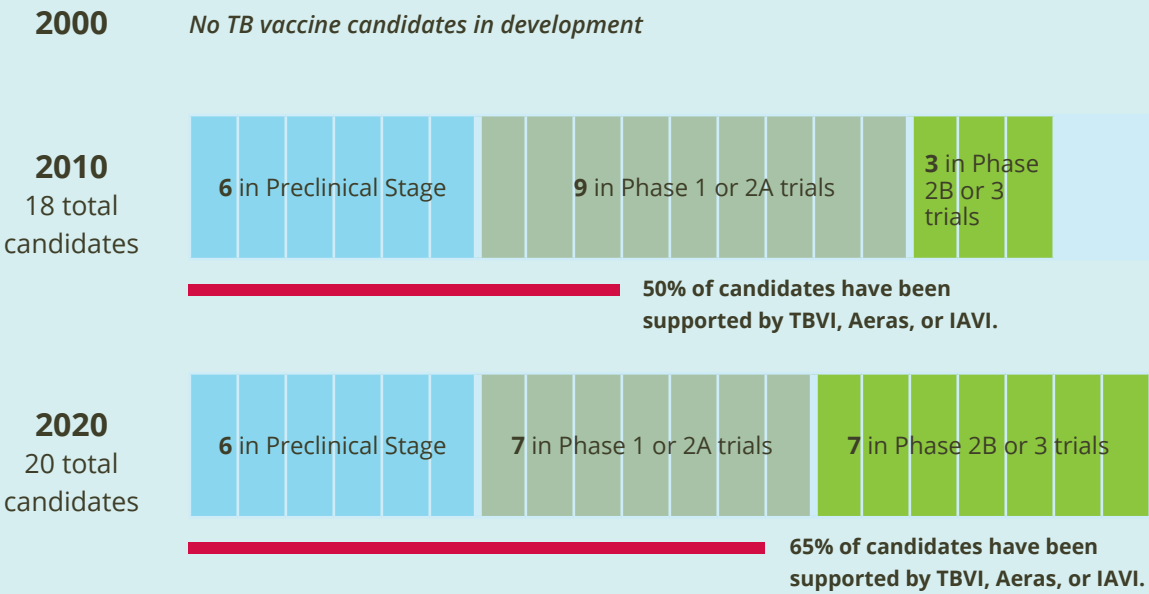
—DR. NICK DRAGER, EXECUTIVE DIRECTOR TBVI

Commission/EU Framework Programmes, DFID UK Government, NORAD Norwegian Government), and private funders (Bill & Melinda Gates Foundation) and PDPs (TBVI and IAVI).

The MTBVAC TB vaccine candidate is being developed for infants as well as adolescents and adults. If development plans proceed as planned, the MTBVAC could be ready to enter the market as a vaccine for infants as early as 2026, and for adolescents and adults as early as 2028–2030.

PROGRESS IN TUBERCULOSIS VACCINE R&D
GLOBAL PIPELINE OVERVIEW

PDPs have played a pivotal role in building a strong global portfolio of TB vaccine candidates. Before the emergence of PDPs, there were no vaccine candidates in development. Today, there are 20, with a third of them in late-stage development. Five of those late-stage candidates have been supported by TBVI, Aeras, or IAVI.



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