Evaluation PDP III Fund 2015-2021

Final Report

Client: Ministry of Foreign Affairs

Rotterdam, 12 November 2021

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The annexes are in a separate document.

List of abbreviations

ACT-A	Access to COVID-19 Tools Accelerator
AGYW	Adolescent Girls and Young Women
AIGHD	Amsterdam Institute for Global Health and Development
AMR	Antimicrobial Resistance
ARV	Antiretrovirals
BFF-DX	Biomarker based fever test
BMBF	German Ministry for Education and Research
BMGF	Bill & Melinda Gates Foundation
BPaL	Bedaquiline, Pretomanid and Linezolid
CAD	Computer-Aided Detection
cAg	Core antigen
CASPR	Coalition to Accelerate and Support Prevention Research
CE	Community Engagement
CHS	Centre for Health Security
CL	Cutaneous Leishmaniasis
DALY	Disability Adjusted Life Year
DFAT	The Department of Foreign Affairs and Trade of Australia
DFID	UK Department for International Development
DHSC	Directorates of Health and Social Care
DNDi	Drugs for Neglected Diseases Initiative
DR-TB	Drug-Resistant forms of Tuberculosis
DVR	Dapivirine Vaginal Ring
EDCTP	European and Developing Countries Clinical Trials Partnerships
EMA	European Medicines Agency
EUL	Emergency Use Listing Procedure
EVI	European Vaccine Initiative
FCDO	Foreign, Commonwealth and Development Office of UK
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
FIND	Foundation for Innovative New Diagnostics
GPP	Good Participatory Practise
HAT	Human African Trypanosomiasis
HCV	Hepatitis C
HIC	High Income Countries
HIV	Human Immunodeficiency Virus
IAVI	International AIDS Vaccine Initiative
IOB	The Policy and Operations Evaluation Department
IPM	International Partnership for Microbicides
IVCC	Innovative Vector Control Consortium
KNCV	Dutch Tuberculosis Foundation
LMIC	Low- and Middle Income Countries
MAA	Marketing Authorization Application
MIC	Middle Income Countries

MMV	Medicines for Malaria Venture
MNC	Multinational pharmaceutical Companies
MoFA	Ministry of Foreign Affairs
MPT	Multipurpose Prevention Technology
MSF	Médecins Sans Frontiéres
MSM	Men who have sex with men
NCE	New Chemical Entities
NEI	Netherlands Economic Institute
NGO	Non-Governmental Organisations
NIH	US National Institute of Health
NTD	Neglected Tropical Disease
OECD/DAC	Organisation for Economic Co-operation and Development/Development Assistance Committee
PAHO	Pan American Health Organization
PDP	Product Development Partnerships
PKDL	Post-Kala Azar Dermal Lesions
POC	Point-Of-Care
POW PDP	Protection Options for Women Product Development Partnership
PRA	Pharmaceutical Research Associates
R&D	Research and Development
RDT	Rapid Diagnostic Test
RUNMC	Radboud University Nijmegen Medical Centre
RVO	The Netherlands Enterprise Agency
rVSV	recombinant Vesicular Stomatitis Virus
SDG	Sustainable Development Goals
SME	Small and Medium sized Enterprises
SRH	Sexual and Reproductive Health and Research
SRHR	Sexual and Reproductive Health and Rights
ST	Self-Testing
TB	Tuberculosis
ToC	Theory of Change
ToR	Terms of References
TPP	Target Product Profile
UHC	Universal Health Coverage
UNGA	United Nations General Assembly
VL	Visceral Leishmaniasis
WHO	World Health Organisation
WoCBP	Woman of Childbearing Potential

Conclusions and recommendations

Introduction

In 2015 the Netherlands government awarded grants to the amount of €83.6 million to six Product Development Partnerships (PDPs): public-private partnerships for research and development of medicines, vaccines and diagnostics to combat poverty-related diseases and conditions related to Sexual and Reproductive Health and Rights (SRHR). In 2020, the grant period was extended by one year and topped up with an amount of €17.3 million. This report describes the findings of an external evaluation of this funding, also known as the PDP III Fund.

The following PDPs have been co-financed under the PDP III Fund:

- Drugs for Neglected Diseases Initiative (DNDi),
- Foundation for Innovative New Diagnostics (FIND),
- International AIDS Vaccine Initiative (IAVI),
- International Partnership for Microbicides (IPM),
- Medicines for Malaria Venture (MMV) and
- TB Alliance.

The overall objective of the evaluation is to review the achievements of the six PDPs and inform decision-making on continuation of the PDP Fund and future funding mechanisms and priorities.

Main findings and recommendations on the individual PDPs during 2015-2021

Relevance

The activities of the six PDPs are highly relevant, as they develop and bring to the market products to combat or prevent poverty-related diseases[1] and conditions associated with sexual and reproductive health and rights (SRHR), which includes HIV/AIDS. Such products are highly needed, as poverty-related diseases are still widespread in Low and Middle Income Countries (LMICs), while they cause substantial loss of (quality of) life, and jeopardise public health. As the target populations lack purchasing power and hence such markets are not commercially interesting for private companies.

Effectiveness

PDPs have made substantial progress in terms of pipeline development of candidate products in 2015-2021. Even though not all activities have been carried out exactly according to the plans submitted to the Ministry of Foreign Affairs (MoFA) in 2015, the adjustments made and the results achieved are generally in line with the original objectives and goals. Since 2015 375 new products are in the pipeline, in total 30 products of the six PDPs moved one phase in the development process, while 12 products developed under PDP III funding have reached marketing stage and have been registered with national authorities or international organisations such as WHO.[2] These products are available for: treatment of patients suffering from sleeping sickness (DNDi), for the

[1] Poverty-related diseases comprise: HIV, TB, malaria and neglected tropical diseases as defined by WHO.

[2] These 12 products are: fexinidazole, for the treatment of sleeping sickness (DNDi); TB Ultra Test, Xpert XDR and Omni, for the diagnosis of tuberculosis; ProBio, Standard Q, for the diagnosis of COVID-19 (FIND); Dapivirine Vaginal Ring, for the prevention of HIV (IPM); pyronaride-artesunate (Pyramax(R)) tablets and paediatric granules, artesunate rectocaps, tafenoquine, for the treatment of various forms of malaria (MMV); pretomanid, as part of treatment for multidrug-resistant tuberculosis (TB Alliance).

diagnosis (FIND) and treatment (TB alliance) of tuberculosis, for the prevention of HIV (IPM) and for the treatment of malaria (MMV).
Besides pipeline development, increasing the accessibility of the products is an important activity for the PDPs. It is estimated that 2.4 billion people around the world have benefitted from the work done by the PDPs. While some PDPs increasingly improve access for specific groups (in particular women of childbearing age, and children), this effort is not seen systematically across all PDPs.
It is recommended that all PDPs follow a systematic approach to accessibility of products for women and children; a cross-cutting standard for PDPs may be helpful in achieving such a standard approach.

Flexibility
The COVID-19 pandemic has inevitably had an impact on operations of the PDPs. PDPs have been successful in minimizing the impact of travelling restrictions and distancing measures, by switching to remote methods of working e.g. in managing trials and keeping contacts with trial participants. COVID-19 has had impact in terms of shifting the attention from donor funding away from neglected tropical diseases (NTDs), as has happened with funding by the UK government. This financial impact is far more important than the impact on operations. At the same time the pandemic has created more attention for product development (particularly vaccines) and hence has created opportunities for several PDPs with respect to the development of COVID-19 vaccines, medicines, or diagnostic tests.

Main findings and recommendations on the funding mechanism

Relevance
Accessibility and pipeline development
The PDP III fund has focused predominantly on product pipeline development. However, accessibility is equally important in order to achieve the desired impact of the funding. Accessibility comprises all steps to reach end users, among which pricing, regulatory approval and reaching communities. With many products now on the market or ready for market introduction, the importance of optimal accessibility is growing.
It is recommended to explicitly include activities aimed at realising better access in the scope of a future PDP Fund by adopting the end-to-end approach (i.e. the whole process from identification of lead substances to the use of the end products by communities) to the funding of PDPs.

Alignment with SRHR policy of the Netherlands
Products for the promotion of sexual and reproductive health constitute one of three priority themes of the PDP III Fund (besides products in relation to poverty-related diseases, and products in relation to new and recurring epidemics). In the present COVID-19 pandemic PDPs experience that attention in funding is shifting. Two major donors, the Bill and Melinda Gates Foundation (BMGF) and the government of the United Kingdom have recently reduced the financing for PDPs. There is a risk of crowding out funding for SRHR and poverty-related diseases. Some PDPs already report feeling the impact of this development.
It is recommended to focus a future PDP Fund on two areas: products for SRH and products for poverty-related diseases.

A further focus in a potential future PDP Fund on products for SRH only would limit the possibilities for product development by PDPs. Such a focus may be less limiting if it includes activities that are related to safety of women during pregnancy and the lactating period, as some PDPs are already doing, Thus, the relevance of product development for a large and hitherto underserved group would increase.

It is recommended that, in case of a focus on SRH in a future PDP Fund, this focus is interpreted broadly, by extending funding also to activities aimed at product development and safety research for groups that are relevant for SRH, like pregnant and lactating women and women of childbearing age.

Alignment with other Dutch funding mechanisms

The Ministry of Foreign Affairs manages several funding mechanisms besides PDP funding, for instance Power of Voices and the SDG5 fund. Especially some funding mechanisms in the SDG5 fund address SRHR and, therefore, have potential synergies with PDP activities on increasing access to essential medicines and diagnostics. Yet, the evaluators did not find evidence of a systematic effort to enhance coherence and coordination between these funding mechanisms. This is a lost opportunity.

It is recommended to explore the possibility to further strengthen the coherence between the work of PDPs and other funding mechanisms of the Ministry of Foreign Affairs that have potential synergies in working on increasing accessibility of the PDP products.

Effectiveness

According to an international survey, the financial contribution of the Netherlands during 2016-2020 equalled around 11% of total funding of all PDPs by bilateral donors. [3] Dutch funding covered slightly over 3% of total expenditures of MMV and approximately 10% of those of IPM during 2016-2020. For the other four PDPs, the funding from PDP III Fund covered 5 to 6.5% of expenditures in these years.

PDPs highly appreciate the characteristics of the Dutch funding under the PDP III Fund, such as it being core funding, it's flexibility in use and the long-term view in the funding. The flexibility for instance complements project funding by other donors and enables the funding of activities that are difficult to allocate to a particular project (like capacity building), or that other donors are not willing to fund, such as exploring a new lead substance. Core funding also helps PDPs to obtain other funding with a co-funding requirement, such as US Funds or ECDTP funds. Core funding is seen as an important added value of Dutch funding.

It is recommended to keep the characteristics such as core funding, flexibility in use and a long-term view in a future PDP fund.

In the past the Dutch government was visible as influencer in the PDP field, e.g. in advocating for SRHR, and in strategy development within the PDP donor community. This role has diminished over time and was significantly lower-key during PDP III years as compared to the level in the beginning period of the PDPs, partly due to high turnover of Dutch government staff.

It is recommended that efforts are being made to step up the leadership role of MoFA in the broader donor and international community regarding PDP funding and strategy (with a view to further enhance PDP's role in SRHR and explore innovative funding mechanisms).

PDPs intensively work together with commercial private sector partners in the discovery and development of their products. In this cooperation, private partners normally participate on a commercial basis. The work of PDPs attracts limited additional funds from commercial companies, in many cases (in kind) as part of their CSR policy. From documents and interviews there appears

[3] The funding from PDP III Fund started 1 October 2015. For this reason the year 2015 has not been taken into account.

no increase in the investment of private sector in the work of PDPs during 2015-2021, whereas an increase of such investments was an important assumption in the PDP III Fund Theory of Change.

All six PDPs work together with research institutes, in several LMICs. PDPs have been investing actively in capacity building in LMICs and employ these institutes in clinical trials. PDP coalition members have performed clinical research at more than 550 sites in more than 80 countries, mostly in LMICs. When a trial is concluded, clinical trial sites experience discontinuity in their workload, which can result in loss of valuable staff. More cooperation between PDPs and other stakeholders in planning clinical trials can improve the sustainability of research capacity in LMICs.
It is recommended that PDPs improve their coordination of clinical trials in LMICs in order to improve the long-term sustainability of the research capacity.

Efficiency

Over the years, the PDP model has proven to be a cost-effective way to develop products for poverty related and neglected tropical diseases and conditions in relation to SRH. Their cost-effectiveness is better than that of commercial pharmaceutical companies. The Lancet Commission on Essential Medicines Policies states that industry-supported estimates of the cost for developed medicines set the average at USD 2.5 billion per new product, whereas DNDi estimates the costs of developing a new chemical entity at € 100-150 million, and the costs of improving a treatment at € 10-40 million. Alternative financing instruments (like direct funding of research institutes in LMICs; or financing via multilateral organisations) are suboptimal in terms of scope and, therefore, potential impact, as compared to the end-to-end approach of the PDP model.

Sustainability

The SWOT analysis shows that a main weakness of the funding mechanism is that it is financially not sustainable without grant funding. Reduction of the dependence on donor grants by increasing other funding would strengthen the sustainability. It is presently not clear to what extent this can be successful. Various ways have been explored to improve the sustainability, such as the use of impact bonds. A few possibilities have been identified to expand the funding basis. More research will be needed to explore the viability of these opportunities.
It is recommended that MoFA explores the possibility, together with PDPs and other funders, to create a common fund that is financed from impact bonds and/or from part of the margin that pharmaceutical companies can make on selling newly developed products in High Income Countries for which intellectual property rights are with PDPs.

1 Introduction

1.1 Background

Only 10% of global health research is devoted to conditions that account for 90% of the global disease burden – an imbalance that has been referred to as the 10/90 disequilibrium, and that persists since the 10/90 report was published. In 2019, spending on neglected tropical diseases and poverty-related diseases was 3,876 million USD, while total global spending on research and development (R&D) for new medicines in that same year was estimated at 190 billion USD. Heavy reliance on a highly competitive multinational drug industry has left the development of lifesaving drugs largely to market forces. Currently, it is largely purchasing power that is defining research agendas and priorities, which means that poor people's health needs are not being met.

This means there is insufficient investment in research and development and innovation in the areas of healthcare products and technologies specifically aimed at diseases and conditions related to poverty and SRHR. Accordingly, such products and technologies are all but non-existent, or unaffordable for the most vulnerable populations lacking access to adequate healthcare.

In 1990 the Product Development Partnerships (PDPs) have been introduced to accelerate the development and availability of products which are unlikely to attract private investments while in development. Since 2006, the PDP model has been deployed to promote research and development and innovation in healthcare.

1.2 The PDP concept

A Product Development Partnership is a not-for-profit public–private partnership that is specifically set up to overcome market failures and other barriers to product research and development PDPs are used for a broad range of neglected diseases, among which the poverty-related diseases which are within the scope of the PDP III Fund.[4] PDPs develop products, such as medicines, vaccines, microbicides, biologics, diagnostics, vector control products, devices, and multipurpose prevention technologies.[5] In a way, PDPs are not different from pharmaceutical companies in that they organise the complete research and development process of new products. This process includes all steps such as basic research, discovery, pre-clinical development, clinical development (phases 1, 2 and 3) and post-registration studies (phase 4).[6] The main difference with commercial pharmaceutical companies is that PDPs focus on the development of products and not on production, and that they focus on products for which there is market failure. The specific failure in this case is that there is an apparent need to prevent and/or cure diseases, but no supply of such products, as their development is not seen as an attractive investment by commercial parties due to expected low revenues.

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4 From here on in this report we will use the term 'poverty-related diseases' to comprise HIV. Tuberculosis and malaria, as well as neglected tropical diseases as defined by WHO, see https://www.who.int/health-topics/neglected-tropical-diseases#tab=tab_1

5 Policy Cures Research, G-Finder 2019. Neglected Disease Research and Development: Uneven Progress, 2019

6 In each of the development phases clinical trials are used. Phase 1 trials focus on the safety and dose range of the medicine; phase 2 trials on the efficacy of the medicine, phase 3 on the effectiveness of the treatment as compared to normal treatment. Once phase 3 is concluded successfully, registration of the medicine can be requested with national authorities and/or WHO. Once registered the product can be made widely available to patients. In this phase the effects of long term use of the medicine are monitored, including possible long term side-effects.

The PDP Delivery chain

Once the clinical trials for a product are successfully concluded and the efficacy and added value of the product is proven, PDPs take care of the registration process of developed products with national authorities and for WHO pre-qualification. Once a product is allowed on a particular market, the production and distribution are taken care of by commercial partners. To this end agreements are made between the PDP and commercial partners, on the use of intellectual property rights and product pricing, ensuring that products are affordable for users in LMICs.

In the development process PDPs use the knowledge of various partners, including commercial partners, patient organisations, scientists, advocacy groups, etc., for instance on the specific needs of patient groups. Financing is provided from a mix of sources, including donor funding from national or philanthropic organisations, donations by private parties and, in some cases, revenues from services provided to other parties.

PDPs operate a flexible model of working, which is inherent to the drug development process. Development of substances that are deemed unsuitable for LMIC contexts are abandoned, and new products are identified that enter the pipeline. PDPs have been adjusting their development model over the years. As some of their products moved through the pipeline to the implementation stage, PDPs increasingly included all aspects of access in their development model, ranging from regulatory approval, via guideline development and –advocacy to training of health workers, and community engagement.

Governance

PDPs are typically managed by a board of directors in which the various aspects of the work are reflected including scientific research, access and external relations. Most PDPs also work with external advisory committees comprising among others civil society organisations and independent scientists. Typically, PDPs have their head office in the United States or Europe, and various regional offices in LMICs.

1.3 The PDP III Fund

In the periods 2006-2009 and 2011-2014 the Dutch MoFA contributed EUR 150 million for the development of medicines, vaccines and diagnostics to combat HIV/AIDS, tuberculosis and malaria. After an evaluation of the PDP Fund II (2011-2014), the Minister for Foreign Trade and Development Cooperation decided to make a third round of funding available.

In 2015, MoFA awarded EUR 83.6 million in grants to six PDPs. The grant was awarded for a period of 5 years, from 2015 to 2020 (PDP III). In 2020, the grant period was extended by one year to cover 2021 as well (EUR 17.3 million).Specifically, the PDP III Fund focuses on the development and availability of affordable, effective medicines, vaccines, diagnostics and innovative products for neglected diseases and conditions, with a view to combating poverty and inequality.

The following organizations received funding from the PDP III Fund in the period 2015-2021:

1. The Medicines for Malaria Venture (MMV) - MMV's mission is to reduce the burden of malaria in disease-endemic countries by discovering, developing and delivering new, effective and affordable antimalarial drugs to cure and protect vulnerable populations. www.mmv.org;
2. The International Partnership for Microbicides (IPM) - IPM's mission is to provide women with safe, effective and affordable products they can use to prevent HIV and protect their sexual and reproductive health. www.ipmglobal.org;
3. The Drugs for Neglected Diseases initiative (DNDi) – DNDi's mission is to improve the quality of life and the health of people suffering from neglected diseases using an alternative model to develop drugs for these diseases and by ensuring equitable access to new and field- health tools. www.dndi.org;
4. The TB alliance - The TB Alliance's mission is to dramatically impact the tuberculosis pandemic by developing new, significantly improved, faster-acting and affordable TB treatments that are available to those who need them. www.tballiance.org;
5. The International AIDS Vaccine Initiative (IAVI) - IAVI's mission is to ensure the development of safe, effective, accessible, preventive AIDS vaccines for use throughout the world. www.iavi.org;
6. FIND - FIND's mission is to turn complex diagnostic challenges into simple solutions to overcome diseases of poverty and transform lives. www.finddiagnostics.org.

Table 1 summarises the activities and amounts per PDP disbursed within the PDP III fund.

Table 1 Overview of funding provided under the PDP III Fund (million Euro)

PDP	Title of activities PDP III	Area of work covered by MoFA funding	Funding 2015-2020	Contracted amounts 2021
DNDi	Support of global control and elimination targets of poverty-related diseases	Human African Trypanosomiasis (HAT), Leishmaniasis, Chagas Disease, Mycetoma	16.00	3.20
FIND	Smart diagnostic solutions to drive effective treatment and elimination of poverty-related diseases	Tuberculosis, Malaria Hepatitis C (HCV)	10.06	2.01
IAVI	Spurring Innovation to bring an aids vaccine to the World	HIV/AIDS	16.00	3.20
IPM	Developing Innovative Products to enhance Women's Sexual and Reproductive Health	HIV/AIDS	14.00	2.80
MMV	Breaking the cycle in malaria: prevention and protection for all	Malaria	14.94	2.99
TB Alliance	Product Development for Tuberculosis Drug Regimens	Tuberculosis	15.30	3.06
			86.3	**17.26**

Source: MoFA.

1.4 Scope of the evaluation

As per Terms of Reference (ToR; Annex A) this external evaluation focuses on whether the original aims of the PDP III fund have been achieved during the funding period 2015 – 2021. It should determine to what extent the PDPs and the used funding instrument – six individual grants over six years – meet their specific objectives in support of their general objective/outcomes. In this

assessment the large-scale effects of the COVID-19 pandemic on the achievements of the PDPs are to be taken into account.

The Dutch funding covers activities of six PDPs working on eight different diseases in more than 40 countries with a considerable network of partners. After more than 16 years of continued funding and in the highly changed context of the COVID-19 pandemic, it is important to evaluate the added value of the PDPs and to evaluate whether the original focus on the six partnerships is still relevant in light of both the Dutch policy objectives and –priorities and current global health context. The overall objective and specific objectives of this evaluation are as follows:[7]

Overall objective

- To inform decision-making on continuation of the PDP Fund and future funding mechanisms and priorities.

Specific objectives

1. To assess the relevance, flexibility, coherence, effectiveness and sustainability of the individual PDPs;
2. To assess to what extent follow-up was given to the recommendations made by the Mid- Term Evaluation of March 2019;
3. To assess the relevance, efficiency and effectiveness of the funding mechanism in reaching the (policy) goals for both the PDPs and the Dutch government – define added value of Dutch funding;
4. To provide recommendations for future funding mechanisms and priorities to promote research and product development to combat poverty-related diseases and conditions related to SRHR based on current challenges.

1.5 Evaluation questions

This evaluation includes questions of relevance, effectiveness, efficiency, sustainability and coherence, as laid down in the OECD/DAC evaluation criteria, as guiding criteria.[8] This evaluation also looks at the governance of the PDPs and how they engage with key external players and stakeholders, whether they are institutions, organizations, networks, programmes, governments or individuals.

Furthermore, this evaluation builds on the Theory of Change (ToC) that stands at the basis of the PDP III funding mechanism (Figure 1, see section 3.3.1).

We have included questions around the added value of the PDPs in the landscape of product development stakeholders, progress of the funding pipeline, and accessibility of the new products for the target groups, while also taking into account the engagement of LMICs in the development process, the role of creating awareness, and leveraging of funds from other donors and the private sector. The evaluation matrix in Annex B shows all evaluation questions and their relationship to the evaluation objectives and OECD/DAC criteria in full detail.

[7] As per Terms of Reference.

[8] https://www.oecd.org/dac/evaluation/daccriteriaforevaluatingdevelopmentassistance.htm

2 Methodology

2.1 Methodology used

We have used a *complexity-aware approach* that acknowledges the complexity of the PDP programme. A complexity-aware approach recognizes the very different types of outcomes in a programme, and the different approaches that may be needed to properly evaluate each type of outcome. A complexity-aware approach also takes into account that processes leading to outcomes may not be linear, and looks at contribution rather than attribution of the evaluation subject. Therefore, we consider this method suitable for a Theory of Change-based programme such as PDP III Fund that recognises complexity, and the many processes and stakeholders that are involved.

We have used two different approaches to evaluate the PDP III programme: 1) Sentinel Indicators and 2) Stakeholder Feedback. We have used *Contribution Analysis* as the main approach to the evaluation. Contribution Analysis is suitable to evaluate programmes that have a solid Theory of Change that clearly articulates the assumptions underlying the intervention. It can therefore test if these assumptions are valid and influential, and thus also test alternative hypotheses. One of the key starting points in Contribution Analysis is, that it has to be verified that the programme has produced (most) outcomes as intended. The PDP III Fund has some very well-defined and easily verifiable outcomes, such as an increased product pipeline for individual PDPs and increased contributions from the private sector. We also have calculated some indicators to provide evidence for the extent to which planned outcomes have been achieved. These are based on available internal or external information, such as estimated number of patients having access to a new product, translated as the number of doses, treatments or tests being distributed.

Stakeholder feedback collected information from stakeholders directly. Using Contribution Analysis, we included a focus on the more complex relationships between the programme and intended and unintended outcomes of the programme, notably the ones related to levels of contribution by various stakeholders or changes in donor policy, target country policies or policies of multilateral organisations such as WHO, and tested whether these have materialised and what the contribution of PDP III was. This left room to test alternative theories of change, for instance if changes in contributions or policy have occurred by public or political pressure, rather than by existence of the PDP III Fund.

For these two approaches, we have used a number of methodologies to collect evidence:
1) *Document review* (see Annex C for a list of reviewed documents and publications)
2) *Key informant interviews* (see Annex D for an overview of interviews by stakeholder)
3) *a Validation workshop* (see Annex F for a short report on the workshop).

With these methodologies a rich body of evidence has been obtained from different sources that enabled us to triangulate the information and obtain robust results for the evaluation.

To formulate and examine alternative theories, we included stakeholders who likely have knowledge of other donor initiatives directed at increasing access to medicines and diagnostics, such as external experts in the field of PDP, staff at relevant global (health) organisations and representatives from relevant research institutes, Civil Society Organisations (CSOs) and Non-Governmental Organisations (NGOs). This allowed us to reflect on the specific contribution of comparable donor initiatives in relation to PDP III.

A summary of the methodology can be found in the evaluation matrix (Annex B), in which the evaluation questions are translated into criteria, indicators and information sources. The guide for interviews is included in Annex E.

2.2 Limitations

Evaluating complex global health initiatives like PDPs requires three main pillars[9] :

1) A Theory of Change that grounds the evaluation;
2) Using multiple methods to help address complexity;
3) Triangulation and synthesis to build confidence in evaluation findings.

There is a Theory of Change (ToC) that forms the basis of the PDP interventions. However, a narrative that explains the thinking, mechanisms and assumptions in this ToC has been lacking.

All evaluation methodologies in a non-experimental setting have as limitation that the counterfactual cannot be established. It is, therefore, tempting to seek a confirmation of results of 'what is there', i.e., the contribution of the PDP-programme. Or, to the contrary, focus on what the programme was not able to contribute to, without formulating alternative theories of change. We aimed to contribute to alternative theories of change by explicitly exploring alternative mechanisms to support product development during our interviews and discussions. While we have done so, more detail in the background of the PDP ToC would have enabled us to more explicitly address underlying mechanisms and assumptions of the PDP III funding by looking for evidence to support or refute these mechanisms and assumptions. Thus, we would have been able construct alternative theories of change based on the Ministry's thinking, rather than our own.

A further main limitation of the evaluation is posed by the limited time span that was available for the evaluation. This means that the time window available for data collection was approximately five weeks. This has restricted the number of methodologies to those that could be implemented. For instance, due to the limited time window, it has not been possible to use methods like surveys, or network analysis by which a broader selection of stakeholders could have been included and thus potentially had provided a more diverse and complete picture that would have done justice to the complex nature of the evaluation subject.

The restricted timespan also limited the possibilities to collect data to construct quantitative indicators and verify data that seem contradictory.

The limit to the number of methodologies for data collection decreased the potential for triangulation of findings. The validation workshop has been the main tool to manage this limitation, next to grading of evidence while triangulating data from interviews and document review.

Another limitation of the current evaluation approach is the sampling strategy. We have purposefully (non-random) sampled stakeholders who know about the PDP III funding by MoFA, and/or are likely to be familiar with the work of one or more PDPs. We have taken care to have representation of all stakeholder groups: the donor, PDPs, Funding Group, industry partners, research partners and civil society partners. To get access to these individuals, we relied on the support of MoFA, RVO and the PDPs. Support by stakeholders with the selection of documents and individuals for key informant interviews is indispensable, but may lead to bias when critical reports or individuals will not be included in this evaluation. We have managed this bias to some extent by

[9] Mookherji S, Meck K. How Can We Better Evaluate Complex Global Health Initiatives? Reflections From the January 2014 Institute of Medicine Workshop. Global Health Science and Practice 2015;3(2):174-179.

triangulation of data, and by compiling a list of interviewees that was larger than the actual need. The evaluation team has decided on the final selection of interviewees, and has included independent experts that were not suggested by either the MoFA or the PDPs.

3 Findings

This chapter presents the main findings from the evaluation. It starts with a short overview in section 3.1 of four evaluations that have been carried out in recent years. Section 3.2 focuses on the evaluation questions that concern the six individual PDPs. As far as possible, general conclusions are drawn for the group of PDPs. In section 3.3 the focus is on the evaluation questions regarding the PDP III fund as a mechanism of MoFA to realise the objective, being the development and availability of affordable, effective medicines, vaccines, diagnostics and innovative products for neglected diseases and conditions. Each section starts with a text box with the relevant evaluation question(s) from the ToR.

3.1 Review of the evidence from previous evaluations

To ensure a complete and efficient implementation of the evaluation, we have built on the analyses made in previous evaluations. In this section the key findings of relevant previous evaluations are summarised.

Review of the Product Development Partnerships Fund 2011-2014 (2014) [10]

In 2014 Technopolis Group carried out a review of the Dutch Ministry of Foreign Affairs PDP Fund II for a period of 2011-2014, covering: Aeras, DNDi, FIND, IAVI, IPM, Sabin and POW PDP. The evaluation concluded that PDPs successfully progressed in their R&D pipelines and stimulated the development of local research capacity.

A number of recommendations to PDPs were provided, specifically:

- The need for more formal structures to **promote mutual learning and information sharing**, in relation to such themes as advocacy and capacity building;
- Potential reduction of costs of non-core activities by **sharing resources and streamlining operations resources** (e.g., clinical trial sites, manufacturing facilities, logistics);
- Targeting policy and decision makers with a **clearer communication and advocacy strategy.**

The PDP II Fund was recognized as an effective funding mechanism, enabling PDPs to carry out activities that would not have been possible otherwise. However, with many products still being under development, it was too early to conclude that the PDP II Fund had achieved its objectives. MoFA was recognized as a valuable partner, especially for the forward-looking and flexible funding approach, which also helped receiving additional funding from other donors. Several recommendations were made to MoFA regarding the PDP II fund and future priorities, including:

(1) consider **PDPs with not just direct linkages to SRHR,** but also connections to the broader international development agenda and the Dutch Top Sector policy;
(2) identify **where in the R&D value chain Dutch funding would have the greatest added value**;
(3) consider a need for **long-term commitment.**

10 Technopolis Group (2014). Review of the Product Development Partnerships Fund 2011-2014. Final report to the Dutch Ministry of Foreign Affairs

Mid-term Review of PDP III Fund (2019)[11]

In 2019 ACT for Performance conducted the mid-term review of the PDP III Fund, covering the 2015-2017 funding period. The mid-term evaluation concluded that PDPs' pipeline development was progressing according to plan and PDPs continued building capacity in LMICs. As in the previous evaluation, flexibility was identified as the main strength of the Dutch funding. PDP III funding was seen as leveraging attention from the PDPs for access and gender issues. The evaluation team drafted several recommendations for MoFA/RVO. For more information see section 3.2.6).

Evaluation of the Product Development Partnerships (PDP) funding activities (2015) [12]

In 2015 evaluation was carried out to inform the UK Department for International Development (DFID) and the German Ministry for Education and Research (BMBF) on the added value of their investment in PDPs. It included the assessment of DNDi, FIND and the European Vaccine Initiative (EVI), in the period of 2009- 2013. The overall recommendations included:

(1) for the governments involved to continue public funding of PDPs with the **long-term financing**, which should mostly be **unrestricted or semi-restricted**;
(2) for PDPs to seek the **diversification of their funding base in order to have flexibility** and ability to **set their own strategy**, instead of being driven by requirements of a particular dominant funder.

Product development partnerships Fund: Mid-term review (2020)[13]

The Department of Foreign Affairs and Trade (DFAT) of the Australian government is currently funding MMV, TB Alliance, FIND and the Innovative Vector Control Consortium (IVCC), for the period of 2018-2023. A mid-term review of Australian Government's support for PDPs, published in 2020, concluded that the PDPs sufficiently progressed against their planned activities. The PDP model was identified as representing value for money, yielding large-scale health and economic impacts. Yet, it was recognized that more can be done to address gender equality. PDPs' increasing role in product access was also noted, acknowledging that access barriers can be addressed by leveraging relative strengths of multiple actors.

Australian government was recommended to:

(1) **continue funding** PDPs at the same level, maintaining **core or equivalent funding flexibility**;
(2) identify critical pathways for specific product access and actors and focus more on **end-to-end solutions with demand-driven access activities**;
(3) help PDPs to strengthen their ability **to address gender equality**.

3.2 Findings regarding the six PDPs

3.2.1 Relevance of individual PDPs

Relevance & flexibility

- What is the relevance of the PDPs for the beneficiaries of the developed products?

[11] ACT for Performance (2019). Mid-term review of PDP III Fund.

[12] Boulton, I.; Meredith, S.; Mertenskoetter, T.; Glaue, F. Evaluation of the Product Development Partnerships (PDP) funding activities. (2015) 71 pp. Retrieved: https://assets.publishing.service.gov.uk/media/57a08971ed915d622c00020d/Evaluation_of_the_PDP_Funding_Activities_of_DFID_and_BMBF_final.pdf.

[13] Retrieved: https://indopacifichealthsecurity.dfat.gov.au/sites/default/files/PDPFund_Mid-Term_Review_Report_2020.pdf?v=1606429211.

All PDPs are making products that are relevant for the end-users in LMICs. These products are relevant in several ways:

- Some diseases represent a considerable loss of (quality of) life on a global scale, as is the case with HIV and AIDS, tuberculosis and malaria, while LMICs bear the brunt of the global burden of these diseases;
- Other diseases represent a relatively modest disease burden globally, but have crippling effects in communities affected by these diseases, like Human African Trypanosomiasis (sleeping sickness), Chagas Disease, or Mycetoma;
- Affordability, and acceptability in terms of side-effects, are among the main criteria in drug development by PDPs, making these products highly relevant for communities with little purchasing power and sparse health care facilities.

Table 2 gives an overview of the burden of disease for the individual diseases involved.

Table 2 Burden of diseases addressed under the PDP III fund

PDP	Disease	Burden of disease[14]
DNDi	Chagas disease	Chagas disease was responsible for 9 490 deaths (95% UI 5 500–16 500) and 275 000 DALYs[15] (184 000–459 000) in 2019. Chagas is endemic in Latin American countries, but cases are also found in other locations due to migration.
DNDi	Human African Trypanosomiasis (HAT/ sleeping sickness)	The global burden of Human African trypanosomiasis (HAT) in 2019 was 82 600 DALYs (95% UI 37 600–156 000) and 1360 deaths (95% UI 609–2580), a 98% decrease in deaths since 1990, reflecting efforts to eliminate transmission and improve case detection. Selected countries in Central Africa (Democratic Republic of Congo, Central African Republic) are among the most affected by HAT.
DNDi	Leishmaniasis (Visceral Leishmaniasis/VL, black fever / kala azar; Cutaneous Leishmaniasis, tropical sore/CL; post-kala azar dermal lesions/PKDL).	Leishmaniasis was responsible for 5 710 deaths (95% UI 1690–18 700) and 697 000 DALYs (375 000–1 620 000) in 2019. The main affected world regions are North Africa and the Middle East, Sub-Sahara Africa and Latin America.
DNDi	Mycetoma	The global burden of mycetoma is unknown. It is endemic in tropical and subtropical areas in the so called 'Mycetoma belt', which includes the Bolivarian Republic of Venezuela, Chad, Ethiopia, India, Mauritania, Mexico, Senegal, Somalia, Sudan, Thailand, and Yemen.[16]
FIND	COVID-19	To date, approximately 247 million people have had COVID-19 since the outbreak of the pandemic, COVID-19 caused 5 million deaths world-wide. Among the or geographical entities win the top-10 of highest mortality rate is only one with high-income: Taiwan. Yemen, Peru and Sudan are in the top 3 by death rate.[17]

[14] The Lancet. Global Burden of Disease. GBD cause and risk summaries. https://www.thelancet.com/gbd/summaries Accessed on 26 October, 2021.

[15] One DALY represents the loss of the equivalent of one year of full health. DALYs for a disease or health condition are the sum of the years of life lost to due to premature mortality (YLLs) and the years lived with a disability (YLDs) due to prevalent cases of the disease or health condition in a population. https://www.who.int/data/gho/indicator-metadata-registry/imr-details/158 Accessed 8 November, 2021

[16] https://www.who.int/news-room/fact-sheets/detail/mycetoma Accessed 26 October, 2021.

[17] https://coronavirus.jhu.edu/ Johns Hopkins University Coronavirus Resource Center. Accessed 1 November, 2021.

PDP	Disease	Burden of disease[14]
FIND	Fever	No estimate available. However, FINDs diagnostics of fever aim to distinguish between viral infections and bacterial infections. As an example, it would be important to distinguish between a viral and bacterial cause lower respiratory tract infections, such as pneumonia. In 2019, there were 489 million new cases of lower respiratory tract infections, causing 2.49 million deaths and 97.2 million DALYs. Lower respiratory tract infection is the number 5 leading cause of death in LMICs. The largest disease burden occurs in sub-Sahara Africa and in countries in South and Central Asia. Latin America also contributes substantially to the burden of lower respiratory tract infections.
FIND	HCV (Hepatitis C)	Globally, 113 million people are estimated to be infected with Hepatitis C in 2019. 542 000 have died of hepatitis C related causes that same year. Hepatitis C resulted in 15.3 million (95% UI 13.3–17.5) global DALYs in 2019 and 0.6% (0.5–0.7) of total global DALYs. Acute hepatitis, cirrhosis, and liver cancer contributed 1.7% (0.9–2.5), 79.5% (76.1–82.7), and 18.9% (15.9–22.2) to DALYs due to hepatitis C, respectively.
FIND, TB Alliance	Tuberculosis	Globally in 2019, tuberculosis was one of the leading causes of death by a single pathogen. Among HIV-negative individuals, the number of deaths was 1.18 million (95% UI 1.08–1.29) and the number of new cases of tuberculosis was 8.50 million (7.45–9.73). 1.8 billion people are estimated to be exposed to tuberculosis. Among the regions with the highest burden are sub-Sahara Africa, South and South-East Asia, and Eastern Europe and Central Asia. Drug-resistant tuberculosis is an increasing problem in many of these countries.
IAVI, IPM	HIV	Globally in 2019, the number of people living with HIV was 36.8 million. HIV-related deaths were 864,000 (95% UI 786,000–996,000) and the number of new HIV infections was 1·99 million (1·76–2·26). People living with HIV have an increasing susceptibility to tuberculosis, and visceral leishmaniasis. The majority of burden was seen in sub-Saharan Africa, which had 74.0% (71.4–76.9) of global HIV-related deaths in 2019. Numbers of new infections are still rising in Eastern Europe and Central Asia, as well in the Middle East and North Africa. Populations most at risk are adolescent girls and young women (highest burden: sub-Sahara Africa), men who have sex with men, and transgender women (highest burden: Latin America), sex workers (highest burden: South East Asia), people who inject drugs and incarcerated people (highest burden: Eastern Europe and Central Asia).

PDP	Disease	Burden of disease[14]
MMV, FIND	Malaria	In 2019, there were 231 million new cases of malaria. Malaria was responsible for 643 000 deaths (95% UI 302 000–1 150 000) in 2019. 356 000 deaths (169 000–626 000) occurred in children under 5 years, comprising 7.1% (4.0–10.4) of total deaths in that age group. These numbers comprise infection by the two most prevalent types of malaria parasites (*Plasmodium falciparum* and *Plasmodium vivax*). Endemic countries comprise most sub-Sahara African countries, as well as countries in South and South-East Asia.

Source: The Lancet

The six PDPs have developed several products that are being used in the diagnosis, prevention and/or cure of these diseases or to improve sexual and reproductive health. This implies that patients are actually being reached. An overview of volume of products distribution is presented in Section 3.2.2.

3.2.2 Effectiveness of individual PDP's

Effectiveness

- What is the progress of the individual PDPs in this period in terms of pipeline development?
- How does this progress compare with the objectives set out in the original grant proposals to the Dutch Government?
- To what extent has the COVID-19 pandemic been an enabling or hindering factor in the achievements of results of the PDPs?
- How do the results/activities so far contribute to increased access for the target group and accelerating delivery of effective products to people most in need? Do all beneficiaries benefit equally from the increases access to products and services?
- What unintended effects/results/outcomes (positive and negative) are being achieved by the PDPs besides the development of the product pipeline (gender equality, jobs created, people trained, etc.).

Pipeline development

Table 3 presents the information on the achievements of the PDPs in terms of pipeline development during 2015-2021; the full overview can be found in Annex G. The table shows that five PDPs together saw 30 products progress at least one phase in the development process. Some 375 new products are reported to be in the pipeline.[18] Some PDPs, such as DNDi, even managed to develop 23 new chemical entities (NCEs), of which now one has led to a marketed drug (fexinidazole),[19] which, according to one PDP representative, and one external publication[20] was initially considered outside the scope and capacities of a PDP.

Table 3 also presents the milestones in regulatory approval that are likely to have an impact on access. Most PDPs had a major breakthrough in 2015-2021 in that (one or more of) their products received a positive scientific opinion or approval from EMA, FDA, or an LMIC regulatory authority, and/or received WHO pre-qualification or were included in the list of essential medicines of the WHO.

18 Netherlands Enterprise Agency, The impact of the Product Development Partnerships. PDP III Programme 2015-2021.
19 DNDi (2021). Summary Report PDPIII 2015-2020.
20 Grace C. (2010). Product Development Partnerships (PDPs): Lessons from PDPs established to develop new health technologies for neglected diseases. DFID human development resource centre (hdrc)

Although PDPs have made substantial progress in terms of pipeline development in 2015-2021, their reports on the achievements in 2015-2020 show that not in all cases all activities have been carried out according to the plans that they had submitted to MoFA in 2015. However, the reports also show that the adjustments made and the results achieved are generally in line with the original objectives and goals.

Table 3 Summary of pipeline development under PDP III: number of substances that moved at least one phase in the development process and regulatory milestones

PDP	No.	Diseases	Regulatory milestones[21]
DNDi	7	HAT: improved combination treatment VL, CL: improved combination treatment Chagas disease: treatment for children	2018: fexinidazole receives a positive opinion from EMA. 2019: WHO includes fexinidazole as first-line treatment into the new WHO-HAT treatment guidelines, and adds fexinidazole to the 2019 WHO-Essential Medicines List. 2020: Democratic Republic of Congo (2018), Guinea, Central African Republic, Chad, Angola, Equatorial Guinea and Gabon approved fexinidazole for the treatment of HAT and updated treatment guidelines. 2021 Ravidasvir, a new drug for treatment of Hepatitis C, receives conditional registration from the Malaysian government.
FIND	11	Tuberculosis: improved tests, tests for drug resistant TB, tests for TB in patients with HIV Malaria: rapid diagnostic test for a specific form of malaria (*P. vivax*); test to distinguish Malaria and other fever Fever: biomarker-based test Hepatitis C: rapid test COVID-19: rapid test	2017: TB Ultra test recommended by WHO 2020: European Commission (CE) approval for Xpert XDR and Omni for TB and MDR-TB; WHO approves two COVID-19 tests under the Emergency Use Listing Procedure (EUL): Panbio, Abbott Rapid Diagnostics and STANDARD Q, SD Biosensor Inc.
IAVI	5	HIV: vaccine candidates; antibody products	(No products at the marketing stage)
IPM	1	HIV: dapivirine vaginal ring (DVR) as HIV prevention for women	2020: EMA Issues a Positive Opinion for the monthly DVR. 2021: WHO Prequalifies the DVR: and received WHO recommendation for use in addition, WHO adds the DVR to the WHO clinical guidelines as a choice for women at substantial risk for HIV infection.
MMV	4	Malaria: treatments adapted to children; prevention of relapse of *P.*	The updated WHO Guidelines for Malaria (February 2021) confirm that pyronaridine-

[21] As reported by the PDPs in their Annual PDP Funder Reports. List is non-exhaustive, as it focuses on products developed under PDP III funding.

PDP	No.	Diseases	Regulatory milestones[21]
		vivax malaria; treatment of severe malaria before referral	artesunate (Pyramax®) is considered a safe and efficacious combination therapy for treatment of uncomplicated malaria in all malaria-endemic areas. 2020: Adult tablet formulation registered in 29 countries; paediatric granule formulation registered in 19 countries, Pyronaridine- artesunate Listed in the national treatment guidelines of Cameroon, Côte d'Ivoire, Guinea, Niger, Nigeria and Republic of Congo. Artesunate rectal capsules for severe malaria in children > 6 months old are WHO prequalified and registered in 17 countries. 2020: marketing authorization application (MAA) approved for tafenoquine in Peru, with regulatory dossiers under review in six additional *P. vivax*-endemic countries.
TB Alliance	2	Multidrug-resistant tuberculosis: new and shorter treatment; new target substance directed against drug-resistant TB.	Approval of pretomanid (Pa) in a combination regimen (BPaL) with bedaquiline (B) and linezolid (L) for the treatment of people with highly drug-resistant forms of TB (DR-TB) by the U.S. FDA, the EMA, and the Drug Controller General of India, as well as its incorporation into WHO guidelines.

Source: PDP annual funder reports, various years

Impact of COVID-19

Relevance & flexibility

- To what extent have the PDPs been able to adjust to changing contexts, including the COVID-19 pandemic?

The COVID-19 pandemic inevitably meant a change in the way the PDPs conduct their operations. The most direct impacts were due the restrictions in travelling and physical contacts. These restrictions have affected the development process as they affected all aspects of the work of PDPs, including clinical trials. For instance, DNDi reported delays in recruiting patients for a Leishmaniasis trial in Uganda,[22] and this example is consistent with reports from other PDP staff and PDP research affiliates. Another impact has been on the availability of medical supplies due to the high demand that suppliers were facing. All in all, the COVID-19 pandemic resulted in temporary interruptions in the work and projects of the PDPs.

PDPs have reacted to these restrictions in various ways and have been successful in minimizing the impact of the restrictions on the activities and results. For instance, much greater use has been made of digital tools and platforms for tracking the situation of patients. Meetings with research

[22] DNDi. Annual Report, 2020.

partners were held digitally.[23] According to a recent report by RVO, most of the activities are running and back on track.[24] This was confirmed in the interviews with PDP representatives.

COVID-19 has caused Ministries of Health in LMICs to focus on the COVID-19 response, at the expense of poverty-related diseases. In addition, COVID-19 has had a huge impact in terms of shifting the attention from donor funding away from poverty-related diseases, as has happened with funding by the UK government (FCDO).[25] Some PDPs already report feeling the impact of this development. In interviews, PDP representatives confirmed that the impact of the pandemic on donor policies and funding is far more important than the impact on operations.

On the other hand, COVID-19 has created more attention for product development (particularly vaccines) and thus has proven the value of the research and development structures developed by PDPs in LMICs. This R&D infrastructure for instance enabled PDPs to carry out clinical trials in LMICs for COVID-19 vaccines. As the RVO report summarizes: "*For example, FIND invested in possibilities for COVID-19 testing, MMV focused on vulnerable children that are affected and DNDi shared their knowledge and network regarding chemical entities against infectious diseases by creating the ANTICOV research platform in 13 African countries. And IAVI leveraged its core technology platforms and expertise in mounting a COVID-19 program to develop antibodies for SARS-CoV2 (currently in the preclinical stage)*."[26] These and other achievements were confirmed in the interviews with staff of the individual PDPs. In Chapter 5 more details can be found on the impact of COVID-19 on operations of each PDP.

Increased access

Distribution of products developed by PDPs

Not only have PDPs brought forward products in the development process, most of them have been able to register newly developed with authorities in LMICs, get them included in treatment guidelines and/or had them included on the WHO list of essential medicines or WHO guidelines. This has been the start of sales of these products. As the products are produced and marketed by commercial partners, sales data are confidential. There are estimates that 2.4 billion people around the world have benefitted from the work done by the PDPs.[27] At the request of the evaluation team, PDPs have provided information on sales of products in recent years. The following table summarizes this information, more details can be found in the PDP sheets (see chapter 5).

Table 4 Market distribution of products developed by PDPs

PDP	Product (group)	Number distributed	First year
DNDi	ASAQ for malaria	over 500 million treatments	2003
	ASMQ for malaria	over 1.3 million treatments	2008
	NECT for HAT	100% of all stage-2 patients are now treated with NECT	
	Paediatric benznidazole for Chagas disease	11,457 children treated	
	HIV-TB Super-booster therapy	Guidelines improve concurrent HIV and TB treatment for 1 million children	
	Fexinidazole for HAT	134 patients treated	2020

[23] E.g. as IAVI reported in the PDP Funders Report 2020
[24] Netherlands Enterprise Agency, *The impact of the Product Development Partnerships, PDP III Programme*, 2021.
[25] Davies, L. (2021). 'A very cruel exit': UK's aid cuts risk rapid return of treatable diseases. The Guardian, 13 September 202
[26] IAVI Funder Report., p. 27.
[27] Netherlands Enterprise Agency, *The impact of the Product Development Partnerships, PDP III Programme*, 2021.

PDP	Product (group)	Number distributed	First year
FIND	Over 95 million products to LMICs		No details
IAVI	IAVI does not yet have products in the implementation stage		
IPM	The monthly dapivirine ring is now in the process of approval in several African countries. Data on the distribution of the ring are not yet available.		
MMV	3 day cure malaria	Approximately 3 billion	2008/2019
	Seasonal malaria chemoprevention:	355 million	2013
	Pre-referal in severe malaria	3.8 million rectocaps	2017
	Severe malaria	175 million vials	2010/18
TB Alliance	RH 75/50 2 FDC DT	1,021,226 treatment courses	
	RH 13 FDC DT	1,011,051 treatment courses	

Source: Information provided to the evaluation team by the PDPs (for more details see Chapter 5 of this report)

Actions aimed at increasing accessibility

Besides pipeline development, increasing the accessibility of the products for the patients in need is an important task for the PDPs. Given that more and more products become available now, even more efforts will be required in the next few years to optimise accessibility of medicinal products in LMICs.

From the interviews and documentation provided, evaluators conclude that PDPs do considerable efforts to secure access, and equity in access, for instance for women and children, by taking into account suitability of products for use during pregnancy and lactation, and acceptability or palatability for young children. All PDPs, albeit to varying degrees, now apply the end-to-end approach in product development in which securing accessibility already starts in the early, basic research stages.

For instance, DNDi includes pricing in the Target Product Profiles (TPPs), as well as access for women and children in terms of suitability for use in pregnancy, and palatability of the formulation. . Also, for FIND an access strategy for any specific intervention is a consideration in the earliest phases of project planning, which includes in-country delivery and uptake. IAVI aims to ensure access to a licensed AIDS vaccine for those individuals and communities who are most vulnerable and at greatest risk of HIV infection. IPM has an access advisory committee to provide strategic guidance to help ensure the dapivirine vaginal ring's successful introduction and uptake in sub-Saharan Africa, where women face the greatest risk for HIV. IPM sees engagement with the community as crucial to realise access to IPM's products. MMV's access strategy is built around supporting introduction of new products (including messaging, education, and mobilising advocates), enhancing reach of marketed products, gathering marketing intelligence and informing R&D such that unmet needs are addressed. TB Alliance worked on multiple fronts to improve access of tuberculosis treatments. It devoted significant resources to facilitate and ensure global adaptation, availability, and affordability of the bedaquiline(B), pretomanid (Pa) and linezolid (L) (BPaL) treatment regimen. It has also made a considerable contribution to addressing a gap in the paediatric TB market.

Intellectual property

All PDPs have particular Intellectual Property (IP) policies that ensure non-exclusive licensing, price limits or other provisions that ensure accessibility and affordability of their products.

DNDi has an intellectual property policy.[28] DNDi aims to secure, non-exclusive, sub-licensable, royalty-free licenses to ensure sustainable manufacturing and distribution at the lowest possible price in endemic countries.

FIND has a Global Access Strategy.[29] FIND considers IP is essential to ensure that the cost structure of new products befits LMICs and is in line with the objective to support affordable products, as well as to maximize freedom for others to use the outputs of our development projects. IP discussions may cover patent-protected intangibles, copyrights, trademark, trade secrets and data rights, for instance.

IAVI's IP management policies and practices are designed to share the results of its research broadly to help enable other researchers in the field, secure IP rights for vaccine candidates in its portfolio to ensure freedom to operate and incentivise collaboration with future industry partners and to ensure ultimate global and equitable access to an HIV/AIDS vaccine.

IPM has secured intellectual property rights to a portfolio of compounds that IPM is working on to develop into various microbicide formulations. IPM is the owner of the intellectual property associated with dapivirine vaginal ring (DVR). Therefore, it has freedom to make changes to manufacturing operations and logistics as needed to achieve the lowest possible cost while maintaining regulatory and quality standards. Generic manufacturers may also be explored for markets outside of the initial target geographical areas.

Management of IP is a key driver of the MMV partnership model. Negotiation of IP value attracts and enables successful collaboration agreements with pharmaceutical partners and researchers, 'de-risking' the venture and guarding against misuse of innovation. For compounds with a novel mechanism of action, MMV or its partners will often seek patent protection in case the compound has application for a profitable indication outside malaria, and to provide control over the quality of manufacture. In turn, there is an understanding that pharmaceutical partners will operate on a 'no profit, no loss', or low-margin "cost-plus" basis, and that patent protection will not extend to malaria-endemic countries (except for India, China and Brazil).

TB Alliance holds the IP to pretomanid, and has licensed its production to pharmaceutical company Mylan. According to its website TB Alliance is committed to ensure access though wide adoption, ensure that products are available and reach those in need, and are affordable to those with TB and their health systems.

Criticism of efforts made by PDPs

Some publications, and at least one interviewee, express concerns as to whether PDPs do enough to ensure affordable prices, or have criticised a lack of transparency about licensing.[30] [31] [32] Others have raised the question to what extent products developed by PDPs are accessible in very

[28] DNDi Intellectual Property Policy https://dndi.org/wp-content/uploads/2018/03/DNDi_Intellectual_Property_Policy.pdf

[29] Maximizing the health impact of diagnostic solutions. https://www.finddx.org/wp-content/uploads/2018/02/FIND_Access-Strategy-Web.pdf Accessed 8 November, 2018.

[30] MSF Access Campaign. Pretomanid - third new TB drug in over half a century must be affordable. https://msfaccess.org/pretomanid-third-new-tb-drug-over-half-century-must-be-affordable

[31] Muñoz, V., et al. (2015). "Can medical products be developed on a non-profit basis? Exploring product development partnerships for neglected diseases." Science and Public Policy **42**(3): 315-338.

[32] Pratt, B. and B. Loff (2013). "Linking Research to Global Health Equity: The Contribution of Product Development Partnerships to Access to Medicines and Research Capacity Building." American Journal of Public Health 103(11): 1968-1978

privatised health care systems, where private services are excluded from concessional pricing schemes, but that are nonetheless used by many patients from poor communities.[33] [34]

Factors hindering access

Despite their actions to ensure access, PDPs report that there are various factors that hinder equity in access. Some of these are beyond their reach, such as the organisation of the health care system, national government policies (or a change in government official), the availability of health care centres and health workers in remote areas, logistical challenges or the availability of other essential infrastructure.

While some PDPs increasingly improve access for specific groups (in particular women of childbearing age, and children), we do not see this effort being done systematically across all PDPs. Therefore, a systematic approach to accessibility of products for women and children is most desirable; a cross-cutting standard for PDPs may be helpful in achieving such a systematic approach and could further enhance the relevance of the products entering and leaving the pipeline of the PDPs.

Unintended effects

PDPs rarely report unintended effects. The identified effects were very mixed. Among positive unintended effects on the level of individuals that have been mentioned are job creation, and more knowledge of trial participants about their own body and HIV prevention, resulting in empowerment and behaviour change. On an organisational level, the fact that PDPs emphasise more and more the importance of access to their products from the beginning of the development process, has led to policy change with pharmaceutical companies to include access in their product development as well.[35] Glaxo, Sanofi and Novartis were mentioned in interviews as big pharmaceutical companies that are now planning systematically about access to their products in an early phase of development. Another unintended influence of PDPs on big pharmaceutical companies is the transparency about the costs of drug development e.g., from DNDi, that according to one of the interviewees, brought about a discussion about the best way of financing research and development with the pharmaceutical industry, and also opened a dialogue on how to spur innovation in other ways than charging high prices for newly developed drugs.

Negative unintended consequences mentioned during interviews were, that in a busy development landscape PDPs sometimes had a competitive rather than collaborative relationships with particular (research) partners. Interviewees mentioned uncertainty of funding as a factor contributing to attrition and turnover of (sometimes very experienced) PDP staff, as well as staff at clinical research centres.

3.2.3 Efficiency of PDPs

Over the years the PDP model has proven to be a cost-effective way to develop medicinal products for poverty-related diseases and conditions in relation to SRH. Asked about cost-effectiveness, one PDP representative stated that their cost-effectiveness was better than that of the commercial pharmaceutical industry, which was backed up by one of the independent experts interviewed as well as by a peer-reviewed report by the Lancet Commission on Essential Medicines Policies. This report states that industry-supported estimates set the average cost for medicines developed at USD 2.5 billion per new product, whereas DNDi estimates the development of a new chemical

[33] Pratt et al., 2013

[34] Puri, L., et al. (2016). "Xpert MTB/RIF for tuberculosis testing: access and price in highly privatised health markets." The Lancet Global Health 4(2): e94-e95.

[35] Access to Medicines Foundation. Access to Medicines Index 2021.

entity to cost € 100-150 million, including the costs of failure,[36] and the costs of improving a treatment at € 10-40 million.[37]

The six PDPs report on the breakdown of their expenditures in their annual reports to funders. Generally these reports show that the vast majority of expenditures is related to research and development and accessibility. Management generally takes 8 to 10% of the total expenditures.[38]

3.2.4 *Coherence of PDP's*

Coherence

- How and to what extent are the PDPs engaging with key external players and stakeholders and what is their specific added value?

Coherence is generally understood as the compatibility of the intervention with other interventions in a country, sector or institution. Focus in this section is on external coherence, which considers the consistency of the intervention with other actors' interventions in the same context.[39] Internal coherence, the consistency of PDPs with Dutch policies and standards, will be dealt with in Chapter 4 of this report.

We operationalise the external coherence of PDPs as how PDPs utilise their (many) partnerships. PDPs have 70 to nearly 500 partnerships (see also table 6). All of them are engaged with donors, research institutions (from basic research to applied research), commercial companies, regulatory authorities, WHO, Ministries of Health, health professionals and community organisations. They are the hub that connects a vast spectrum of information to serve the entire chain of development of health products for LMICs: from identification of lead substances to ensuring access and availability in communities. Some PDPs and external researchers see this 'spider in the web model' as their very essence and added value as 'system integrators'[40] over other research organisations or product developers, which is very well compatible with the OECD notion of external coherence.

PDPs sometimes also partner with each other, as is the case of FIND working closely with DNDi, TB Alliance and MMV to provide companion diagnostics for the introduction of new treatment regimens as well as advocating for better tools for LMICs. MMV has also collaborated with DNDi and taken several antimalarials from DNDi in its portfolio. These are partnerships directly related to the development of particular products for particular diseases. PDPs do not report broader collaboration or partnerships among each other, e.g., in coordination of clinical trial capacity, sharing experience with regulatory approvals, or setting standards in the field of not-for-profit product development.

[36] Wirtz, V. J., et al. (2017). Essential medicines for universal health coverage. The Lancet 389(10067): 453.
[37] DNDi (2015). PDP Annual Funder Report.
[38] Funders reports of the PDPs, various years.
[39] OECD DAC. Evaluation Criteria. https://www.oecd.org/dac/evaluation/daccriteriaforevaluatingdevelopmentassistance.htm#coherence-block Accessed 8 November, 2021.
[40] Muñoz, V., et al. (2015). "Can medical products be developed on a non-profit basis? Exploring product development partnerships for neglected diseases." Science and Public Policy **42**(3): 315-338.

3.2.5 *Sustainability of individual PDP's*

Sustainability

- What is the added value of and dependency on Dutch funding in terms of sustainability of results and financial sustainability of the individual PDPs? What other donors are supporting the PDP's?
- What other stakeholders have joined the PDP Funders Group – an informal network of donors of which the Dutch MoFA is an active member – during the period the PDPs have received support from the Dutch MoFA?

In applying for funding from the PDP III Fund, the PDPs have put forward proposals. These clearly describe for what activities financing is requested and what outcomes are to be expected. There is variation between the PDPs in terms of the part of total activities for which financing is sought, and the level of co-financing requested for those activities. In general terms, the co-financing rate ranges from 10-20% in case a major part of the activities of the PDP are put forward for co-financing, to 50-90% in case the co-financing relates to a smaller part of the activities of the PDP.[41]

The Dutch co-financing thus has a substantial role in the activities put forward for co-financing. When related to the total expenditures of the PDPs in the years 2016-2020, the Dutch funding under PDP III was responsible for approximately 3% in the case of MMV, to up to 10% in the case of IPM; for the four other PDPs this share was 5 to 6.5 %.[42]

Under the PDP III Fund MoFA provides core financing to the PDPs. This characteristic is broadly appreciated by the PDPs for its flexibility. This was already found in previous evaluations of the PDP Fund and was confirmed by the interviews for this evaluation. The core financing in principle makes it easier for PDPs to complete the financing plan. As many donors use project financing this leaves some activities potentially uncovered that are deemed necessary for the portfolio approach of the PDPs. Core funding can then be used to fill in the gaps.

The PDPs do not see the conditions as valid under the financing as a problem to use the funding. They all complied with at least one of the priority themes described in the administrative rules, i.e. products for SRHR, products for neglected tropical diseases or products for new or recurring epidemics.

All PDPs have a large portfolio of donors. Although at overall level (all PDPs together) the top 12 financing organisations are relatively stable, at the level of individual PDPs shifts occur in the donor financing regularly. PDPs report annually on the status of the (newly attracted) donor funding. These report show a broad range of donors, with varying levels of financing. For instance the DNDi Funders Report for 2020 shows a list of 37 grants that were already secured before 2020 and grants secured in 2020. Grant sizes for DNDi range from GBP 40.000 up to GBP 64 million.[43] The Dutch grant under PDP III is among the larger individual grants for DNDi. The lists of grants of other PDPs show a similar picture.

Most of the PDPs are wholly or predominantly dependent on donor funding. In the case of FIND the revenue basis was expanded substantially due to the revenues generated by the work carried out in relation to the COVID-19 pandemic. However, in all other cases PDPs continuously have to acquire new funding. The long term financial sustainability is therefore seen as a weakness (see also section 3.3.3). For instance, in the past IPM has temporarily halted development of a product due to insufficient funding (see section 5.4).

41 Based on the information contained in the proposals submitted by the PDPs to MoFA in 2015.

42 Calculated from the information based in the annual PDP Funder Reports submitted by the PDPs and the actual co-financing received.

43 See: DNDi, PDP Annual Funder Report 2020.

3.2.6 *Mid-Term Evaluation*

Relevance & flexibility

- To what extent follow-up was given to the recommendations made by the Mid-Term Evaluation of March 2019.

In the Mid-Term evaluation of 2019 various recommendations were drafted aimed at various parties: PDPs, Funders Group and the Dutch government (see text box). It is noted that the Steering Committee of this Mid-Term Evaluation did not endorse all recommendations.[44] The committee in particular expressed doubts on recommendations I (stronger focus) and IV (earmarking of funds for few specific products) and questioned details of recommendation VIII (in particular regarding the levies on products and services).

Main recommendations

i. The evaluation team recommends the PDPs to consider for the future a stronger focus on a fewer products and diagnostic tools that have a irrefutable potential to service vulnerable populations, which may strengthen even further the effectiveness of PDP III funding;
ii. Continued work could be done to ensure reporting is streamlined and coordination is reinforced;
iii. The recommendations from PDP II, as well from this mid-term review and any future evaluation, may be provided to the grantees with a strong advice to apply these in their work, and with a monitoring mechanism (e.g. mandatory section in progress reports);
iv. The evaluation team recommends MoFA to continue its funding to the PDPs while strengthening the earmarking of its funds for a few specific products relevant for SRHR and vulnerable populations. A notional earmarking is suggested, keeping the funding flexible (not earmarked on expenditures but on process results, hence providing flexibility in re-allocation of funds), while agreeing on targets related to the products;
v. MoFA could develop a communication strategy, in close collaboration with the grantees, to better inform the Dutch public and Parliament on PDP III and its concrete results;
vi. Forward looking, the evaluation team recommends MoFA to strengthen the relevance of PDP III (or a possible PDP IV) by paying more attention to neglected tropical diseases (NTDs), relatively underfunded compared to malaria, TB, and HIV;
vii. MoFA could start discussions with like-minded donors to develop a common (pooled) fund that finances the next phase of a PDP fund. A common fund will reduce the transaction costs for the grantees;
viii. The PDPs and the Funder's Group could start a joint study and initiate reflections on a sustainable funding mechanism that is less dependent on aid flows, such as an air levy system, a small tax on drugs and vaccines, or an additional levy on unhealthy industries, such as tobacco and soft drinks industries.

Source: ACT for Performance, 2019, p X (summarised by Ecorys).

In our interviews it appeared that most, if not all, PDP representatives and government officials were not aware of these recommendations. The evaluators also did not find evidence that anyone of the recommendations had been implemented.

Nevertheless, it is acknowledged that some of the recommendations touch upon issues that are still relevant, such as those with respect to communication strategy of the Dutch government (V) and exploring ways to improve financial sustainability (VII, VIII).

[44] See: Management response to the Mid-Term Review of the PDP III Fund.

3.3 The funding mechanism

3.3.1 Introduction

The PDP III Fund

With the PDP III Fund the Dutch government made EUR 86.3 million available for the period 2015-2020 to PDPs that adhered to the criteria of the fund. PDPs could submit proposals for co-financing for the whole period. In 2020 an additional EUR 17.3 million was made available for 2021. By this the time span of the funding was effectively prolonged up to 31 December 2021.

Proposals from PDPs for financing were in principle eligible for funding if they met the following criteria:

- the products to be developed are specifically meant for use in countries that are included in the List of Recipients of Official Development Assistance;
- the activities proposed for financing could relate to any phase of the project development cycle;
- the subsidy was to be used for the development of at least one of the following types of products:
  - Promotion of sexual and reproductive health;
  - Treatment, prevention and diagnostics of poverty-related diseases;
  - Treatment, prevention and diagnostics of potentially new and recurring epidemics.

Theory of change

The overall objective of the PDP III fund is defined as: "*to promote the development of medicines, vaccines, diagnostics and other devices to prevent, diagnose and treat diseases and conditions related to poverty and SRHR more quickly, cheaply, effectively and simply".* [45]

By promoting the development of such medicinal products (main objective), the PDP III fund aims to realise the following (additional) objectives[46]:

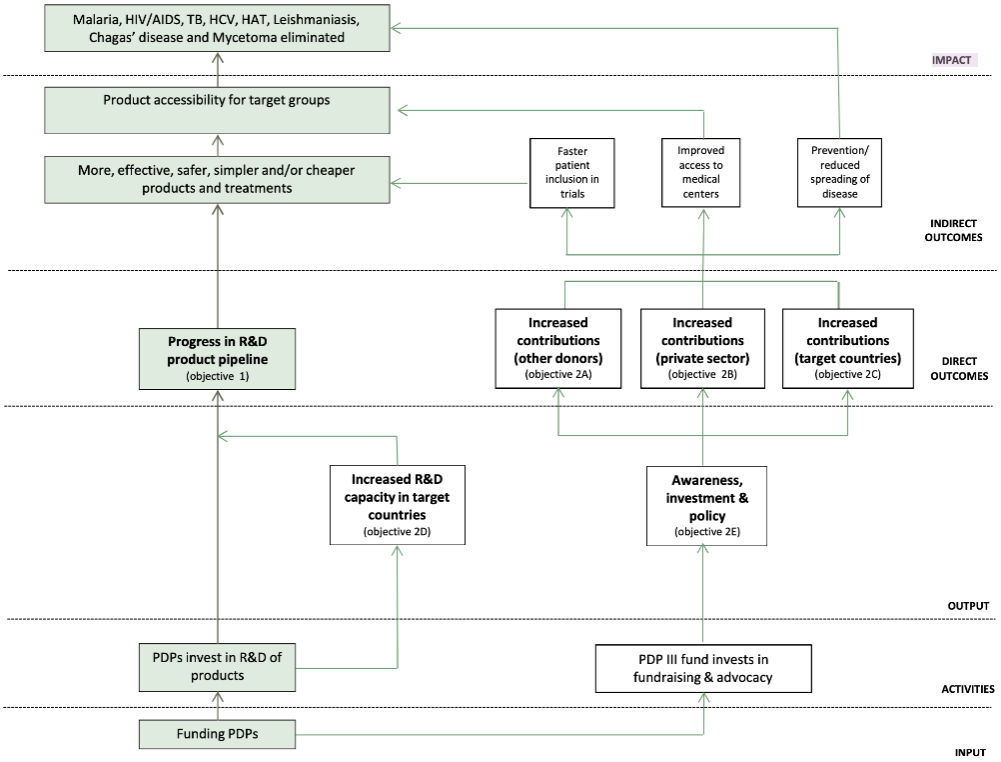
A. Increased investment in R&D and innovation in these areas by other donors (public and private);
B. Increased interest in and/or contributions from the private sector towards product development for poverty-related diseases and conditions related to SRHR;
C. Increased involvement and active participation of developing countries in product development partnerships;
D. Increased R&D capacity in the target countries regarding the research and production of medicines, vaccines and diagnostics for diseases and conditions related to poverty and SRHR;
E. More investment in and awareness of diseases and conditions related to poverty and SRHR, as well as a coherent policy approach towards this topic.

In defining these main and additional objectives, the Terms of Reference deviates somewhat from the administrative rules, as published in the Staatscourant in 2015, as well as the Theory of Change (ToC) that accompanies the ToR (see Figure 1).

[45] As stated in the Annexe to the publication of the grant in the Staatscourant.

[46] See Annexe to: Order of the Minister for Foreign Trade and Development Cooperation of 20 April 2015, no. MinBuza-2015.BZ-2015.198527, laying down administrative rules and a ceiling for grants awarded under the Ministry of Foreign Affairs Grant Regulations 2006 (Product Development Partnerships III Fund).

Figure 1 Theory of Change of the PDP III Fund



Source: MoFA.

In the administrative rules the above-described objectives (main; A-E) are called results. A distinction is made between primary results (pipeline development; A-C) and secondary results (D and E). In the ToC these results areas are divided over outputs (D and E; considered outputs of the activities of the PDPs and PDP III Fund respectively) and outcomes (pipeline development; A to C). In addition, it is noted that the administrative rules define two other results, which are neither mentioned in the ToR nor in the ToC, namely:[47]

- Primary result: Strengthened image of the Netherlands as a country with expertise in poverty-related diseases and conditions;
- Secondary result: Increased access for Dutch businesses and knowledge institutes to international public and private funding for product development in the areas of SRHR and/or poverty-related diseases.

For this evaluation a slightly revised ToC has been drafted. The core of the ToC is that the activities of the PDPs that are co-financed are being seen as the Activities, which lead to progress in the R&D product pipeline (output). In being able to carry out their activities PDPs use additional funds from other donors (A), private parties (B) and target countries (C), and develop and use R&D capacity in target countries (D). Next to pipeline development the PDPs develop activities which increase accessibility of the developed medicinal products, among others by raising awareness (E). In this respect pipeline development (objective 1) and increased awareness (objective 2E) are seen as outputs of the work of PDP's whereas results relating to A-D are seen as direct outcomes.

In other words, our interpretation of the Terms of Reference and the Theory of Change is that the main objective of the PDP III Fund is to stimulate the development of medicinal products by financing activities of PDPs in terms of pipeline development and in terms of advocacy. These are

47 Ibid.

the two main outputs of the funding of the PDPs. In realising these outputs progress may be made in realising objectives A to D as described above, which should be seen as expected outcomes of the financing of the PDP's during 2015-2021.

The expected impact of the PDP III Fund is that the greater availability of suitable products and treatments and the increased awareness result in an increase in their accessibility for target groups, thereby having an impact on the number of people suffering from diseases such as malaria, HIV/AIDS and tuberculosis. This slightly revised ToC is shown in Annex I.

The following sections should be read with this conclusion in mind. It for instance means that the expected results and impacts are to be rather seen as a result of the financed activities of PDPs and not so much as a direct consequence of the PDP III Fund itself as the Theory of Change suggests.

3.3.2 Relevance

Relevance

- What is the relevance of the PDPs regarding the current SRHR ToC and SRHR Results Framework of the MoFA?
- To what extent are the PDPs aligned to the current Dutch (SRHR) policy objectives and priorities?
- To what extent are the PDPs aligned to the current global health agenda and the Dutch Top Sector policy?

The relevance of the PDP III Fund has been assessed with a view to the policies of the Dutch Ministry of Foreign Affairs, the life sciences and health top sector and the European Commission.

SRHR policy: policy objectives and priorities, results framework

The SRHR policy of the Dutch Ministry of Foreign Affairs has the following four objectives:

1. Better information and greater freedom of choice for young people about their sexuality;
2. Improved access to SRH and HIV/AIDS medicines and commodities;
3. Better public and private health care for family planning, pregnancies and childbirth, including safe abortions;
4. The sexual and reproductive rights of all people, including those belonging to marginalized groups, are institutionally respected & protected.

In the SRHR Results Framework these objectives have been translated in several objectives for each result areas with accompanying indicators. The framework comprises in total 10 objectives (see Annex H). For these objectives the Framework defines in total 27 indicators.

Relation of PDP III Funded activities with SRHR policy

One of the three themes for which PDPs could propose financing relates to promotion of sexual and reproductive health. Three of the PDP's have defined their application as relating to this theme, such as IPM, FIND and IAVI. For others, such as MMV, TB Alliance and DNDi the focus of their application for PDP III funding is not on this theme specifically.

As the PDPs are mainly aimed at product development and accessibility, the main relation of the output and impact of their activities is with two of the 10 objectives, namely:

- Objective D: Support innovation for SRH and HIV/AIDS medicines and commodities
- Objective E: Promote access to and correct usage of safe, effective, quality and affordable medicines and commodities for:

1. Safe pregnancy and delivery, modern family planning, post-abortion care and safe abortion;
2. Prevention and treatment of HIV/AIDS.

None of the other objectives appear to be directly affected by the results of the PDP III Fund. Of course, the availability of diagnostics and medicinal products can help to stimulate the availability of services to the target group of SRHR policy (women of child bearing age, youths), but this relation is more indirect and it would not directly affect any of the other indicators in the framework.

The PDP III Fund is thus relevant in terms of contributing to one of the four policy objectives of the SRHR policy. Therefore, the PDP III Fund is considered to be to some extent relevant for the SRHR policy, given that part of the PDP's activities are beyond the scope of the policy, whereas the policy focus is much broader than availability of medicinal products.

Top sector policy

The goal of the international strategy of the Dutch Life Science and Health Top-sector (Health-Holland) is increasing the competitiveness of the sector, thereby increasing the size and impact of their international activities. [48] One of the ambitions of the strategy is to contribute to the development of solutions for global health problems in realising the sustainable development goals. The strategy poses that the Dutch health sector has much to "Ensure healthy lives and promote well-being for all at all ages" as described in SDG3. It states: through international cooperation the Netherlands can help partner countries with knowledge and technology transfer. This cooperation is expected to be also beneficial for the Netherlands, in terms of gathering new insights and strengthening the earning capacity.

The work of the PDP's fits well with this policy and several Dutch companies and research institutes are active in the various PDPs (see section 3.3.3). This is not to say that these links are the result of the PDP III Fund, as partnerships with Dutch entities would most likely have been established also in absence of the Dutch funding through the PDP III Fund. Nevertheless, it can be concluded that the PDPs fits well with the Dutch top sector policy.

Alignment of PDPs to the global health agenda

The mission of all PDPs directly supports the global health agenda, including the Sustainable Development Goals (SDGs) and WHO's Universal Health Coverage (UHC). All PDPs align with SDG3: Ensure healthy lives and promote wellbeing for all at all ages.

Within SDG3 all PDPs particularly align with the following SDG3 health targets:

- 3.3 By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases;
- 3.8 Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all;
- 3.b Support the research and development of vaccines and medicines for the communicable and non-communicable diseases that primarily affect developing countries, provide access to affordable essential medicines and vaccines, in accordance with the Doha Declaration on the TRIPS Agreement and Public Health, which affirms the right of developing countries to use to the full the provisions in the Agreement on Trade-Related Aspects of Intellectual Property Rights regarding flexibilities to protect public health, and, in particular, provide access to medicines for all.

[48] Health-Holland, Strategie Internationaal 2020-2023, p 3.

The PDPs that focus on developing products directly related SRH, like IPM, are also aligned with target 3.7:

- 3.7 By 2030, ensure universal access to sexual and reproductive health-care services, including for family planning, information and education, and the integration of reproductive health into national strategies and programmes.

The PDPs that develop products targeted for children also contribute to SDG target 3.2:

- 3.2 By 2030, end preventable deaths of new-borns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1000 live births and under-5 mortality to at least as low as 25 per 1000 live births.

PDPs have a significant role in achieving SDG3, by realising access to quality medicines through their contacts with large donors such as the Global Fund to fight AIDS, tuberculosis and malaria, PEPFAR/USAID. The Netherlands is the tenth largest public donor of The Global Fund, with a total contribution of €1,077 million to date.[49] Once a product is WHO approved and included in guidelines, these large actors can wield major influence on the availability of new products. The Global Fund can do so by procuring new products to (national) programmes in LMICs that it funds.

3.3.3 Effectiveness

Effectiveness

- Have there been significant developments in expenditure, costs and investments for PDPs by other donors?
- Has the funding mechanism provided leverage for Dutch policy priorities in international fora?
- What is the relative contribution of the Netherlands to the funding of other donors in terms of both finance and influence?
- Is there an increased interest in and/or are there investments from the private sector in product development for poverty-related diseases and conditions related to SRHR? And how and to what extent are the 6 PDPs contributing to that?
- Is there increased involvement and participation of developing countries in product development partnerships? And how and to what extent are the 6 PDPs contributing to that?
- Is there an increase in R&D capacity in target countries (training and job creation are important overall indicators for many of the programmes funded by MoFA)?
- Is there more investment in (see point E), and awareness of disease related to poverty and SRHR, as well as a coherent policy approach towards this topic? As the aspect of awareness is difficult to measure, suggested evaluation questions are:
  - Has the visibility of the PDP III Fund in the Netherlands increased?
  - Has the number of Dutch companies and knowledge institutes involved in the PDPs increased?

Trends in financing of research and development of neglected diseases

The annual G-Finder report is an important source of information on the overall financing of PDPs and the role of the Dutch PDP III Fund in this. The table below shows some relevant data for the years 2015-2019 (data on 2020 not yet available). In interpreting these data, it should be kept in mind that the G-Finder report covers a broader range of neglected diseases in developing countries than the PDP III Fund.

The table shows that almost all of the funding of PDPs comes from 12 large donors, and that the share of this group has even grown over the years. The Dutch contribution to PDPs accounted for 4

[49] https://www.theglobalfund.org/en/government/profiles/netherlands/ Accessed 9 November, 2021

to 5% of the total funding of all PDPs in 2016-2019. The low share in 2015 is due to the fact that PDP III Fund only started late 2015. Since 2016 the Netherlands has been among the top 12 funders. The G-Finder reports also show that in recent years no new bilateral donor has emerged with a substantial additional contribution.

Table 5 Funding of PDPs (million US Dollar) a)

	2015	2016	2017	2018	2019 b)
Total financing PDPs	508	467	526	553	492
Of which by top 12 funders	484	449	504	537	n.a.
Idem as % of total	95%	96%	96%	97%	n.a.
Of which PDP III Fund	5	24	24	20	19
Idem as % of total	1%	5%	5%	4%	4%
Private investments MNC	410	418	466	598	500
Private investments SME	86	106	110	96	13

Source: G-Finder 2019 Final Report; G-Finder 2020 Final Report.
a: NB: the scope of the G-Finder survey includes all PDPs, also those not co-financed from the PDP III Fund.
b: note that the data for 2015-2018 are in US dollars of 2019; data for 2019 are in US dollars of 2019.

These figures illustrate that the PDP III Fund is an important source of financing for the PDPs. It also shows the decline in overall funding in 2019, which is attributed to lower contributions from for instance Gates Foundation and UK Government (previously DFID, now DHSC).

The G-Finder report also shows investment by private companies with respect to neglected diseases. These relate to the investments for own account of these companies (multinational pharmaceutical companies – MNCs; small and medium sized enterprises- SMEs) in relation to neglected diseases and are thus not related to investments in relation to the activities of PDPs. The vast majority (71%) of this financing is related to clinical development and post registration studies, while only 20% is devoted to early stage research.[50] In addition, the majority of private investments (64 to 76% in 2015-2019) were related to three diseases: HIV/AIDS, malaria and tuberculosis; an additional 10% to neglected tropical diseases as identified by WHO. Despite their high level of investments, MNCs are responsible for only 16% of total investments in neglected tropical diseases. [51]

Involvement of developing countries

The review of the achievements of the six PDPs reveals that they have established many partnerships over time. A differing number of the partnerships are with organisations within LMICs. The following table presents a partial overview.

Table 6 Overview of partnerships of PDPs

PDP	Number of partnerships	Idem in LMICs	Among which research institutes in LMICs	Dutch knowledge partners in PDP
DNDi	Over 200		52% of research partners are in LMICs	7
FIND	332			17
IAVI	190		34	4
IPM	70	26		4
MMV	323	51		7
TB Alliance	482	94		8

Source: various documents provided by the PDPs. See also PDP sheets in chapter 5.

[50] G-Finder 2019, Final report, p. 9.
[51] Ibid., p 11.

Among these partnerships there are research institutes in target countries. The level to which PDPs have been instrumental in setting up or increasing the capacity of these institutes differs considerably between them. This is partly due to the emphasis in their activities. For instance, phase 2 and phase 3 clinical trials are more frequently organised in LMICs than phase 1 trials. Another factor that explains the difference relates to the character or scope of the PDPs. DNDi and IPM, for instance, put substantial effort in capacity building in developing countries.

The overall view from the documentation and interviews is that PDPs have had a substantial impact on R&D capacity in LMICs. PDP coalition members have performed clinical research at more than 550 sites in more than 80 countries, mostly in LMICs, according to the Netherlands Enterprise Agency.[52] In various cases, clinical research capacity in LMICs was available for testing newly developed COVID-19 vaccines. Interviewees also pointed out, though, that the lack of continuity in clinical trials is a potential threat for the continuity of these research centres.

Despite their capacity to generate much-needed interventions for neglected diseases, PDPs are not without their critics. It has been suggested that the paradigm perpetuates research disparities and power inequities between high-income countries and LMICs. Financial control and decision making power within PDPs rest with first-world head offices and senior staff primarily from the United States and Europe,[53] and many production partners who can benefit from work of PDPs are pharmaceutical companies in high-income countries. Some PDP representatives acknowledged that PDPs could step up their role for instance in enhancing phase 1 research capacity and manufacturing capacity, particularly in Africa.

Dutch policies

With respect to the leverage of Dutch policies in international fora, frequently interviewees mentioned that the Dutch focus on SRHR is generally well known and highly appreciated. With respect to the role of PDPs in tackling global health issues in general or in tackling neglected tropical diseases, the long-standing presence of the Netherlands is most telling. In this area, though, it is noted that the input by the Netherlands has been less prominent in recent years than it has been in the earlier years of PDPs

Investments in poverty-related diseases and products for SRH

According to the G-Finder survey of 2020, total investments in R&D for neglected diseases increased from 3.4 billion US dollars in 2015 to 3.9 billion US dollars in 2019.[54] It should be noted, though, that over 75% of all investments are geared to three diseases: HIV/AIDS, malaria and TB. These data are therefore not representative for investments in diseases related to poverty. The report also shows, for instance that only a small part of total investments is related to neglected tropical diseases:[55]

"Global R&D funding for neglected tropical diseases […] included in the G-FINDER survey scope has been stagnant for a decade, and this situation continued in 2019. After adjusting for participation, funding for NTDs increased by just $7.5m (2.4%), to $328m [..], marginally above the record-low share of overall neglected disease funding they received in 2018. [..] In addition to seeing little overall change, most NTDs saw little change to their individual funding levels in 2019, although the majority received small increases."

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52 Netherlands Enterprise Agency, The impact of the Product Development Partnerships PDP III Programme, 2015-2021

53 Pratt, B. and B. Loff (2013). "Linking Research to Global Health Equity: The Contribution of Product Development Partnerships to Access to Medicines and Research Capacity Building." American Journal of Public Health 103(11): 1968-1978.

54 Policy Cures Research, G-FINDER 2020, Neglected disease research and development: where to now?

55 Ibid, p. 14. Note that not all NTDs recognised by the WHO are included in the survey.

Visibility and involvement of Dutch companies

Among the partnerships shown in Table 6 there are various Dutch companies and knowledge institutions. The number reported in recent years is slightly higher than as was reported in 2015, with many partnerships that were present in 2015 still being in place.[56] It is thus concluded that the cooperation with Dutch knowledge partners has been quite stable over time. The role of PDP III Fund in this is assessed to be limited, based on the interviews.

The number of partnerships may not be the best metric to look at the Dutch input into product development. Most of these relations either were already established earlier, or are driven by the knowledge and capabilities that the Dutch partners can bring for the PDP's development processes. Also, the we have not found indications from interview partners that the visibility of the PDP Fund in the Netherlands has grown vis-à-vis the previous funding period.

3.3.4 Efficiency

Efficiency

- What are the strengths and weaknesses of the current funding mechanism? What are threats and opportunities?
- What is the role of the European & Developing Countries Clinical Trials Partnership (EDCTP) and how efficient is the collaboration between EDCTP and the Netherlands MoFA regarding the PDPs?

Alternative financing instruments

As explained in section 3.2.3, the PDP model is a cost effective way of developing medical products for poverty-related diseases and making them accessible for the people in need in LMICs. By co-financing the activities of six PDPs, the PDP III Fund contributes to this development and accessibility, thereby realising the expected impact. Although are alternative financing instruments can be envisaged to stimulate development and/or accessibility of products for poverty-related diseases, most of these alternatives would address only part of the activities of PDPs, and may therefore have more limited outcomes and impact.

One alternative to PDP co-financing would be direct funding of research institutes, either in LMICs or elsewhere. In this way Dutch financing would concentrate on the development phase of products, without necessarily adding to increased accessibility. Also the funding might involve more partners, each with a narrow scope in terms of products. Another alternative would be to directly fund multilateral organisations that stimulate development or accessibility of products for poverty-related diseases. Also in this situation the focus would be on only a part of the development and accessibility process, thereby limiting the scope of outcomes and impact.

SWOT of the PDP mechanism

Despite its cost-effectiveness, the PDP model has some drawbacks. For this evaluation an analysis has been made of the strengths, weaknesses, opportunities and threats of the PDP model from a financial and government point of view.

[56] The overview of Dutch partners of the six PDPs was derived from Netherlands Enterprise Agency (RVO).

Figure 2 A SWOT analysis of the PDP delivery model from a finance (and governance) perspective

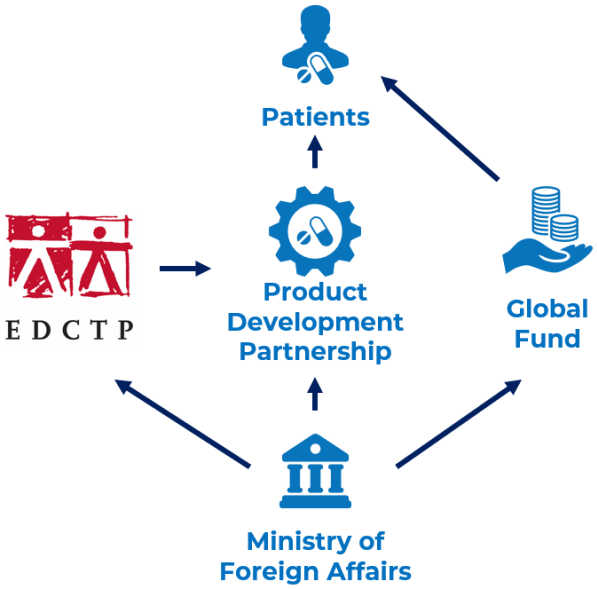
Strength: 1. Proven PPP model with long term (complex) partnerships between private and public sector 2. Mitigation / repair of 'market failure' (medicines are developed for financially unattractive markets) 3. Mitigated product development risks for private sector 4. Track-record of product delivery	***Weakness:*** 1. Relative indirect relation between funding of R&D and; • resulting medicines / products; • product delivery (uptake/access), and • 'impact' (public health indicators) 2. Not sustainable without grant funding 3. Portfolio approach requires freedom of manoeuvring (less focus on specific medicines / diseases)
Opportunity: 1. Provide core and long-term budget support 2. Strengthen / extending 'delivery chain' 3. Secure revenue upside (via development fund) 4. Social impact bonds 5. Direct funding other players in 'delivery chain' 6. Combined donor approach	***Threat:*** 1. (Other/ non-NL) Donor grants fall away 2. Weak governance / deviation of focus of donor administrations 3. 'Control' over 'trust' (micro managing PDPs) 4. Short-term budgeting 5. Overhead squeeze

One of the weaknesses of the PDP mechanism is its high dependency on donor financing. Due to reducing financing by some of the donors (UK, Gates Foundation), as well as the shifting focus due to the COVID-19 pandemic, this weakness is becoming a serious threat.

In this respect the PDP III Fund contributes to this weakness as it provides financing for 5 years, which is quite short given the time it takes to develop new medicinal products, which can easily take up to 20 years or more. This drawback is somewhat counterbalanced by the way in which the Dutch financing works. The core financing applied by the PDP III Fund provides flexibility for the PDPs which is relatively unique among donor organisations.

Dutch PDP funding has leveraged other funding, according to PDP staff. Sometimes it is not very tangible, when interviewees say the Dutch government has a good reputation as a donor, and therefore getting Dutch money is a good sign for your organisation. More concretely, more than one interviewee has mentioned that for some EDCTP or US funding calls, co-funding was required, in which case the PDP brought up the unearmarked Dutch money that helped them attract the EDCTP or US funding.

Figure 3 Synergy in Dutch funding of product development



Dutch funding not only creates major synergies in product development through its in-kind funding of EDCTP and PDPs, but also in market-shaping through its contribution to The Global Fund to fight AIDS, tuberculosis and malaria as the Fund' 10th largest donor (see Figure 3). Once the Global Fund includes a product in its procurement system, a substantial number of orders can be expected and therefore places a new product firmly on the market.

Nevertheless, a broadening of the financing basis for the PDPs is required in order to increase their financial sustainability. Various options have been explored to increase the financial sustainability, by means of a development fund or by making use of social impact bonds.

Possible opportunity: Secure possible revenue upside (via development fund)

In principle, PDPs address a market failure that arises from a low revenue expectation in a certain market in developing countries. It may however be possible that a product/medicine is relevant in other more affluent markets as well (a HIV medicine for instance) which could create additional revenue returns for a PDP. A PDP could agree with its associated pharmaceutical companies a premium on the sale price for any product that is sold outside the developing countries market. Such upside revenue sharing mechanism could stimulate PDPs and their partners to also cease these market opportunities.

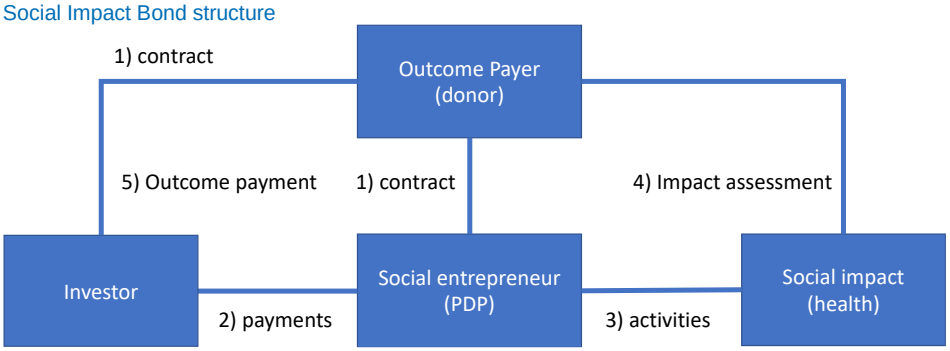
The premium could be secured in a designated 'development fund' that provides future R&D budgets for PDPs. Those budgets would enhance the sustainability and capacity of PDPs to deliver the required health / societal impact objectives. Such fund may ideally be linked to a group of PDPs, otherwise individual PDPs may prefer developing only medicines that also have a market potential in developed markets. Which would be a partial return to the market failures PDPs were designed for to overcome.

Recommendation: explore whether donors and PDPs would consider this as a proper incentive, then explore the development fund's governance principles.

Possible opportunity: Social Impact bonds

Social Impact Bonds have been in use in various sectors to help donors, social entrepreneurs and investors with measuring, financing and enhancing societal impact. See the figure below for an overview of a social impact bond structure. It is structured around a contract (1) between an outcome payer (donor), an impact investor and a social entrepreneur (read a PDP). The investor pays out working capital budgets (2) for the PDP to perform their activities (3). An outcome payment (5) is eventually made if an independent third party (4) acknowledges that the impact is realised.

Social Impact Bond structure



These bonds could be instrumental for further enhancing the impact of PDPs and / or for attracting other investor groups into the sector. Social impact bonds may be more relevant for the latter than for the former objective; PDPs have shown to be effective and efficient whilst the present funding mechanism is input and best effort based. It may be opportune to at least further explore whether a social impact bond for this sector is relevant for attracting other investor groups.

Recommendation: Explore whether a social bond structure is feasible for this sector, whether investors are available and whether donors and PDPs see opportunities for this type of support.

EDCTP

Part of the Dutch financing of PDPs is earmarked as a contribution "in kind" of the Netherlands for the work of EDCTP. This contribution is matched by a similar extra funding by the European Commission. Based on these funding EDCTP finances capacity building and clinical trials in Africa, thereby giving extra financing opportunities to PDPs.

The PDP III Fund thus fits well in with and strengthens the activities of the EDCTP. PDP staff mentioned more than once the positive contribution of EDCTP in strengthening their work *("We would not have the support we needed on many products without them").* Interviewees also wondered whether such a good partnership could not be extended to other continents outside Africa.

On a more critical note, more than once interviewees also commented on the quite heavy bureaucracy at EDCTP, especially when something in the project changes – as often happens, particularly when the pandemic struck.

4 Discussion and recommendations

In this chapter recommendations are formulated on the basis of the evidence presented and findings formulated in the previous chapter. In line with the ToR, the recommendations focus on future funding mechanisms and priorities to promote research and product development to combat poverty-related diseases and conditions related to SRHR based on current challenges. Also aspects that might become relevant in the future are taken into account.

The recommendations address the following questions from the ToR:

- What can be done to improve the relevance, efficiency and effectiveness of a new PDP funding mechanism, taking into account the current policy focus of the Dutch Ministry of Foreign Affairs, in specific the policies related to SRHR and the balance between aid and trade?
- Is the instrument of the PDP the most appropriate to stimulate research and product development to combat poverty-related diseases and conditions related to SRHR or are there any other instruments recommended?

Recommendations on a new PDP funding mechanism

On the focus in funding: accessibility and pipeline development

Although the criteria for the PDP III Fund are broadly described, the fund has focused predominantly on product pipeline development. However, accessibility is equally important in order to achieve the desired impact of the funding. Whereas pipeline development stimulates supply of products (medicines, vaccines, diagnostics, etc.), accessibility deals with the demand for these products.

Accessibility comprises all steps to reach end users, among which pricing, regulatory approval and reaching communities. This means that the product needs to be approved for marketing, needs to fit the conditions of the specific patient groups (e.g. children, women of childbearing age), need to be user friendly for these groups, etc. It also means that national governments need to stimulate the use and health professionals need to be aware of the value of the products and how they need to be applied.

Over time the PDPs have developed new products for specific patient groups. With more products becoming available or ready for market introduction, the importance of optimal accessibility is growing. Based on these observations:

It is recommended to explicitly include activities aimed at realising better access in the scope of a future PDP Fund by adopting the end-to-end approach (i.e. the whole process from identification of lead substances to the use of the end products by communities) to the funding of PDPs.

On the relation between PDP's and SRHR policy

Products for the promotion of sexual and reproductive health constitute one of three priority themes of the PDP III Fund (besides products in relation to poverty-related diseases, and products in relation to new and recurring epidemics). While there is a clear need for innovative products directly related to SRHR, particularly an effective AIDS vaccine, the needs for innovative medicinal

products for poverty-related diseases remain in a context where new and recurring epidemics have an impact on the funding landscape for poverty-related diseases.

In the present COVID-19 pandemic PDPs experience that attention in funding is shifting. Two major donors, the Bill and Melinda Gates Foundation (BMGF) and the government of the United Kingdom have recently reduced the financing for PDPs. There is a risk that COVID-19 is crowding out funding for SRHR and poverty-related diseases. Some PDPs already report feeling the impact of this development. In the past, funding for diseases new and recurring epidemics has been considerable, once such an epidemic occurred. For instance, when Ebola hit West Africa in the previous decade, $165 million were made available for R&D, masking the general decline in funding for poverty-related disease and making Ebola the fifth-best funded neglected diseases, directly behind HIV, tuberculosis, malaria and diarrhoeal diseases.[57] Therefore, based on current and past trends in funding for new and recurring epidemics, one can conclude that such diseases will be able to attract sufficient R&D funding when circumstances so dictate. Based on these observations:

It is recommended to focus a future PDP Fund on two areas: products for SRH and products for poverty-related diseases.

A further focus in a potential future PDP Fund on products for SRH only would limit the possibilities for product development by PDPs. Such a focus may be less limiting if it includes activities that are related to safety of women during pregnancy and the lactating period, as some PDPs are already doing, Thus, the relevance of product development for a large and hitherto underserved group would increase.

It is recommended that, in case of a focus on SRH in a future PDP Fund, this focus is interpreted broadly, by extending funding also to activities aimed at product development and safety research for groups that are relevant for SRH, like pregnant and lactating women and women of childbearing age.

Coherence between future PDP fund and other Dutch funding mechanisms

Accessibility for all patient groups to the newly developed products is important to realise their full impact. PDPs have been increasing their efforts into the access of their products in recent years (end-to-end approach). Increasing accessibility of the products can improve the effectiveness of the PDPs.

The Ministry of Foreign Affairs manages several funding mechanisms besides PDP funding, for instance Power of Voices and the SDG5 fund. Especially some funding mechanisms in the SDG5 fund address SRHR and, therefore, have potential synergies with PDP activities on increasing access to relevant essential medicines and diagnostics. Yet, the evaluators did not find evidence of a systematic effort to enhance coherence and coordination between these funding mechanisms. This is a lost opportunity.

It is recommended to explore the possibility to further strengthen the coherence between the work of PDPs and other funding mechanisms of the Ministry of Foreign Affairs that have potential synergies in working on increasing accessibility of the PDP products.

[57] Ebola funding boost hides ongoing decline in neglected disease R&D https://www.ghtcoalition.org/blog/ebola-funding-boost-hides-ongoing-decline-in-neglected-disease-r-d

On funding characteristics

PDPs highly appreciate the characteristics of the Dutch funding under the PDP III Fund, such as it being core funding, it's flexibility in use and the long-term view in the funding. The flexibility for instance complements project funding by other donors and enables the funding of activities that are difficult to allocate to a particular project (like capacity building) or that other donors are not willing to fund, such as exploring a new lead substance. Core funding also helps PDPs to obtain other funding with a co-funding requirement, such as US Funds or ECDTP funds. Core funding is seen as an important added value of Dutch funding.

It is recommended to keep the characteristics such as core funding, flexibility in use and a long-term view in a future PDP fund.

On the PDP instrument

Effectiveness of PDP III Fund in realising the desired impact

As described in section 3.3.1, the objective of the PDP III Fund is to reduce the burden of poverty-related diseases and improve the availability and accessibility of products related to sexual and reproductive health. The evidence presented in this report underlines that indeed more products, which were developed by the PDPs co-financed from the PDP III Fund, have become available for, and have been distributed to, patients since 2015. Other products advanced in the product development cycle of the PDPs.

Over the years, the PDP model has proven to be a cost-effective way to develop products for poverty related and neglected tropical diseases and conditions in relation to SRH. Their cost-effectiveness is better than that of commercial pharmaceutical companies. The Lancet Commission on Essential Medicines Policies states that industry-supported estimates of the cost for developed medicines set the average at USD 2.5 billion per new product, whereas DNDi estimates the costs of developing a new chemical entity at € 100-150 million, and the costs of improving a treatment at € 10-40 million. Alternative financing instruments (like direct funding of research institutes in LMICs; or financing via multilateral organisations) are suboptimal in terms of scope and, therefore, potential impact, as compared to the end-to-end approach of the PDP model.

The PDPs are thus effective in reaching the goal of product pipeline development for poverty-related diseases and conditions in relation to SRH. Alternative financing instrument (such like direct funding of research institutes in LMICs; or financing via multilateral organisations) are suboptimal in terms of scope and potential impact, as compared to the PDP model, mostly because such models would address only part of the product development and accessibility pipeline. They would either stimulate part of product development or focus on increasing accessibility.

Although the PDP III Fund has contributed to this success, it is difficult to exactly pinpoint what part of that success is due to this financing. If the PDP III Fund would not have been available, it is not likely that other donors would have stepped in. Each donor makes an individual appraisal and there is no sign found that donors directly react on each other's actions. For instance, there is no indication that the recent reductions in PDP funding by BMGF and UK government has been reason for other new donors to step in or for existing donors to increase their funding.

Given this, and given the way in which PDPs manage their portfolios of donors and activities, it is more likely that fewer activities would have taken place if the PDP III Fund had not been available. In practice this most probably means that fewer new products would have been explored and that development of products would slow down. Also, without Dutch funding the PDPs could not have applied for funding for some EDCTP funding applications for which co-funding was a requirement,

as the Dutch funding has been used as co-funding. The same holds true for applications to some US donors.

It therefore seems fair to conclude that without PDP III Funding less would have been achieved in terms of product development, and therefor in terms of (future) availability of products for people in need. Although an exact estimate of the impact of PDP III funding is not possible, some tentative remarks can be made. The funding provided by the Netherlands government in 2015-2021 equalled just over € 100 million Euro. Given this funding and the cost estimates presented above from DNDi, the size of the budget of the PDP III Fund is slightly below the cost of one successful new product development or equal to 2.5 to 10 improved treatments. This does not yet take into account the synergy that is realised via EDCTP and the Dutch contribution to the Global Fund.

Alternatively, the Dutch funding catered for approximately 5 to 6 percent of total expenditures over the past 5 years. This may indicate that due to Dutch funding 5 to 6 percent of the results of the PDPs have been realised, i.e. 5 to 6 percent of the products that progressed one stage (30), or of products that were brought to the market (12), or of other outcomes such as research capacity developed and persons trained.

At the same time there is pressure on financing and the risk of crowding out financing by COVID-19 is substantial. This would limit the possibilities for PDPs and negatively affect the realisation of impact.

Given the above observations the evaluators conclude that, in case developing and making accessible products to combat poverty-related diseases or conditions relating to sexual and reproductive health remains a policy priority, the PDP model potentially is the optimal instrument to realise this, provided that potential threats can be successfully addressed, such as with respect to financial sustainability.

Explore possibilities to improve financial sustainability

The SWOT analysis shows that a main weakness of the funding mechanism is that it is financially not sustainable without grant funding. Reduction of the dependence on donor grants by increasing other funding would strengthen the sustainability. It is presently not clear to what extent this can be successful. Various ways have been explored to improve the sustainability. A few possibilities have been identified to expand the funding basis. More research will be needed to explore the viability of these opportunities.

It is recommended that MoFA explores the possibility, together with PDPs and other funders, to create a common fund that is financed from impact bonds and/or from part of the margin that pharmaceutical companies can make on selling newly developed products in High Income Countries for which intellectual property rights are with PDPs.

Reintroduce thought-leadership of Dutch government

In the past the Dutch government was visible as influencer in the PDP field, e.g. in advocating for SRHR, and in strategy development within the PDP donor community. This role has diminished over time and was significantly lower-key during PDP III years as compared to the level in the beginning period of the PDPs, partly due to high turnover of Dutch government staff. The leadership role in the recent past of the Dutch government in strategic issues has been acknowledged and appreciated by the PDPs. In addition, PDP representatives feel that the Dutch government, with like-minded partners such as the Swiss government, could play a leadership role in the donor community and the PDP Funders Group in advocacy on issues like core funding.

It is recommended that efforts are being made to step up the leadership role of MoFA in the broader donor and international community regarding PDP funding and strategy (with a view to further enhance PDP's role in SRHR and explore innovative funding mechanisms).

Recommendations to PDPs

Besides pipeline development, increasing the accessibility of the products is an important activity for the PDPs. While some PDPs increasingly improve access for specific groups (in particular women of childbearing age, and children), this effort is not seen systematically across all PDPs.

It is recommended that all PDPs follow a systematic approach to accessibility of products for women and children; a cross-cutting standard for PDPs may be helpful in achieving such a standard approach.

All six PDPs work together with research institutes, in several LMICs. PDPs have been investing actively in capacity building in LMICs and employ these institutes in clinical trials. When a trial is concluded, clinical trial sites experience discontinuity in their workload, which can result in loss of valuable staff. More cooperation between PDPs and other stakeholders in planning clinical trials can improve the sustainability of research capacity in LMICs.

It is recommended that PDPs improve their coordination of clinical trials in LMICs in order to improve the long-term sustainability of the research capacity.

5 PDP Sheets

In this chapter summarised information is presented for each of the six PDPs financed under the PDP III Fund. The information is based on documentation received from the PDPs, such as Annual Funder Reports and the Applications for financing under PDP III, and documentation received from Netherlands Enterprise Agency (RVO). The sections are organised along the various evaluation criteria and contain information that is used in the main report. Some sections, in particular those relating to relevance, are based on additional research and assessments by the evaluation team.

5.1 Drugs for Neglected Diseases Initiative (DNDi)

MoFA Awards to DNDi	
DNDi-1	Grant of € 3 million for the period 2006-2009
DNDi-2	Grant of € 14 million for the period 2011-2014
DNDi-3	Grant of € 16 million for the period 2015-2020
Extension 2021	Grant of € 3.2 million for 2021

Source: Netherlands Enterprise Agency (RVO)

Relevance

Relevance of the developed products for the individuals in need

The Drugs for Neglected Diseases initiative's (DNDi) mission is to save lives and improve the health of people living with neglected diseases by using an alternative model to develop drugs for these diseases, and by ensuring equitable access to treatment. Table 7 shows the burden and geographical spread of the diseases for which DNDi has been developing products under the PDP III fund. These diseases mainly affect LMICs and are diseases which disproportionately impact the poorest and most vulnerable.

Table 7 Burden and geographical spread of diseases targeted by DNDi

Disease	Burden of disease[58]
Leishmaniasis (Visceral Leishmaniasis/VL, black fever / kala azar; Cutaneous Leishmaniasis, tropical sore/CL; post-kala azar dermal lesions/PKDL).	Leishmaniasis was responsible for 5 710 deaths (95% UI 1690–18 700) and 697 000 DALYs (375 000–1 620 000) in 2019. The main affected world regions are North Africa and the Middle East, Sub-Sahara Africa and Latin America.
Chagas disease	Chagas disease was responsible for 9 490 deaths (95% UI 5 500–16 500) and 275 000 DALYs (184 000–459 000) in 2019. Chagas is endemic in Latin American countries, but cases are also found in other locations due to migration.
Human African Trypanosomiasis (HAT/ sleeping sickness)	The global burden of human African trypanosomiasis (HAT) in 2019 was 82 600 DALYs (95% UI 37 600–156 000) and 1360 deaths (95% UI 609–2580), a 98% decrease in

[58] The Lancet. Global Burden of Disease. GBD cause and risk summaries. https://www.thelancet.com/gbd/summaries Accessed on 26 October, 2021.

Disease	Burden of disease[58]
	deaths since 1990, reflecting efforts to eliminate transmission and improve case detection. Selected countries in Central Africa (Democratic Republic of Congo, Central African Republic) are among the most affected by HAT.
Mycetoma	The global burden of mycetoma is unknown. It is endemic in tropical and subtropical areas in the so called 'Mycetoma belt', which includes the Bolivarian Republic of Venezuela, Chad, Ethiopia, India, Mauritania, Mexico, Senegal, Somalia, Sudan, Thailand, and Yemen.[59]

Source: The Lancet

Relevance regarding SRHR policy of MoFA

DNDi has not developed products directly related to SRH or to HIV/AIDS under PDP III funding. The only direct relationship to SRH in DNDi's overall portfolio is the development of paediatric formulations for antiretrovirals used in HIV, to improve quality of life for children living with HIV. One of DNDi's current strategic imperatives in its Strategic Plan 2021-2028 is to *"contribute to building a proactive agenda for maternal and child health and gender-responsive R&D"*[60]*.* Therefore, more broadly speaking there is alignment with the SRHR Theory of Change and Results Framework (especially pillar 2 and 3) of the Netherlands Ministry of Foreign Affairs.

Alignment Dutch Top Sector policy

The innovative character of PDPs such as DNDi is fully aligned with one of the Dutch Top Sector policy's foundations, i.e. innovation. DNDi's collaboration with selected Dutch knowledge institutes and partners contribute to the Dutch Top Sector policy. Dutch partners of DNDi include:

- Amsterdam UMC;
- Netherlands Cancer Institute;
- MSF-Netherlands;
- Rotterdam Centre for Tropical Medicine;
- Free University Amsterdam;
- Radboud University Medical Center;
- Erasmus Medical Center.

Effectiveness

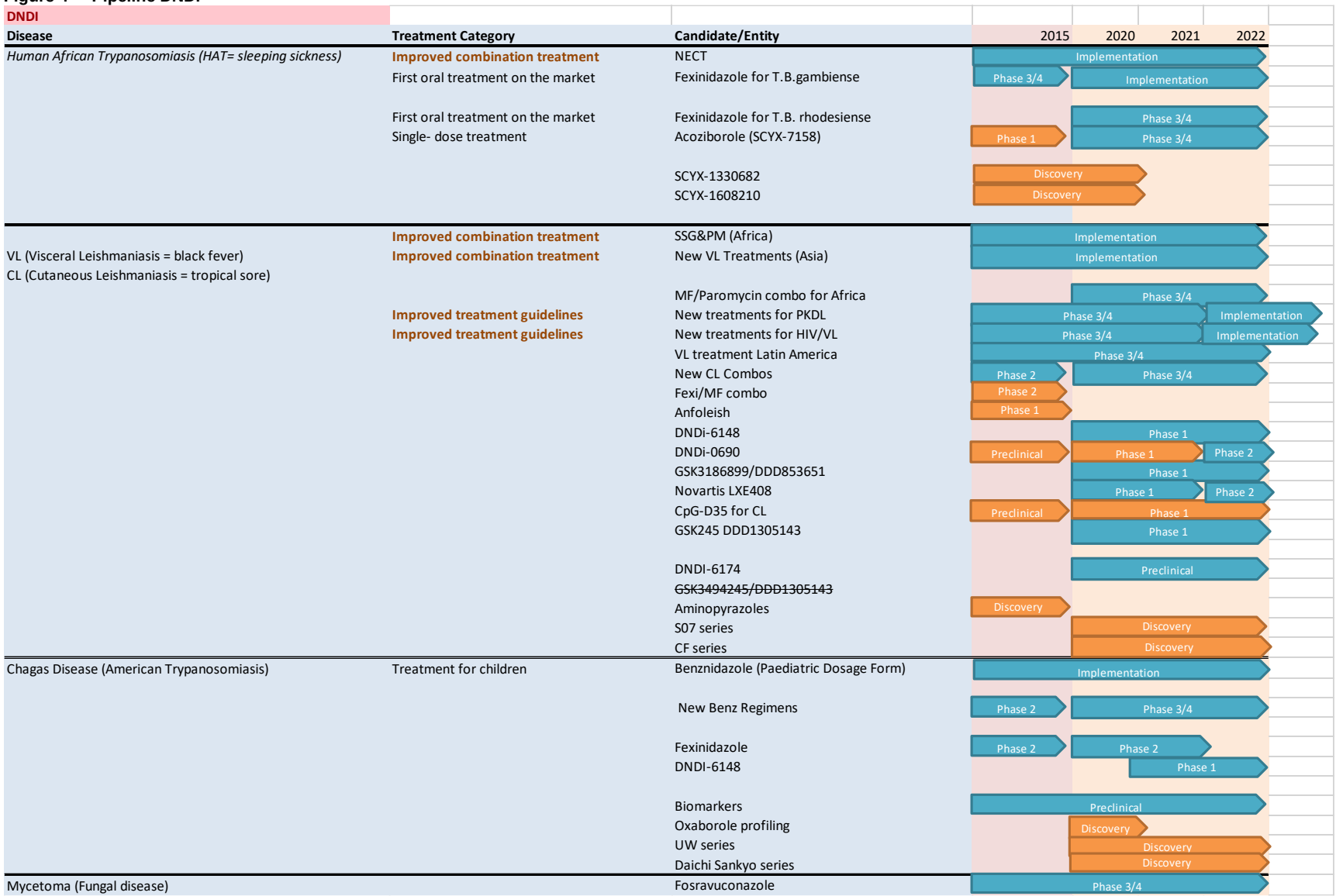
Pipeline and original targets

Figure 4 shows the progression of the funding pipeline from 2015 – 2021 funded under PDP III, with a projection for 2022. At least 7 products moved one phase or more through the pipeline. It is expected that an additional four products move one phase up in 2022, including two to implementation after registration and/ or national guideline change.

59 https://www.who.int/news-room/fact-sheets/detail/mycetoma Accessed 26 October, 2021

60 DNDi Strategic Plan 2021-2028 – 25 treatments in 25 years

Figure 4 Pipeline DNDi



The PDP III funding proposal anticipated assessment of 5-6 preclinical candidates from internally-driven programmes, supplemented by 1-2 in-licensing opportunities for Chagas disease and Leishmaniasis. Figure 4**Error! Reference source not found.** shows 8 substances in the discovery phase and 4 substances as Preclinical, which means that with 12 substances in initial phases, DNDi outperforms the original targets. In addition, 3 substances from external sources have entered the development process.

Two of the aforementioned preclinical candidates for Leishmaniasis moved up in the pipeline to phase 1 studies, while one of them is anticipated making it until phase 2 trials at the beginning of 2022. This meets the originally planned target in the funding proposal, which was to obtain 2 new drug candidates for clinical development in leishmaniasis, with one of them entering phase 2 studies. The latter was anticipated for 2018 instead of 2022, as seems to be the case now.

As to HAT, finalizing development of fexinidazole for the two types of Trypanosoma parasite is on track, as well as completion of clinical development of acoziborole. All substances are in the in phase 3 or 4 trials or fully in the implementation phase.
For Mycetoma, the PDP III proposal plans clinical trials of an already developed substance, which is in accordance with the reported funding pipeline.

Impact of COVID-19

The COVID-19 pandemic has partly hampered DNDi's work, but also provided opportunities. During the beginning of the pandemic DNDi has had weekly meetings with support teams in countries and to assess how to best monitor activities remotely.

Opportunities

- In response to the COVID-19 pandemic and inequities in research and access, DNDi launched into action to address the underserved and specific challenges of resource-constrained countries with fragile health systems.
- DNDi's core attributes placed it in a prime position to contribute its expertise and leverage its networks for COVID-19. DNDi was called to contribute to the ACT-A therapeutic partnership, notably in therapeutic selection and clinical trials in low-resource settings. DNDi established the COVID-19 Clinical Research Coalition, which has grown to nearly 700 members including close to 200 member institutions (including: Amsterdam UMC, and Radboud UMC), and launched ANTICOV, the largest clinical trial in Africa testing multiple early treatment options for COVID-19.[61]

Challenges

- DNDi has secured access to sizable compound libraries to feed its discovery pipeline. In 2020 the numbers of compounds processed from commercial sources decreased due to the delays experienced by partners during the COVID-19 lockdowns.
- The DNDi PDP III Final Report expresses concerns around funding because of the pandemic situation. With limited resources, objectives to combat the COVID-19 pandemic and the fight against neglected tropical diseases, both might compete with one another – and NTDs may lose traction on the global agenda. This may have a negative influence on donor contributions to be expected for DNDi's work.

Access for the target groups and equity in access

DNDi has realised multiple actions to improve and realise access to new treatments. Below are some examples of actions geared towards improving access, without pretending to be exhaustive.

[61] PDP III Final Report. DNDi, 2020.

Pricing

TPPs take into account the concept of affordable pricing. Contracts with pharmaceutical companies stipulate affordable pricing arrangements. As part of its commitment to cost transparency and fair pricing of medicines, DNDi publishes its drug R&D costs based on its latest historical data set.

Regulatory approval and clinical guidelines

Fexinidazole has been included as first-line treatment into the new WHO-HAT treatment guidelines and added to the 2019 WHO-Essential Medicines Lists for adults and children.
The paediatric formulation of benznidazole for Chagas disease was registered in two countries during the evaluation period (USA (2017) Argentina (2018)). The drug was already registered in Brazil and included on the WHO Model List of Essential Medicines for Children prior to the period.
DNDi is working with Ministries of Health of affected countries in Africa to adapt guidelines for HIV /VL co-infection to novel drug combinations.
DNDi provides training of health workers in new guidelines. For example, DNDi has provided training of 1519 health workers on Good Clinical Practice and Leishmaniasis during the evaluation period.

Equity

DNDi has put effort in ensuring access of children and women to new products. For instance, special drug dosing studies in children have been done for Leishmaniasis products, as well as DNDi's continued efforts to expand testing and treatment of children with Chagas disease. DNDi plans to conduct at least 6 new studies
on indications for paediatric use in its next work period (2021-2028). DNDi also has a gender strategy to help increase gender-inclusive data and research for the development of drugs and diagnostics, including proposals for a safe, ethical framework for the recruitment of women of childbearing age in clinical trials of new drugs for NTDs. DNDi developed a proposal for a safe, ethical framework for the recruitment of women susceptible to becoming pregnant in clinical trials of new drugs against NTDs. DNDi has advocated to the WHO for inclusion of the framework into the WHO's Global Strategy for Women's, Children's and Adolescents' Health (2016−2030).

Advocacy

DNDi has participated in various advocacy activities for equitable access to medicines for NTDs within the global health agenda. DNDi realised this, for instance, within UNGA High Level Meeting on UHC, and in the 2019 G20 Health Ministerial Declaration.

Distribution of developed products

Over the years DNDi has developed 9 products and/or improved treatments which have been introduced into health systems. Exact distribution or uptake numbers are not available from DNDi as much of the distribution is in the hands of its partners (WHO, PAHO, National health agencies, pharmaceutical manufacturers). A recent overview received from DNDi shows that since 2015 three products were registered (and made available to patients). One of these products (paediatric HIV) is registered in one country (South Africa, 2016), one product (regarding HAT) in 7 countries in Africa (2019), and the third product (hepatitis C, 2021) has received a conditional registration in Malaysia. The market introductions before 2015 concern six products. These treatments are registered or in treatment guidelines in 79 countries in Africa, Asia and the Americas.

Patients reached (2003-2020 cumulative):
ASAQ for malaria: over 500 million treatments distributed since 2007
ASMQ for malaria: over 1.3 million treatments distributed since 2008
NECT for HAT: 100% of all stage-2 patients are now treated with NECT

Patients reached (2003-2020 cumulative):
Paediatric benznidazole for Chagas disease: 11,457 children treated 2017-2020 (approximately 25-50% of number of infants born with Chagas disease)
HIV-TB Super-booster therapy: Guidelines improve concurrent HIV and TB treatment for 1 million children
Fexinidazole for HAT: 134 patients treated in 2020 (over 20% of all diagnosed patients; all others treated with NECT).

Involvement and increase in R&D capacity of LMICs

DNDi supports four regional clinical research platforms. These "knowledge hubs" promote scientific exchange, identify patients' needs and R&D gaps, strengthen and sustain clinical research capacity, facilitate access to new treatments, and advocate for an enabling policy and regulatory environment for needs-driven R&D.

The disease platforms have been integral in supporting DNDi operations, and in particular its clinical trials and in access activities. In total DNDi trained almost 4500 people during the evaluation period through these platforms. During the years 2015-2020 DNDi conducted an average of 18 clinical trials each year in over 18 countries. Through DNDi's clinical work over 17,000 people were enrolled in DNDi clinical studies in the five-year period. DNDi prepared or maintained around 60 trial sites on average annually during the evaluation period, in countries like Bolivia, Brazil, DRC, Guinea, Panama, Peru, Ethiopia, Kenya, Sudan and Uganda.

Sustainability

DNDi secured EUR 56 million in new funding in 2020. The 2020 Annual Report shows a large, varied number of donors, in line with DNDi's Fundraising Policy which does not allow any one donor to contribute over 25% of all donations. This diminishes the risk of depending on one (or a few) donors, thus contributing to sustainability of the organisation. Besides the Netherlands Ministry of Foreign Affairs, the report lists 17 other public institutional donors, and includes 33 named private donors, some of which are institutional donors. DNDi also receives funding from anonymous individual donors.

In DNDi's 2021-2028 Strategic Plan it reports DNDi raised EUR 630 million since 2003 and estimates a projected budget of EUR 600 million for the strategic plan through 2028.
DNDi receives substantial unrestricted funding. While unrestricted funding comprised 52% of total funding in 2020, it is a decrease from 71% in 2018.

5.2 Foundation for Innovative New Diagnostics (FIND)

MoFA Awards to FIND	
FIND-1	Grant of € 7.9 million for the period 2006-2009
FIND-2	Grant of € 10.2 million for the period 2011-2014
FIND-3	Grant of € 10.1 million for the period 2015-2020
Extension 2021	Grant of € 2.0 million for 2021
Support to ACT-A/ Covid-19	Grant of € 5.0 million for 2021

Source: Netherlands Enterprise Agency (RVO)

Relevance

Relevance of the developed products for the individuals in need

FIND, the global alliance for diagnostics, takes on the roles of connecting communities, funders, decision makers, healthcare providers and developers to advance diagnostic innovation, to ensure equitable access to reliable diagnosis around the world. The goal is to strengthen testing at primary

health care level for the vulnerable populations in LMICs, by removing the barriers that prevent accurate and timely diagnosis and providing access to diagnostic tools that are available and affordable.

Table 8 Burden of disease of FIND's PDP III portfolio

Disease	Burden of disease
HCV (Hepatitis C)	Globally, 113 million people are estimated to be infected with Hepatitis C in 2019. 542 000 have died of hepatitis C related causes that same year. Hepatitis C resulted in 15.3 million (95% UI 13.3–17.5) global DALYs in 2019 and 0.6% (0.5–0.7) of total global DALYs. Acute hepatitis, cirrhosis, and liver cancer contributed 1.7% (0.9–2.5), 79.5% (76.1–82.7), and 18.9% (15.9–22.2) to DALYs due to hepatitis C, respectively.
Tuberculosis	Globally in 2019, tuberculosis was one of the leading causes of death by a single pathogen. Among HIV-negative individuals, the number of deaths was 1.18 million (95% UI 1.08–1.29) and the number of new cases of tuberculosis was 8.50 million (7.45–9.73). 1.8 billion people are estimated to be exposed to tuberculosis. Among the regions with the highest burden are sub-Sahara Africa, South and South-East Asia, and Eastern Europe and Central Asia. Drug-resistant tuberculosis is an increasing problem in many of these countries.
Fever	No estimate available. However, FINDs diagnostics of fever aim to distinguish between viral infections and bacterial infections. As an example, it would be important to distinguish between a viral and bacterial cause lower respiratory tract infections, such as pneumonia. In 2019, there were 489 million new cases of lower respiratory tract infections, causing 2.49 million deaths and 97.2 million DALYs. Lower respiratory tract infections is the number 5 leading cause of death in LMICs. The largest disease burden occurs in sub-Sahara Africa and in countries in South and Central Asia. Latin America also contributes substantially to the burden of lower respiratory tract infections.
COVID-19	To date, approximately 247 million people have had COVID-19 since the outbreak of the pandemic, COVID-19 caused 5 million deaths world-wide. Among the or geographical entities win the top-10 of highest mortality rate is only one with high-income: Taiwan. Yemen, Peru and Sudan are in the top 3 by death rate.62

Source: The Lancet (Hepatitis C, Tuberculosis, Fever); John Hopkins University (COVID-19)

Within the PDP III, FIND facilitates access to diagnostics, focusing on Hepatitis C, TB, and malaria/fever management. In addition, FIND has received financial support from the Dutch government to support FIND's COVID-19 work within Access to COVID-19 Tools Accelerator (ACT-A). Table 8 shows the burden and geographical spread of these diseases.

Relevance regarding SRHR policy of MoFA

FIND has not developed products directly related to SRH or to HIV/AIDS under PDP III funding, although its wider product portfolio includes products directly related to SRH, such as a test to detect gonorrhoea resistance to antibiotics, a test to distinguish gonorrhoea from chlamydia in primary care, and a test to detect recent HIV infection.

62 https://coronavirus.jhu.edu/ Johns Hopkins University Coronavirus Resource Center. Accessed 1 November, 2021.

FIND also contributed to the evaluation of a sex-based treatment algorithm for the malaria treatment (P. vivax malaria with tafenoquine) as a new strategy to accelerate policy changes for P. vivax radical cure using available tools.

Three studies have been conducted on high sensitivity RDTs to detect malaria in pregnancy, which show that low-density infections, detected by these tests, are linked to increased risk of anaemia in pregnant women.
In 2020 FIND co-hosted the event together with G20 Health and Development Partnership, Women Political Leaders, and the International Council of Nurses, titled “Test to exit COVID-19: Engaging women political leaders as champions for testing”63, which focused on highlighting women leadership and engagement as champions for testing. The event was hosted on 22 June with 120+ participants from across the world.

As defined in the high-level workplan for the next 36 months, included in PDP Annual Funder Report of 2020, FIND also covers women and children as a specific field of focus and defines multiple objectives, e.g. improving antenatal NCD testing; increasing access to testing for women targeting HIV, syphilis, malaria and hepatitis B testing in antenatal care; support malaria elimination by improving tools for P. vivax.

With all aforementioned activities in mind, FIND is aligned in a broad sense with the SRHR ToC and Results Framework (especially results areas 2 and 3) of the Netherlands Ministry of Foreign Affairs.

Alignment Dutch Top Sector policy

FIND has been working with various Dutch partners with respect to academic research, policy and advocacy. Below is the overview of Dutch partners that FIND has been working with:

Organisation Name	Disease
Academic Medical Centre	Tuberculosis
Access to Medicine Foundation	Tuberculosis
Amsterdam Institute for Global Health and Development	Hepatitis C
Crucell	
Delft Imaging Systems	
Delta Diagnostics	Tuberculosis
eNose	Tuberculosis
European and Developing Countries Clinical Trial Partnership	Tuberculosis
Grand Challenges Europe	
Health Action International (HAI)	
Health Action International Europe	
Institute of Tropical Medicine Belgium	
International AIDS Vaccine Initiative	
kinetic evaluation instruments bv	Tuberculosis
KIT Biomedical research	Tuberculosis
KNCV Tuberculosis Foundation	
Leiden University Medical Center	Malaria
LUMC	Tuberculosis
Médecins Sans Frontières Netherlands	Malaria
Ministry of Foreign Affairs - Netherlands	
Philips	
RAPDIF (Rapid Diagnosis of Febrile Illnesses)	
Royal Philips	Tuberculosis
Top Institute Pharma	
Total	

Source: “Achievements FIND PDPIII 2015-2020"

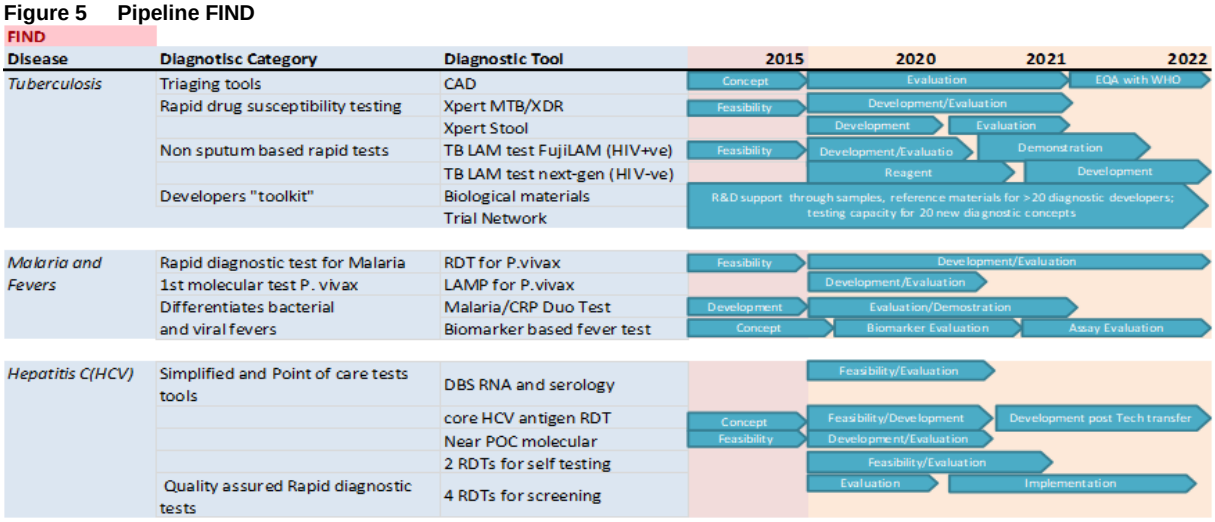
63 https://www.finddx.org/newsroom/test-to-exit/

Effectiveness

Pipeline and original targets

Figure 5 shows the progression of the funding pipeline from 2015 – 2021, with a projection for 2022, which covers three disease areas supported by the PDP III fund: Tuberculosis, Malaria/Fever and Hepatitis C. FIND has made progress in each of these focus areas. The majority of diagnostic tools that FIND started with in 2015 and those that got introduced at a later stage progressed through at least one phase through the pipeline.

Figure 5 Pipeline FIND



Source: Netherlands Enterprise Agency (RVO)

Tuberculosis

- FIND has supported the development of next-generation TB LAM and point of care urine tests. Together with partners FIND developed a suite of superior reagents for a prototype next generation unite test to detect TB in HIV-negative people.
- To inform the WHO screening guidelines, FIND conducted evaluations of three computer-aided detection (CAD) for chest X-ray tools as a class of technology for triage and screening. This technology is now formally recommended by WHO. FIND also conducted a landscape assessment of the portable and ultra-portable X-ray systems regarding CAD implementation for TB programs, to support CAD implementation in LMICs.
- FIND has contributed to improving the detection of drug resistant TB, by partnering with Cepheid to develop and evaluate the Xpert MTB/XDR test.
- During the PDP II funding period, FIND has also started to develop a biomarker database which allows identification of the best biomarkers for test development, which helps solving the siloed research at individual institutions level.

Malaria and fevers

FIND has been supporting novel molecular tools for P. vivax and lead the development of a serology P. vivax rapid test (RDT) for identification of patients with liver stage infections. It has also worked on developing and validating tests for malarial and non-malarial fevers, covering tools to differentiate bacterial and viral fevers. This has included work on Biomarker based fever test (BFF-DX), which aims at improving care in non-sever patients in low resource settings. By 2020 the study has collected data from Brazil and Malawi for approx. 10 host biomarkers. FIND has also progressed with Malaria/CRP DUO test to support care of patients with fever in LMICs. In 2020 CRP-Malaria combo test evaluation study was conducted in India. Th results have been made available to manufacturers in order to support the test registration in India. Further impacts studies

have been carried out in Myanmar and Cambodia and early CRP implementation studies in Vietnam, Thailand and Myanmar.

Hepatitis C

- Since 2017 FIND delivered two point-of-care (POC) molecular tests. Together with partners FIND has identified 4 quality assured rapid diagnostic tests (RTDs) for screening and self-testing (ST) for WHO pre-qualification clearance.
- 10 studies have been conducted on HCV self-testing to collect evidence on feasibility, acceptability, and usability, to be used by WHO for HVC self-testing recommendation, with a focus on marginalized populations.
- FIND together with partners successfully completed cAg RDT prototype development, which facilitates cheap and simple confirmatory test using the HCV core antigen (cAg) as a marker.

Impact of COVID-19

The COVID-19 pandemic presented not only challenges for FIND, but also substantial opportunities. As described FIND is presently a main actor in the diagnostic response as a co-convenor with the Global Fund of the ACT-A Diagnostic Pillar. The ACT-Accelerator offers a springboard for accelerated diagnostics innovation and implementation. For instance, FIND works in ACT-A to develop capacity for sequencing of new health threats, variants and resistant bacteria (AMR) globally. The strong focus on COVID-19 since February 2020 has not negatively affected the effort to address diagnostic needs for the other diseases.

Access for the target groups and equity in access

FIND has a global access policy that is shaped around the “four A’s”, which means that diagnostics developed by FIND are Available, Appropriate, Affordable and Adopted. Developing a global access strategy for any specific intervention is a consideration in the earliest phases of project planning, which includes in-country delivery and uptake. The importance of access has evolved in the past years in FIND. Since 2015 there is an access team and program. That program focuses on making sure that tests not only are used but then are linked to health outcomes that lead to treatments or prevention interventions. This approach has been used in the development of tests for HAT, together with DNDi, as a contribution to eradicating HAT.

By working on ensuring equitable access to diagnostics for poverty-related diseases as well as COVID-19, FIND has undertaken multiple activities in order to improve access for vulnerable groups including women and girls. Together with Women in Global Health, FIND gathered the evidence on women’s access to testing and explored the potential role of women as drivers of change in health systems, which resulted in the report published in 2020 “Health in their hands: testing & women’s empowerment means better health for all”[64].

In terms of special target groups for access to diagnostics, FIND is developing diagnostic tests for TB in children, for which there are very few good tools to date. Besides, FIND is developing a fever screening tool that has great relevance for children.

FIND has a gender equality policy. The gender equality policy addresses the organisation itself, as well as programmatic activities. The latter includes assessments ‘to identify gender dynamics that affect the disease and its control that will better enable the creation of innovative solutions’. In addition, FIND commits to provide gender disaggregated data ‘for all interventions, to indicate if/how gender impacts outcomes’. See the section ‘Relevance regarding Sexual and Reproductive Health and Rights (SRHR) policy of MoFA’ for an overview of FIND’s activities to foster gender-equity in diagnostics development.

[64] https://www.finddx.org/wp-content/uploads/2021/03/Health-in-their-hands_FULL_Nov-2020.pdf

Distribution of developed products

FIND reports in its review of activities over 2015-2021 that it has provided "*over 95 million products [….] to LMICs. Of the supported products, 10 were in use in LMICs by end 2020, 67% of the target*".[65] No details are available on the type of products, timing and/or geographic spread of these distributions.

Involvement and increase in R&D capacity of LMICs

In 2020, FIND trained 2 318 health workers (48% women) and strengthened 233 laboratories or testing sites. In 2015, the number of trained health workers was 1 786. While FIND doesn't state where these health workers were situated, it is assumed that the majority of them come from LMICs given FIND's product portfolio.

FIND representatives have stressed the bi-directional relationship in their capacity building activities.

FIND staff report a gap in local manufacturing capacity, while the need to enhance the actual production of diagnostic tests is clearly there. COVID-19 has accelerated this need.

Sustainability

The FIND Annual lists 18 institutional donors in 2015. The latest annual report published, over 2019, reports 14 institutional donors. In this period, the total of contributions received by FIND (USD 63.0 million) more than doubled. In 2019, the UK government (DFID) was the single largest donor contributing to over one-fourth of FINDs budget that year. FINDs growing budget and its role in developing diagnostics for the current COVID-19 pandemic is likely to contribute to its sustainability, within the restrictions that PDPs face in developing products for which the patients or consumers have no purchasing power.

5.3 International AIDS Vaccine Initiative (IAVI)

MoFA Awards to IAVI	
IAVI-1	Grant of NLG 5 million for 1999
IAVI-2	Grant of NLG 45 million over four years awarded in 2000
IAVI-3	Grant of * over three years awarded in 2004
IAVI-3 suppl.	Supplementary grant of € 4 million
IAVI-4	Grant of € 16.2 million for the period 2006-2009
IAVI-5	Grant of € 13.3 million for the period 2011-2014
IAVI-6	Grant of € 16 million for the period 2015-2020
Extension 2021	Grant of € 3.2 million for 2021

Source: Netherlands Enterprise Agency (RVO)

Relevance

Relevance of the developed products for the individuals in need

IAVI is a Product Development Partnership established in 1996 to develop safe, effective, accessible, preventive HIV vaccines for use throughout the world. IAVI has applied for PDP III funding to advance the clinical development of HIV vaccine candidates working in close collaboration with public and private partners worldwide, especially in Africa, to deliver the Programme Goal of an expanded pipeline of novel HIV vaccine candidates, as well as other biomedical HIV prevention methods, developed, designed and tested by IAVI and partners across

[65] FIND, Summary of progress under PDPIII 2015-2020 (and 2021) supported by the Government of Netherlands, 2021, p. 5.

the world, which meet the needs of those most vulnerable to and disproportionately affected by AIDS. Africa is the continent still disproportionally affected by HIV, with 1.4 million (93%) of all new HIV infections globally each year occurring in SSA and women and girls accounting for 63% of those new infections in 2020; there is still a global burden with LMICs on each continent harbouring different key populations most at risk for HIV (and AIDS), see Table 9 for more details.

Table 9 Burden and geographical spread of HIV

Disease	Burden of disease[66]
HIV	Globally in 2019, the number of people living with HIV was 36.8 million. HIV-related deaths were 864,000 (95% UI 786,000–996,000) and the number of new HIV infections was 1·99 million (1·76–2·26). People living with HIV have an increasing susceptibility to tuberculosis, and visceral leishmaniasis. The majority of burden was seen in sub-Saharan Africa, which had 74.0% (71.4–76.9) of global HIV-related deaths in 2019. Numbers of new infections are still rising in Eastern Europe and Central Asia, as well in the Middle East and North Africa. Populations most at risk are adolescent girls and young women (highest burden: sub-Sahara Africa), men who have sex with men, and transgender women (highest burden: Latin America), sex workers (highest burden: South East Asia), people who inject drugs and incarcerated people (highest burden: Eastern Europe and Central Asia).

Source: The Lancet

Relevance regarding SRHR policy of MoFA

The SRHR policy priority of the Netherlands MoFA includes HIV/AIDS. As such, IAVI fully aligns with the current Theory of Change and Results Framework of this policy, particularly the result "Support innovation for SRH and HIV/AIDS medicines and commodities" (result area 2, objective D).

Alignment Dutch Top Sector policy

In spurring its vaccine development, IAVI has liaised with the following Dutch organisations amidst of its 190 partners from academia, biotechnology, and pharmaceutical sector, as well as civil society and global health initiatives:

- Amsterdam Medical Centre;
- Crucell/Janssen Pharmaceutical Companies;
- Batavia Biosciences;
- Erasmus University Medical Centre.

In addition, IAVI has long-standing advocacy partnerships with Aidsfonds, Share-Net, AIGHD and KNCV.

Effectiveness

Pipeline and original targets

The pipeline (Figure 6) shows that IAVI has advanced a pipeline of 5 novel HIV prevention approaches including those designed to ensure a durable and broad cellular and antibody response. It also shows that one of these candidates progressed to phase 2b studies. This is in line with the expected result in the project proposal, that anticipated 5-6 such novel vaccine approaches, and to support the most advanced candidates towards phase 2b efficacy trials. Additionally, in early 2021, IAVI and Scripps scientists released results from a germline targeting vaccine (eOD GT 60mer) that successfully initiated the complex process of development of broadly neutralizing antibodies (bnAb) in a Phase I clinical trial. Building on these positive results, IAVI will

[66] The Lancet. Global Burden of Disease. GBD cause and risk summaries. https://www.thelancet.com/gbd/summaries Accessed on 26 October, 2021.

leverage mRNA technology to advance an mRNA eOD GT8 60mer vaccine later in 2021 in Phase 1 testing with an aim to ultimately generate potent and broadly protective antibodies.

Figure 6 IAVI's product pipeline 2015-2022

Disease	Treatment Category	Candidate/Entity	2015	2020	2021	2022
HIV/AIDS	Vaccine candidates	Ad26, gp140 (HPX2006/HVTN705)	Phase 1	Phase 2b		
		Cabotegravir (HPTN084)		Phase 3		
		PrEPVacc		Phase 3		
		eOD-GT8	Preclinical	Phase 1		
		eOD-GT8 mRNA	Preclinical		Phase 1	
		BG505 GT1.1 gp140			Phase 1	
		BG505 SOSIP gp140	Preclinical	Phase 1		
		HIVconsv	Preclinical		Phase 1	
		VSV-HIV		Preclinical		
	Antibody product	VxPDC:PGT121, PGDM1400, VRC07-523LS		Phase 1 / 2a		
	Antibody product	VxPDC: 3BNC117-LS-J and 10-1074-LS-J		Phase 1 / 2		
	Antibody product	enhanced bNabs		Preclinical	Phase 1	

Source: Netherlands Enterprise Agency (RVO)

Moreover, IAVI advanced four broadly neutralizing antibodies to preclinical development with three first generation antibodies having completed evaluation in Phase I trials. With IAVI's partner, the US National Institute of Health (NIH), having established proof of concept in early 2021 for antibody-based prevention through the Phase IIb AMP trial, it is anticipated that antibody-based prevention and the development of vaccines designed to generate such antibodies, can be accelerated.

Impact of COVID-19

As with most PDPs, the COVID-19 pandemic provided some opportunities and posed some challenges for IAVI.

Opportunities

- In the initial phase of the pandemic, February 2020, IAVI scientists responded rapidly and began applying one of its HIV vaccine technologies — recombinant vesicular stomatitis virus (rVSV) as a vaccine vector — to COVID-19.
- While initial results of the candidate rVSV vaccine were disappointing, this has urged the organisation to go back to the design lab to make improvements (ongoing) To strengthen protective immune responses and apply formulations that can be especially suited to use in resource-low settings. IAVI also applied its knowledge on neutralizing antibodies to identify potent neutralizing antibodies from recovered COVID-19 patients. This portfolio of antibodies is the foundation of a program designed to develop affordable and accessible antibodies with potential application to COVID-19 and to new coronaviruses that may arise.

Challenges

- COVID-19 presented a set of challenges for enrolment in and conduct of ongoing clinical trials. The IAVI clinical research team and their partners met these challenges with new solutions, by quickly deploying tools and methods to move many site monitoring visits and participant follow-up visits to virtual platforms with the aim of protecting the health and safety of staff, partners, and participants. Direct data capture to reduce paper handling is also being increasingly used and is improving efficiencies in data management for trials.
- While some trials and trial sites experienced slower or lower enrolment due to the pandemic, most trial targets are back on track, thanks to creative adaptations to local situations. IAVI implemented other creative methods such as having trial staff contact volunteers by telephone or WhatsApp for follow up. Planned in-person meetings, trainings and travel were also adapted to virtual platforms where possible to ensure study activities continued.

Access for the target groups and equity in access

IAVI pays attention to gender balance in trial participation, having succeeded through gender-mainstreaming in its actions to increase the participation by women to an average of 53.8%. Through participation in the Coalition to Accelerate and Support Prevention Research (CASPR), IAVI is strengthening the capacity of African CSOs representing adolescent girls and young women (AGYW) and female sex workers (FSW) to champion their rights to exercise greater involvement in decision making that affects them and creating an enabling environment for these female populations to participate in the development of acceptable and needed HIV prevention tools (incl. multi-purpose prevention technologies) to close critical gaps in women's prevention toolkit/options.

Several IAVI publications address special issues of key populations for their effective involvement in HIV research. IAVI's approach to community engagement is essential to conduct safe and ethical HIV research in a way that avoids the potential for social harm such as discrimination, gender-based violence and stigma to study participants, especially those most vulnerable, including AGYW, men who have sex with men (MSM), transgender women, and fishing communities.

IAVI is also participating in research among key populations at risk for HIV and vulnerable communities, garnering research insights in these communities that are relevant to guide policy making in the AIDS response and for future product development. For instance, IAVI, in partnership with the Uganda AIDS Commission, has developed guidelines and a road map for delivering HIV and AIDS services in vulnerable Ugandan fishing communities; and helped develop National Implementation Guidelines for HIV and STI Programming Among Young Key Populations, in Kenya.

Distribution of developed products

As Figure 6 shows, IAVI does not yet have products in the implementation stage.

Involvement and increase in R&D capacity of LMICs

IAVI has forty clinical research partners in Africa and India as of 2020, including 11 state-of-the-art clinical research centre partners with 12 GCLP-accredited laboratories capable of conducting clinical research at international standards.

As part of the IAVI-led ADVANCE programme, that drives IAVI's HIV Prevention & Community Engagement work, IAVI collaborates through the CASPR Advocacy network of strategic partnerships and activities toward supporting and strengthening India- and Africa-led biomedical HIV prevention research, implementation, and advocacy. The CASPR network, led by AVAC, brings together several Africa- and India-based partners — including the Wits Reproductive Health and HIV Institute, WACI Health, HIV/AIDS Vaccine Ethics Group, the New HIV Vaccine and Microbicide Advocacy Society, and Advocacy for Prevention of HIV and AIDS — to accelerate HIV prevention research in Africa and India.

IAVI and partners published a total of **333 scientific publications** during PDP III period with an increase in articles co-authored or lead by African researchers from 29% to 64%**.** On average 28% were female author. Through its Capacity Building Program, scientists in Africa were strengthened in their basic science research skills to be able to more meaningfully contribute to HIV vaccine design and become qualified scientists through degree training (Masters/PhD) with a total of 42 individuals supported by the International Training Program to date. Twenty-nine HIV vaccine candidates have been advanced to clinical trials across 11 countries. To date, Phase I trials are rarely conducted in LMICs, for regulatory and capacity reasons. IAVI managed its first ever Phase I trials in Kenya, Rwanda, Zambia, India, (and Germany) in 2001. IAVI trained 970 Scientists in

LMICs in Good Clinical Practices and GCLP to international standards for conducting clinical trials in the years 2018 - 2020.

Sustainability

The 2020 IAVI Annual Report mentions across IAVI's entire portfolio, 40 governments, foundations and other donors, of which 12 government institutional donors. At December 31, 2020, grants from U.S. Government agencies and foreign government agencies represented approximately 20% and 61% of grants receivable, respectively. In 2020, Dutch funding represented about 3% of total HIV-related revenue, and about 4.6% of governmental donor funding.

5.4 International Partnership for Microbicides (IPM)

MoFA Awards to IPM	
	Core Funding to IPM of € 10 million for the period 2002-2008
IPM-1	Grant of € 12 million for the period 2006-2009
IPM-2	Grant of € 9.4 million for the period 2011-2014
IPM-3	Grant of € 14 million for the period 2015-June 2021
Extension 2021	Grant of € 2.8 million for 2021

Source: Netherlands Enterprise Agency (RVO)

Relevance

Relevance of the developed products for the individuals in need

Since its inception in 2002, IPM is dedicated to preventing HIV/AIDS and improving women's sexual and reproductive health by developing new HIV prevention and multipurpose prevention technologies (MPTs). IPM works to improve women's health by accelerating the development and availability of safe, effective products women could use discreetly to protect themselves against HIV, addressing a critical gap in the HIV prevention strategies currently available.

Table 10 Burden and geographical spread of HIV

Disease	Burden of disease
HIV	Globally in 2019, the number of people living with HIV was 36.8 million. HIV-related deaths were 864 000 (95% UI 786 000–996 000) and the number of new HIV infections was 1.99 million (1.76–2.26). People living with HIV have an increasing susceptibility to tuberculosis, and visceral leishmaniasis. The majority of burden was seen in sub-Saharan Africa, which had 74.0% (71.4–76.9) of global HIV-related deaths in 2019. Numbers of new infections are still rising in Eastern Europe and Central Asia, as well in the Middle East and North Africa. Populations most at risk for HIV are adolescent girls and young women (highest burden: sub-Sahara Africa), men who have sex with men, and transgender women (highest burden: Latin America), sex workers (highest burden: South East Asia), people who inject drugs and incarcerated people (highest burden: Eastern Europe and Central Asia).

Source: The Lancet

IPM has advanced HIV prevention products for women that harness potent antiretrovirals (ARVs) to address the urgent need for prevention methods that women can control themselves. Every minute 6 people under the age of 25 become infected with HIV. Among newly infected 15 –25 year olds in

LMICs, females outnumber males two to one.[67] This highlights the need for affordable, effective, female-controlled HIV prevention methods such as the ones under IPM's development.

Relevance regarding SRHR policy of MoFA

The SRHR policy priority of the Netherlands MoFA includes HIV/AIDS. As such, IPM fully aligns with the current Theory of Change and Results Framework of this policy, particularly the result "Support innovation for SRH and HIV/AIDS medicines and commodities" (result area 2, objective D). IPM's focus on female-controlled HIV prevention, which is hitherto underrepresented in product development, is also broadly aligned with the result area 1 "Better information and greater freedom of choice for young people about their sexuality".

Alignment Dutch Top Sector policy

IPM has an extensive partnership network of 68 organisations. Among these, IPM lists the following Dutch organisations:

- Aidsfonds;
- Global Network of People Living with HIV (GNP+);
- Pharmaceutical Research Associates (PRA);
- Venn Life Sciences (formerly Kinesis Pharma B.V.).

Effectiveness

Pipeline and original targets

IPM's current product pipeline has moved the dapivirine vaginal ring from Phase 3 trials to marketing stage. Further development focuses on products closely related to this ring, such as a combination with a contraceptive, and a longer-acting dapivirine ring that could be used for 3 months instead of 1 month. Active development of the other 6 products in the pipeline has been halted.

Figure 7 Pipeline IPM

Source: Netherlands Enterprise Agency (RVO)

Testing the dapivirine vaginal ring beyond Phase III trials to obtain priority regulatory approvals, and provide early access to the ring to Phase III trial participants, is within the original objectives as stated in the PDP III funding proposal.

The planned subsequent implementation and market introduction and delivery programs in at least four African countries to support access to the dapivirine ring is also largely within the original objectives as stated in the PDP III funding proposal. Approval has been received in Zimbabwe and is pending in: Botswana, Eswatini, Kenya, Lesotho, Malawi, Namibia, Rwanda, South Africa, Tanzania, Uganda and Zambia. Reportedly, four of these countries have also approved the ring without yet having made their decision public.

[67] UNAIDS. Gender & AIDS fact sheets: HIV/AIDS and young people. https://data.unaids.org/topics/gender/youngpeople_en.pdf Accessed 28 October, 2021.

Further development of the 3-month dapivirine-levonorgestrel ring for HIV prevention and contraception to Phase III trials and the 3-month dapivirine-only ring to clinical trials, as outlined in the PDP III funding proposal, has not been achieved. This is due to technical challenges related to the ring device. Phase I safety-trials of the 3-month ring have been completed.

The planned preclinical/nonclinical studies on products based on various ARVs that were mentioned in the PDP III proposal have been put on hold in response to advise from IPM's Scientific Advisory Board to focus IPM's limited resources on:1. The monthly DVR (the licensure program); 2. Dapivirine-contraceptive ring (MPT ring); and 3.

Impact of COVID-19

The impacts of COVID-19 on IPM's work were monitored throughout 2020 across IPM's departments. Given IPM's virtual work model and that there were no IPM-led clinical trials ongoing, the impact on IPM's programs was manageable. Some examples of the impact of COVID-19 and how negative impacts were managed:

- COVID-19 Impact on Regulatory and Quality Affairs Activities: Given imposed remote working conditions, there were continued delays in compiling and transferring essential information for drug regulators. IPM has put strategies in place to overcome and manage these delays.
- COVID-19 Impact on Community Engagement Activities: In-person community outreach activities - which form a significant part of IPM's outreach activities - were halted in line with country guidelines. To ensure continued outreach, IPM supported community-based partners efforts to revise workplans so educational and support activities could progress, albeit on a smaller scale.
- COVID-19 provided an opportunity to examine how work and outreach could be continued without face-to-face engagement. In response to the COVID-19 the situation, IPM provided partners with non-pharmaceutical interventions (masks and hand sanitizers) and technical support to host engagements using virtual platforms. Many successful engagements, trainings, and dialogue sessions were implemented remotely. In 2020, 2,379 people (1,885 women and 494 men) attended community level training and skills building events. Online community activities were hampered in rural and poor communities, where connectivity was limited because people cannot afford smart phones or large data bundles.

Access for the target groups and equity in access

IPM has an access advisory committee to provide strategic guidance to help ensure the ring's successful introduction and uptake in sub-Saharan Africa, where women face the greatest risk for HIV.

By developing and delivering safe, effective and affordable prevention products for women, IPM incorporates demographic, geographic and gender equity in all its work.
To achieve maximum public health impact, equity is a necessary and vital component of any future rollout strategy of IPM microbicide products. IPM conducts market and end-user research that includes analysis by age, sex, geographic location and socioeconomic status, to address potential inequities in product access and use.

IPM sees engagement with the community as crucial to realise access to IPM's products. Woman-centred healthcare can only be effective if women are part of the process. To support adolescent girls and young women to stay informed and engaged, IPM continued to sponsor and utilize Inside My Purse, a blog for and by young women in Africa to discuss topics of SRH and well-being in a non-judgmental environment. This is just one example of ways IPM stays engaged with the communities where the monthly dapivirine ring trials took place and market introduction is expected.

IPM has started an engagement with health care workers, particularly making sure that they don't become the barrier for the ring for young people. According to IPM, a judgmental attitude about sex may hamper access to HIV-prevention methods such as the dapivirine ring.

Distribution of developed products

As explained above the monthly dapivirine ring is now in the process of approval in several African countries. Data on the distribution of the ring to the target group in these countries are not yet available.

Involvement and increase in R&D capacity of LMICs

IPM has actively focused resources to build research capacity in sub-Saharan Africa. Over the course of IPM's clinical research, achievements included:

- Increasing and developing physical infrastructure and strengthening human resource capacity at research centres;
- Developing research centre capability to conduct ethical and high-quality clinical trials
- Providing professional development opportunities for research centre staff, including doctors, nurses, counsellors, laboratory technicians, finance, community and administrative staff, among others
- During 2015-2020 IPM published 67 articles in peer-reviewed journals, of which 21 were LMIC-led.

Sustainability

In 2015 IPM reported having 10 grants for their work, from 8 different donors. In 2020 IPM reports 7 grants, by 7 donors (including PDP III). Although IPM planned to receive a new donor funding commitment by the end of 2020, this did not materialise. IPM reports having submitted two funding applications that could result in such a commitment. IPM staff report that the funding situation currently is difficult. Taking all this into account, the funding situation and hence the sustainability of IPM is a known risk that is included in IPM's risk analysis and mitigation plan.

5.5 Medicines for Malaria Venture (MMV)

MoFA Awards to MMV	
MMV	Grant of € 14,942,667 for the period 2015–2020
Extension 2021	Grant of € 2,988,533 for 2021

Source: Netherlands Enterprise Agency (RVO)

Relevance

Relevance of the developed products for the individuals in need

Medicines for Malaria Venture (MMV) is a Product Development Partnership (PDP) established as a Not-for-Profit Swiss foundation in 1999. Its mission is to reduce the burden of malaria in disease-endemic countries by discovering, developing and delivering new, effective and affordable antimalarial drugs for vulnerable and under-served populations. Infants and women of childbearing potential (WoCBP) currently represent two of the most vulnerable and underserved groups, between them carrying the majority of the global malaria disease burden. Pregnant women are more likely to bitten than other women, and are more likely to suffer severe consequences of malaria, in part because pregnancy reduces a woman's immunity, and also because the placenta provides a location where malaria parasites can reside. A variable level of access to healthcare decreases women's access to malaria prevention and treatment and increases their vulnerability.

Table 11 Burden and geographical spread of Malaria

Disease	Burden of disease[68]
Malaria	In 2019, there were 231 million new cases of malaria. Malaria was responsible for 643 000 deaths (95% UI 302 000–1 150 000) in 2019. 356 000 deaths (169 000–626 000) occurred in children under 5 years, comprising 7.1% (4.0–10.4) of total deaths in that age group. These numbers comprise infection by the two most prevalent types of malaria parasites (*Plasmodium falciparum* and *Plasmodium vivax*). Endemic countries comprise most sub-Sahara African countries, as well as countries in South and South-East Asia.

Source: The Lancet

Relevance regarding SRHR policy of MoFA

Although MMV does not develop products with a direct relationship with SRH, MMV's mission aligns with Ministry of Foreign Affairs' objectives to support the development of innovative and novel medicines designed for use in the most vulnerable patients (such as pregnant women and very young children) and reduce maternal mortality rates. There is a clear focus on the main target groups of the Dutch policy on SRHR (women of childbearing age; youths) and there is a direct link with the SRHR Results Framework, since malaria treatment and prophylaxis during pregnancy contributes to safe pregnancy and delivery in results area 2, objective E "Promote access to and correct usage of safe, effective, quality and affordable medicines and commodities for: 1. Safe pregnancy and delivery, modern family planning, post-abortion care and safe abortion 2. Prevention and treatment of HIV/AIDS."

Alignment Dutch Top Sector policy

Throughout the 5-year reporting period, MMV successfully collaborated with a number of Dutch research organizations to complete the planned activities for PDP III, including:

- TropIQ Health Sciences, Nijmegen;
- Radboud University Medical Center, Nijmegen;
- Pivot Park Screening Centre, Oss;
- Lygature, Utrecht;
- Biomedical Primate Research Centre, Rijswijk;
- Mercachem, Nijmegen;
- Consultants, e.g. Hermkens Consultancy.

These organizations assisted with the development and completion of drug screenings and mosquito feeding assays, evaluation of mosquitocidal compounds, training of African scientists and/or project management.

Effectiveness

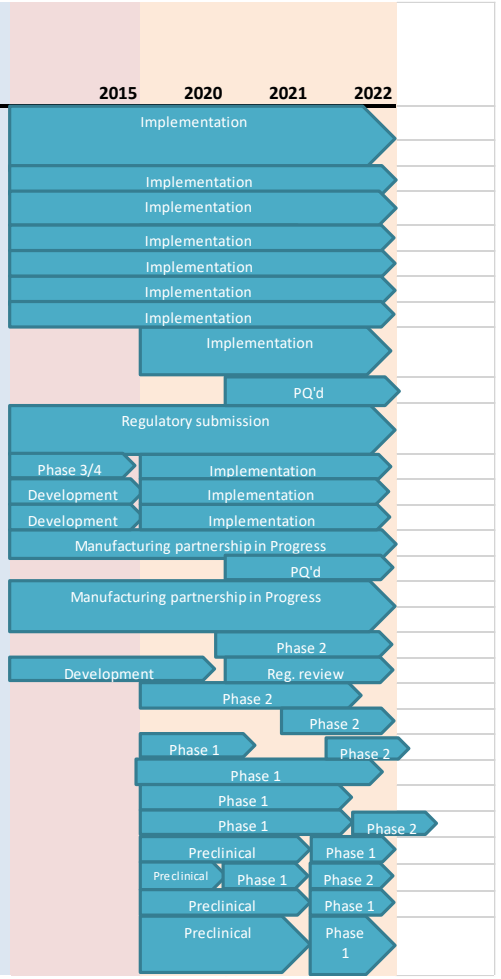
Pipeline and original targets

Ten components or treatments for malaria moved up the pipeline one phase or more. This includes transmission blocking agents mentioned in the PDP III funding proposal, developed in partnership with Dutch partner TropIQ. Further progress during the funding period includes replenishing the pipeline with the eyes on the emerging artemisinin resistance. This includes next generation tools to replace today's artemisinin-based therapies in Africa, and repurposing tools for severe malaria as replacement for artemisinin monotherapies used today.

[68] The Lancet. Global burden of disease. GBD cause and risk summaries. https://www.thelancet.com/gbd/summaries Accessed 27 October, 2021.

Figure 8 Pipeline MMV

Disease	Indication/treatment category*	Candidate/Entity/Manufacturer
Malaria	3 day cure, uncomplicated malaria, artemisinin-based combination therapy	Coartem® dispersible (artemether-lumefrantine), Novartis
	Severe malaria	Larinate® 60 mg for injection (artesunate for injection), Ipca
	Severe malaria	Artesun® (artesunate for injection), Fosun Pharma
	3 day cure, uncomplicated malaria, artemisinin-based combination therapy	Eurartesim ® (dihydroartemisinin - piperaquine), Alfasigma
	3 day cure, uncomplicated malaria, artemisinin-based combination therapy	Pyramax ® (pyronaridine-artesunate), Shin Poong
	3 day cure, uncomplicated malaria, artemisinin-based combination therapy	Pyramax® granules pediatric (pyronaridine-artesunate), Shing Poong
	3 day cure, uncomplicated malaria, artemisinin-based combination therapy	ASAQ Winthrop® (artesunate-amodiaquine), Sanofi
	3 day cure, uncomplicated malaria, artemisinin-based combination therapy	ASMQ (artesunate-mefloquine), Cipla
	Seasonal Malaria Chemoprevention	SPAQ-CO™ dispersible (sulfaxodine-pyrimethamine+amodiaquine), Fosun Pharma
	Seasonal Malaria Chemoprevention	Supyra® (sulfaxodine-pyrimethamine+amodiaquine), S Kant
	3 day cure, uncomplicated malaria, artemisinin-based combination therapy	DHA-PQP dispersible (dihydroartemisinin-piperaquine dispersible), Alfasigma
	P.vivax relapse prevention	Tafenoquine (Kozenis/ Krintafel), GSK
	Pre-referal in severe malaria	Artesunate Rectocaps (artesunate rectal capsules), Cipla
	Pre-referal in severe malaria	Artecap™ (artesunate rectal capsules), Strides Pharma
	Intermittent preventive treatment of malaria in pregnancy (IPTp)	Sulfaxodine- pyrimethamine, Universal Corporation
		Sulfaxodine- pyrimethamine, S Kant
Malaria	Intermittent preventive treatment of malaria in pregnancy (IPTp)	Sulfaxodine- pyrimethamine, Swhipha/Biogaran
	Intermittent preventive treatment of malaria in pregnancy (IPTp)	Sulfaxodine-pyrimethamine, Emzor Pharmaceutical Industries Ltd.
	3 day cure, uncomplicated malaria, artemisinin-based combination therapy for patients < 5k	Artemether-Lumefantrine for <5kg, Novartis
	P. vivax relapse prevention	Tafenoquine paediatric, GSK
	2-3 day cure, uncomplicated malaria, non-artemisinin based	Ganaplacide/Lumefantrine, Novartis
	Non-artemisinin treatment for severe malaria	Cipargamin, Novartis
	1-3 day cure, uncomplicated malaria, non-artemisinin based	M5717, Merck KGaA
	Prophylaxis	Atoquanil, Ipca
	1-3 day cure, uncomplicated malaria, non-artemisinin based; potential for severe malaria	MMV533
	1-3 day cure, uncomplicated malaria, non-artemisinin based	ZY19489 (MMV253), Zydus Cadila
	Prophylaxis	MMV371, Janssen
	1-3 day cure, uncomplicated malaria, non-artemisinin based	INE693, Novartis
	Transmission blocking, 1-3 day cure, uncomplicated malaria, non-artemisinin based	MMV183, TropIQ
	Uncomplicated malaria treatment for single-exposure radical cure (SERC) and/or resistance management (TPP-1)	GSK701, GSK



Source: MMV

Not reflected in the funding pipeline but significant for the PDP III grant as it was mentioned in the original funding proposal, is the research to establish the safety of artemisinine combination treatments (ACTs) in early pregnancy. This includes setting up a registry, in cooperation with the Liverpool School of Tropical Medicine, to monitor the use of different antimalarials during pregnancy with an emphasis on the first trimester. This project started in 2020, with Dutch funding from 2021.

Impact of COVID-19

The global COVID-19 pandemic resulted in massive and unprecedented disruptions to all forms of global industry, including scientific research and medical care. Main impacts on the activities of MMV included:

- many nations were forced to adopt strict restrictions on travel, which has limited the collaboration of international research staff, preventing site visits and in-person training activities.
- Disruptions in global health supply chains and shortages of key medical products have been experienced due to competition for manufacturing capacity between COVID-19 interventions and other global health commodities, blocking and suspension of imports and exports of goods, fluctuations in demand and panic buying.
- The pandemic has placed a particular burden on the already restricted healthcare infrastructure, staff, supply and storage facilities of resource-limited countries. As many of these countries are also endemic for malaria, there have been significant concerns that pandemic-induced shortages might oblige governments to shift their limited healthcare resources (financial and human) to COVID-19 emergency care. This is predicted to result in a significant increase in the number of cases and deaths for malaria. To illustrate this: 73% of malaria programmes have been reported as disrupted.

MMV was nonetheless able to move a lot of its projects forwards. An important factor in this respect was the global nature of MMV's portfolio. In order to further mitigate the impact of the pandemic-induced challenges, various approaches had to be implemented:

- For some partners doing experimental or clinical work there have been periods where scientists working with MMV have been unable to do practical work, because of strict restrictions and lockdowns. They focused on doing their work in other ways, just not experimentally.
- Careful diligence of some of MMV's CRO partners who had proactive measures in place, resulted in hardly any days of work and productivity lost.
- MMV helped establish medication stockpiles to mitigate shortages in antimalarial treatments and preventative therapies.
- At WHO's request, MMV coordinated a multi-partner workstream to monitor on a weekly basis any global risks to supply chain production and distribution of key antimalarial commodities (primarily medicines, LLINs, diagnostics) as well as PPE.
- Compounds from MMV's portfolio with predicted antiviral activity were shared with researchers free of charge as part of efforts to identify novel COVID-19 treatments. Consequently, two treatments that have displayed good distribution to the lung and promising activity against SARS-CoV-2 are currently being evaluated in clinical trials in South Africa.
- MMV collaborated with organizations such as the WHO Global Malaria Programme, the Wellcome Trust and the Bill & Melinda Gates Foundation to develop malaria/COVID-19 response policies designed to minimize the impact of the pandemic on malarial elimination efforts.
- Several nations were able to adapt existing malaria programmes to respond to the challenges presented by COVID-19. In Zambia, healthcare workers were able to make use of communication skills learned through MMV-sponsored training programmes to disseminate public health messages on COVID-19 safety. In Ethiopia, two medical centres equipped with

state-of-the-art laboratory equipment by MMV were transformed into fully functional COVID-19 testing facilities operated by MMV-trained clinical staff.

Access for the target groups and equity in access

MMV partners with 'last-mile organisations' who work hand in hand with the Ministries of Health to build access strategies and routine systems that allow regular delivery of Malaria case management. Examples are Catholic Relief Services, Clinton Health Access Initiative and the Malaria Consortium. MMV has used data from malaria indicator surveys to make (very conservative) estimates about patient impact of its medicines, by analysing each step of the access delivery challenge: (a) drugs delivered to country, (b) drugs being available at the point of care where needed; (c) at point of care, drugs being used correctly for malaria versus incorrectly for something else.

Distribution of developed products

The pipeline of MMV shows 13 different products that are ready to be marketed (registration obtained) or already being marketed. Six of these products were brought to the market after 2015 Total disbursements to date are higher for the eight older products. Table 12 gives a summary overview. The older products have been registered in 10 to 50 countries (average: 27 countries). For newer products the number of countries in which the products are registered is lower, at 1 to 13 countries.

Table 12 Distribution of products developed by MMV

	Year Approved	Treatments distributed since Launch	Data Source	Estimated Annual Cases requiring treatment	Data Source(s)
3 day cure, uncomplicated malaria, artemisinin-based combination therapy:					
Coartem® dispersible (artemether-lumefrantine), Novartis	2008	430 million	MMV website: https://www.mmv.org/node/11210/overlay	230 million uncomplicated malaria cases per annum	World Malaria Report 2020
Generic copies of Coartem Dispersible (by Ajanta, Cipla, Ipca, Strides Pharma, Macleods, Mylan)	2009-2021	1,530 million	Unitaid ACT Forecast and additional analysis from GF PQR database		
Eurartesim ® (dihydroartemisinin - piperaquine), Alfasigma	2011	7.8 million	MMV website: https://www.mmv.org/node/11211/overlay		
Generic copy of Eurartesim (Guilin)	2019	3.5 million	Global Fund dashboard		
Pyramax ® (pyronaridine-artesunate), Shin Poong	2012	~1 million	Company data		
Pyramax® granules pediatric (pyronaridine-artesunate), Shing Poong	2015	~1 million	Company data		
ASAQ Winthrop® (artesunate-amodiaquine), Sanofi	2008	537 million	MMV Website: https://www.mmv.org/node/11529/overlay		
Generic copies of ASAQ (Generics by Ajanta, Cipla, Fosun Pharma, Ipca, Strides Pharma, Macleods)	2009-2021	419 million	Unitaid ACT Forecast and additional analysis from GF PQR database		
ASMQ (artesunate-mefloquine), Cipla	2012	1.3 million	MMV Website: https://www.mmv.org/node/11530/overlay		
Seasonal Malaria Chemoprevention					
SPAQ-CO™ dispersible (sulfaxodine-pyrimethamine+amodiaquine), Fosun Pharma	2013	355 million	MMV Website: https://www.mmv.org/node/11531/overlay	39 million children per year	"Estimating the potential public health impact of seasonal malaria chemoprevention in African children" DOI: 10.1038/ncomms1879
P.vivax relapse prevention					
Tafenoquine (Kozenis/ Krintafel), GSK	2018	no full product launch yet -- only small scale feasibility studies to date		7 million cases per year	WHO MWR 2020
Pre-referal in severe malaria					
Artesunate Rectocaps (artesunate rectal capsules), Cipla	2017	3.8 million rectocaps total	MMV website: https://www.mmv.org/node/11235/overlay	10 million severe malaria cases per annum	Most recent multi-country model/ survey about prevalence of severe malaria establishes estimate of 4.5%: https://assets.researchsquare.com/files/rs-32066/v1/6665691e-2834-4f2b-a680-544b44f0dd9f.pdf?c=1631842221
Artecap™ (artesunate rectal capsules), Strides Pharma			MMV website: https://www.mmv.org/node/12560/overlay		
Severe malaria					
Larinate® 60 mg for injection (artesunate for injection), Ipca	2018	8.9 million vials	MMV website: https://www.mmv.org/node/12997/overlay		
Artesun® (artesunate for injection), Fosun Pharma	2010	166 million vials	MMV website: https://www.mmv.org/node/11206/overlay		

Source: MMV

Involvement and increase in R&D capacity of LMICs

MMV has built up a network of 107 clinical and discovery centres, increasing the research capacity of 30 malaria-endemic countries.

Sustainability

The Dutch financing has been responsible for 1.4 to 4.7% of total income of MMV over the years 2015-2020. The total contribution of € 14.9 million represented about 9% of total governmental funding during these years. Other governmental donors comprise United Kingdom, Germany, Switzerland, Ireland, United States, Australia, Korea, Monaco and Norway.

5.6 TB Alliance

MoFA Awards to TB Alliance	
TB Alliance-1	Grant of € 2 million awarded in 2005
TB Alliance-2	Grant of € 2 million awarded in 2006
TB Alliance-3	Grant of € 8 million for the period 2006-2009
TB Alliance-4	Grant of € 15.3 million for the period 2015-2020
Extension 2021	Grant of € 3.1 million for 2021

Source: Netherlands Enterprise Agency (RVO)

Relevance

Relevance of the developed products for the individuals in need

Since TB Alliance was established in 2000, it has led the global search and development of new tuberculosis (TB) medicines, leveraging cross-sector partnerships to advance urgently needed TB drug development. TB Alliance sees as their core mission to develop new, faster-acting and affordable tuberculosis treatments for those in need, especially for the most vulnerable populations, and in doing so have a considerable impact on the tuberculosis pandemic. TB Alliance defines as their ultimate goal the development of *"an ultra-short "universal" treatment that can cure all forms of TB"*[69].

Table 13 shows the burden and geographical spread of tuberculosis, for which TB Alliance has been developing treatments under the PDP III fund.

Table 13 Burden and geographical spread of tuberculosis

Disease	Burden of disease[70]
Tuberculosis	Globally in 2019, tuberculosis was one of the leading causes of death by a single pathogen. Among HIV-negative individuals, the number of deaths was 1·18 million (95% UI 1·08–1·29) and the number of new cases of tuberculosis was 8·50 million (7·45–9·73). 1.8 billion people are estimated to be exposed to tuberculosis. Among the regions with the highest burden are sub-Sahara Africa, South and South-East Asia, and Eastern Europe and Central Asia. Drug-resistant tuberculosis is an increasing problem in many of these countries.

Source: The Lancet

Relevance regarding SRHR policy of MoFA

There is no direct link between the actual products that TB Alliance develops, and SRHR. Tuberculosis is still the leading cause of death of people living with HIV, and TB/HIV co-infection is

[69] Achievements report: Achievements TB Alliance PDPIII 2015-2020

[70] The Lancet. Global Burden of Disease. GBD cause and risk summaries. https://www.thelancet.com/gbd/summaries Accessed on 26 October, 2021.

common, certainly in sub-Sahara Africa where the new drug-resistant TB treatments will be deployed.

The TB Alliance reports that it participated in a learning exchange led by MMV on the topic of R&D, gender, and pregnant and lactating women. TB Alliance aims to contribute to this discussion, to ensure that pregnant and lactating women are safely included into clinical studies according to internationally defined legal, ethical, medical, safety, and scientific standards.

Based on the aforementioned actions, there is some, albeit indirect, alignment with the SRHR Theory of Change and Results Framework (especially result 2 and 3) of the Netherlands Ministry of Foreign Affairs.

Alignment Dutch Top Sector policy

TB Alliance has developed an extensive network of partnerships with Dutch parties, collaborating with Dutch partners on execution of clinical trials, including clinical trial site for first-ever Phase 1 study of the compound TBAJ- 587 in the Netherlands (partner QPS Holdings LLC in Groningen), as well as conducting market and costing analysis of TB products. Dutch partners include:

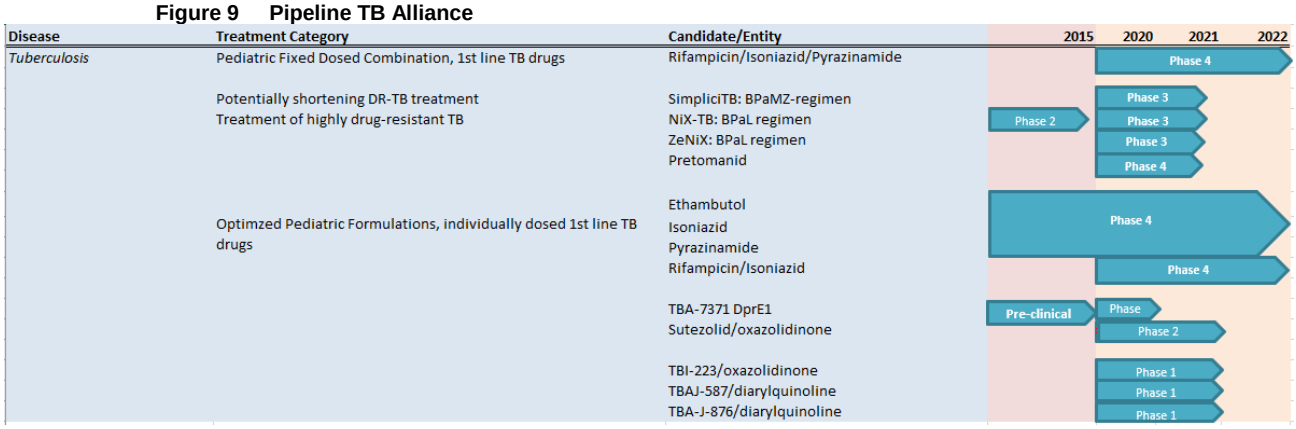
- Erasmus University Medical Center;
- KNCV Royal Netherlands Tuberculosis Association;
- Médecins Sans Frontières Netherlands-Artsen Zonder Grenzen (MSF);
- Radboud University Nijmegen Medical Centre (RUNMC);
- Sonsbeek Pharma Consultancy B.V.;
- Stichting Amsterdam Institute for Global Health and Development (AIGHD);
- TropIQ Health Sciences;
- VU Medical Center.

Effectiveness

Pipeline and original targets

Figure 9 shows the progression of the funding pipeline from 2015 – 2021 funded under PDP III, with a projection for 2022. The most notable achievement is the approval of a new chemical entity developed by TB Alliance pretomanid (Pa) as part of the BPaL regimen with bedaquiline (B) and linezolid (L) for the treatment of people with highly drug-resistant forms of TB (DR-TB). It has been approved by the U.S. Food and Drug Administration (FDA), the European Commission (EMA), the Drug Controller General of India and incorporated into World Health Organization (WHO) guidelines. TB Alliance reported that taking into account multiple approvals and guidelines, in 2020 pretomanid was available in 150 countries worldwide.

Figure 9 Pipeline TB Alliance



Source: Netherlands Enterprise Agency (RVO)

Since 2015 TB Alliance executed late-stage Phase 3 pretomanid containing trials including Nix-TB, ZeNix-TB, and SimpliciTB, potentially shortening DR-TB treatment from between 9-18 months to six

months and drug-susceptible TB treatment from six to four months. Regarding the earlier stage clinical portfolio, in 2020 TB Alliance had five Phase 1 / 2 stage entities, namely TBA-7371 DprE1, Sutezolid/oxazolidinone, TBI-223/oxazolidinone, TBAJ-587/diarylquinoline and TBA-J-876/diarylquinoline.

TB Alliance also made progress in Paediatric Fixed Dose Combination (FDC) initiatives for drug-susceptible tuberculosis, although it was not directly supported by the DGIS funding. In 2020 Rifampicin / Isoniazid / Pyrazinamide were in Phase 4 phase.
These pipeline achievements of TB Alliance are broadly in line with the proposed objectives for receiving the PDP III fund set out in 2015.

Impact of COVID-19

The outbreak of COVID-19 presented challenges to many aspects of TB Alliance work. Yet, TB Alliance was able to respond quickly and adapt to the changing circumstances in order to continue the planned activities. Various areas got impacted by the evolving COVID-19 pandemic situation across regions:

Operations
The COVI-19 pandemic placed TB Alliance staff, contractors and consultants in difficult situation in terms of the workload and uncertainly about the security. TB Alliance utilized already existing virtual infrastructure to ensure the most effective way of working for personnel.

Pre-clinical activities and drug discovery
Since many of the TB Alliance's pre-clinical partners are in Asia, the discovery and innovation activities were impacted early on. TB Alliance responded to the situation by making use of the partner model and quickly moving work to other partners (e.g. when China went into the lock down at the beginning of 2020, the situation was mitigated by temporarily moving the research projects to U.S, which then later on got moved back to China, once labs there got reopened.)

Clinical trials
Clinical trial activities faced multiple challenges, such as shipping drug products, transporting samples to labs, and performing medical monitoring, which were addressed by regular meeting of all Principle Investigators to find the needed solutions. TB Alliance also had to address disruptions in continuation of community engagement, interruptions in supply chain, staff retention, travel restrictions, increased costs of supplies and equipment.

New ways of patient retention and community support were created (e.g. ad-hoc dialogue groups on COVID-19). When TB hospitals were shut down, for different clinical studies TB Alliance had to modify protocols and find new techniques to continue the activities, e.g. telephonic meetings and monitoring instead of in-person, delivery of drugs directly to patient's homes, consolidating testing schedules to minimize time at a clinic.

Financial uncertainty
TB Alliance also expressed the difficult financing climate caused by COVID-19 pandemic and its economic impact on countries' economies more generally, which translates into uncertain future of PDP funding particularly coming from bilateral donors.

Access for the target groups and equity in access

TB Alliance worked on multiple fronts to improve access of tuberculosis treatments. It devoted significant resources to facilitate and ensure global adaptation, availability, and affordability of BPal regimen. TB Alliance progressed in BPaL registration and rollout. In 2020 TB Alliance (1) secured

marketing authorization from European Commission for pretomanid in BPaI, (2) its commercialization partner Viatris secured approval in India, (3) BPaL was also included in WHO treatment guidelines for DR-TB. Operational research to accelerate BPaI implementation is planned in key countries across Africa, Asia, Eastern Europe.

TB Alliance adopted a unique commercialization strategy within a broader PDP field, by recognizing that generic pharmaceutical suppliers are needed to obtain high-quality and affordable (low-cost) manufacturing. To that end by 2020 TB Alliance already made commercialization agreement with three partners, which have complementary market reach but foster competition, to make sure that the regimen is affordable, accessible and widely available. By bringing together industry partners and procurement institutions like the Global Drug Facility and the Global Fund, TB alliance seeks to ensure that countries can get access to new treatments at affordable prices.

TB Alliance addresses marginalized groups (e.g. people with disabilities, people living with HIV/AIDS, groups who identify as having same-sex partners), by making sure that trial recruitment plans consider these vulnerable populations.

TB Alliance also made a considerable contribution to addressing a gap in the paediatric TB market. New TB cures for children in the appropriate dose and form were introduced by TB alliance in 2016. By 2020 these child-friendly TB treatments have been ordered by 116 countries, covering 75% of the estimated global childhood TB burden.[71]

In 2019 a paediatric investigation plan (PIP) for Pretomanid was submitted to the EMA. TB Alliance is working together with the U.S government funded International Maternal Paediatric Adolescent AIDS Clinical Trials Network (IMPAACT) to develop a paediatric pharmacokinetic and safety study protocol for Pretomanid, [72] making this new product available for children with TB.

In high-burden countries in Sub-Saharan Africa, Eastern Europe, South and Southeast Asia new TB regimens have to be tested which also provides access to special populations. TB Alliance follows clinical research standards enrolling women in all its clinical trials (ranging from 30-50 % of women participants). By following Good Participatory Practice (GPP), TB Alliance also puts emphasis on community participation in clinical trials including women.[73]

Distribution of developed products

TB Alliance provided information on the supplies ordered by LMICs over the last five years for two groups of products, namely 2 FDC DT (Rifampicin/Isoniazid (paediatric formulations) and 3 FDC DT (including Rifampicin / Isoniazid / Pyrazinamide (paediatric formulations). It shows that a growing number of countries have ordered such supplies since 2016-17 until 2019-2020. The number of products ordered increased by more than 50% in these years, from roughly 1 million to 1,6 million doses.

Table 14 Supplies ordered (in thousands) and number of LMICs ordering products developed by TB Alliance

product	# of tablets sold	Packs of 84 sold	Treatment courses
RH 75/50 (2FDC DT)	367,641,288	4,376,682	1,021,226
RHZ 75/50/150 (3FDC DT)	182,007,168	2,166,752	1,011,151

Source: TB Alliance

71 Achievements report: Achievements TB Alliance PDPIII 2015-2020
72 Achievements report: Achievements TB Alliance PDPIII 2015-2020
73 PDP Funder Reporting 2020

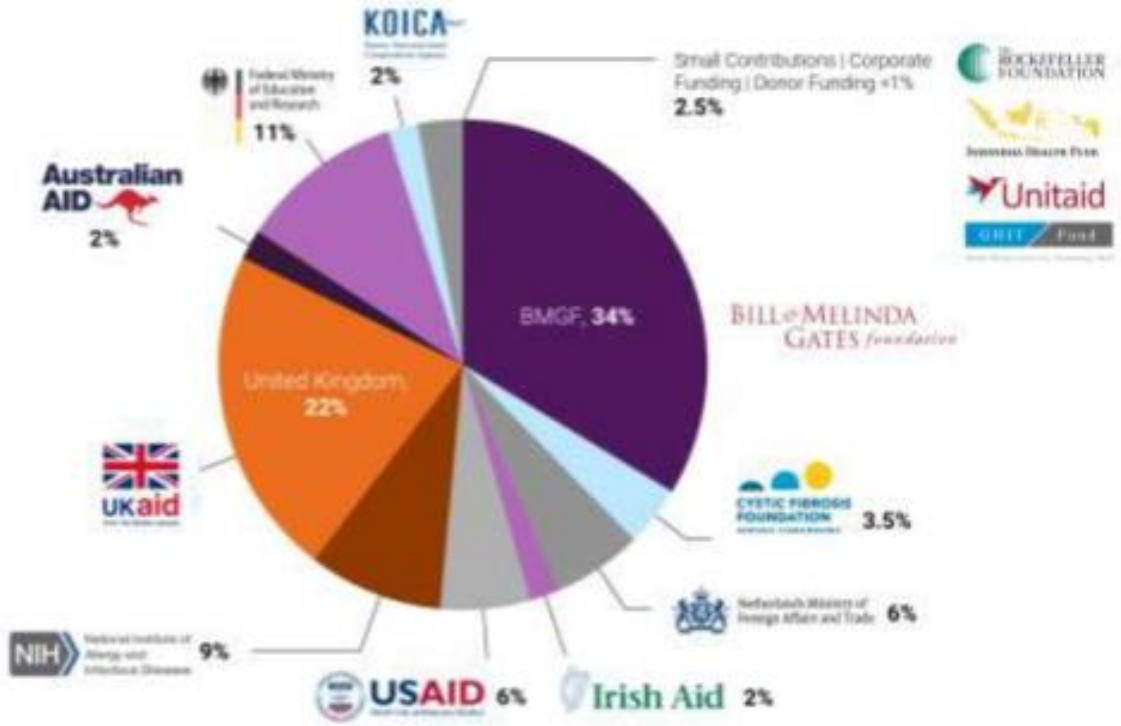
Involvement and increase in R&D capacity of LMICs

Most of TB Alliance's clinical trial sites are located in LMICs, which means setting up trial capacity, training and brining in the equipment to be able to carry out trials to the global standards that meet registration requirements.

TB Alliance is working with clinical trial sites, coordinators and communities on the ground. It runs Community Engagement (CE) programs, which provide technical assistance, skills training, and small grant initiatives to the trial communities. Strong emphasis is put on research literacy and dialogue with key local stakeholders, including trial participants.

Sustainability

During the PDP III grant period of 2015-2020 TB Alliance continued diversification of funding by securing new donors and partnerships. Prior to 2015 TB Alliance funding was based on a few key donors (such as BMGF, UK FCDO, USAID and US FDA). Since then donor base expanded and TB Alliance added nine new donors, including both government bilateral funding agencies and private foundations. In 2020 TB Alliance the total donor funding amounted to approx. US$62.5 million. The graph below shows the donors and the percentage of their respective funding.



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