A Report to the Norwegian Agency for Development Cooperation (Norad)

A review of MFA/Norad's support to global health product development

NORWEGIAN INSTITUTE OF PUBLIC HEALTH (NIPH)
DEPARTMENT OF INTERNATIONAL PUBLIC HEALTH

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This report is part of a framework agreement between Norad and NIPH, under which NIPH receives financial support by Norad for the provision of technical advisory services on various health-related issues for development cooperation, including on global health access and innovation. Under this agreement, the lead author of this report, Gouglas, has performed the technical appraisal of applications for MFA/Norad funding by five PDPs (the same five evaluated in this report) in 2013; and he has been responsible for the ongoing technical monitoring and evaluation of the five PDPs' implementation of MFA/Norad funded activities since January 2014, including participation in coordination meetings with other funders under the PDP Funders Group (PFG).

NIPH has received numerous research grants over time from the GLOBVAC programme of the Research Council of Norway, including for the participation in the ongoing Ebola vaccine efficacy trial in Guinea and the implementation of carrier studies to support the clinical development of MenAfriVac™ previously. The lead author of this report has been involved in the drafting of the Report to the Norwegian Ministry of Health: Vaccine-based mitigation of the 2014 Ebola Viral Disease (EVD) epidemic: Gap analysis and proposal for Norwegian initiatives;[1] and previously in the drafting of a Discussion note for the WHO urgent Ebola vaccine access meeting held in October 21st, 2014.[2] The two authors are also currently funded by the GLOBVAC programme of the Research Council of Norway for the research and development of novel policy interventions on Strengthening International Collaboration for Capitalizing on Cost-Effective and Life-Saving Commodities (i4C).[3]

The authors certify that they have no other involvement with any financial interest, or non-financial interest in the subject matter or materials discussed in this report.

Oslo, June 2015

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ACRONYMS

ACT	Artemisinin Combination Therapy
APIs	active pharmaceutical ingredients
ART	antiretroviral therapy
ARV	Anti-RetroViral
BCG	Bacille Calmette-Guérin
BD	Becton, Dickinson and Company
BMGF	Bill & Melinda Gates Foundation
BMZ	Federal Ministry for Economic Cooperation and Development, Germany
bNAbs	broadly neutralizing antibodies
BVGH	BioVentures for Global Health
CAR	Central African Republic
CDT	Clinical Development Team
CDV	Canine Distemper Virus vector
CEWG	Consultative Expert Working Group
CHMI	Controlled human malaria infection
CMOs	contract manufacturing organizations
CRCs	clinical research centers
DAC	Development Assistance Committee
DALYs	Disability Adjusted Life Years
DNDi	Drugs for Neglected Diseases Initiative
DRC	Congo Democratic Republic
DSMB	Data Safety Monitoring Board
DSW	German Foundation for World Population
EC	European Commission
EDCTP	European Developing Countries Clinical Trial Partnership
EDCTP	European & Developing Countries Clinical Trials Partnership
EEIG	European Economic Interest Grouping
EIC	European Investment Bank
EMA	European Medicines Agency
ESAC	Expert Scientific Advisory Committee
EU	European Union
FTEs	Full-Time Equivalents
GAVI	Gavi, the Vaccine Alliance
GCLP	Good Clinical Laboratory Practice
GCP	Good Clinical Practice
GDP	Gross Domestic Product
GHIF	Global Health Investment Fund
GHIT Fund	Global Health Innovation and Technology Fund
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
GLOBVAC	Norwegian Research Programme for Global Health and Vaccination Research
GMAP	Global Malaria Action Plan
GMP	Good Manufacturing Practices
GSK	GlaxoSmithKline
HAT	Human African Trypanosomiasis
HICs	high income countries
HIV/AIDS	Human immunodeficiency virus infection / acquired immune deficiency syndrome
HPV	Human papillomavirus
HVTR	HIV Vaccine Translational Research Laboratory
IAVI	International AIDS Vaccine Initiative
ICPD	International Conference on Population and Development

ICT	Information Communication Technology
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
IND	Investigational New Drug
IP	Intellectual Property
IPM	International Partnership for Microbicides
IPTp	intermittent preventive treatment in pregnancy
IT	Information Technology
iVSV	inactivated Vesicular Stomatitis Virus
LMICs	Low and Middle Income Countries
M&E	Monitoring & Evaluation
malERA	malaria research eradication agenda
MCC	Medicines Control Council, South Africa
MDGs	Millennium Development Goals
MESA	Malaria Eradication Scientific Alliance
MFA/Norad	Norwegian Ministry of Foreign Affairs / Norwegian Agency for Development Cooperation
MFA/DANIDA	Danish Ministry of Foreign Affairs / Danish International Development Agency
MMV	Medicines for Malaria Venture
MoFA/DGIS	Dutch Ministry of Foreign Affairs / Directorate-General for International Cooperation
MPTs	multi-purpose technologies
MSF	Doctors Without Borders
MSM	men who have sex with men
NCEs	New chemical entities
NEA	Netherlands Enterprise Agency
NGOs	Non-Governmental Organizations
NHP	Non-Human Primate
NIPH	Norwegian Institute of Public Health
NMBU	Norwegian
NOK	Norwegian krone
NTDs	Neglected Tropical Diseases
ODA	Official Development Assistance
PATH MVI	PATH Malaria Vaccine Initiative
PDP III	Product Development Partnerships III Fund
PDT	Product Development Team
PFG	PDP Funders Group
PNLTHA	National Program for the Fight Against Human African Trypanosomiasis
PRIND	poverty related infectious and neglected disease
PS	Participating States
PSIAs	Participating States' Initiated Activities
R&D	Research and Development
RBM	Roll Back Malaria
RCs	research centers
RIAs	Research & Innovation Actions
RMNCH	reproductive, maternal, new born and child health
SAC	Scientific Advisory Committee
SATVI	South African TB Vaccine Initiative
SCAs	Coordination & Support Actions
SDC	Swiss Agency for Development and Cooperation
SDGs	Sustainable Development Goals
SERCaP	single-encounter radical cure and prophylaxis
SIDA	Swedish International Development Cooperation Agency
SLAB	Saving Lives at Birth: A Grand Challenge for Development
SMC	Seasonal Malarial Chemoprevention
SO	strategic objective
SOPs	Standard Operating Procedures

SP + AQ	sulfaxine-pyrimethamine + amodiaquine
SRHR	sexual and reproductive health and rights
SRIAs	Strategic Research & Innovation Actions
TAG	Treatment Action Group
TB	Tuberculosis
TBCC	TB Biomarker Core Group
TBVI	TuBerculosis Vaccine Initiative
TMA	Training & Mobility Actions
TPPs	Target Product Profiles
UCT	University of Cape Town
UK	United Kingdom
UK DFID	UK Department for International Development
UK MRC	UK Medical Research Council
UN	United Nations
UNAIDS	United Nations Program on HIV/AIDS
UNCLSC	UN Commission on Life-Saving Commodities for Women and Children
UNDP	United Nations Development Program
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
UNITAID	International Drug Purchasing Facility
US FDA	US Food and Drug Administration
US NIH	US National Institutes of Health
US$	US dollars
USA	United States of America
USAID	US Agency for International Development
VISTA	Vaccine, Immunology, Science and Technology for Africa
VSV	Vesicular Stomatitis Virus vector
VxPDC	Vaccine Product Development Centre
WHA	World Health Assembly
WHO	World Health Organization
WHO TDR	WHO Special Program for Research and Training in Tropical Diseases

Executive summary

The Norwegian Agency for Development Cooperation (Norad) has commissioned the Norwegian Institute of Public Health (NIPH) to conduct a review of the Norwegian Ministry of Foreign Affairs (MFA)/Norad support to global health product development against poverty related infectious and neglected diseases (PRINDs), reproductive, maternal, new born and child health (RMNCH) conditions.

This report aims to:

- provide Norad with strategic and technical input to the monitoring of progress met vis-à-vis planned activities in the MFA/Norad's existing PDP grants for the period 2013-2015
- provide strategic input to MFA/Norad's goals and priorities for global health product development funding in the future, demonstrating the importance of global health product development funding, identifying opportunities for synergies and value-for-money

Based on these objectives, the report addresses the following policy questions:

- What have MFA/Norad's contributions in global health product development been to date?
- What are the results of these investments?
- Have investments been appropriate in terms of strategic orientation, funding levels, grantees selected, and accompanying financing and coordination measures?
- Should MFA/Norad be recommended to alter their course of action in any of these aspects?

Background

Progress made - Progress in global health product development over the past two decades has been unprecedented. Government and philanthropic funding, the Bill & Melinda Gates Foundation being the most profiled, has been catalytic to product development efforts throughout this time, and a growing community of product developers has also emerged. Collectively, these institutional arrangements and investments have built a powerful research and development (R&D) pipeline of new drugs, vaccines, diagnostics and other products against poverty related diseases and health conditions.

Challenges ahead - PRINDs and RMNCH conditions remain heavy burdens for the world's poor, causing over 11 million deaths each year, hampering child growth, harming labour productivity, perpetuating poverty and underdevelopment for the world's bottom billion. Norway is an important funder of global interventions through initiatives like Gavi, the Vaccine Alliance and the Global Fund, to improve access to existing life-saving commodities. However, new or improved biomedical products are still needed for controlling these diseases, for saving lives and improving the quality of life of millions of people.

Product development processes can be highly complex, lengthy and costly. Although important results can be achieved throughout the R&D process in terms of scientific and

technical progress, most commonly health outcomes are not achieved until after the product has been registered, scaled-up and rolled out. In order for R&D investments to create impact on health, they must be sustained over several years. R&D projects that are discontinued will easily be perceived as a financial 'loss', despite whatever scientific progress has been made during the project period. This risk is particular to product development as opposed to distribution oriented interventions, where health outcomes can manifest themselves in the very short term.

MFA/Norad's investments

Small and smart – MFA/Norad has been a small and smart funder of global health product development, long recognizing the need for new and improved biomedical products to improve global health and human security through health. Driven by a commitment to high impact interventions against global killer- and regional disruptor- diseases, MFA/Norad investments in the field have aligned with international health priorities and have been responsive to health crises. The organization has supported several Product Development Partnerships (PDPs) and international initiatives, based on a pragmatic mix of technical and policy criteria to create a balanced and diversified portfolio in terms of disease areas, development timeframes (long/short), risk and cost levels (high/low). The distribution of its investments has increased substantially across diseases and products in recent years, in response to expanding priorities in global health and emerging research strategy objectives.

Funding levels – From 1974 to 2015, MFA/Norad's cumulative investments in global health product development surpassed NOK 1.4 billion. And from 2001 to 2015 MFA/Norad invested an accumulated NOK 933 million in the field.

Table 1: MFA/Norad investments into global health product development, 1974-2015 (current NOK)

Recipient (NOK)	1974-2000	2001-2012	2013	2014	2015
WHO TDR (1974-2015)	474,961,012	230,252,339	14,546,537	5,000,000	-
GLOBVAC (2008-2015)	-	101,377,890	23,859,508	41,116,667	41,116,667
IPM (2002-2015)	-	182,000,000	8,000,000	-	12,000,000
IAVI (2001-2015)	-	169,500,000	6,000,000	6,000,000	6,000,000
SLAB (2011-2015)	-	28,500,000	10,500,000	10,500,000	10,500,000
DNDi (2013-2015)	-	-	5,000,000	5,000,000	5,000,000
MMV (2013-2015)	-	-	5,000,000	5,000,000	5,000,000
TBVI (2013-2015)	-	-	5,000,000	5,000,000	5,000,000
TOTAL (NOK)	**474,961,012**	**711,630,229**	**77,906,045**	**77,616,667**	**84,616,667**

These are small amounts considering that total development costs for a single drug or vaccine in this field cost hundreds of millions of NOK (e.g. MenAfrivac™ cost approximately NOK 520 million to develop;[4] and costs of developing an improved treatment of marginal innovation in neglected tropical diseases are estimated at NOK 80 - 320 million).[5]

Funding distribution – MFA/Norad has funded a number of WHO initiatives, Product Development Partnerships, pooled funding initiatives such as the Saving Lives at Birth Initiative, and Norwegian R&D institutions via its contributions to the Norwegian Research Programme for Global Health and Vaccination Research (GLOBVAC). Through these platforms and networks, MFA/Norad R&D investments have been distributed across

many diseases and health conditions. Investments have been concentrated on the main global killers such as: malaria and other neglected tropical diseases; HIV/AIDS; TB; diarrheal diseases; and RMNCH conditions; as well as a couple of more geographically restricted illnesses which have had severe disruptive social impacts: meningococcal disease and Ebola. Diarrheal diseases, TB and RMNCH conditions have historically received less MFA/Norad funding in relation to their morbidity and mortality, although their funding has been increasing in recent years. Diseases such as HIV/AIDS and malaria, which are important drivers of maternal morbidity and mortality, have received proportionate attention. Other diseases however have not (e.g. helminth infections).

Funding as part of aid and economic growth – Although MFA/Norad ranks number seven among DAC members in terms of ODA, it ranks only number 17 in terms of total public funding in global health product development. Moreover, the Norwegian product development contributions would have to be multiplied more than four-fold to comply with the CEWG recommendation of spending 0.01% of GDP for this purpose. This suggests that Norway could increase its investment in product development in the longer term.

Results of MFA/Norad's recent investments

Although MFA/Norad has supported product development targeting tropical diseases since the mid-1970s it is not until 2000 that this investment gained momentum. Previously, and partly with the small core funding support from MFA/Norad, WHO TDR had contributed to the development of multiple drugs and several diagnostics for neglected tropical diseases. More recently, and largely with contributions of MFA/Norad, GLOBVAC supported R&D related to two vaccines which are affordable and suitable for LMIC settings; one against meningococcal disease (MenAfriVac™), and one against rotavirus (ROTAVAC®).

Investing in PDPs – PDPs are independent non-profit enterprises that bring together financial and technical resources from public, private and philanthropic sectors to accelerate the development of new products that can meet the health needs of the poorest populations in LMICs. The entities operate in environments where sufficient commercial demand to incentivize pharmaceutical industry engagement is absent. MFA/Norad's modest investments of NOK 83 million into five Product Development Partnerships from 2013 to 2015 have contributed to the support of a cumulative pipeline of 136 different R&D projects across four diseases (HIV/AIDS, malaria, sleeping sickness, tuberculosis) and three product types (drugs, vaccines, microbicides). PDPs included: the Drugs for Neglected Diseases Initiative (DNDi); the International AIDS Vaccine Initiative (IAVI); the International Partnership for Microbicides (IPM); the Medicines for Malaria Venture (MMV); and the TuBerculosis Vaccine Initiative (TBVI).

Despite the highly complex, lengthy, and costly nature of this type of R&D, all five PDPs have made substantial progress in their product development efforts, with technical or other difficulties creating minor delays to development timelines or leading to a limited number of R&D failures.

- **DNDi has made considerable progress with its drug development program against sleeping sickness**, advancing a novel drug through late stage clinical trials and anticipating a positive opinion for approval by regulatory authorities by 2018.
- **IAVI has made stepwise progress with its discovery and development efforts towards advancing AIDS vaccines to efficacy trials over the next five years**, building

on an accumulated knowledge base and demonstrated technical and human capacity to design novel vaccine immunogens[i] for the broader field.

- **IPM has made breakthrough progress with its dapivirine ring licensure program**, completing enrolment in a pivotal large scale efficacy study of what is hoped to become the first licensed ring technology for prevention of HIV through sexual transmission in women.
- **MMV has made remarkable progress in R&D and access activities**, including: obtaining WHO prequalification for a pediatric antimalarial (SP+AQ); awaiting another WHO prequalification for an affordable rectal artesunate; submitting the pediatric formulation of a new antimalarial, Pyramax® for regulatory approval; advancing a potential single-dose cure for relapsing malaria into phase III studies and many other promising new compounds through to preclinical or clinical stages of development.
- **TBVI has made significant progress in advancing TB vaccine candidates through its pipeline**, including the clinical testing of a novel vaccine that aims to replace BCG as priming vaccine for global use in newborns and that can also act as a 'boosting vaccine' for adolescents and adults; developing new models for TB vaccine candidate comparisons and efficient R&D prioritization; launching new discovery projects and extending R&D partnerships.

Despite differing scientific challenges, disease areas, product types, and operational models, these PDPs have been facing common technical and managerial challenges and have been struggling to attract diversified and sustainable R&D funding over time. PDP funding is becoming increasingly earmarked to specific R&D projects, reducing PDPs' ability to manage R&D portfolios flexibly and independently. In this sense, MFA/Norad core funding to the PDPs has been highly beneficial, as it has been flexible enough to allow PDPs to manage R&D portfolios efficiently and to avoid duplications in funding, while sending a positive signal for other funders to continue to support the PDPs.

PDPs currently funded by MFA/Norad promise to deliver significant health gains to LMIC populations. The development of the first ever female-initiated prevention technology against HIV is nearing completion. If successful, this product will be the world's proof-of-concept for next generation multi-purpose technologies on HIV prevention and contraception to improve women's health. Similarly, new simplified, safer and effective drugs against resistance in sleeping sickness and malaria are close to registration. Promising new TB vaccines have just entered clinical trials and recent new evidence from basic science has reinvigorated hopes for an HIV/AIDS vaccine for global use in the future.

Investing in RMNCH R&D – Since 2011, MFA/Norad's investments in product innovations for improving RMNCH through the UN Commission on Life-Saving Commodities for Women and Children, and via the Saving Lives at Birth: A Grand Challenge for Development (SLAB), have resulted in over 91 low cost innovation ideas being tested or transitioned to scale-up, including:

- a time-temperature sensor for oxytocin
- a new formulation for inhaled oxytocin that is user-friendly and suitable for tropical temperatures
- a user-friendly product presentation of amoxicillin dispersible tablets to treat childhood pneumonia in low-resource settings

[i] antigens that are capable of inducing an immune response

- a traction device to deliver babies through the birth canal when complications arise in second-stage labour (BD Odon Device ™)

These two initiatives have incubated funds for scale up and commercialization of much needed low cost innovations for improving RMNCH. They have facilitated the transfer of low cost research into implementation, and fostered the participation of South-based innovators.

Investing in Ebola vaccine development – In response to the Ebola epidemic in West Africa in 2014, GLOBVAC contributed NOK 20 million on behalf of MFA/Norad to an international trial of an Ebola vaccine in Guinea. Conclusive results are not yet possible given that the clinical trial is still underway. However, MFA/Norad funding was catalytic for the clinical trial to take place when no other funder had indicated willingness to launch clinical trials in Guinea. Also in this case, MFA/Norad's quick and flexible funding response guaranteed the timely planning and setup of the vaccine trial in a country that continues to suffer from the disease epidemic as this report is being written. However, future funding efforts of Ebola vaccine R&D are likely to require greater pooling and coordination of investments at international level.

Options for future investments

Looking into the future and as the development agenda is becoming broader, the prioritization of global health product development investments is becoming increasingly challenging. As per MFA/Norad's current priorities in global health and strategic objectives, any future investments in the field would have to revolve around improving women's and children's health; reducing the global burden of disease with an emphasis on prevention, diagnosis and treatment of communicable diseases; and promoting human security through health. In light of these priorities and objectives, there are potential benefits and options for financing and coordination to be considered for future MFA/Norad investments in the field.

Potential benefits - There can be significant health benefits from investments into global health product development. Overall, new products are associated with a decrease in the under-5 mortality rate of about 2% per year. There are health economic benefits from investments in global health product development too. On average, one healthy year of life can be gained for every US$ 71 invested into product development for PRINDs. Other benefits include the potential strengthening of links between Norwegian R&D institutions and international initiatives, which have recently started to gain some momentum.

The PDP model - The PDP model is an appropriate model for pooling resources and spreading funding risk across portfolios of costly, lengthy and complex R&D projects; and it is suitable for MFA/Norad investments in the development of drugs, vaccines and devices against PRINDs and RMNCH conditions. In order to sustain their growing R&D pipelines that can deliver products, PDPs need substantial funding provided *flexibly and predictably over a long period of time*. Small funders like MFA/Norad can benefit from investing in PDPs by leveraging resources with other similar-minded funders, and spreading funding risk across diverse R&D portfolios.

Pooled financing schemes - Saving Lives at Birth is a prime example of how funders can pool resources together and coordinate effectively to support the development of needed low cost product innovations for RMNCH. And the establishment of new pooled R&D fund under the auspices of WHO TDR signalizes an opportunity for greater synergies

between funders supporting the development of products against disrupting diseases like Ebola, where PDP or other effective international structures are currently lacking. Pooled financing schemes are not involved in R&D management activities the same way as PDPs, which act more like virtual biopharmaceutical R&D organizations. However there can be many restrictions with pooled financing. These include participation rules and reporting requirements that add complexities in terms of aligning individual funder objectives; as well as significant costs including overhead and administration. Provided that funders are content with certain principles based on which pooled financing schemes are set up (e.g. on open knowledge innovation; geographic restrictions; disease-, product- or R&D stage-related scope restrictions, etc.), pooled schemes can share funding risks and decrease the burden of interactions between funders and product developers.

Improved coordination with other funders - Coordination of global health product development investments holds the potential to preempt underfunding or duplication of funding, given the engagement of multiple funders supporting broad R&D portfolios with long term commitments. Efforts with great scope for improvement include: continued engagement in PDP Funders Group (PFG) coordination activities; increased engagements with other funders on monitoring and evaluation of commonly funded R&D projects and/or organizations.

Recommendations

MFA/Norad would sustain and reinforce its role as a 'small and smart' funder of global health product development in the coming years, by:

1. **Maintaining its current levels of global health product development funding; and, if possible, increasing its funding in the longer term**

The current funding level has been beneficial and effective, and should be sustained. An increase in the long term would make Norway approach the internationally endorsed target of spending 0.01% of GDP on product development for poverty related diseases and conditions, and would respond to the great funding needs in this field.

2. **Continuing to support the currently funded PDPs, while maintaining its flexible funding approach based on core funding and increasing the predictability of its funding through expanded grant cycles**

Several of these PDPs are now on the brink of achieving tangible outputs, and others have recently achieved critical milestones that are promising significant R&D advancements in the next few years. Sustained MFA/Norad investments into the five PDPs can contribute to the continuation of their important R&D efforts, and can maintain momentum for greater strategic synergies between PDP funding and Norwegian research capacities in the future.

Core funding is crucial to dealing with risks and complexities that are inherent in product development processes, and should continue to be the preferred way of PDP funding. Moreover, MFA/Norad should consider increasing its PDP grant cycles from three years to at least six years, matching PDP business cycles more closely, and signalizing more clearly its long term commitments to individual PDP strategies. Besides the benefit of more predictable funding for PDPs, such an increase would also benefit MFA/Norad, by reducing transaction and administration costs related to grant management processes.

3. **Continuing to invest in pooled financing mechanisms for RMNCH related product innovations and considering channeling any future funds for Ebola vaccine R&D into the newly established Pooled R&D Fund hosted by the WHO TDR**

On one hand, SLAB provides a good platform for the transfer of low cost research into product innovations for RMNCH in LMICs, by brokering deals between early innovation ideas and commercialization platforms between small sized innovators and larger scale private sector actors. The mechanism also offers certain advantages to MFA/Norad investments, such as the opportunity for ICT, eHealth and other app-based technologies developed by Norwegian researchers for the domestic market which may also be applicable abroad (and vice versa). Continued support of SLAB's product innovation elements would not only contribute to MFA/Norad's sustained commitment in RMNCH R&D as per its first priority in global health; it would also potentially foster greater synergies in the sense that investments in new products for national use by the Norwegian government could turn out to have global applicability.

On the other hand, despite its flexible and responsive funding of Ebola vaccine R&D, MFA/Norad remains a small funder in comparison to total funding requirements for the continuation of these costly and risky R&D efforts in the future. In light of an emerging consensus between governments to support future Ebola R&D efforts through a pooled R&D fund hosted by WHO TDR, MFA/Norad should consider the opportunity to leverage its limited resources in the field through such a fund. This would be in line with MFA/Norad's global health priority on improving human security through health; and would also be in line with the CEWG recommendation that funders dedicate at least 20% of their funding obligations in the field into a single pooled financing mechanism. Potential trade-offs to alternative financing options (e.g. GLOBVAC) should be considered prior to any final decision, such as: differences in overhead and administration costs; ability to channel funds quickly and flexibly; restrictions on participation or other operational principles.

4. **Improving coordination of global health product development funding with other funders**

First, MFA/Norad should continue to engage in PFG-led coordination activities, including standardizing reporting requirements to PDPs, exploring opportunities for joint PDP evaluations, and sharing information on PDP assessments through meetings and other communication tools proposed by the PFG.

Second, MFA/Norad should more proactively explore information sharing options on a bilateral basis with other funders supporting common R&D projects and/or PDPs, who may have a deeper understanding of technical aspects of projects and/or organizations that are commonly supported.

Third, MFA/Norad should explore options for joint financing schemes in the future with other funders in special areas of common interest (e.g. late stage TB vaccine R&D supported by MFA/Norad, where MFA/Norad funded PDPs can no longer support due to scope restrictions). Joint financing schemes would make sense depending on economic and strategic cost-benefit trade-offs for the organization.

METHODOLOGY

Scope, objectives and methods were finalized during an inception phase from January 2015 to February 2015, comprising a detailed activity plan; a meeting with MFA/Norad officials to finalize data collection methods and lists of potential interviewees; and a Terms of Reference document noting the focus areas of the review. The review was conducted by researchers of the Department of International Public Health, NIPH between March and June 2015.

Scope & definitions

This report is focused on MFA/Norad global health product development funding for: (1) Poverty-related infectious and neglected diseases (PRINDs) that disproportionately affect LMIC populations, and for which there are insufficient commercial markets to attract R&D by industry; (2) Maternal, child and reproductive health conditions that persist in LMIC settings.

Product development in this report is defined in terms of[ii]:

- **Geography**: Investments that are specifically targeted at LMIC R&D needs, according to World Bank national income classification.
- **Product types**: Health products types include drugs, vaccines (preventive and therapeutic), diagnostics, microbicides, vector control products (pesticides, biological control agents and vaccines targeting animal reservoirs), as well as platform technologies (adjuvants, diagnostic platforms and delivery devices). The latter category concerns technologies that can potentially be applied to a range of neglected diseases, RMNCH conditions, and respective products, but which have not yet been attached to a specific product for a specific disease or health condition.
- **Parts of the R&D process that is being addressed:** Basic science is excluded, and so is applied research that is not directly linked to development of a specific product. For instance prevalence and disease burden studies are not included in this definition. All activities in the product development process up to and including market approval are included. Post-marketing approval activities such as pharmacovigilance, manufacturing scale-up, commercialization, market shaping, etc., are not included.

Methods

To perform this review we gathered and analyzed three different types of data:

- Review of published and grey literature between 2009 and February 2015
- Expert consultations with representatives from 35 institutions (see annex 6)
- Data analysis of R&D pipelines, financial and cost-effectiveness information, gathered from MFA/Norad, PDPs, databases and published reports.
- PDP performance assessments using a framework that builds on the OECD DAC evaluation criteria and the MFA/Norad PDP funding appraisal framework.

Our findings are based upon the triangulation of the above mentioned data. For more description regarding our methods, please see Annex 8: Detailed methodology.

[ii] This definition is adapted from G-FINDER .

1. Introduction

The Norwegian Ministry of Foreign Affairs supported by the Norwegian Agency for Development Cooperation (MFA/Norad) has funded global health product development against poverty-related diseases for many decades. From the support of WHO initiatives since 1974 to the more recent support of Product Development Partnerships (PDPs), MFA/Norad has been a small but smart funder of new and improved biomedical products that have contributed to global health improvement.

As poverty related infectious and neglected diseases (PRINDs), reproductive, maternal, new born and child health (RMNCH) conditions continue to claim the lives of over 11 million people, MFA/Norad has maintained its commitment to support the development of new and improved products that can contribute to reducing the burden of these diseases and conditions; improving population health; and promoting human security through health.

In an evolving landscape of priorities, mechanisms for financing and coordination of product development in global health, it is an opportunity to take stock of MFA/Norad's contributions in global health product development and examine its future role in this space.

This report aims to:

- provide Norad with strategic and technical input to the monitoring of progress met vis-à-vis planned activities in the MFA/Norad's existing PDP grants for the period 2013-2015
- provide strategic input to MFA/Norad's goals and priorities for global health product development funding in the future, demonstrating the importance of global health product development funding, identifying opportunities for synergies and value-for-money

Based on these objectives, the report addresses the following policy questions:

- What have MFA/Norad's contributions in global health product development been to date?
- What are the results of these investments?
- Have investments been appropriate in terms of strategic orientation, funding levels, grantees selected, and accompanying financing and coordination measures?
- Should MFA/Norad be recommended to alter their course of action in any of these aspects?

Background

Progress to date

Progress in global health product development has been unprecedented. Between 1975 and 2000, only 13 out of 1,393 new products had been approved globally against diseases that primarily affected vulnerable populations in the developing world.[6] In stark contrast, between 2000 and 2010, 43 new or improved drugs, vaccines and diagnostics reached the market, tackling a wide variety of poverty related infectious diseases. Many of these products, such as improved combination treatments against sleeping sickness,

leishmaniasis, and malaria, have already saved over 1.6 million lives[iii]; whereas a life-saving vaccine against Meningitis A - to which Norwegian funders and researchers have contributed in clinical testing - will be reaching more than 300 million children and adults across 25 countries in Africa by 2016.[7] Overall, historical evidence suggests that the adoption of new products is associated with a decrease in the under-5 mortality rate of about 2% per year;[8] and that the story of global health improvement in the past two decades has largely been based on the development of new products.[9]

Government and philanthropic funding has been catalytic to product development efforts. For instance, eight neglected disease drugs had been developed with public input by the WHO Special Program for Research and Training in Tropical Diseases (TDR) prior to 2004, associated with improved access, including through negotiating lower public sector prices or free donation programs.[10] More recently, from 2007 to 2013, governments around the world invested US$ 15 billion for the development of new drugs, vaccines, diagnostics and vector control products across more than 30 disease areas.[11] This represents 67% of global investments made by public, private, philanthropic and multilateral sectors during the seven year period. Excluding the US National Institutes of Health (US NIH)[iv], 30% of government funding internationally comes from aid agencies.[12] Moreover, non-profit organizations like the Bill & Melinda Gates Foundation (BMGF) and the Wellcome Trust have been investing over half a billion dollars annually in R&D for new products to tackle a number of neglected diseases, representing approximately 17% of global funding in the field .[11]

A growing community of product developers has also emerged, capitalizing on the investments made by governments in high-income countries. Innovative financing and R&D management mechanisms have sprung out from collaborative initiatives between governments, non-profits and the private sector, such as a number of Product Development Partnerships (PDPs), the European Developing Countries Clinical Trial Partnership (EDCTP), the Global Health Investment Fund (GHIF), and the Global Health Innovation and Technology Fund (GHIT Fund). With a noticeable lag, new initiatives have been emerging lately also in the area of women's, maternal and child health, such as the Grand Challenges initiative 'Saving Lives at Birth' (SLAB). And despite its recent financial challenges,[13] the WHO has recently initiated new efforts for establishing a voluntary pooled R&D fund for neglected diseases.[14] The overall purpose of all these structures has been to pool resources and incentivize R&D in the absence of sufficient incentives for industry to take the lead.

Collectively, these institutional arrangements and investments have built a powerful R&D pipeline for the development of new drugs, vaccines, diagnostics and other products against PRINDs. For instance, in 2012 the global R&D pipeline for new products against 23 PRINDs consisted of over 370 projects, according to one estimate[15]. Based on information collated from 14 PDPs[v], their combined R&D pipelines for a number of neglected diseases increased from 44 projects in 2004[vi] to 126 projects in 2014[vii]. And according to IFPMA

[iii] Coartem dispersible: 500k lives saved; Injectable Artesunate: 165k lives saved; ASAQ & ASMQ: 963,600 lives saved; NECT: 13,000 lives saved; Combination therapies for leishmaniasis: 2,660 lives saved
[iv] Excluding the US National Institutes of Health (US NIH) - NIH is the single biggest funder of neglected disease R&D in the world, occupying approximately a third of the total global annual investments in the field, though most of its investments are intramurally allocated.
[v] Websites, annual progress reports and direct consultations
[vi] PDPs included are: AERAS; DNDI; EVI; FIND; IAVI; IDRI; IOWH; IPM; IVCC; IVI; MMV; PATH; Sabin Vaccine Institute PDP; TB Alliance
[vii] PDPs included are the same as in the 2004 figure, excluding IOWH which has been merged with PATH and including TBVI which was founded after 2004.

data[16], the industry's combined R&D pipeline for 11 neglected conditions grew from 32 projects in 2004 to 186 projects in 2014. Almost half of all industry PRIND R&D projects in 2014 were implemented in partnership with PDPs (90 projects in total).

Challenges ahead

PRINDs and RMNCH conditions are continuing to create a heavy burden for the world's poor, causing over 11 million deaths each year, hampering child growth, harming labor productivity, perpetuating poverty and underdevelopment for the world's 'bottom billion'.[17] Each year 255,000 women die from different maternal disorders[viii]. Diseases such as helminth infections,[18, 19] malaria,[20] and HIV/AIDS[21] contribute, directly or indirectly, to over 25% of maternal morbidity and mortality.[22] And each year 45,000 maternal deaths, 1.45 million neonatal deaths, and 1.2 million stillbirths occur due to hemorrhage, labor, delivery and other complications - debilitating families, communities and nations.[23]

New or improved biomedical products are needed for controlling these diseases, for saving lives and improving the quality of life of millions of people. HIV/AIDS, malaria and tuberculosis remain a global health threat due to a combination of limited advances in the development of effective vaccines and growing resistance to existing treatments. Although biomedical products exist for many other PRINDs, these are often ineffective or prone to resistance; in lack of proper diagnostics leading to wrong treatment; unaffordable to poor populations; and unsuitable for tropical environments and underdeveloped health systems. While strengthening health systems is pivotal to reducing RMNCH mortality – an activity in which MFA/Norad is also committed – new and improved multi-purpose technologies for disease prevention and contraception, drugs and devices against pregnancy, birth and post-birth maternal and child conditions can greatly improve women's and children's health.[20] Emerging infectious diseases like Ebola, whose health burden has been historically low, are also increasingly at risk of new epidemics. In these cases, effective biomedical products for disease control and prevention, such as drugs and vaccines, are entirely lacking.

Narrowing R&D gaps is not always easy, as the product development process can be highly complex, lengthy and costly. Drugs and vaccines can take 10 to 15 years to develop with less than 6% probability of success at point of discovery.[24] As product candidates advance to later stages of R&D their probability of success increases, but so do the investment requirements, which can add up to tens of millions of dollars per product, only for clinical testing[ix]. Overall, average costs of developing a single new drug or vaccine can range from around US$ 100 million [25] to many billion dollars, [26] according to different estimates. Diagnostics and other devices can be quicker and cost less money to develop.[27]

Enhanced investments are pivotal for sustaining product development efforts against PRINDs and RMNCH conditions. As the recently published Global Health 2035 Report[28] suggests, enhanced investments in new products over the next 20 years can help in the reduction of women's and children's deaths due to infections in LMICs down to levels currently observed in some of the best-performing middle income countries (MICs). And as recent research suggests,[29] over 14 Disability Adjusted Life Years (DALYs) can be averted for every US$ 1000 spent in PRIND R&D, which implies great life-year gaining potential for the right amounts invested. However, from the US$ 248 billion spent globally on health

[viii] GBD data 2010, deaths due to maternal disorders
[ix] According to Medicines for Malaria Ventures (MMV) statistics, the clinical development of a novel malaria drug exceeds US$ 50 million in R&D costs

research in 2009,[30] only US$ 3 billion was invested in R&D for products against infectious diseases affecting LMIC populations.[31] This represents a mere 1% of total health research investments, and indicates a large mismatch between R&D priorities and R&D investments.[28] Both the Consultative Expert Working Group (CEWG) on R&D Financing and Coordination at WHO[32] and the Lancet Commission on Investing in Health[28] have called for a doubling of global health product development funding to US$ 6 billion annually for PRINDs'. Without sustained investments in global health product development, advocates suggest,[33] the world may never see new drugs to tackle resistant malaria and TB; microbicide and reproductive health technologies to prevent HIV infections and maternal deaths; drugs and vaccines against HIV and other neglected diseases.

MFA/Norad's response

The recognition of the need for new and improved biomedical products to improve global health and human security through health has led MFA/Norad to increasingly engage in global health product development funding over time.

From the 1970s onwards

Following a World Health Assembly (WHA) resolution in the early 1970s urging the WHO to intensify research on tropical diseases, MFA/Norad became an important supporter of the WHO Special Program for Research and Training in Tropical Diseases (WHO TDR).[34] For many decades to come TDR would be the only international partnership supported by public funds to conduct R&D for the development and evaluation of new medicines, diagnostics and vector control products (such as insecticide-treated bed nets) against a number of PRINDs. TDR is still the recipient of Norwegian investments, even though it has not engaged in product development for a few years.

Passing the 1990s and entering the millennium

A Commission on Health Research for Development in 1990[35] demonstrated that only 10% of health research investments globally were dedicated to developing country needs, where 90% of all deaths worldwide occurred (what was later coined as the 10/90 gap). A World Development Report by the World Bank in 1993[36] demonstrated a clear and central role for governments to support health in order to combat worldwide poverty. Coupled with concerns about emerging global HIV/AIDS, malaria and tuberculosis epidemics in the 1990s,[37] these findings were catalytic to an increased engagement by MFA/Norad in the support of newly established national and international global health initiatives to support R&D and access. Domestically, MFA/Norad supported the launch of the Global Health and Vaccination Research program (GLOBVAC),[38] demonstrating the central position that vaccines would obtain in Norway's global health efforts. Internationally, MFA/Norad supported a number of initiatives, including Gavi, the Vaccine Alliance (GAVI),[39] the Global Fund to Fight AIDS, Tuberculosis and Malaria (The Global Fund),[40] and the International Drug Purchasing Facility (UNITAID)[41] on the access front; the International AIDS Vaccine Initiative (IAVI)[42] and the International Partnership for Microbicides (IPM)[43] on the R&D front.

MFA/Norad's prioritization of these global health initiatives in the 2000s was facilitated by a game changing set of targets agreed among nations at the beginning of the millennium, linking disease-specific challenges with poverty alleviation and development goals. A United Nations Millennium Declaration in 2000 urged nations to a new global partnership to reduce

extreme poverty, leading to the launch of the Millennium Development Goals (MDGs)[44] on, among others, combating women's and children health, HIV/AIDS, malaria and other diseases (MDGs 4 - 6). Placing HIV as a leading priority, MFA/Norad developed its own HIV and AIDS policy, following UN guidelines for achieving universal access to prevention, care and support; and prioritizing areas in which Norway could play a leading role, such as women, gender and empowerment (including sexual and reproductive health and rights), and prevention of mother-to-child transmission[45].

Nearing towards 2015

As it became increasingly clear by the end of the first decade of this century that the MDG targets would not be met by 2015 for a number of diseases and health conditions, including women's and children's health, MFA/Norad expanded its priorities and commitments to global health product development further.

MFA/Norad had already been supporting UNFPA for its work on RMNCH in response to a UN led International Conference on Population and Development (ICPD) in Cairo's Plan of Action in 1994 that had recognized reproductive rights as human rights for the first time.[46] The plan linked poverty, hunger and disease with securing women's sexual and reproductive health and rights, but little was done until the 2010s. An Every Woman Every Child[47] effort and an accompanying Strategy for Women's and Children's Health[48] in 2010 urged nations to intensify efforts to improve women's and children's health. In response, Norway spearheaded the establishment of a UN Commission on Life-Saving Commodities for Women and Children,[49] including the support of product innovations to improve women's and children's health. It also helped establish the Saving Lives at Birth Initiative[50] in 2011, part of a broader family of Grand Challenge Initiatives in health and development, to support the development and transition to scale of low cost innovations for saving women's and children's lives at their most vulnerable days around birth.

MFA/Norad renewed its commitment to the global health related MDGs in the early 2010s, as reflected in the White Paper "Global health in foreign and development policy"[51], and particularly policy priority "Reducing the burden of disease with emphasis on prevention". In 2013 MFA/Norad started funding three additional PDPs: Drugs for Neglected Diseases Initiative (DNDi), Medicines for Malaria Venture (MMV), and Tuberculosis Vaccine Initiative (TBVI). This was partly because of concerns about growing resistance to existing treatments (e.g. malaria drugs); partly because of a renewed commitment to eliminating a number of diseases by 2020 led by the WHO[52] (e.g. sleeping sickness); partly because of the belief that MFA/Norad investments could focus on areas of comparative advantages for Norwegian researchers to engage with international networks for translating their scientific outputs into products, especially vaccines (e.g. TB vaccines); and partly because of the desire to create more funding synergies with international donor and development partner communities in areas of market failure.

Recognizing that, despite past efforts, insufficient resources were being devoted globally to R&D for PRINDs as concluded by CEWG,[53] MFA/Norad recently extended its commitment to the support of a number of demonstration projects facilitated by the WHO to address identified gaps that disproportionately affect developing countries (see chapter 2).

And in its ongoing commitment to contribute to containing the spread of diseases with pandemic potential and human security implications related to health, MFA/Norad recently supported the Ebola vaccine development efforts led again by the WHO.

Planning for 2030

Today, MFA/Norad shares the international community's vision for a grand convergence in health between the rich and the poor parts of the world within a generation.[28] And the organization is supporting a new framework replacing the MDGs – the Sustainable Development Goals (SDGs) – as part of its strategy for investing in global health product development in the next few years. Although still under development, the SDGs are likely to include the unfinished agenda of reducing maternal, newborn and child deaths, as well as reducing the burden of infectious diseases, areas where Norway has long been engaged in. It is likely, however, that SDGs will also cover broader health issues, such as non-communicable diseases, often caused by non-health related, social determinants that require cross-sectorial interventions.

To shed some light on what a longer term investment strategy in product innovations towards the 2030 targets could be, MFA/Norad recently commissioned PATH to issue a call for innovation ideas supporting the 2030 SDGs' health targets, including on reducing preventable maternal, newborn, and child deaths; ensuring universal access to reproductive health supplies and services; preventing and treating infectious diseases such as HIV/AIDS, malaria and TB; and reducing the toll of diabetes, cancer and chronic respiratory and cardiovascular disease.[54] The goal is to select a set of 20 to 30 product innovations across diverse disease and/or health condition areas, using independent experts in the process.

MFA/Norad' strategy for ODA research support that is under development revolves around three strategic objectives: (1) new knowledge; (2) more systematic use of research-based knowledge in policy making and practice in developing countries and in Norway; (3) strengthened research capacity in developing countries[55]. Its current global health priorities are:[51] improving women's and children's health, reducing the global burden of disease with an emphasis on prevention, and promoting human security through health. And the research priorities within global health revolve around: prevention, diagnosis and treatment of communicable diseases; reproductive, maternal, neonatal, child and adolescent health; health systems strengthening and health security; with determinants of health as a potential new area in addition. Types of research include: product development and innovation; and implementation research.

Product development in health is an integral, albeit not prominent, part of the current strategy's objective 1. As the development agenda is becoming broader, the prioritization of global health product development investments is becoming increasingly challenging. It is crucial to take stock of what MFA/Norad has invested in global health product development to date, what the results have been from its investments, and what the options for future investments are in light of its current priorities in health and aid.

2. MFA/Norad's investments in global health product development

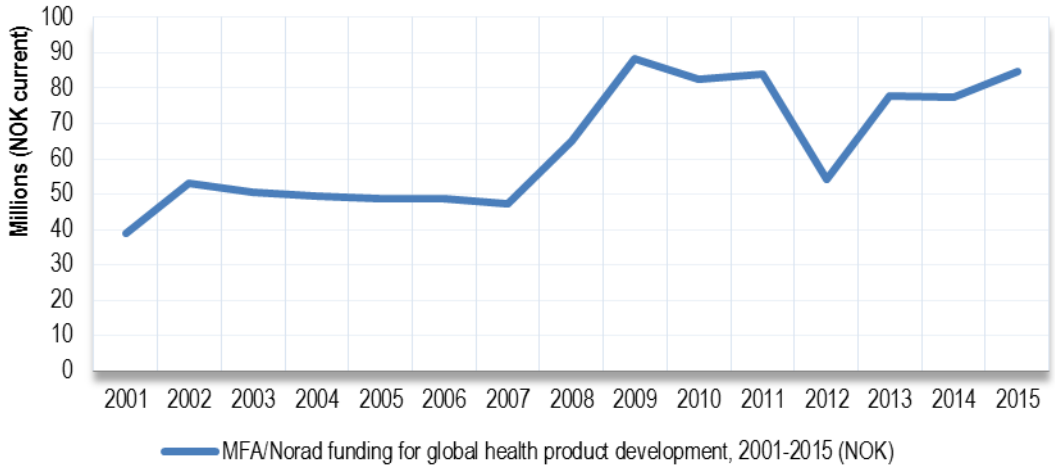
MFA/Norad has been a small and smart funder of global health product development, guided by international health priorities and responses to health crises. Its investments since 1974 have spanned across several organizations and international initiatives; and have been distributed across multiple diseases and products, particularly in recent years, in response to the organization's expanding priorities in global health and research strategy objectives. This chapter presents the MFA/Norad investments into global health product development between 1974 and 2015.

Product development funding levels and distribution

Funding levels

From 1974 to 2015, MFA/Norad's cumulative investments in global health product development surpassed NOK 1.4 billion, 34% of which was invested prior to 2001. From 2001 to 2015 MFA/Norad invested an accumulated NOK 933 million in the field, increasing its contributions from NOK 51.1 million in 2001 to NOK 84.7 million in 2015[x].

Figure 1: MFA/Norad funding in global health product development, 2001-2015 (current NOK)



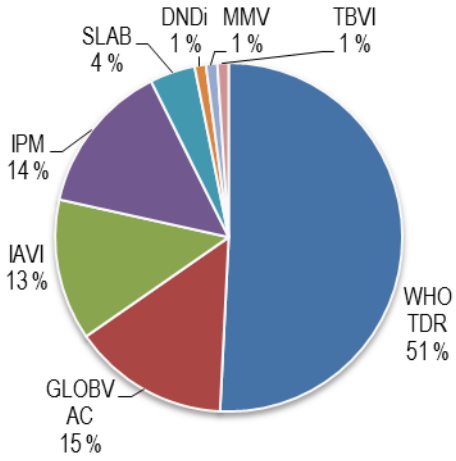
[x] The following disclaimer applies to all graphics included in chapter 2:

- Data sources: MFA/Norad data on investments into DNDi, IAVI, IPM, MMV, DNDi, SLAB; WHO TDR published data on investments into WHO TDR; G-FINDER data on investments into GLOBVAC 2007-2013; GLOBVAC annual reports and Projects Bank of the Research Council of Norway on investments into GLOBVAC 2013-2015.
- Data extrapolations: MFA/Norad investment data for GLOBVAC have been extrapolated from G-FINDER and the Research Council of Norway's Projects Bank assuming that MFA/Norad project-by-project contributions proportionate to MFA/Norad's share of total annual contributions to GLOBVAC. For 2013-2015 specifically, the Projects Bank of the Research Council of Norway was mined to identify eligible R&D projects and corresponding investment data was included in the analysis if within scope of the product development definition applied in this report.
- Reported currency: All figures are reported in current NOK, and are not inflation-adjusted. Regarding MFA/Norad investment data on GLOBVAC between 2007 and 2013, G-FINDER data was converted from US$ 2013 to current US$, then to current NOK values. Moreover, MFA/Norad investment data for WHO TDR between 1974 and 2013 was converted from current US$ to current NOK after distributing total investments for this period equally across all respective years.

From 1974 to 2015, MFA/Norad provided core funding of approximately NOK 725 million to the WHO Special Program for Research and Training in Tropical Diseases (WHO TDR), part of which was invested in drug, diagnostic and vector control product R&D for PRINDs. This included a NOK 5 million investment in 2014 for the implementation of a number of health R&D demonstration projects facilitated by WHO TDR, aiming to address identified gaps that disproportionately affect developing countries.

From 2001 to 2015 NOK 434.5 million was invested into five PDPs undertaking R&D for HIV/AIDS vaccines and microbicides, drugs for malaria and sleeping sickness, and TB vaccines (IAVI since 2001; IPM since 2002; MMV, DNDi and TBVI since 2013).

Figure 2: MFA/Norad's global health product development funding by recipient, 1974-2015



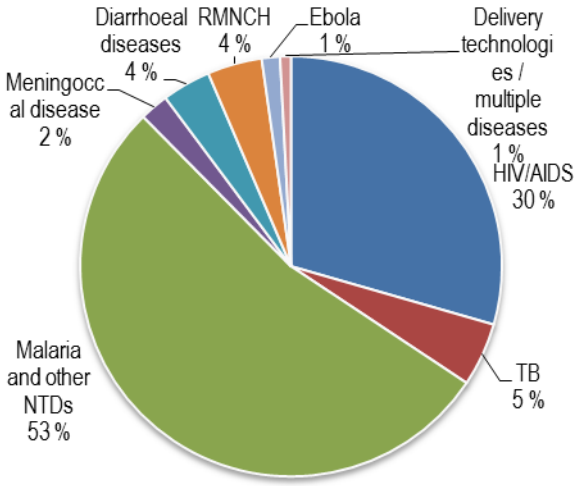
Since GLOBVAC's inception in the mid-2000s, an approximate NOK 207.5 million of MFA/Norad core contributions to the program was invested in product development related activities, such as R&D for affordable and LMIC- specific vaccines against meningococcal disease, TB, HIV/AIDS, malaria, diarrheal disease vaccines, and Ebola; as well as additional research supporting the development of diagnostics and new treatment regimens for TB, delivery technologies for safer and more affordable vaccines.

And from 2011 to 2015, MFA/Norad invested NOK 60 million to the Saving Lives at Birth Initiative (SLAB) for the support of RMNCH related product innovations. This comes on top of MFA/Norad's previous support of product innovations through the UN Commission for Life Saving Commodities for Women and Children, which is not included in these figures.

Funding distribution

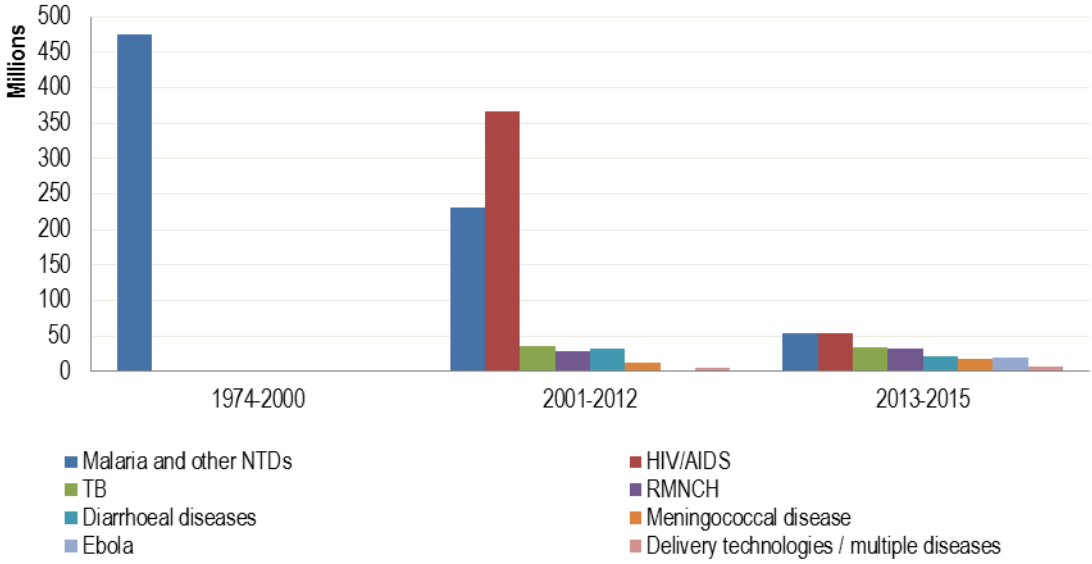
MFA/Norad funding for global health product development has been distributed across many diseases and health conditions. The largest share of funds has been allocated to malaria and other neglected tropical diseases, such as sleeping sickness, leishmaniasis, onchocerciasis and leprosy (53%). The second largest portion of MFA/Norad funds has been allocated to HIV/AIDS (30%). The remaining diseases and conditions have received 1-5% of total MFA/Norad investments each, including TB (5%), diarrheal diseases (4%), RMNCH conditions (4%), meningococcal disease (2%), Ebola (1%), and delivery technologies for multiple diseases (1%).

Figure 3: MFA/Norad funding for global health product development by disease, 1974-2015



The distribution of MFA/Norad global health product development funding has spread significantly across diseases and health conditions over time. From 1974 to 2000 malaria and other NTDs received the bulk of MFA/Norad funding through its contributions to WHO TDR (NOK 475 million). Between 2001 and 2012 HIV/AIDS received most of MFA/Norad funding (NOK 367 million) through contributions to IAVI and IPM, followed by malaria and other NTDs (NOK 230 million) through contributions to WHO TDR and GLOBVAC. The emergence of GLOBVAC during this period signalized a modest start in product development funding against other diseases, such as TB (NOK 36 million), diarrheal diseases (NOK 32 million) and delivery technologies for multiple diseases (NOK 6 million). MFA/Norad also invested NOK 29 million to RMNCH R&D following the launch of SLAB in 2011. From 2013 to 2015, MFA/Norad funding has been distributed more equitably across diseases and conditions. Although malaria & other NTDs and HIV/AIDS have remained at the top of MFA/Norad's investment portfolio (NOK 55 million and NOK 53 million respectively), these investments have been proportionately less in relation to other diseases and conditions including TB (NOK 34 million), RMNCH (NOK 32 million), diarrheal diseases (NOK 22 million), meningococcal disease (NOK 19 million), Ebola (NOK 20 million) and delivery technologies for multiple diseases (NOK 6 million).

Figure 4: Change in the distribution of MFA/Norad global health product development funding by disease over time, 1974-2015



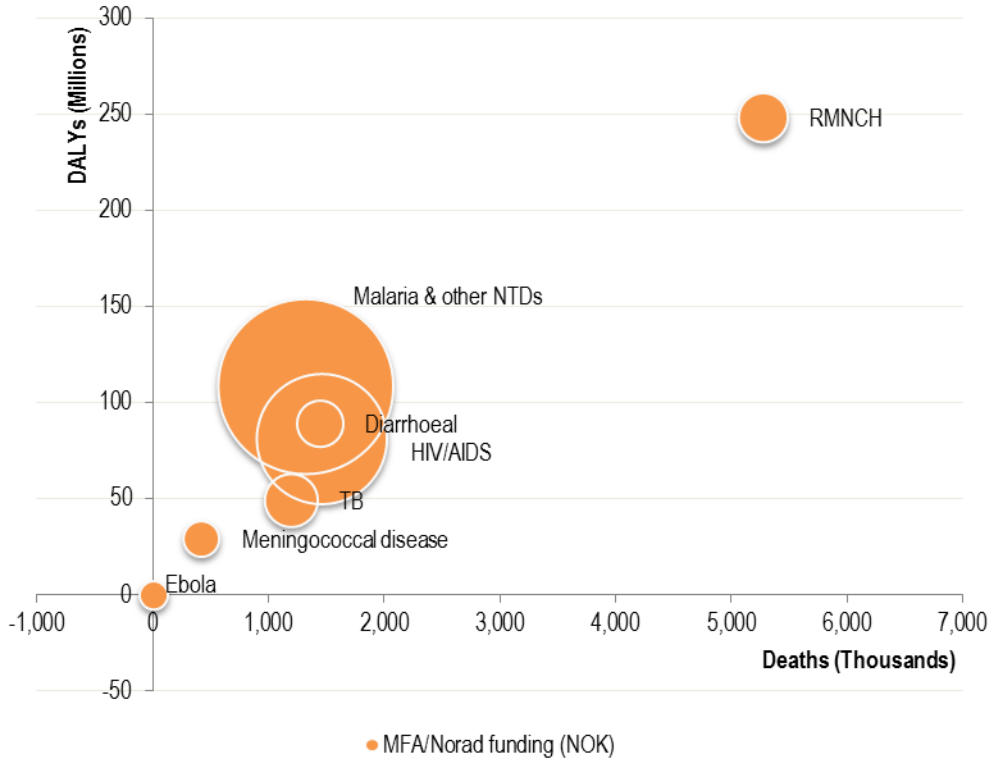
The distribution of this funding partly reflects the global health priorities and the research strategy objectives of MFA/Norad, as they have evolved over time in alignment with global development goals (see chapter 1). For instance, for six disease areas and conditions[xi] MDG targets have not been met and in our assessment funding is well aligned with the unfinished MDG agenda. Six disease areas represent an ongoing risk for outbreaks and epidemics[xii]. And all disease areas and conditions are highly relevant to women's and children's health.

As figure 4 demonstrates, funding has been distributed across most disease areas in proportion to their global disease burden (measured by deaths and DALYs). However,

[xi] HIV/AIDS, TB, malaria and other NTDs, Meningococcal Disease, Diarrheal Diseases, RMNCH
[xii] HIV/AIDS, TB, malaria and other NTDs, Meningococcal Disease, Diarrheal Diseases, Ebola

diarrheal diseases, TB and RMNCH conditions have received less funding in relation to their morbidity and mortality. Finally, in alignment with MFA/Norad's priority to vaccines, a quarter (25%) of MFA/Norad funding into global health product development has been allocated to this product type since 1975. This almost doubled to 38% of total MFA/Norad funding between 2001 and 2015, mainly due funding to IAVI since 2001. The remaining portion of investments has been distributed across drugs, vector control products, diagnostics, and other devices.

Figure 5: MFA/Norad funding for global health product development by disease (1974-2015) and Global Burden of Disease (2010)



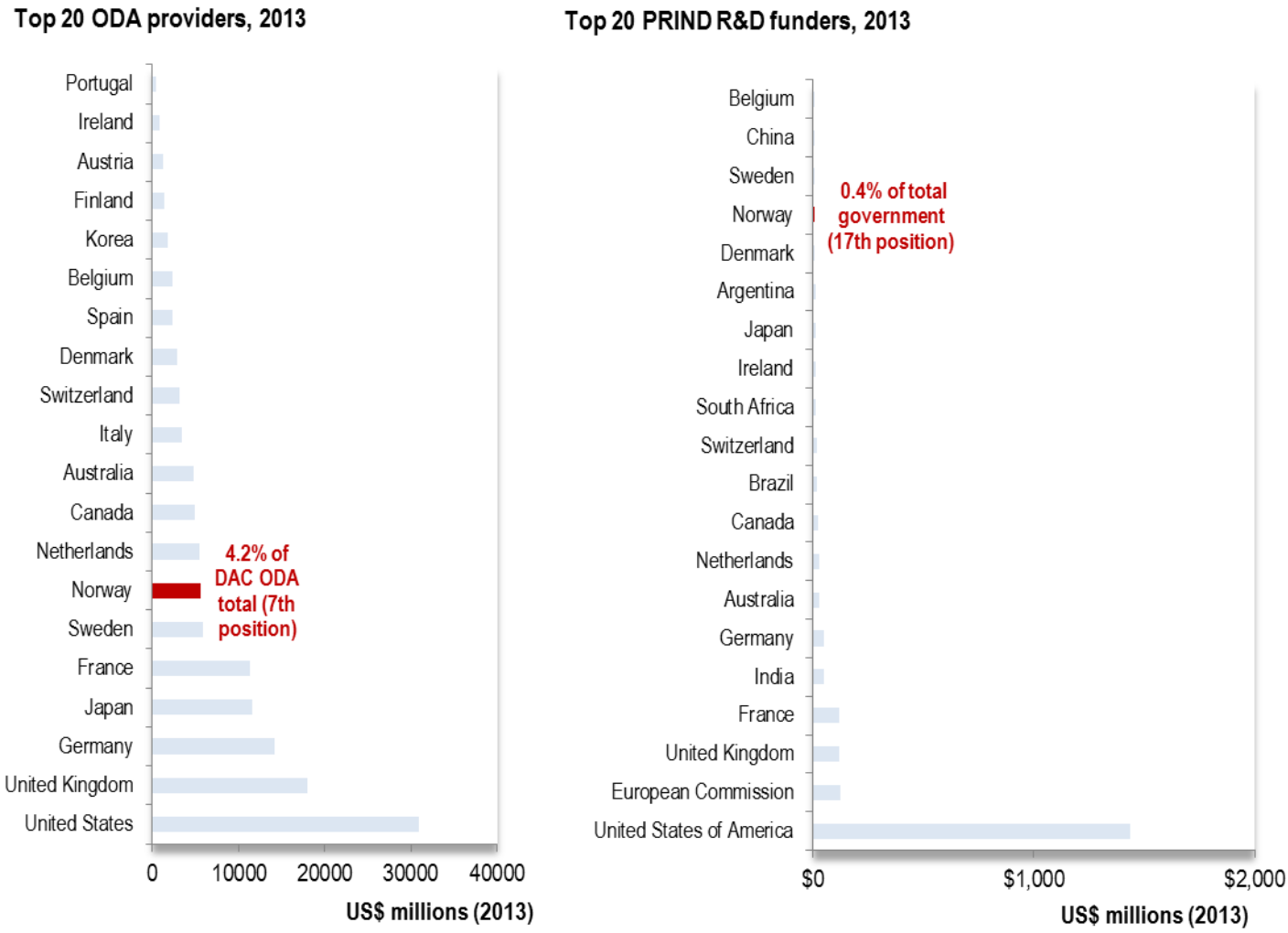
Out of the total MFA/Norad investments in global health product development, the five PDPs (DNDi, IAVI, IPM, MMV, TBVI) have received core funding following non-competitive grant financing procedures (see chapter 3). WHO TDR has received core funding support through MFA/Norad contributions to the WHO. R&D projects on Ebola, diarrheal diseases, meningococcal disease and some HIV/AIDS, TB and malaria related activities have been supported through GLOBVAC, which is a competitive grant financing mechanism. Finally, pooled financing schemes at the international level have been utilized to support product innovations for RMNCH. These processes carry with them different strengths and limitations, which are discussed in greater detail in chapters 3 to 5.

Product development as part of aid and economic growth

Funding in relation to aid

MFA/Norad is a significant contributor of development assistance (ODA). In 2013, it provided NOK 32.8 billion in aid (or 4.2% of DAC members' ODA total), ranking in the 7th position among all DAC members that year. In comparison, according to the G-FINDER survey, MFA/Norad investments in 2013 constituted 0.4% of total public funding in global health product development, ranking at the 17th position among government funders worldwide. As figure 6 demonstrates, MFA/Norad spends relatively less on global health product development than most major ODA donor countries. It is worth noting that several of the countries surpassing Norway in PRIND R&D investments, including Brazil and India, have significant domestic pharmaceutical sectors, suggesting that these countries are seeking strategic synergies with their PRIND R&D funding similar to the way Norway is.

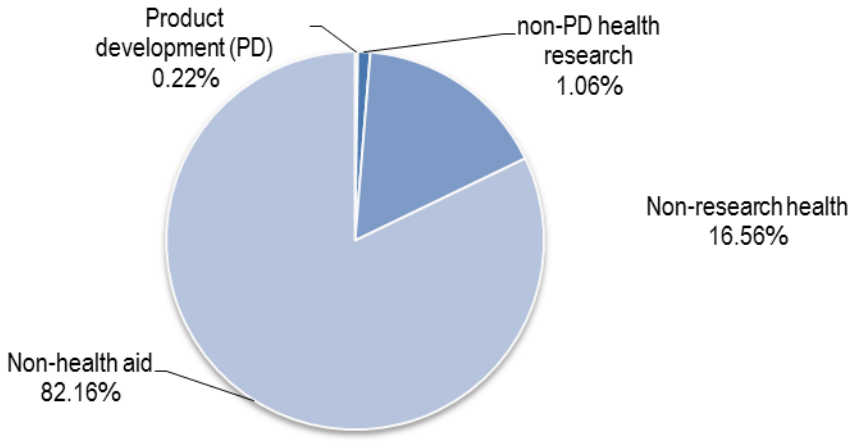
Figure 6: MFA/Norad ranking in ODA vs PRIND R&D funding, 2013



Funding in relation to other research and health

Based on a mapping exercise of investments for global health research conducted by MFA/Norad for 2013,[56] product development absorbs only a small share of MFA/Norad total investments in aid. Out of the entire 2013 aid portfolio, health investments constituted 18% of total aid (NOK 5.9 billion). Health research investments constituted 1.3% of total aid (NOK 421.8 million). And product development constituted 0.2% (NOK 73.4 million).

Figure 7: Distribution of MFA/Norad aid funding in relation to health, 2013



MFA/Norad's broader *non-research health* related product rollout[xiii] and access[xiv] portfolio includes contributions to the WHO (TDR, HRP and other programs), GAVI, GFATM, UNITAID, UNFPA, UNAIDS, UNICEF, Family Planning (including previously the UN Commission for Life Saving Commodities), and a number of LMICs on a bilateral basis (e.g. Ethiopia, India, Malawi, Nigeria, Pakistan, and Tanzania).

MFA/Norad's broader *non-product development health research* related portfolio includes funding for:

- GLOBVAC, Research Council of Norway
- the WHO for biomedical and clinical research on infectious diseases and reproductive health
- multiple recipients for implementation and operational research in infectious diseases and reproductive, maternal and child health
- Norwegian, LMIC and WHO recipients for capacity building in infectious disease, reproductive health, IT and education, health policy and systems research
- Norwegian, North American, WHO and other UN related recipients for knowledge summary and/or dissemination of research on infectious diseases, reproductive, maternal and child health, health policy and systems research.

MFA/Norad classifies its total global health *research* investments into five domains, out of which implementation and operational research absorbs the largest portion (55%), followed by product development (17%) and other biomedical and clinical research (15%). The two

[xiii] Including distribution of drugs, vaccines, diagnostics, devices and other commodities for poverty related infectious diseases, maternal and child health, and other conditions targeting LMICs populations.
[xiv] Including product-specific activities, as well as: broader health system strengthening; core support to multilateral organizations; gender equality and strengthening of women's rights; maternal and child health; and policy development.

remaining domains, capacity building for research and knowledge summary and/or dissemination, absorb 7% and 5% respectively.

It is clear from the above that health research is a small component of MFA/Norad investments in aid. MFA/Norad investments in health research in 2013 constituted 1.3% of total aid. MFA/Norad funding of global health product development as a share of health research funding in 2013 was 17%, it was a mere 1% of total health funding, and 0.2% of total aid funding for the year.

However, it is worth noting that MFA/Norad investments in health research in 2013 constituted 0.014% of GDP for that year. The CEWG recommended that '*All countries should commit to spend at least 0.01% of GDP on government-funded R&D devoted to meeting the health needs of developing countries*'. Presuming that the greatest part of Norwegian global health research is funded over the MFA/Norad budget, and assuming that the CEWG benchmark refers to a broader definition of R&D that covers both product development and biomedical R&D supported by GLOBVAC, Norway appears to comply with the CEWG recommendation.

Under a narrower, and perhaps more accurate, interpretation of the CEWG recommendation, MFA/Norad investments into global health product development fall short from this key international benchmark. MFA/Norad investments in global health product development in 2013 constituted 0.002% of GDP for that year. For Norway it would require NOK 294 million to reach that target for product development funding. Again, presuming that the greatest part of Norwegian global health product development is funded over the MFA/Norad budget, the annual NOK 70 – 90 million budgets would have to be multiplied more than four-fold to comply with the CEWG recommendation if only product development funding was to be considered. It is worth noting that no country other than the USA currently satisfies this benchmark on product development funding.

3. Results of MFA/Norad's recent investments

Although MFA/Norad has supported product development targeting tropical diseases since the mid-1970s it is not until 2000 that this kind of investment gained any significant momentum. Previously, and partly with the small core funding support from MFA/Norad, WHO TDR had contributed to the development of multiple drugs and several diagnostics for neglected tropical diseases. More recently, and largely with contributions of MFA/Norad, GLOBVAC supported R&D activities related to two licensed vaccines; one against meningococcal disease (MenAfriVac™)[57] and one against rotavirus (ROTAVAC®),[58] which are affordable and suitable for LMIC settings. However, as chapter 2 demonstrates, since 2001 the bulk of MFA/Norad investments in the field have been directed to PDPs, as well as initiatives for RMNCH product innovations and access. This chapter presents the results from MFA/Norad's recent investments in these initiatives.

Investing in PDPs

The value of PDPs

The most prominent group of recipients of MFA/Norad investments in global health product development has been Product Development Partnerships (PDPs). These are independent non-profit enterprises that bring together public, private, academic and philanthropic sectors to accelerate the development of drugs, vaccines, diagnostics, devices and other health technologies against PRINDs, RMNCH or other health conditions. The rationale of PDPs is to address R&D gaps for biomedical products to meet the needs of the poorest populations in LMICs, in the absence of sufficient commercial demand to incentivize pharmaceutical industry engagement. PDPs achieve this by leveraging resources and expertise from multiple sectors and by managing R&D portfolios which can target single or multiple disease and product areas.

The first PDPs in the fields of PRIND R&D and RMNCH R&D were WHO TDR and PATH[xv] respectively, both established in the 1970s. From the mid- 1990s to the mid- 2000s there was an explosion of next generation PDPs in the field, partly in response to an unprecedented interest in R&D against PRINDs by governments in high-income countries and partly due to the emergence of game changing non-profit funders like BMGF. Accounts of the exact number of PDPs active in global health product development today vary according to different definitions and different classifications. However, we know according to the G-FINDER survey that there are at least 16 PDPs active in PRIND R&D,[59] four of which are also engaged in RMNCH R&D[xvi].

Between 2007 and 2013, PDPs in the field of PRINDs received US$ 3.8 billion (on average US$ 549 million per year), absorbing 27% of all government funding for product development[xvii]. In response PDPs have built robust R&D pipelines in a number of PRINDs. Over 40% of all drugs, vaccines and diagnostics that were approved from 2000 to 2010 had been supported by PDPs.[60] Additional technologies have been developed since 2000 to facilitate lower costs and better access (e.g. PATH's semi-synthetic artemisinin and Vaccine

[xv] Initially called the Program for the Introduction and Adaptation of Contraceptive Technology, or PIACT
[xvi] PATH, CONRAD, FHI 360, and IPM since 2013
[xvii] excluding NIH which is largely conducting intramural investments

Vial Monitors;[61] TB Alliance's Critical Path to TB Drug Regimens). An increasingly larger share of the global R&D pipelines in PRINDs has been supported by PDPs, not least because pre-2000, newly-merged multinational pharmaceutical companies were actively closing down neglected disease research[10]. In 2004, 25% of all drug R&D projects in the field were conducted by PDPs[10]. By 2012, PDPs were engaged in 40% of the neglected disease R&D pipeline globally,[15] and by 2014, over 53% of the drug and diagnostic pipelines for the 10 neglected tropical diseases selected as priorities by Uniting to Combat NTDs in the London Declaration, were conducted by PDPs.[62] By 2014, PDPs were partnering with industry to support R&D across almost half its combined R&D pipeline for 11 neglected conditions.[16]

The build-up of this unprecedented R&D pipeline has been driven by PDPs' overall ability to diversify funding risk and reduce risk of failure by:

- **pooling infrastructure and expertise** from diverse groups of researchers and developers, industry facilities, and clinical trial partners in LMICs
- **managing effective partnerships** through the use of collaborative R&D arrangements and business-oriented approaches reducing development times, open access innovation and use of rational criteria for R&D project prioritization[63]
- **licensing for access,** managing intellectual property and conflicts of interest with industry
- **prioritizing innovations** with lower risk of failure and high benefit potential if redesigned according to affordability and LMIC suitability criteria

Results from recent investments in five PDPs

As mentioned in chapter 2, MFA/Norad has been financially supporting five PDPs in the field of PRINDs: the Drugs for Neglected Diseases Initiative (DNDi); the International AIDS Vaccine Initiative (IAVI); the International Partnership for Microbicides (IPM); the Medicines for Malaria Venture (MMV); and the Tuberculosis Vaccine Initiative (TBVI). The most recent funding cycle started in 2013 and it is coming to an end in December 2015.

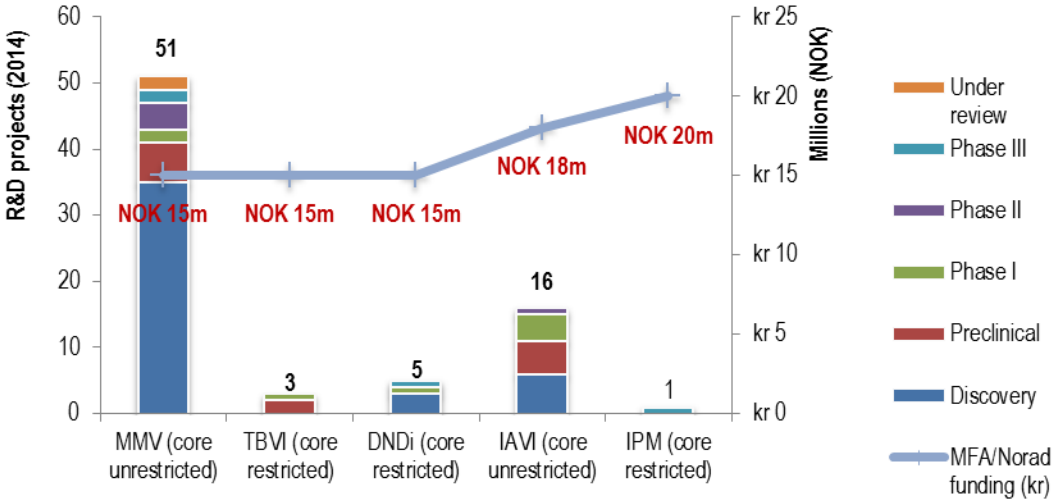
Whereas all PDPs received core funding between 2013 and 2015, only MMV and IAVI received core unrestricted funding, i.e. funding that could be flexibly allocated across the entire R&D portfolio of the organizations, without any particular earmarking. DNDi received core semi-restricted funding, i.e. funding that could be flexibly allocated across a disease-specific R&D portfolio (in this case sleeping sickness), without any further earmarking. TBVI and IPM received core restricted funding, i.e. funding that could be flexibly allocated across specific R&D projects or other pre-defined activities. In TBVI's case this was for work on a number of preclinical and clinical TB vaccine candidates as well as additional discovery or portfolio management activities. In IPM's case funding was directed to support the dapivirine ring clinical development and licensure program. Overall, the differences in the type of MFA/Norad funding across the five PDPs entirely reflects the PDPs' own choices over means of MFA/Norad support, to which the organization has been fully accommodating.

The five PDPs were selected through a non-competitive grant financing process, initiated by MFA/Norad invitations to the PDPs to submit funding applications for the three year period; and concluded by technical appraisals conducted by Norad in collaboration with consultants from the NIPH. PDPs were invited based on relevance of their R&D portfolios to MFA/Norad polies and strategies around specific diseases and products (for more details see annexes 1 to 5). All PDPs that had initially been invited received MFA/Norad funding. Norad has been the implementing agency and has dealt with all direct contact and grant agreements. MFA

directives are given to Norad through StProp1S and allocation letters, and Norad has had all direct follow-up with respect to grant management, i.e. invitation letters, proposals, grant letters, reporting, annual meetings etc.

Due to the differences in the type of core funding allocated to the PDPs by MFA/Norad during the three year period, it is difficult to pinpoint the exact number of R&D projects supported by Norwegian investments, particularly in the case of MMV and IAVI where funding has been fully unrestricted. Based on these differences, a total of NOK 83 million was invested during 2013-2015, which PDPs could flexibly distribute across 136 different R&D projects (see figure 8).

Figure 8: Flexible distribution of MFA/Norad funding to R&D projects of five PDPs



Detailed assessments of each PDP's performance during the period 2013-2015 are provided in annexes 1 to 5, and textboxes on PDP achievements, pipelines and recent trends and innovations are provided below. Overall, despite the complex nature of this field of work, all five PDPs have made substantial progress in their product development efforts, with technical or other difficulties creating only minor delays to development timelines or leading to only a limited number of R&D failures. In summary:

- **DNDi has made considerable progress with its drug development program against sleeping sickness (HAT).** The PDP has been conducting a phase II/III safety and efficacy study for fexinidazole, a novel drug against HAT starting in 2012. The follow-up period for the pivotal study is ongoing and submission of the file to the regulatory authority is likely due by end of 2017. Patient recruitment is ongoing and additional studies have been initiated for different ages and different stages of the disease. Patient enrolment to the study has been slow and new clinical trial sites have been set up to ensure adequate numbers of study participants, stretching timelines and somewhat increasing clinical development costs. The advancement of another novel drug against HAT to phase II/III testing has been delayed by over a year due to the difficulty to define the dose regimen due to the very long half-live of the product in an earlier phase I dosing study. SCYX-7158, an Orally-Active Benzoxaborole for the Treatment of Stage 2 HAT,[64] is not expected to begin before 2016. DNDi is working closely with partners including through a regional Platform to ensure smooth and timely implementation of clinical development, staff training and regulatory dossier submissions.

- **IAVI has made stepwise progress with its discovery and development efforts towards advancing AIDS vaccines to efficacy trials over the next five years.** Since 2013, the PDP has advanced two vaccine candidates to clinical phase I trials, and three candidates to preclinical development, each of which is testing a distinct approach to inducing broadly neutralizing antibodies (bNAbs) to HIV. Additionally, in its replicating vector program, the lead candidate Sendai, entered phase I clinical testing in 2013. This failed to meet immunogenicity targets and was terminated, with a decision made in 2014 not to fund a next-generation candidate. However, two other replicating vector based vaccines are currently being tested in preclinical models; with at least one prioritized for clinical development given sufficient funding is made available. IAVI has entered new partnerships for the clinical testing (and planned large-scale trials) of conserved and mosaic HIV antigen candidates and has expanded its technical support services to a broad community of HIV vaccine developers along with further diversifying its R&D portfolio including early stage development and smaller experimental trials for novel (innovative) concepts led by the PDP. IAVI has also maintained its global leadership and contributions to advocacy and policy for AIDS vaccine R&D and global health; has expanded its South-South collaboration networks in Africa and in India spanning from discovery to clinical and epidemiological research to further support and inform future efficacy trials.

- **IPM has made breakthrough progress with its dapivirine ring licensure program.** The PDP has been conducting a phase III clinical trial since 2012, testing the long term safety and efficacy of the dapivirine vaginal ring for monthly replacement. Clinical trial data will be an important milestone to demonstrating proof-of-concept as to whether microbicides are effective prevention tools against sexually transmitted HIV. In 2014 the study reached a milestone by completing enrolment at multiple sites in two African countries. Enrolment was also completed in a parallel study funded by the US NIH, the successful completion of which is a prerequisite for sufficient clinical data generation and dossier submission for approval to regulatory authorities. The dossier will be submitted to both the European Medicines Agency (EMA) and the South African Medicines Control Council by the end of 2016. A series of additional studies have been requested by the US FDA, which will push timelines for FDA review of the product further into the future. Manufacturing activities for the clinical trials have run smoothly to date, however future manufacturing capacity remains a potential challenge for commercial supply of and access to the product. In this regard, IPM has a signed contract with its current manufacturer, QPharma, to meet launch requirements up to 1.6 million rings per year post marketing approval. In addition, IPM has partnered with NuSil Drug Delivery to transfer the current ring manufacturing process and conduct studies to demonstrate comparability between rings manufactured at NuSil and at QPharma. If successful, these studies will be used to establish a long-term manufacturing partnership to meet increased demands for commercial supply, at a lower cost per ring.

- **MMV has made remarkable progress with its R&D and access portfolio activities.** One antimalarial for children has obtained WHO prequalification (SP+AQ) and WHO prequalification is pending for an affordable rectal artesunate in late 2015. A dossier for registration of a third antimalarial pediatric formulation (Pyramax®) has been submitted to EMA, with results expected by end-2015. A phase III trial of tafenoquine for single dose cure for P. *vivax* relapse prevention started in 2014. A phase IIb dose-ranging

study in patients with single-dose cure of another antimalarial (OZ439-piperaquine) was initiated ahead of schedule in 2014. MMV is currently working with partners to test more affordable formulation approaches. Two new compounds reached Proof of Concept (DSM265 and MMV048); the former has already advanced to phase II studies. Seven new compounds have moved from discovery to preclinical development. One candidate (ELQ300) has been terminated due to formulation issues. Another candidate (21A092) is currently on hold, whereas the AstraZeneca mini-portfolio project has been terminated due to the closure of the AstraZeneca facility in India. MMV's R&D efforts towards its short term goal for pregnant women have not fully materialized, as the AZ-CQ candidate for intermittent preventive treatment in pregnancy (IPTp) showed poor efficacy.

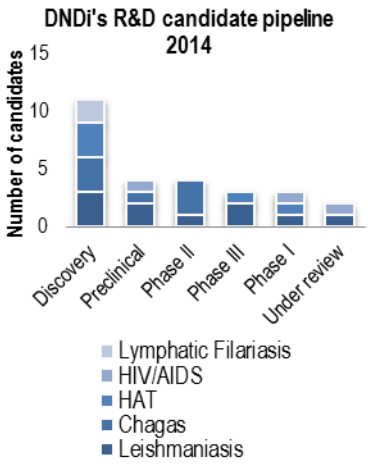
- **TBVI has made significant progress in advancing TB vaccine candidates through the pipeline**, launching new discovery projects and extending R&D partnerships over the last couple of years. A phase I trial of MTBVAC, a live-attenuated vaccine against TB, was successfully completed in Switzerland in 2014 and a new safety, tolerability and immunogenicity trial is being planned in South Africa following TBVI recommendations. The launch of the trial has been delayed by approximately half a year due to requests for data and design clarifications by the South African Health Authorities, partly reflecting also TBVI's limited presence of clinical research networks in LMICs. Another four TB vaccine candidates advanced to early clinical and preclinical development and a new EC funded discovery network was launched in 2014, bringing in 13 new R&D partners and aspiring to explore 20 different strategies to TB vaccine development in the coming years. A novel preclinical model for head-to-head comparisons of vaccine candidates was successfully developed, which now requires further standardization and funding to support TBVI's R&D prioritization and portfolio management processes. Several TB biomarkers were identified to guide R&D prioritization and population stratification for clinical trials.

MFA/Norad funding has been flexible, allowing PDPs to manage their R&D portfolios more efficiently and to avoid duplications in funding. Although MFA/Norad funding levels to individual PDPs have been considerably small, there is a wide appreciation by stakeholders of the positive signal generated within the donor community because of MFA/Norad's ongoing commitment to supporting PDPs. For instance, the breadth of support by different funders is a great signal politically for IPM, as well as financially helpful when this is flexibly provided (e.g. core funding). MFA/Norad funding to DNDi has allowed the PDP to make resource allocation decisions within its HAT drug R&D program more flexibly, and it has contributed to the further diversification of its funder-base promoting independence of the PDP's overall strategy in R&D. Similarly, gaining new public funders sends positive signals to other funders in the case of MMV, promoting independence of the organization. In the case of IAVI, MFA/Norad has been one of the longest lasting funders, and its core funding approach has allowed the PDP to manage its R&D portfolio effectively while maintaining alignment with Norwegian strategies in the field. MFA/Norad funding has been catalytic in the case of TBVI particularly, where it has served as a bridge investment between two major EC grants supporting TBVI's ongoing R&D activities on biomarkers, preclinical models for R&D candidate prioritization and other projects in the PDP's pipeline.

Textbox 1: Investing in the Drugs for Neglected Diseases Initiative (DNDi)

DNDi is a non-profit R&D organization set up in 2003 to develop treatments against the most neglected diseases. It has headquarters in Geneva and offices in Congo Democratic Republic (DRC), Brazil, India, Japan, Kenya, Malaysia, and USA; with total staff of 108.

DNDi has historically focused its R&D efforts on Human African Trypanosomiasis (HAT), leishmaniasis, Chagas disease and malaria. In these disease areas it has delivered 6 new improved treatments, including 1 HAT combination therapy (NECT); 2 Artemisinin Combination Therapies for malaria (ASAQ, ASMQ); 1 Visceral Leishmaniasis combination therapy for East Africa (SSG & PM); 3 Visceral Leishmaniasis combination therapies for East Asia; and 1 Chagas pediatric dosage formulation (Benznidazole 12.5mg).[65] Its current portfolio comprises 27 R&D projects, mostly in kinetoplastid drugs but recently also in HIV/AIDS pediatric drugs and drugs for lymphatic filariasis. DNDi's R&D portfolio today no longer includes malaria drugs.



Case study : DNDI's fexinidazole for HAT (sleeping sickness)

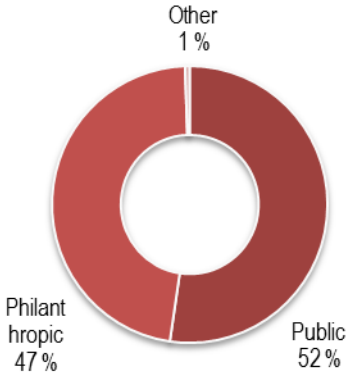
Fexinidazole is a rediscovered chemical entity through DNDi's compound mining efforts within the nitroimidazole project initiated in 2005.[66] The drug is an oral, short course treatment for both stages of HAT, caused by T.b. gambiense or T.b. rhodesiense. Fexinidazole has the potential to change the dynamics of HAT patient management and HAT elimination efforts.

Today there are 69 million people at risk of HAT infection, especially remote populations in sub-Saharan Africa. The disease is fatal if untreated. HAT elimination requires universal disease detection, development of an effective and affordable treatment for both stages and access at all areas of prevalence. Current treatments are either effective against one stage of the disease (NECT); require hospitalization; are toxic - 5% mortality - and painful when delivered (melasoprol); or are expensive and prone to resistance (eflornithine). Choice of treatment is determined by lumbar puncture, a complex and painful diagnostic procedure.

Clinical phase II/III safety and efficacy testing is now underway across eight sites in DRC. Enrollment is ongoing (537 patients to date) in three different studies for different ages and stages of the disease caused by T.b. gambiense. A fourth study is planned in Uganda and Malawi for HAT rhodesiense. The main study has completed recruitment in April 2015 (18 months follow-up period) to facilitate a submission under article 58 to the European Medicines Agency (EMA)by end of 2017. The goal is to obtain approval in 2018 for use of fexinidazole against both stages of the disease. A positive opinion by EMA would facilitate registration in affected countries and allow fexinidazole's use to treat HAT without need for lumbar puncture.

The drug's development started in 2007, led by DNDi,[66] entering first-in-human clinical trials in 2009[67] and phase II/III in 2012. The PDP has been collaborating with the Swiss Tropical Public Health Institute on designing the drug's Target Product Profile and clinical development plan. MSF, the Human African Trypanosomiasis National Control Programme of DRC and Central African Republic (CAR) have been contributing to the drug's clinical development. The PDP's key industry partner, Sanofi, has been responsible for the industrial development, registration and manufacturing of the drug. Another industry partner, Aptuit, has been responsible for its pharmaceutical development. Over 12 public and other funders have supported this project since 2007, including MFA/Norad since 2013.

US$ 286 million disbursed to DNDi, 2007-2014 (US$ 2013)



Recent trends and innovations:

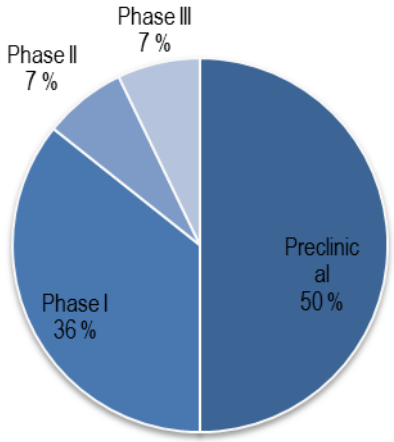
- ✓ 15 New Chemical Entities (NCEs) comprising over 50% of DNDi's R&D portfolio
- ✓ Improved Target Product Profiles (TPPs) for HAT drugs to better suit patients' needs and meet HAT elimination targets
- ✓ Expansion to Lymphatic Filariasis and HIV/AIDS paediatric drug R&D
- ✓ Improved regulatory models through Regional Disease Platforms

Textbox 2: Investing in the International Partnership for Microbicides (IPM)

The International Partnership for Microbicides (IPM) is a Product Development Partnership (PDP) focusing on the development and availability of safe and effective microbicides and other HIV prevention, sexual and reproductive health technologies for women in LMICs. Established in 2002 as a non-profit organization, the PDP has headquarters in Silver Spring, Maryland, USA, and an office in Paarl, Western Cape, South Africa; with a total staff of 74.

Since inception, IPM has led R&D efforts globally in developing the first long-acting ARV-based microbicide for HIV prevention in women. It has worked in over 10 countries in Africa, Europe and North America to conduct 25 clinical trials on several microbicide candidates, and 13 epidemiological studies. It has helped strengthen capacity at 15 research centers (RCs) in Africa (10 of these newly established by IPM), and has trained 850 clinical staff and community advisors on microbicide trial implementation. The PDP has developed competencies in: developing and evaluating microbicides and multi-purpose technologies (MPTs) to address women's health needs; negotiating royalty-free licenses for ARVs as microbicides; and streamlining manufacturing processes.

IPM's R&D candidate pipeline 2014



Case study : IPM's dapivirine ring

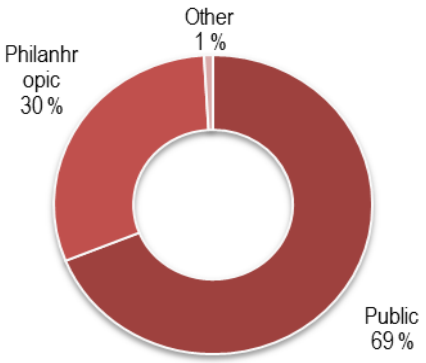
The dapirivirine ring is a vaginal ring that slowly releases the ARV drug dapivirine over time, and is designed to remain in place for at least 30 days to provide long-acting, discreet and easy-to-use protection against HIV in women.[68] The ring is a novel formulation made out of silicone material with dapivirine dispersed uniformly throughout a matrix ring. Dapivirine is an ARV drug that works by preventing HIV from replicating inside a healthy cell.[69] If effective this ring will be the first long-acting female-initiated prevention tool that women can use to protect themselves against HIV.

Two parallel phase III safety and efficacy studies are now underway across 21 sites in Malawi, South Africa, Uganda, and Zimbabwe, led by IPM and a US NIH-funded consortium, the Microbicide Trials Network. The studies have completed enrolment of 4,588 women ages 18-45. Efficacy results are expected by early 2016. Should the ring prove to be safe and effective, IPM – the ring's regulatory sponsor - will seek approval for the ring's licensure.

IPM's Phase III trial of the dapivirine ring started in 2012. The PDP has been able to establish long-term, sustainable contract relationships for the development of the dapivirine ring including collaborations with a Sweden-based contract developer and pharmaceuticals manufacturer, QPharma, for the development of this novel drug delivery method; NuSil Drug Delivery for the long-term supply of silicone; and Omnichem for the production of dapivirine to support the licensure program at as low a cost as possible.

IPM began developing dapivirine as a microbicide in 2004 through a royalty-free licensing agreement with Janssen Sciences Ireland UC, and has previously tested dapivirine as a vaginal gel or ring in 16 safety studies. This license has since been expanded to a worldwide rights agreement. The company provides ongoing data management, quality management and other in-kind support.

US$ 291 million disbursed to IPM, 2007-2014 (US$ 2013)



Recent trends and innovations:

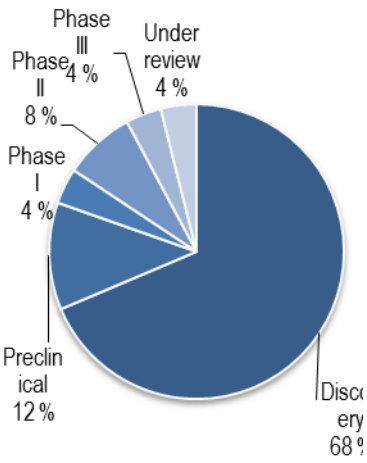
- ✓ 3 active pharmaceutical ingredients (APIs) at clinical and 1 NCE at preclinical development (making up 50% of IPM's R&D portfolio)
- ✓ Expansion to multi-purpose prevention ring development combining ARVs with contraceptive hormones, if proof-of-concept in dapivirine ring licensure is achieved
- ✓ Improved models for pharmacodynamic testing in early clinical trials
- ✓ Increased leadership on vaginal ring formulation and polymer chemistry
- ✓ Evidence-based processes for selection of suitable ARVs and stage-gating for candidates

Textbox 3: Investing in Medicines for Malaria Venture (MMV)

Medicines for Malaria Venture (MMV) is Product Development Partnership (PDP) established in 1999 as a non-profit foundation to discover, develop and deliver new, effective, and affordable antimalarial drugs to malaria-endemic countries. Its focus is on building a strong R&D pipeline leading to a new generation of medicines that will form a critical part of malaria eradication efforts.

Since inception, MMV has built the largest and most diverse portfolio of antimalarial drug projects in history. It has helped bring forward five antimalarial product modifications: Coartem® dispersible; artesunate injection for severe malaria; Pyramax®; Eurartesim®; sulphadoxine-pyremethamine + amodiaquine (SP+AQ). Its current R&D portfolio includes 35 projects in discovery, 7 projects in preclinical, 8 projects in clinical development, and 2 projects under regulatory review, targeting a range of mechanisms of action and chemo types. Its extensive malaria screening campaign of 6 million compounds has been continuously supplying MMV's R&D pipeline as well as assisting the broader malaria R&D community through open access innovations and data sharing.

MMV's pipeline 2014



Case study : An Africa-led next-generation single-dose cure for malaria

MMV048 is a novel malarial kinase inhibitor belonging to the aminopyridine class.[70] The compound aims to stop relapse, block transmission, and has full activity against drug-resistant strains of malaria. MMV048 has the potential to become a single-dose cure for uncomplicated malaria in children and adults, reducing treatment from three days to one. Its availability can increase the operational feasibility of malaria elimination and eradication programs, potentially replacing lead compounds currently in late stages of development.

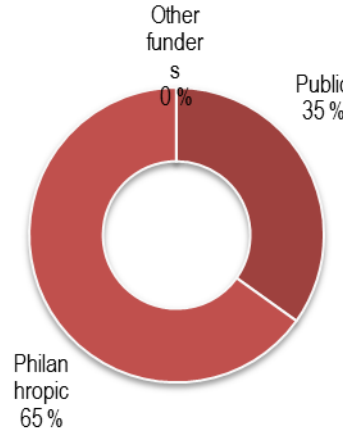
A clinical phase I study was successfully completed in 2014 at the University of Cape Town, South Africa (UCT). This was the first ever first-in-human study of a new chemical entity against malaria ever conducted in Africa. MMV worked closely with the clinical pharmacology group at UCT to set up the systems and structures for the implementation of the study. Additional formulation development is under way that will determine decisions over further clinical development of the drug.

The project started in 2011 with the identification of chemical series by scientists of the Eskitis Institute for Drug Discovery at the Griffith University, Australia,[71] as part of an extensive malaria compound screening activity organized by MMV in a commercial compound library of Biofocus, a UK based biotechnology company. Scientists from the Drug Discovery and Development Centre (H3-D) at UCT further explored the series, with parasitological and pharmaceutical support from the Swiss Tropical and Public Health Institute and Monash University, Australia. Following optimization and re-testing of leads with the greatest antimalarial potential, UCT selected MMV048 for preclinical safety testing and pharmacokinetic modelling, due to its potent activity against multiple stages of the P. *falciparum's* lifecycle and its potential to block malaria transmission.[72]

MMV048 is the first novel malaria drug candidate to have been discovered and proposed for clinical development by an Africa-led team. And it is the first antimalarial R&D project to be co-funded by the South African Technology Innovation Agency. MMV048 is an example of how collaborative efforts among public, private and non-profit R&D institutions across three continents including partners from disease-endemic countries can generate novel R&D outcomes against poverty-related infectious diseases.

MFA/Norad has provided core funding to MMV since 2013, part of which has supported the development of MMV048.

US$ 518 million invested in MMV, 2007-2014



Recent trends and innovations:

- ✓ New chemical entities comprise 73% of the R&D portfolio from preclinical development to registration
- ✓ 5 new innovations improving development timelines at preclinical and early clinical testing
- ✓ Expanded networks in drug manufacturing and development with 7 industry and 1 regional access partners
- ✓ New competitive selection processes for novel partners at discovery
- ✓ Transfer of both of DNDi's approved ACTs to MMV for inclusion in its access and delivery portfolio

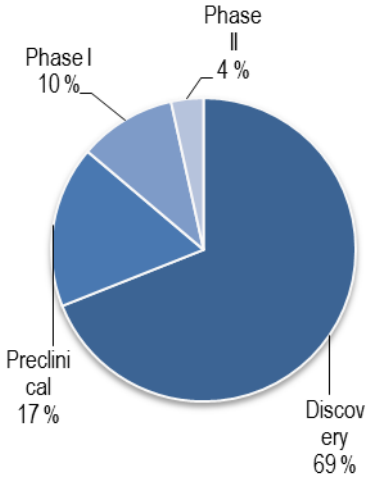
Textbox 4: Investing in the Tuberculosis Vaccine Initiative (TBVI)

TuBerculosis Vaccine Initiative (TBVI) is a non-profit foundation that facilitates the discovery and development of new, safe and effective TB vaccines that are accessible and affordable for all people. As a Product Development Partnership (PDP), TBVI integrates, translates and prioritizes R&D efforts to discover and develop new TB vaccines and biomarkers for global use. The PDP has sprung off a Tuberculosis Vaccine Cluster funded by the European Commission (EC) since the early 2000s, and was established as an independent non-profit organization in 2008. TBVI has headquarters in the Netherlands, with a network of 50 universities, institutes and industry partners from about 20 countries.

TBVI acts as a support structure to TB vaccine developers, without taking ownership of vaccines or claiming intellectual acquisition. Its main focus is on boosting and priming vaccines from discovery to Phase IIa clinical testing, in line with WHO strategy on TB vaccines. The PDP does not support late stage safety and efficacy studies.

Since inception, TBVI has supported a broad number of new vaccine candidates, of which 8 are currently being evaluated in clinical trials. In addition, TBVI characterized and validated 17 biomarkers, and has identified another 18 new such correlates in humans. The PDP has supported, or is currently supporting, 50% of all TB vaccine candidates being developed from preclinical to clinical stages worldwide. Its current R&D portfolio comprises of 29 projects.

TBVI's R&D candidate pipeline 2014



Case study : TBVI's MTBVAC – a live attenuated vaccine for TB

MTBVAC is a live-attenuated strain of Mycobacterium tuberculosis (MTB) and is the first vaccine candidate developed fulfilling the Geneva consensus requirements for live mycobacterial vaccines. MTBVAC is a single-dose intradermal vaccine that aspires to replace Bacille Calmette-Guérin (BCG), the only TB vaccine available today, as priming vaccine for global use in newborns and adults.

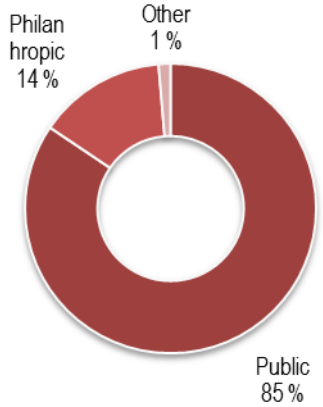
New vaccines are pivotal for stopping the global TB epidemic and for preventing the spread of tuberculosis. A modestly efficacious adult preventive vaccine could avert 30-50 million new TB cases by 2050; and a significantly improved newborn vaccine over BCG could avert an extra 7-10 million new cases over this timeframe.[73]

Preparations for a clinical phase I trial are currently underway in South Africa, a TB-endemic country. The trial is expected to start in mid-2015 following a positive opinion by the South African Health Authorities, ending in mid-2016. Biofabri, a Spanish biopharmaceutical company, is the clinical trial sponsor. In collaboration with the University of Zaragoza Biofabri and the South African TB Vaccine Initiative (SATVI), Biofabri will be testing MTBVAC's safety, tolerability and immunogenicity in healthy neonates.

Preclinical studies have previously demonstrated robust safety and efficacy comparable to BCG, and a clinical phase I study completed in 2014 at the University of Lausanne showed satisfactory safety and immunogenicity outcomes.[74]

The development of MTBVAC started in the early 2000s by the University of Zaragoza and Institut Pasteur. Over 12 partners have been engaged in preclinical and early clinical studies since.[75] Throughout the process TBVI has provided a platform of financial, scientific and technical advisory support, originating through the coordination of an EC grant. MFA/Norad has funded the project since 2013.

US$ 31.4 million disbursed to TBVI, 2007-2014 (US$ 2013)



Recent trends and innovations:

- ✓ New leadership, which includes strengthened Scientific Team
- ✓ New Portfolio Management Committee and improved R&D portfolio management process at entry, stage gating and priority setting of TB vaccine candidates
- ✓ New preclinical model for head-to-head comparison of TB vaccine R&D candidates and their selection for further clinical testing (including a preclinical prime-boost model)
- ✓ New EC funded TB vaccine discovery network for €6.4 million (TBVAC 2020)

Textbox 5: Investing in the International AIDS Vaccine Initiative (IAVI)

IAVI is a Product Development Partnership (PDP) established in 1996 to develop AIDS vaccines for global use, conduct policy analysis and advocate for the AIDS vaccine field. Its current focus in on the discovery and development of vaccine candidates able to elicit broadly neutralizing antibodies (bNAbs) to prevent HIV infection, as well as replicating viral vector-based vaccine candidates capable of preventing and controlling HIV infection.[76] IAVI is also a force of clinical research capacity building in Africa, vaccine design and technical support services to the AIDS vaccine field more broadly.[77]

Since inception, IAVI has evaluated 15 AIDS vaccine candidates in 27 early-stage human trials in 11 countries on four continents. In recent years the PDP has contributed to the discovery of dozens of bNAbs, revealing new vulnerable sites on the virus which researchers can target for vaccine design.[78] Its current R&D portfolio comprises of 10 projects in preclinical and early clinical development; and six different approaches to the design of novel immunogens with the potential of inducing neutralizing antibodies requiring further development.

Case study : Developing a vaccine to elicit broadly neutralizing antibodies

One out of four chronically HIV-infected individuals naturally produces antibodies that are capable of neutralizing a broad range of HIV strains. The human immune system generates these so- called bNAbs in response to an HIV infection, but too slowly and too late to help people prevent or control infection.[78] Isolating bNAbs can help scientists design novel vaccine immunogens with the potential of developing effective AIDS vaccines that elicit these special antibodies before exposure to HIV. An effective AIDS vaccine would offer the most effective prevention tool against new cases of this killer disease, which since 1983 has cost 39 million lives.[79]

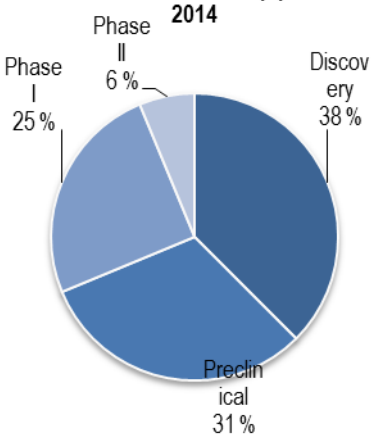
IAVI and partners are now testing five strategies to inducing bNAbs to HIV. At the preclinical stage, three approaches are being tested, including: an immunogen that mimics the HIV envelope trimer (BG505-SOSIP trimer immunogen);[80, 81] a computationally derived HIV immunogen assembled on nanoparticles that can bind multiple bNAbs and can be used as a priming vaccination to kick off the process of immune system response (eOD-GT8);[82] and a set of inactivated Vesicular Stomatitis Virus (iVSV) particles that are used as delivery platforms for HIV envelope trimers to elicit bNAbs against HIV.[83] These diverse strategies are expected to provide key immunology data to improve immunogen design and to validate preclinical screening models in the future. At early clinical stage, one approach is exploring whether a gene transfer technique can be used to produce bNAbs in humans as a means of preventing HIV infection (AAV1-PG9).[84] Another approach is testing clinical immune responses to an HIV Envelope protein (CN54gp140).[85] Safety and immunogenicity results will inform immunogen design, dosing, and manufacturing decisions.

IAVI and partners have been studying the molecular structure and biochemistry of known bNAbs since 2002, when the Neutralizing Antibody Consortium (NAC) was set up.[86] In 2009 two highly potent bNAbs were isolated from donors in HIV-endemic countries,[87] setting off a discovery spree of dozens of bNAbs since, which have contributed to the design of novel immunogens by IAVI as well as by a broader community of HIV/AIDS vaccine developers.

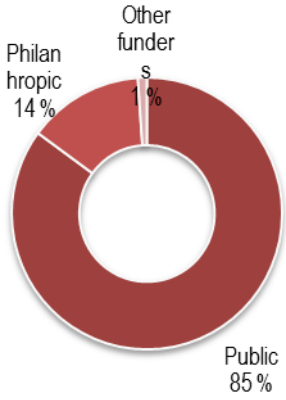
The discovery of bNAbs has generated a new momentum to AIDS vaccine R&D, which has suffered from some disappointing results of large, late-stage clinical trials in recent years.[88-90] bNAbs have potentially both immune-prophylactic and immunotherapeutic benefits, including for use in HIV cure approaches.[91] Additionally, approaches to creating neutralizing antibody responses to HIV are now being employed successfully for other viral diseases, such as respiratory syncytial virus[92, 93] and influenza;[94] and their preventive use can contribute to better directions in AIDS care in the future.[95]

MFA/Norad has provided core funding to IAVI since 2001.

IAVI's R&D candidate pipeline 2014



US$ 583 million disbursed to IAVI, 2007-2014 (US$ 2013)



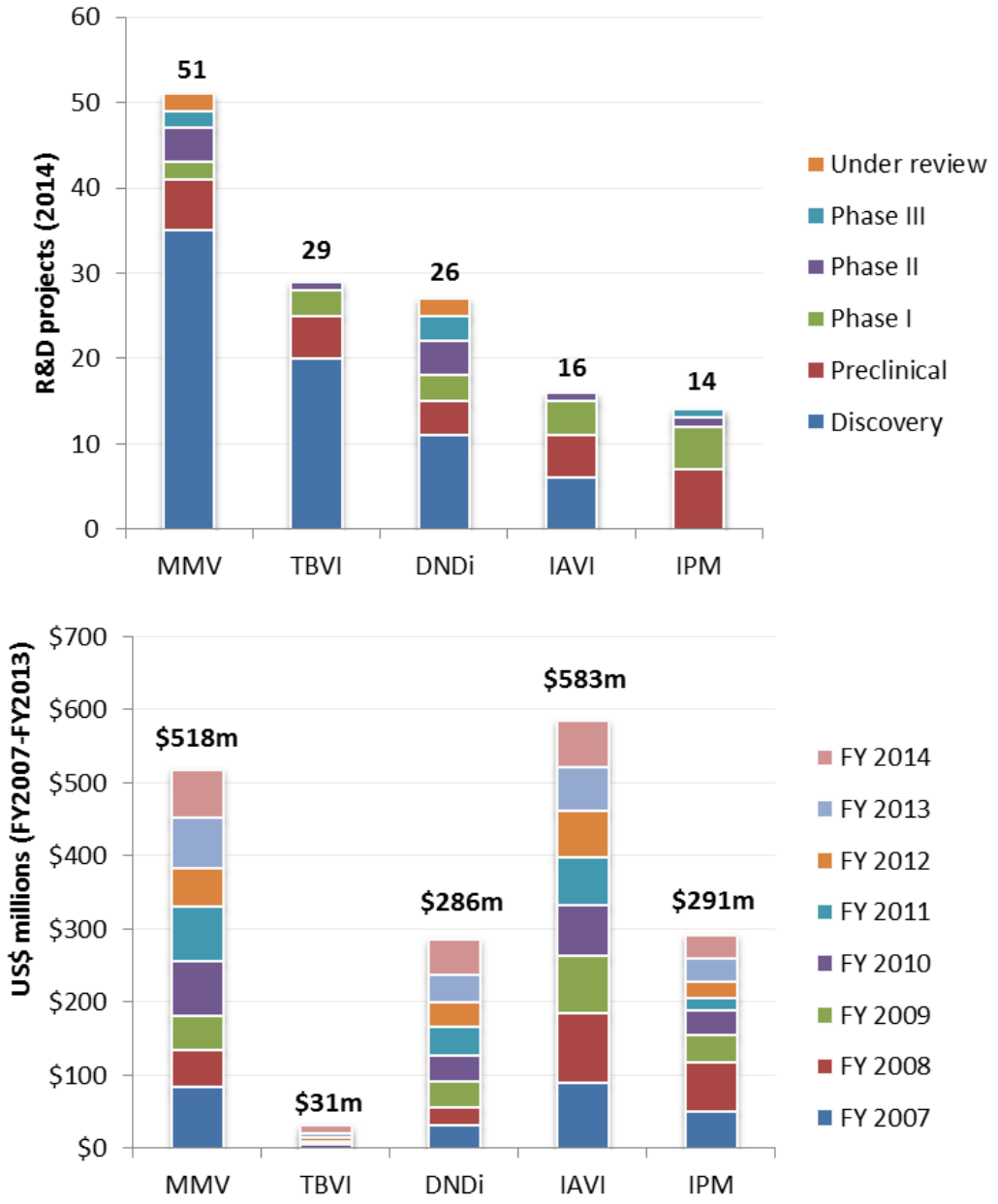
Recent trends and innovations:

- ✓ R&D portfolio diversified with early development, smaller experimental trials and technical support services to non-IAVI vaccine developers
- ✓ New discovery, development and access networks: Indo-East Africa Collaboration; VISTA Eastern and Southern Africa
- ✓ New PDP partnerships: PATH MVI for use of Human Immunology Lab; Aeras for manufacturing
- ✓ New industry partnership: Johnson & Johnson for clinical testing of HIV mosaic immunogens
- ✓ New immunogen screening platforms (crystallography, cyoroelectron microscopy) and preclinical models (humanized mouse models)

Differences between the five PDPs

There is some variation in the size of PDPs' pipelines and the levels of funding received to support their pipelines over time, as figure 8 demonstrates. For instance, IAVI and IPM have the smallest pipelines but have received the first and third largest volume of funding since 2007. TBVI has the second largest pipeline but has received by far the smallest amount of funding in the eight year period. MMV and DNDi have a more balanced pipeline structure in relation to investments received between 2007 and 2014. The reasons behind these differences are multi-faceted, including different scientific gaps among disease and product areas (i.e. for prevention, treatment and diagnosis); different compositions of PDP pipelines and distributions of R&D candidates between early and late stages of development; and different operational models and partnership compositions.

Figure 9: R&D pipelines of DNDi, IAVI, IPM, MMV and TBVI in 2014 vs PDP expenditures 2007 – 2014 (in 2013 US$)



The development of AIDS vaccines has been extremely challenging partly due to multiple knowledge gaps including on antigenic variation and immunity. And the world is still lacking an effective microbicide technology for female-initiated HIV prevention. The quest for a proof-of-concept in these product areas has led to numerous and expensive clinical trials over time. In recent years IPM has placed an even greater focus on late stage clinical development and licensure efforts for its lead candidate – the dapivirine ring - increasing funding requirements for clinical testing, ring manufacturing and regulatory preparations. Lack of well-established regulatory frameworks for this novel type of product is an additional hurdle. Since 2012, IAVI has placed a particular focus on early stage development and early (phase I) clinical trials to continue to optimize vaccine candidates (learning from results from past trials, as well as ongoing epidemiology studies in Africa and new scientific insights and technologies). But the PDP is still facing extremely high attrition rates at early clinical development stages, sustaining high average development costs. Failed candidates often result in a move back to earlier R&D stages with the hope that improved vaccines can be designed based on data generated from failed trials. This process allows for comprehensive comparison between vaccine approaches, and supports decision making on which approach or candidate to ultimately advance to large scale testing. Although this lengthy and complex, iterative process, is common practice in the field of biopharmaceutical R&D, it sheds some light as to why HIV vaccine R&D can be so much more expensive than other types of R&D. In short, it is a daunting task to devise an immunological defence against a virus that attacks the immune system itself.

Moreover, among the five PDPs, IAVI has the largest number of staff and partners working in laboratories or research centers across the world. Although its vaccine design and development capabilities give it a comparative advantage to becoming a hub for technical support to other vaccine developers, it also makes it a more expensive operational model to maintain over time. IPM outsourced its in-house manufacturing services in the late 2000s and has achieved significant economic gains ever since. However, like IAVI, the PDP maintains regulatory sponsorship of its products, increasing costs for managing R&D and licensure processes. TBVI, MMV and DNDi have been maintaining smaller teams of core staff and delegating regulatory sponsorship of products to their R&D partners. The setup for in-kind contributions by R&D partners in these models is potentially more inviting, which in some cases has arguably almost doubled PDPs' contributions in cash (e.g. as per MMV's own estimates on own financial to industry in-kind contribution ratio).

It is worth noting that TBVI does not support late stage clinical trials for its TB vaccines. For instance, in comparison to 2012, TBVI has four fewer projects in clinical development, which have been transferred to other developers for late stage clinical testing in the last couple of years. Its focus on discovery, preclinical and early clinical development allows TBVI to keep funding requirements of its R&D portfolio at much lower levels than other PDPs. Lower resource requirements are also driven by its limited engagement in IP management and by not maintaining a significant clinical research network in LMICs. It is likely that the PDP is underspending in these two areas, which are crucial for bringing appropriate and affordable products to market over time.

MMV and DNDi have a policy of not being marketing authorization holders of their products, although they have robust IP management and licensing practices in place. Increasingly the PDPs have been advocating for open innovation policies in neglected disease R&D according to the principles laid out by the WHO. The PDPs have balanced portfolios across all R&D stages with a good mix of incremental and breakthrough innovations in their pipelines (50-

70% of their portfolios comprises new chemical entities). The PDPs engage with industry partners on a project-by-project basis as early as possible in the R&D process, including on economic and financing aspects against clearly defined target product profiles that are in alignment with WHO and disease eradication strategy objectives. In recent years, MMV has developed various preclinical and early clinical models that have reduced development timelines by two years and have decreased attrition and R&D costs significantly[xviii] ; and DNDi has set up innovative region- and disease- specific platforms, reducing risks and costs including human resources (e.g. by avoiding duplication of training), and preparing the ground for product roll-out (e.g. by early inclusion of national regulatory authorities to regulatory discussions with EMA and the WHO).

Common challenges to the five PDPs

All PDPs are facing ongoing scientific and managerial challenges. The science is challenging for HIV prevention technologies and new TB vaccines; and the development of new chemical entities for malaria and HAT is not as easy as reformulating existing products to meet LMIC specific suitability and affordability criteria. There are numerous hurdles related to IP, clinical development, manufacturing and regulatory issues, which PDPs have to overcome, including getting the right partners engaged across different R&D stages.

All PDPs are struggling to attract diversified and sustainable R&D funding. In the absence of sufficient industry investment, each of the PDPs is highly dependent on one to two donors, such as the BMGF, USAID, UK DFID, or the EC. Even though DNDi has a 50:50 funding ratio policy by public and private sectors and places a 25% cap on the share of total funding by any single funder, the PDP is still heavily dependent on three donors including MSF. Greater diversification of PDPs' donor bases means greater independence of R&D strategies, clearer signals of confidence to potential investors and greater risk sharing for small funders already engaged in funding these PDPs.

PDP funding is becoming increasingly inflexible for PDPs and risky for smaller PDP funders. Although some funders have extended their PDP funding cycles in recent years to allow for greater predictability of investments, there has been a trend towards 'line item by line item' or results-based financing of PDPs, especially by some of the major PDP funders, such as USAID and the BMGF (and the EC which has always been a project-based funding entity). This restricted funding approach is challenging PDPs' ability to manage R&D portfolios flexibly and, arguably, to achieve greater R&D efficiencies over time; and it is forcing them to spend more on fundraising activities to secure core funding; and it is increasing the risk of smaller donor investments to PDPs, which, if also restricted to specific projects, are exposed to changes in funding decisions by larger funders who support PDPs in this way.[xix]

[xviii] (1) Controlled human malaria infection (CHMI) model; (2) High-throughput Plasmodium vivax liver-stage assay; (3) Standard membrane feeding assay; (4) Drug-resistance assay; (4) Pharmacokinetic modelling in SCID mice

[xix] For small funders, core funding is preferable to earmarked funding. A PDP may receive funding earmarked for a specific project in its portfolio from several funders. These allocations may vary considerably in size, to the extent that withdrawal of one big funder leaves that particular project infeasible. Thus, smaller funders may find themselves at the mercy of one or a few big funders with respect to declaring 'failure' of any specific project, and withdrawal of a critical funder will inevitably lead to considerations on part of the small funders of whether to reallocate their contributions across that PDP's portfolio. Core funding, on the contrary, has the dual advantage of leaving it up to the PDP to allocate funding flexibly and independently to achieve the greatest impact, and of increasing visibility by making it possible for the funder to claim credit for contributing to the entire portfolio of that PDP, instead of just one or a select few projects.

Investing in RMNCH R&D

The second group of recipients of MFA/Norad investments in global health product development has been a variety of initiatives for scaling up RMNCH commodities. These are a mix of pooled funding structures to identify and scale up product innovations that can save lives of women, mothers and children in the world's poorest countries. The rationale is to support low cost innovations which can have high life-saving impact, by leveraging resources and by setting clear targets against which scale up innovations are to be supported.

UN Commission on Life-Saving Commodities for Women and Children

Following a call by the UN Secretary-General's Global Strategy for Women's and Children's Health (2010) on the global community to work towards saving 16 million lives by 2015, a UN Commission on Life-Saving Commodities for Women and Children was set up in 2012 to identify overlooked commodities and to recommend actions to address access barriers that could save over six million lives of women and children by 2017 for less than US$ 2.6 billion investments.[96] Some years on, the Commission's recommendations have translated into specific measures undertaken under the UN Secretary General's Every Woman Every Child banner, and together with other RMNCH initiatives they contribute to making progress towards the unfinished agenda of MDGs 4 and 5.[97]

Table 2: Life-Saving Commodities prioritized by the UN Commission on Life-Saving Commodities for Women and Children

Area	Commodity	Usage
Reproductive Health	Female condoms	Family planning / Contraception
	Implants	Family planning / Contraception
	Emergency Contraception	Family planning / Contraception
Maternal Health	Oxytocin	Post-Partum Hemorrhage
	Misoprostol	Post-Partum Hemorrhage
	Magnesium sulfate	Eclampsia and Severe Pre-Eclampsia / Toxemia of Pregnancy
Newborn Health	Injectable antibiotics	Newborn Sepsis
	Antenatal Corticosteroid (ANCS)	Respiratory Distress Syndrome for preterm babies
	Chlorhexidine	Newborn Cord Care
	Resuscitation Equipment	Newborn Asphyxia
Child Health	Amoxicillin	Pneumonia
	Oral Rehydration Salts (ORS)	Diarrhea
	Zinc	Diarrhea

Although its focus has been on broader access and utilization issues around market shaping, quality and regulation, supply chain and advocacy building, the Commission has also been supporting innovation for new product formulations to reduce the cost and increase the ease of use of the commodities; or new packaging so that commodities can be easily transported and stocked. Examples include a time-temperature sensor for oxytocin, to be included in the packaging for each batch to assess whether products are likely to be viable and effective at the point of administration; a new formulation for inhaled oxytocin, which

obviates the need for syringes/injections and cold storage; and a user-friendly product presentation of amoxicillin dispersible tablets in order to facilitate adherence to the treatment of childhood pneumonia in low-resource settings.[98]

The identification of product innovations through country work plans, commodity group meetings and other bottom up approaches to idea generation has been an interesting process that led to the gathering of a substantial list of innovation ideas. And it has created a precedent on how to identify low cost innovations collaboratively and how to identify barriers to specific RMNCH commodities to help prioritize strategic planning and implementation of commodity manufacturing, import, procurement, regulation, quality control, supply and utilization.

Saving Lives at Birth: A Grand Challenge for Development (SLAB)

In 2011 five funding partners – USAID, MFA/Norad, BMGF, Grand Challenges Canada, and DFID – pooled resources to collectively support low cost innovations to help pregnant women and their families to practice healthy behaviors and access health care during pregnancy, childbirth and the early postnatal period.[50] These include simplified technologies to prevent, detect or treat maternal and newborn problems at the time of birth; service delivery approaches for higher quality care at time of birth; and demand-side information technology or other communication innovations.

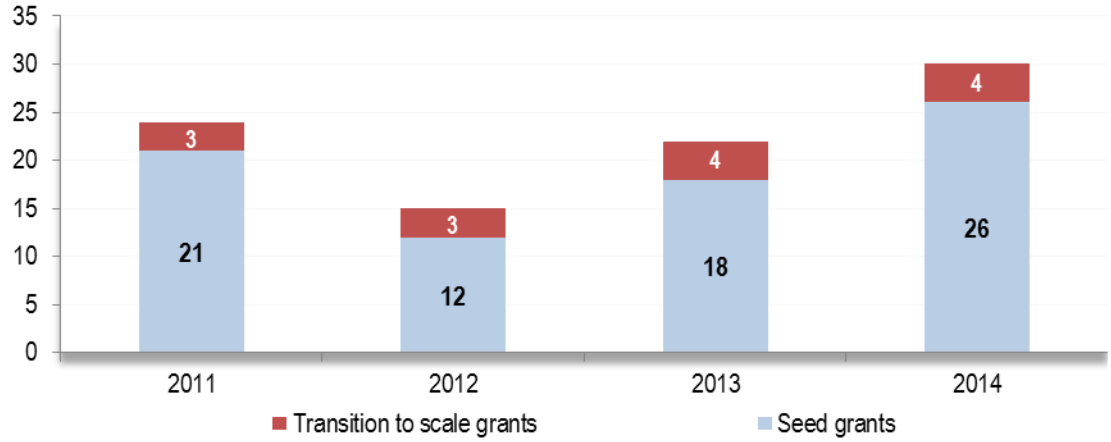
SLAB is part of the Grand Challenges family of initiatives, supporting innovations on the principles of highest impact and access to those most in need. Through competitive grant financing processes SLAB provides three types of funds:

- **Seed funds** of up to US$ 0.25 million for two years, to support the development of innovations to reach validation of effectiveness
- **Validation funds** for up to two years, to introduce and validate the effectiveness of innovations to reach proof-of-concept
- **Transition to scale funds** of up to US$ 2 million for four years, to develop, refine, and rigorously test the impact of innovations that have previously demonstrated promising results and have scale up potential

Funding partners nominate reviewers and USAID manages the overall commissioning process. Although the overall process is competitive, there are selection criteria that aim to encourage greater participation by LMIC innovators.

After four rounds of competitive calls between 2011 and 2014, rigorous reviews and stepwise project selection processes, a total of 91 innovations were funded, out of which 77 were seed grants and 14 were transition to scale grants.

Figure 10: Grants awarded through the Saving Lives at Birth Initiative, 2011-2014



Since 2011, only a handful of projects have moved from seed grants to transition to scale grants with success[xx]. And as some stakeholders suggest, an increasing number of innovators have applied for new seed grants in order to support further development work required to finalize proof-of-concept. Validation funds have therefore been introduced, in response to the realization that seed grants had been too small in size or too narrow in timelines required for projects to reach proof-of-concept.

Despite its challenges, SLAB has been influential in incubating funds required for scale up and commercialization of much needed low cost innovations. For instance, a traction device to deliver babies through the birth canal when complications arise in second-stage labor, which was invented by a car mechanic in Argentina, has now entered clinical trials organized by the WHO to demonstrate safety and effectiveness. The so called BD Odon Device ™ is currently being developed by Becton, Dickinson and Company (BD) in collaboration with SLAB.[99] Another product, Monash University's inhaled oxytocin, which had previously received some funding by the UNCLSC and more recently seed funding by SLAB , is now licensed to GlaxoSmithKline (GSK) to bring the concept from preclinical through to trial stage for a combined investment of US$ 16.6 million by GSK, the McCall MacBain Foundation, Grand Challenges Canada, and Planet Wheeler Foundation.[100]

Although this type of funding structure would not be suitable for higher risk and higher cost R&D (such as for instance the development of drugs or vaccines), SLAB provides an interesting platform that allows for the transfer of low cost research into implementation, by brokering deals between early innovation ideas and commercialization platforms between small sized innovators and larger scale private sector actors, while fostering an increasing amount of participation by innovators based in LMICs.

On a final note, SLAB offers certain advantages to MFA/Norad investments, such as the opportunity for ICT, eHealth and other app- based technologies developed by Norwegian researchers for the domestic market which can probably be used abroad (and vice versa). In the long run, stakeholders suggest, synergies might arise in the sense that investments in new products for national use by the Ministry of Health could turn out to have global applicability.

[xx] Moved from seed grant in 2011 (round 1) to transition grant in 2012 (round 2): Rice University 'Low-Cost Respiratory Support: Reducing Early Neonatal Death in Malawi'.

Moved from seed grant in 2011 (round 1) to transition grant in 2014: Changamka Microhealth Kenya 'Scale-up proven e-voucher program to reduce financial and informational barriers to care in rural Kenya'; Trustees of Boston University, USA 'Scale-upan affordable, effective, and portable counterfeit and substandard drug detector device'

Investing in Ebola vaccines

In late 2014 the Norwegian Research Program for Global Health and Vaccination Research (GLOBVAC) financially contributed NOK 20 million on behalf of the Norwegian Ministry of Foreign Affairs to an international trial of an Ebola vaccine. Given the urgent nature of the spread of Ebola in West Africa, Norad asked the Research Council of Norway to conduct a speedy decision concerning financing a safety and efficacy study of Ebola vaccines in Guinea, planned by the WHO, MSF, the Norwegian Institute of Public Health (NIPH), and others.[101]

The Efficacy and safety evaluation of Ebola vaccines in Guinea is now underway but conclusive results are not yet available. Despite some time delays in decisions around clinical study design, WHO and partners played an important role in setting up the trial in the context of ring vaccination of the population in communities where the Ebola-virus is active.

Early release of MFA/Norad funding was instrumental for the trial to start when no other funder had indicated willingness to launch clinical trials in Guinea, as some stakeholders have argued. At the time the country had the lowest prevalence among affected countries and setting up a trial there was risky. Given the evolution of the disease outbreak over the past few months, Guinea is providing a hopeful ground for conclusive vaccine safety and immunogenicity results to be produced. New cases of the disease have been dropping in neighboring countries, creating bottlenecks to the completion of parallel clinical trials led by other R&D consortia.

Although MFA/Norad has been a flexible funder that has complemented and filled in clear gaps in the planning and setup of Ebola vaccine clinical trials, it remains a small funder in comparison to global investments in Ebola product development. As some stakeholders suggest, maintaining a leading role in the field will depend on decisions to support future Ebola R&D efforts through multilateral, pooled mechanisms. There appears to be an emerging consensus among member states of the WHO that the WHO TDR can have a pooled financing function in Ebola R&D through a new pooled R&D fund.[102]

4. Financing approaches

Funders have considered a number of options over the years to support R&D of biomedical products to tackle PRINDs and RMNCH conditions. Using competitive, non-competitive, pooled or guarantee-based financing tools, governments in high income countries (HICs) have been experimenting with different models to leverage resources and incentivize product development efforts in global health. Although an extensive literature on innovative global health R&D financing models has developed over time,[103-108] few of these novel mechanisms have gained the support by governments in practice. This chapter provides a high-level overview of options relevant to MFA/Norad investments in global health product development, presenting examples or case studies to demonstrate lessons for future MFA/Norad investment decisions in the field.

Competitive grant financing

Description

Competitive grant financing is the most common approach to global health product development funding by governments, especially by national Science and Technology (S&T) agencies in Europe and European Union (EU) funding programs. Competitive grant financing is usually provided through Calls for Proposals (or Requests for Proposals). Participation rules are defined by the commissioning authorities, which usually maintain tight oversight of the selection process, and close implementation monitoring.

Under competitive grant financing there is usually a restricted number of final grantees, after having been selected against openly pre-defined technical and financial criteria. Depending on the degree of in-house expertise, commissioning authorities may self-manage or outsource components of the project selection and implementation monitoring process. Competitive grant financing schemes also tend to have pre-determined scope, time horizons, milestones and targets for R&D implementation. Such schemes can be restricted – in the sense that they are project-specific – or unrestricted – in the sense that they target broader R&D portfolios in the form of core support to fund recipient organizations. However the same participation rules and regulations apply across the board for all grantees of any particular scheme.

Example 1: GLOBVAC, Research Council of Norway

The Research Council of Norway's GLOBVAC program is a competitive grant financing scheme that supports research to improve health and health equity for poor populations in LMICs.[38] MFA/Norad provides over 85% of the Program's funding. The Program issues annual calls for research proposals that can demonstrate high impact around five thematic areas: Prevention and treatment of, and diagnostics for, communicable diseases with particular relevance to LMICs; Family planning, reproductive, maternal, neonatal, child and youth health; Health systems and health policy research; Implementation research; Innovation in technology and methods development for maternal and child health in setting where appropriate technologies are lacking. Project proposals are reviewed by independent experts and the best proposals are prioritized for final selection by the GLOBVAC Program Board.

Although GLOBVAC's focus is on broader research, capacity building of Norwegian institutions and partnerships with LMIC groups, product development projects can be supported if projects meet the requirements and priorities of the program. For instance, GLOBVAC has funded among others: the development of an affordable rotavirus vaccine;[58] an HIV therapeutic vaccine; an instrument for the removal of implants; carrier studies to support the clinical testing of MenAfriVac™ in a number of African countries; and the clinical testing of an Ebola vaccine in Guinea. Only Norwegian companies or public research institutions are eligible as project owners.

Example 2: Product Development Partnerships III Fund (PDP III)

The PDP III Fund is financially supported by the Dutch Ministry of Foreign Affairs (MoFA/DGIS) and managed by the Netherlands Enterprise Agency (NEA), to support the development and availability of biomedical products against PRINDs, sexual and reproductive health and rights (SRHR). PDP III is the third competitive grant financing scheme for PDPs that MoFA/DGIS has launched since 2006. Only PDPs can apply for funding. Funds are allocated through a competitive call for proposals. The funding cycle is five years and funding is largely unrestricted and in the form of core support, while the monitoring and evaluation are outsourced to NEA. Based on stakeholder impressions and evidence from previously published evaluations[109] investments under this fund are disbursed annually, based on annual meetings with PDPs, progress reports and approvals. Outsourcing M&E procedures to NEA ensures greater efficiencies and options for policy brokering by MoFA/DGIS in relation to previous funding cycles.

Between 2006 and 2014, MoFA/DGIS invested € 150 million to 10 PDPs[xxi] and WHO TDR, through its PDP Fund. The organization was the 13th largest funder of PRINDs in the world based on cumulative investment data provided by G-FINDER for the period 2007-2013;[11] and the 4th largest funder of PDPs operating in the field for the seven year period. Its available budget for the period 2015-2020 is € 86.3 million, with annual investments per PDP ranging from € 1 million to € 4 million.

Lessons for MFA/Norad

Competitive financing can add transparency and ensure quality of product development funding. Competitive selection of fund recipients can assure high quality of R&D if the right review and selection processes are in place. Greater transparency is also guaranteed as selection criteria tend to be more explicitly defined. Funding predictability through calls for proposals and explicit objectives therein can also foster collaborative arrangements and linkages between different R&D institutions. Competitive funding has also the potential to attract a broad range of applicant organizations.

Competitive financing can be costly, lengthy, and technically cumbersome for development agencies, adding to transaction costs. Where funding is project-based, this can create time constraints, budget rigidities and managerial inefficiencies. Selection processes can be lengthy, requiring technical expertise. If this is not available in-house, outsourcing parts of the processes to peer institutions can increase overall efficiencies in commissioning funds. In extreme situations, slow processes can prevent decisions from being made swiftly enough to respond to urgent public health needs. Writing proposals for competitive financing calls can be more demanding, and the unsuccessful proposals must be counted as transaction costs.

[xxi] Aeras; DNDi; EVI; FIND; TB Alliance; IAVI; IPM; MMV; SVI PDP; POW PDP

Non-competitive grant financing

Description

Non-competitive grant financing is common among small sized aid agencies supporting PDPs. Participation rules are defined by the commissioning authorities that maintain oversight of the selection process. Implementation monitoring can be lighter than under competitive grants. Under non-competitive grant financing grantees are usually invited to submit proposals for funding against commissioning authorities' strategic and programmatic priorities. Depending on the degree of in-house expertise, commissioning authorities may self-manage or outsource components of the selection, monitoring and evaluation process.

In non-competitive financing schemes the scope of R&D can be fully or partially determined by the applicants; time horizons for implementation can be longer; whereas milestones and targets for R&D implementation tend to be more flexible across different fund recipient organizations. Such schemes can be unrestricted in the sense that they are organization or R&D portfolio specific; semi-restricted in the sense that they are R&D portfolio-specific but limited to a specific disease or product area. Non-competitive grant financing schemes can also be flexible in terms of the conditions applied to different grantees participating in these.

Example: Non-competitive aid agency financing for PDPs

A number of aid agencies in high-income countries, including MFA/Norad, Irish Aid, the Danish Ministry of Foreign Affairs / Danish International Development Agency (MFA / DANIDA) and the Swiss Agency for Development and Cooperation (SDC), have been supporting PDPs through non-competitive grant financing processes for many years. This type of PDP financing has been considered suitable to aid agencies' needs to tailor investments around national priorities, development policies and health portfolio strategies flexibly; their human resource and technical expertise constraints in managing competitive financing processes in-house effectively; and the opportunity for them to utilize PDPs as platforms for global policy dialogue and coordination with other funders and development partners on the ground.

An acknowledgement of the need for new and improved biomedical products to address poverty reduction and development challenges linked to health and a conviction of the role that PDPs can play in accelerating the development and rollout of such products have been the driving forces behind aid agencies' long standing commitments to PDPs. Although funding cycles among aid agencies providing this type of funding vary from three to five years on average, the unrestricted nature of core funding to PDPs is common, and like in competitive financing schemes supporting PDPs there are clear milestones and targets for R&D implementation, which tend to be determined in a more collaborative manner with PDPs. Invitation of PDPs is based on an a priori understanding of these PDPs' governance structures, strategies and capacities to deliver high quality results in order to meet funding priorities; in the absence of open processes that would encourage PDPs to demonstrate how their proposed strategies and capacities would work better than others.

Lessons for MFA/Norad

Non-competitive financing can reduce complexity of managing R&D grants by resource constrained and technical capacity-limited aid agencies. If funding is unrestricted, it allows for an attribution of public investments across a wider portfolio of R&D projects. If restricted, it increases complexity of managing R&D grants - including commissioning, M&E activities - and restricts attribution to specific projects, exposing public investments to higher risks of failure.

Non-competitive financing can add speed to funding decisions in alignment with political priorities but it limits transparency in selection processes. Funding decisions under non-competitive financing schemes can be much more flexible than in competitive financing schemes without being constrained by pre-defined recipient eligibility or R&D scope criteria. The shortfall of these processes is that they do not always allow comparison of recipient organization capacities for quality and excellence in innovation, as these are usually preselected, even though there might be others able to conduct similar type of R&D but who are not given the opportunity to demonstrate this.

Pooled financing

Description

Pooled financing is an increasingly popular approach to global health product development funding by some government agencies, EU and international institutions, as reflected for instance by the recent agreement of the World Health Assembly (WHA 67) to create a voluntary pooled R&D fund for PRINDs at the WHO.[14] Based on cost sharing and risk spreading principles, pooled funding at the bilateral (i.e. between two agencies) or multilateral (i.e. more than two agencies) level can leverage resources by bringing individual agency funds into a common pool to provide larger funding volumes or to support more projects or organizations conducting R&D.

Pooled funding can be provided either via competitive and/or non-competitive processes. Participation rules can be defined either by the intermediaries managing the funds or jointly by the intermediaries and the agencies participating in the pool. Intermediaries maintain

tight oversight of the selection process, close implementation monitoring, and full or at least partial ownership of the R&D outputs.

Under pooled funding, priorities of participating agencies are aligned with the mission of the intermediary managing the funds. There is a high level of in-house expertise within the intermediary organization who can self-manage the entire chain of commissioning and implementation monitoring. To date, pooled funding schemes are restricted in the sense that they are project- or program- specific and that the same rules and regulations apply across the board for all grantees participating in these.

Case study 1: European & Developing Countries Clinical Trials Partnership (EDCTP)

Description

EDCTP is a pooled financing mechanism supporting the clinical development of new or improved interventions to prevent or treat HIV/AIDS, TB, malaria and neglected infectious diseases in sub-Saharan Africa. Launched in 2003 as a European Union (EU) program under the legal structure of an European Economic Interest Grouping (EEIG), and transferred in 2014 to an Association under Dutch Law, EDCTP is a public-public partnership between 14 countries in Europe[xxii], 13 countries in sub-Saharan Africa[xxiii] ('Participating States' (PS)), and the European Union (EU). EDCTP's second program (EDCTP2), covering the period 2014-2024, will be pooling resources from the EU in cash and from PSs, both in cash and in-kind. The EU has committed up to a maximum of € 683 million, conditional to European PSs matching this sum. Besides contributing cash, one means of PSs matching the EU contribution is through so-called Participating States' Initiated Activities (PSIAs), which are national activities, funded and implemented independently from EDCTP by one or more PSs, which contribute to the objectives of EDCTP2 and can therefore be counted as in-kind contributions to EDCTP. EDCTP also aims to attract an extra € 500 million from industry or others.

Activities in the EDCTP2 program are therefore funded and managed through two different streams: :

- **Participating States Initiated Activities –** activities and projects that are funded and managed directly from a participating state, using public funds of that state (i.e. no EU funds), and implemented and managed according to the national rules of the participating state. This can be counted as an in kind contribution from the participating state if the activity has been included in the EDCTP2 annual work plan, and therefore pre-approved as falling within the scope of the EDCTP2 program.
- **Centrally managed activities -** commissioned by EDCTP using EU funds and cash contributions (either restricted or unrestricted) from participating states and third parties. Activities are focused on clinical trials and capacity building and are commissioned through open and transparent calls for proposals that are centrally managed by the EDCTP Secretariat. The centrally managed activities are either:
  - A) Research & Innovation Actions (RIA) consisting primarily of clinical trials and other clinical research activities related to PRDs that are implemented in partnership with research teams in sub-Saharan Africa. RIAs are collaborative research actions, which normally must comprise a minimum of two legal entities from Europe and at least one legal entity from sub-Saharan Africa.
  - B) Strategic Research & Innovation Actions (SRIA), a special type of RIA that support large and strategically important, large-scale clinical trials. Strategic RIAs have the special feature that EDCTP only provides 50% (or less) of the total project costs. The Strategic RIAs require therefore co-funding from other funders (private or public), and this instrument is therefore specially designed to facilitate collaboration with other funders for large-scale projects.
  - C) Coordination & Support Actions (CSA), small projects to develop or strengthen clinical research capacities in sub-Saharan Africa or to promote networking and collaboration between researchers.
- Training & Mobility Actions (TMA), which are fellowships. EDCTP offers individual fellowships to junior and senior fellows from sub-Saharan Africa in order to support their training and career development

Achievements

In its first program (EDCTP1, 2003-2015), EDCTP supported 100 clinical trials in 30 different sub-Saharan countries and facilitated the registration of new pediatric formulation of an ARV drug and the improvement of eight existing medical treatments; launched a Pan-African Clinical Trials Registry and supported the development of four Regional Networks of Excellence in Africa as well as an

[xxii] Austria, Denmark, Finland, France, Germany, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, UK

[xxiii] Burkina Faso, Cameroon, Congo, The Gambia, Ghana, Mali, Mozambique, Niger, Senegal, South Africa, Tanzania, Uganda and Zambia

African Vaccine Regulators Forum.[110]

EDCTP1 got off to a bumpy start, as stakeholders acknowledge. Industry participation was restricted due to public management regulations, with in-kind contributions such as drug donations being the main form of industry engagement. Co-funding was required on a project-by-project basis in the early years, restricting projects with otherwise better funding potential. The EEIG legal structure meant that it was not possible for African countries to be members and thus did not allow for a true European-African partnership. Key changes under EDCTP2 include:

- **Diversifying sources and beneficiaries of funding** through a tiered competitive grant financing system spanning across the entire R&D chain, encouraging industry to participate more clearly (the private sector can now also receive funds under EDCTP2) and promoting greater ownership of funding by co-funders
- **Improving its governance structure** by encouraging African countries to become members of its General Assembly, giving them voice at the highest level and ensuring greater ownership of R&D efforts concerning their populations
- **Expanding its scope** by covering a broader range of disease areas (in addition to HIV, malaria and tuberculosis, neglected infectious diseases prevalent in sub-Saharan Africa and other emerging infectious diseases of particular relevance for Africa, such as Ebola, will also be supported) and a wider spectrum of activities (phase I-IV clinical trials and health services optimization research)
- **No co-funding requirement for the majority of the Calls,** projects can be funded 100% by EDCTP
- **Broadening calls for proposals** so that they are less prescriptive and more bottom-up, open calls that are responsive to the needs identified by the scientific research community
- **Increasing budget levels** as enabled by an enlarged program budget, which allows the possibility to support more ambitious, impactful projects of strategic importance (from €3-4m previously to €15m now), which is key if EDCTP wants to be a big player in clinical R&D

Lessons for MFA/Norad

EDCTP2 offers an interesting resource leveraging option for public funders who wish to commit their funds to global health product development, demonstrated by its capacity to manage competitive funding processes and its decision to conduct joint calls with co-funders. EDCTP has already launched a joint call on Ebola R&D with WHO TDR and UK MRC, focusing on research capacity development in sub-Saharan Africa to conduct high quality health research during infectious disease outbreaks resulting in health emergencies.

EDCTP2 offers a more attractive option for funding to PDPs as funding ceilings for projects of strategic importance have more than trebled. PDPs have already submitted three pre-registration project proposals for funding to EDCTP2. Since EDCTP funds are expected to only cover up to 50% of these types of projects, there is an incentive for third parties to match EU funding for recipients of common interest.

There are ongoing challenges in terms of participation rules and reporting requirements which could add complexities in terms of joint funding initiatives in practice. Given the focus of EDCTP on collaborative projects, there are ongoing challenges related to participation rules. However, EDCTP is the only public-public pooled financing structure in Europe that partners directly with sub-Saharan African countries and focuses on global health product development, offering a platform for greater transparency and inclusiveness of public investments in the long term, especially for smaller sized countries.

Case study 2: Global Health Innovative Technology Fund (GHIT Fund)

Description

The Global Health Innovative Technology Fund (GHIT Fund) is a Product Development Funding Partnership supporting the discovery and development of new health technologies, for PRNIDs, through the facilitation of international collaborations that utilize Japanese innovation, investment and leadership. Launched as a non-profit organization in Japan in 2013, the GHIT Fund is a PDP set up by the Japanese Government, Japan's pharmaceutical industry, the United Nations Development Program (UNDP) and the Bill & Melinda Gates Foundation.[111]

The GHIT Fund is set up as a matching fund structure. The Japanese Government provides 50% of the funding, followed by BMGF (25%) and the Japanese industry (25%). There are six major pharmaceutical companies currently supporting the GHIT Fund. Through competitive grant financing processes, the GHIT Fund prioritizes international partnerships where Japanese product developers can contribute with own investments, infrastructure and R&D expertise.

Achievements

Between 2007 and 2013, Japan invested US$49 million in PRIND R&D, representing 0.2% of global investments and ranking in 18th position out of 54 countries investing in the field.[11] This was in contrast to Japan's 2nd position worldwide in terms of size of its pharmaceutical market in 2013.[112] Since 2013, the GHIT Fund has incubated US$ 32 million for the development of malaria drugs and vaccines; TB drugs and vaccines; Chagas drugs and vaccines; schistosomiasis drugs; lymphatic filariasis drugs; dengue vaccines; and drugs against leishmaniasis and sleeping sickness. Its total R&D portfolio is comprised of 30 projects. The majority of the supported projects concern early discovery (43%), followed by preclinical development (37%), and by clinical development projects (20%). The majority of the supported projects (80%) are implemented by PDPs in collaboration with Japanese industry and other research institutions.

Lessons for MFA/Norad

Global health product development investments that can capitalize on domestic R&D capabilities require strong domestic R&D institutions and the right long term funding structures in place to incentivize international partnerships. The GHIT Fund follows a portfolio management approach which focuses strictly on product development, attracting Japan's pharma industry as a co-funder and a co-developer in an organic manner. Beyond catalyzing industry engagement, the GHIT Fund also provides a platform of funding and collaboration for PDPs. Since 2013, PDPs have absorbed over US$21 million (or 67%) of all investments disbursed by the GHIT Fund, engaging in 80% of all projects included in the organization's portfolio. It is worth noting that the potential of translating the GHIT Fund model to Norway would be extremely challenging, given that the potential in the Norwegian pharmaceutical industry is much smaller than in Japan.

Funding multiple diseases and products can better keep up with global health product development needs, but narrowing investments to product development is key for focused results in the long term. The GHIT Fund has a broad disease and product scope that spans across the entire R&D chain, allowing it to adjust its investments according to evolving global health R&D needs. As it does not engage in R&D implementation, the organization makes a more targeted use of its available resources on product development activities. This is a key difference to PDPs, which otherwise share a common mission; and a significant difference to public funders (e.g. Science and Technology Agencies) who spread their investments more broadly across health research activities.

Case study 3: WHO TDR - Pooled R&D Fund

Description

WHO TDR, the Special Program for Research and Training in Tropical Diseases, is a global program of scientific collaboration that helps facilitate, support and influence efforts to combat diseases of poverty.[113] WHO TDR was established in 1974 as a pooled funding mechanism, supported mainly by public funders including Norway, and it operated in some ways like a PDP structure. WHO TDR was one of the first initiatives worldwide that focused on global health R&D against PRINDs and the translation of research into new products to prevent and control these diseases in LMICs. WHO TDR is hosted at the WHO; and it is sponsored by the United Nations Children's Fund (UNICEF), the United Nations Development Program (UNDP), the World Bank and the WHO.

Under review is the establishment at WHO TDR of a pooled R&D fund for voluntary contributions towards LMIC- specific R&D needs against PRINDs.[102] The creation of this Fund was endorsed by the World Health Assembly (WHA 67) in 2014.[14] The rationale is to support product development guided by priority areas identified by the WHO Global Health Research Observatory, which is currently also under development. Although the final shape of this fund is yet to be determined, stakeholders suggest that it is likely for the pooled funds to be allocated via both competitive (e.g. calls for proposals) and non-competitive (e.g. partnership-based) grant financing processes. To date over US$ 10 million has been pooled from various governments, including commitments from Brazil, India, Norway, South Africa and Switzerland. Some of these funds have helped establish the pooled R&D fund, and some have been earmarked to R&D demonstration projects on alternative financing and coordination approaches to address identified R&D gaps[114] due to end by 2017.

Achievements

The list of WHO TDR achievements is long. Indicatively in 40 years of operation, WHO TDR has contributed to the development of 12 drugs against malaria, leishmaniasis, leprosy, onchocerciasis and sleeping sickness;[115] has helped develop and evaluate new diagnostics for malaria, TB, onchocerciasis and sleeping sickness;[115] has helped establish the effectiveness of insecticide-treated bed nets against vector-borne diseases[116] and artemisinin therapy against malaria[117]; has provided research evidence to five elimination campaigns for PRINDs;[115] has trained thousands of LMIC researchers;[118] has identified access barriers to treatment and care;[119] and has incubated the development of a number of PDPs, such as MMV and FIND, as well as other global health research and access initiatives, such as the Global Forum for Health Research and the African Network for Drugs and Diagnostics Innovation.

Moving towards the establishment of the Pooled R&D Fund, WHO TDR has commissioned three studies to help identify how to set up this fund and what is needed financially and operationally.[102] The studies include: a financial modelling exercise; a consultation exercise to determine the remit of a WHO TDR-based Scientific Working Group; and a consultation exercise on the roles of target product profiles (TPPs) in the neglected diseases. Several stakeholders have recommended that WHO TDR takes forward this fund due to its demonstrated ability to manage R&D and deliver results; its balanced governance structure that is representative of public

funders from different geographies; and its ability to set up robust R&D partnerships in response to evolving health needs over time.

Lessons for MFA/Norad

A Pooled R&D Fund at WHO TDR can share risks, reduce costs, focus on a health needs- driven R&D agenda and compress timelines between identified needs and funding decisions. WHO TDR is committed to de-linkage of R&D from product prices, following the 67th WHA decision. It can allow for portfolio management across diseases and products, building on the WHO agenda on health R&D and LMIC R&D capacities, without competing against other product developers but in contrast by complementing resources to allow them to implement their product development missions. Defining TPPs based on public health needs is a starting point for consensus building around affordability, suitability and other access-related issues of R&D efforts. The evidence-based priority setting conducted by the Health R&D Observatory increases the likelihood of a public health focus and the presence of a global public R&D fund can have positive implications for industry. Importantly, WHO TDR is in a unique position within the UN family to maintain a co-sponsorship relationship with UNDP, UNICEF, and the World Bank within the WHO. This suggests that there is a very short chain between the research networks supported by the organization in LMICs right through to the World Health Assembly.

The burden of interactions between donors and product developers can be significantly reduced. Smaller donors, including from LMICs, are either not able to, or not willing to, maintain interactions with product developers due to cost, time or technical requirements. A pooled fund hosted by the WHO TDR would provide cost-time efficiencies and would bring in the necessary expertise and specialized knowledge that WHO and collaborating partners have accumulated over time.

Decision making authority can be more evenly spread across public funders from different geographies, allowing for an equitable distribution of agenda setting authority between sectors and nations. This is because WHO TDR has a representative governance structure built in to its committees with balanced representation from disease endemic countries and donors.

There are funding and prioritization challenges, creating uncertainties about operational feasibility. The R&D demonstration projects require US$ 50 million, yet only 25% has been committed to date. The fund's size has yet to be worked out, but consistency and flexibility of funds and homogeneity of priorities are crucial, as the EDCTP experience suggests. Several stakeholders, including PDPs implementing some of the R&D demonstration projects, see aid agency investments via this mechanism as influential, but highlight the importance that any resources allocated to pooled mechanisms should strike a balance between pooled and national funding, suggesting that only new, and not diverted, resources should be dedicated to such structures.

Guarantee-based financing

Description

Guarantee-based financing is a special approach to supporting global health product development. This type of financing is built on initial investments by the funders capitalizing the relevant fund, and guarantees that future disbursements will be made under a set of pre-defined conditions, allowing for additional financing to be acquired in secondary capital markets by the intermediary managing the fund.

Example: Global Health Investment Fund (GHIF)

GHIF aims to capitalize on the late stage commercialization phase of product development processes in global health. The rationale is to fill a funding gap for products with marginal profitability or, in other words, that are 'partially commercial' by offering an investment guarantee. The gap is a result of development agencies and philanthropies focusing on non-commercial projects on the one hand, while commercial investors preferring lower-risk options on the other. The GHIF guarantee reduces the risk exposure of the investors. The two guarantors, BMGF and SIDA, offer investors a risk sharing model by which the first loss up to 20% of invested capital and 50% of the remaining investment is fully covered by the guarantors. On average, this is a 60% loss protection guarantee. On these premises the Fund has obtained a total of US$ 108 million in investments from Grand Challenges of Canada, BMZ (Germany), International Finance Corporation (IFC), GSK, Merck, Pfizer, AXA, Storebrand and JP Morgan, and individual investors. GHIF is currently in the process of developing its investment portfolio. The first three projects include a PCR-based TB diagnostics tablet; a cholera vaccine manufacturing scale-up project; and a re-registration of a veterinary drug for use against onchocerciasis. These will soak up close to US$ 23 million.

Lessons for MFA/Norad

- The guarantee instrument has good potential but has not been exploited to its maximum. It is likely that organizations other than MFA/Norad within the Norwegian investment sector would be more suitable to consider such a financing vehicle.
- The guarantee instrument is best applied to disease and product areas where there is a certain degree of effective demand and in the late stages of the product development process. It is therefore likely that this financing vehicle is not very well-suited to MFA/Norad given its current global health product development funding portfolio.

5. Coordination issues

Coordination of global health product development investments holds the potential to preempt underfunding or duplication of funding, given the engagement of multiple funders supporting broad R&D portfolios with long term commitments.

Coordination can relate to many aspects of the financing continuum, such as evidence generation and data sharing, priority setting and investment decision making, and commissioning of R&D (from selecting to monitoring and evaluating). Coordination among stakeholders can take place at a bilateral or multilateral level, and it can concern interactions within domestic or international settings.

At the national level, MFA/Norad occupies one seat on the GLOBVAC Program Board. At the international level, MFA/Norad shares a position on the Joint Coordinating Board of WHO TDR with Switzerland.[120] MFA/Norad is also a member of the PDP Funders Group (PFG), an informal network of public and private organizations funding one or more PDPs in the fields of PRINDs and RMNCH.[121] PFG functions essentially as a forum for information sharing and coordination of activities that can benefit funders as well as PDPs by making them all work more effectively.

These formal governance and informal network structures provide fruitful platforms for policy dialogue and decision making. However, as several stakeholders have suggested, a lot more could be done to improve data sharing and harmonization or strengthening of existing processes among funders. This chapter summarizes a number of options and restrictions on various aspects of coordination of global health product development funding identified in stakeholder consultations.

Evidence generation and data sharing

Global health product development is a complex process. Funding operations require technical understanding of scientific and management aspects of R&D activities and partnerships, and frequently there are information asymmetries between funders and product developers, which can create significant knowledge gaps for funders. This is particularly the case in R&D portfolio financing. Therefore it is crucial to develop evidence-based tools for understanding what is being done for the money invested and/or sharing available evidence among stakeholders. Such tools and processes can facilitate funders and governance structures to make more informed investment decisions. Two examples of such tools and processes were identified by stakeholders:

- **PFG- led information sharing activities**, such as newsletters, reports, presentations and meetings. These activities are helpful for funders to obtain an overview of trends and issues around PDPs, PDP funders and other programs such as EDTCP, Horizon 2020, etc.

- **Information sharing between funders about commonly supported R&D projects or product development organizations**. Some stakeholders have stated that these types of interactions are usually limited to a few organizations such as BMGF, the Wellcome Trust, DFID, and pooled financing mechanisms. Other stakeholders argued that although there are regional communication platforms for aid discussions among certain aid agencies, similar relationships for global health product development are lacking. Data

sharing could start at the point of proposals for funding knocking on funders' doors, some stakeholders suggest, for instance by creating a database of proposals based on which further discussions on content can be made. Information sharing could also take place at the point of assessing the quality of R&D portfolios funders support in common. BMGF has recently developed an Integrated Portfolio Management approach to monitoring the ongoing status of R&D portfolios and to better understanding the relative risk and value of R&D projects included in R&D pipelines of organizations it supports. R&D portfolio information on target product profiles, cost effectiveness and other features is gathered and presented under a single visual framework. Although this approach might not be the best fit for how many government funders monitor their global health product development investments today, it is an example of how deeper dive analyses of R&D pipeline data could be conducted to inform coordination efforts between funders commonly supporting R&D projects or product development organizations.

Priority setting and investment decision making

Without alignment of priorities in areas that require multiple funders and broad portfolios for R&D to succeed progress in developing new products can slow down. Two examples of actions to improve coordination on this front were recommended by stakeholders, including:

- **Developing a common understanding of the added value of investments in global health product development.** This requires taking stock of past results and achievements, generating lessons learnt and identifying success drivers for maintaining momentum of investments over time. Since funding levels are often politically determined, several stakeholders suggest, it is important for decision making organizations to communicate to their political constituencies how much funding is really required in order to make an impact in health.

- **Clarifying individual funding agency objectives in global health product development.** The differences in objectives among funders in the field are large, several stakeholders argue. Some prioritize rapid scale up approaches, and others focus on capacity building or building the science in specific disease and product areas. Lack of clarification of objectives in areas that require multiple funders and broad portfolios to succeed can slow down progress in developing new products. Some stakeholders suggest that greater clarification can be achieved through the expressed positioning of funders around certain normative principles (e.g. on open access innovation, product pricing, etc.) and around different models for managing R&D funds (e.g. the PDP model, or public-public partnerships such as the EDCTP or the WHO Pooled R&D Fund). Such clarity would benefit decisions by smaller funders on long-term commitments to global health product development funding.

Commissioning

Commissioning processes such as selection procedures over projects or recipient organizations, grant management, and monitoring and evaluation (M&E) processes can be cumbersome, lengthy, and sometimes unnecessarily duplicative. Improved coordination on

commissioning R&D can take many forms and a number of opportunities have been identified by stakeholders:

- **Implementing joint competitive financing schemes.** Some stakeholders suggested that joint calls for proposals could be done relatively easily if there was an agreement on criteria, scope, funding contributions, timing and structure of decision making. As the EDCTP case study in chapter 4 demonstrated, this mechanism is in a position today to apply a joint call model, which it has already deployed in collaboration with WHO TDR and UK MRC. Some stakeholders argued that government funders may not be ready for such schemes, or that the participation rules of joint financing schemes would simply not match the priorities of individual funders in the field.

- **Outsourcing appraisal, selection and M&E processes –** Some aid agencies have moved in this direction in recent years, for instance the PDP Fund III (see chapter 4). Other programs like GLOBVAC have highly robust processes and tools for peer reviews and selection of projects for funding. The use of such processes by MFA/Norad however may be challenging, as stakeholders suggest, unless the entirety of its product development funding is outsourced. Outsourcing technical components of the selection and M&E process is operationally feasible, according to other stakeholders. However clarity is required in terms of roles and responsibilities between the agencies involved in funding and technically supporting the schemes, respectively. MFA/Norad commissioned the NIPH for the technical appraisal and ongoing M&E of the five PDPs that recently received funding from the organization. Therefore it is worth noting that there are potential conflicts of interest with making this particular point.

- **Harmonizing specific features of otherwise independent financing schemes** –most important being the harmonization of reporting requirements to commonly funded recipients, which is already done quite effectively in the case of PDPs via the PFG; followed by a greater harmonization of funding cycles and types of funding provided to recipients of common interest. For instance, the PDP model requires flexible and predictable financing over time, as demonstrated in chapter 3. Improving the conditions for efficient R&D portfolio management by PDPs is desirable and operationally feasible, as previous analysis (see chapter 3) and impressions by several stakeholders suggest. Some stakeholders have suggested the implementation of more joint evaluations, which have been recently tested successfully by the Germany and UK based aid agencies in the case of PDPs.

6. Options for future investments

The analysis conducted in this report has assessed MFA/Norad contributions in global health product development to date; and has assessed these investments against their results, strategic orientation over funding levels, beneficiaries and accompanying financing and coordination measures. This analysis has demonstrated that MFA/Norad has been a 'small and smart' funder of global health product development, guiding its investments according to international health priorities and responses to health crises.

Looking into the future and as the development agenda is becoming broader, the prioritization of global health product development investments is becoming increasingly challenging. As per MFA/Norad's current priorities in global health and strategic objectives, any future investments in the field would have to revolve around improving women's and children's health; reducing the global burden of disease with an emphasis on prevention, diagnosis and treatment of communicable diseases; and promoting human security through health. In light of these priorities and objectives, this section discusses the potential benefits and options for financing and coordination of future MFA/Norad investments in the field.

Potential benefits

Health benefits

Investments in global health product development can contribute to improving health in LMICs. Several products to which Norway has financially and/or scientifically contributed since 1974 showcase the health benefits of such investments. As chapters 2 and 3 demonstrate, these include vaccines against meningococcal disease and diarrheal diseases, drugs and diagnostics against malaria and other PRINDs. New projects currently in the R&D pipeline promise to deliver additional health gains to LMIC populations. The development of the first ever female-initiated prevention technology against HIV is nearing completion. If successful, this product will be the world's proof-of-concept for next generation multi-purpose technologies on HIV prevention and contraception to improve women's health. Similarly, new simplified, safer and effective drugs against sleeping sickness and malaria are close to registration. Thanks to MFA/Norad's quick and flexible funding response a novel vaccine against Ebola is being clinically tested in an African country that continues to suffer from the disease epidemic as this report is being written. Promising new TB vaccines have just entered clinical trials and recent new evidence from basic science has reinvigorated hopes for an HIV/AIDS vaccine for global use in the future. Sustained MFA/Norad investments can contribute to the continuation of these important R&D efforts made partly thanks to the almost NOK 1 billion spent by the organization in the field since 2001.

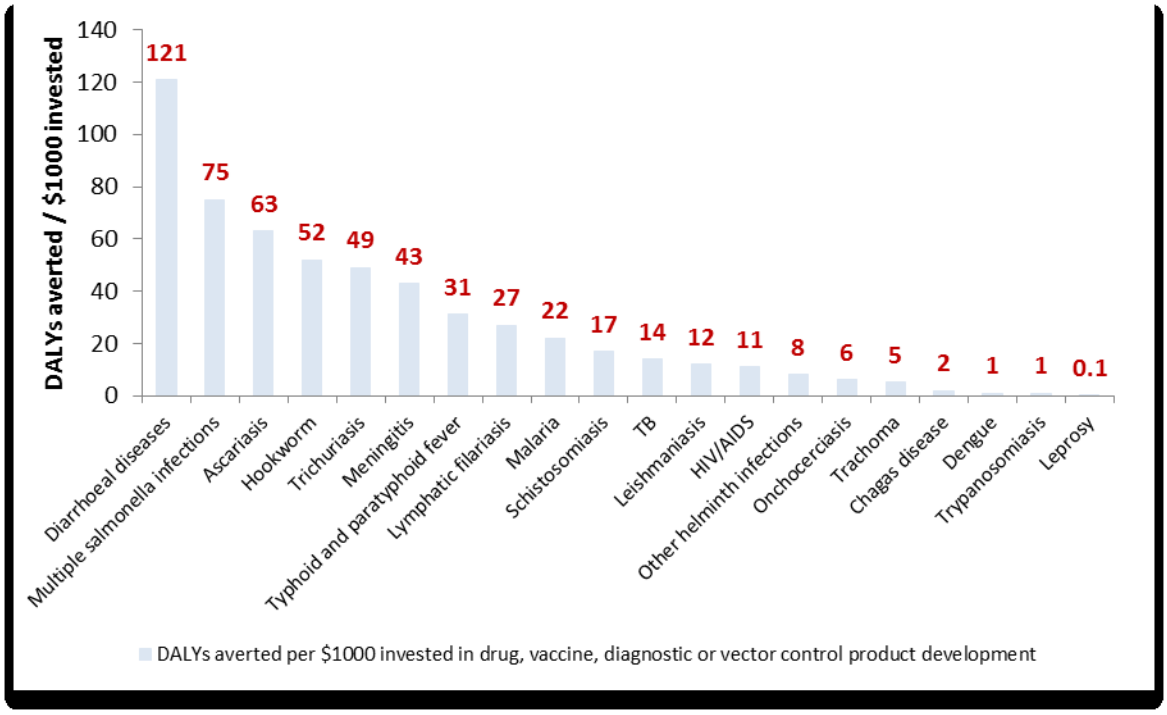
Health economic benefits

There are potential health economic benefits from investments in global health product development too. As research suggests,[29] on average, 14 Disability Adjusted Life Years (DALYs) can be averted for every US 1000 invested in PRIND R&D, which broadly means one healthy year of life gained for every US$ 71 invested[xxiv]. As figure 10 shows, R&D investments for new products against diarrhoeal diseases, helminth infections, meningococcal disease, salmonella and typhoid / paratyphoid fevers, malaria, TB, HIV/AIDS

[xxiv] According to the research conducted to calculate these returns, different returns are largely driven by widely divergent burdens of disease - e.g. 89 million DALYs annually for diarrhoeal disease vs 5.5 thousand DALYs for leprosy.

and certain kinetoplastids, can all have great life-saving potential; provided that the right amounts are invested and the appropriate technical expertise is available.

Figure 11: Investment returns to R&D into 20 PRINDs



Other strategic benefits

Other benefits include the potential strengthening of links between Norwegian R&D institutions and international initiatives, which have recently started to gain some momentum. This is demonstrated for instance by new collaborations emerging between TBVI and Norwegian academic R&D institutions in the last two years. Another example is the partnership between NIPH and the WHO to clinically test an Ebola vaccine candidate in Guinea

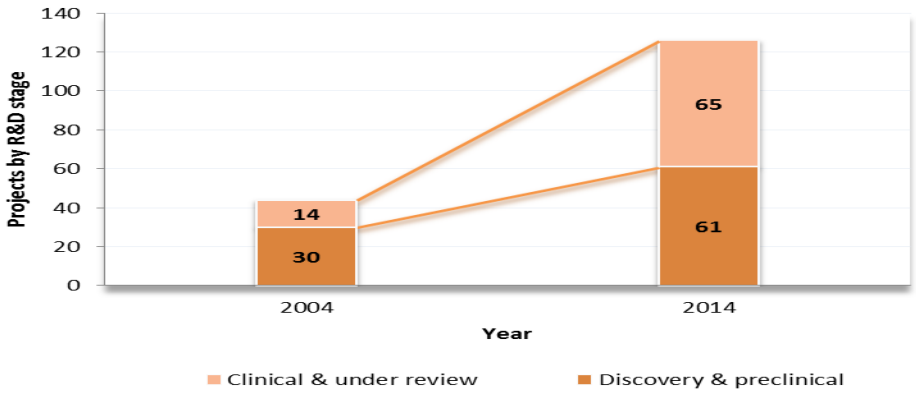
Options for future investments

Investing in PDPs

As chapter 3 demonstrates, the PDP model is an appropriate model for pooling resources and spreading funding risk across portfolios of costly, lengthy and complex R&D projects. Additional evidence from the collective performance of numerous PDPs over the past 15 years suggests that the PDP model is suitable for MFA/Norad investments in global health product development. There are at least 16 PDPs engaged in PRIND and RMNCH R&D today. From 2000 to 2015, over 50 products have been licensed, which PDPs have contributed in developing or in re-purposing for LMIC- specific needs. These include drugs, vaccines, vector control products diagnostics and other devices for 12 PRINDs and various RMNCH conditions (see detailed table in annex 8). As chapter 3 demonstrates, these successes have relied heavily on sustained public funding over time.

According to information collated from 14 PDPs[xxv], their combined R&D pipelines for a number of neglected diseases increased from 44 projects in 2004[xxvi] to 126 projects in 2014[xxvii], signalizing almost a trebling of discovery, preclinical and clinical development activity (see figure 13).

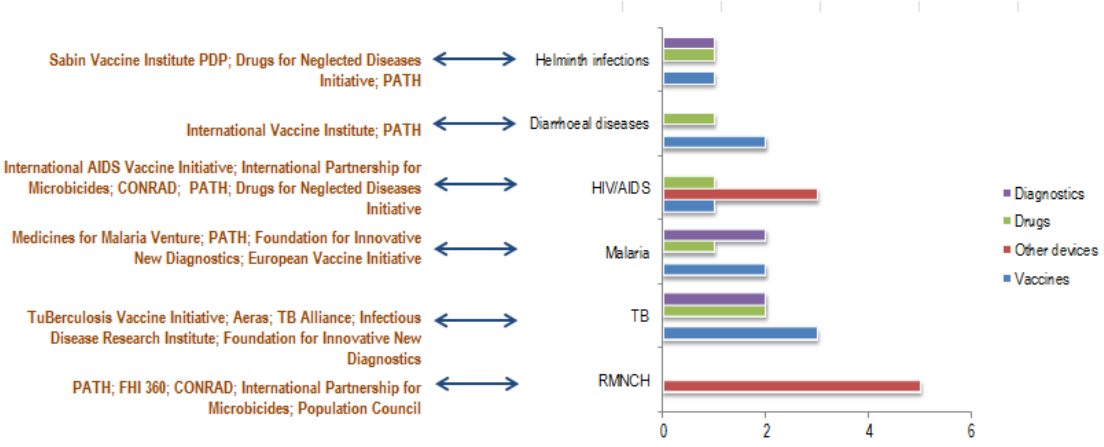
Figure 13: The cumulative R&D pipeline of 14 PDPs, 2004[xxviii] vs 2014[xxix]



Chapter 2 demonstrates that 38% of MFA/Norad global health product investments between 2001 and 2015 focused on vaccines, which is a high priority for the organization. The analysis conducted in the chapter also shows that diarrheal diseases, TB and RMNCH conditions have historically received less funding by MFA/Norad proportionately to their morbidity and mortality, although funding for these has been increasing in recent years. Moreover, evidence suggests that helminth infections[18, 19], malaria,[20] and HIV/AIDS[21] contribute, directly or indirectly, to over 25% of maternal morbidity and mortality[22].

Matching this evidence against operational PDPs on the ground shows that there are several options for MFA/Norad to consider if it decides to expand its list PDP recipients in the future.

Figure 14: PDPs active by disease and by product where MFA/Norad could provide new funding for R&D



[xxv] Websites, annual progress reports and direct consultations
[xxvi] PDPs included are: AERAS; DNDI; EVI; FIND; IAVI; IDRI; IOWH; IPM; IVCC; IVI; MMV; PATH; Sabin Vaccine Institute PDP; TB Alliance
[xxvii] PDPs included are the same as in the 2004 figure, excluding IOWH which has been merged with PATH and including TBVI which was founded after 2004.
[xxviii] PDPs included are: AERAS; DNDI; EVI; FIND; IAVI; IDRI; IOWH; IPM; IVCC; IVI; MMV; PATH; Sabin Vaccine Institute PDP; TB Alliance
[xxix] PDPs included are the same as in the 2004 figure, excluding IOWH which has been merged with PATH and including TBVI which was founded after 2004.

Options for financing & coordination

Competitive vs non-competitive schemes

Similarly to other aid agencies in Europe, MFA/Norad applies a non-competitive selection process for PDPs (see chapter 3). This process reinforces the image of the 'small and smart' funder. It allows for quick responses to crises, and the application-by-invitation has saved on the considerable managerial resources.

The number of operational PDPs in PRIND and RMNCH R&D has increased over time, and so have potential PDP options for MFA/Norad to consider for future investments. Competitive selection processes would potentially allow for larger number of PDP applicants to demonstrate how their R&D strategies would fit with organizational priorities and objectives. However, competition would in any case be limited, given the limited 'population' of PDPs (all in all less than 20 operational PDPs in PRIND and RMNCH R&D. Selection processes in competitive schemes can be lengthy, requiring technical expertise that MFA/Norad may not be in the position to provide in the near future.

In non-competitive processes selection and evaluation criteria are likely to be more implicit, and there is a minor theoretical risk that the portfolio formulation process can become politically determined at the cost of technical considerations of quality and excellence in innovation. However, MFA/Norad's track record in global health product development funding to date demonstrates that its investment portfolio can be tailored effectively to align with national priorities, and can be balanced across disease areas, geographical orientation, different risk levels and product development timelines. This is an important consideration for the organization to make, in light of potentially undesirable transaction costs and administration burdens that a competitive selection process would induce.

Pooled financing schemes

The CEWG has recommended that funders should dedicate at least 20% of their total global health R&D funding obligation into a single pooled financing mechanism.[122] However there can be many restrictions with pooled financing, including on participation rules and reporting requirements that add complexities in terms of aligning individual funder objectives; and there can be significant costs including overhead and administration. Provided that funders are content with certain principles based on which pooled financing schemes are set up (e.g. on open knowledge innovation; geographic restrictions; disease-, product- or R&D stage- related scope restrictions, etc.), pooled schemes can share funding risks and decrease the burden of interactions between funders and product developers.

Saving Lives at Birth is a prime example of how funders can pool resources together and coordinate effectively to support the development of needed product innovations for RMNCH. And the establishment of new pooled R&D fund under the auspices of WHO TDR signalizes an opportunity for greater synergies between funders supporting the development of products against diseases like Ebola, where PDP or other effective structures are currently lacking.

Coordination measures

As chapter 5 demonstrates, there is great scope for improved coordination and synergies with other funders for MFA/Norad to support global health product development.

The PFG provides a fruitful platform for policy dialogue and coordination between funders of PDPs. PFG-led activities help funders obtain updates on funding trends and R&D challenges around PDPs, and facilitate more efficient PDP operations, for instance through the standardization of reporting requirements and the implementation of joint meetings between PDPs and multiple PDP funders. Continuing to engage with PFG-led activities can benefit MFA/Norad by reducing administrative costs for the organization as well as MFA/Norad supported PDPs, revolving around duplicative meetings and excessive reporting requirements to PDPs.

Given the complexity of scientific and management aspects of R&D activities and partnerships, information sharing between funders on commonly supported R&D projects or R&D organizations can facilitate a better understanding of the relative risk and value of R&D MFA/Norad supports. Various funders have expressed the desire for greater synergies in R&D pipeline data sharing, joint assessments of R&D projects and/or product development organizations. Such tools and processes can help MFA/Norad to make more informed investment decisions in the future, and which to date remain largely unexplored.

Finally, improved coordination on commissioning R&D can reduce duplications of certain processes, for instance funding proposal assessments via joint financing schemes on special areas of common interest between funders. Such arrangements presume that the participating funders in any particular scheme can reach an agreement on criteria, scope, funding contributions, timing and structure of decision making. The key is to reduce transactions costs by avoiding duplication of efforts, while avoiding creation of an additional administrative layer, which would increase transaction costs. It is worth noting that the EDCTP has the structure and the desire to explore such opportunities with European governments in the future. Although few government funders may be ready for joint financing schemes today, some aid agencies do not exclude the possibility of joint financing in the future, if the participation rules were to adequately match their funding priorities in the field.

7. Recommendations

The following recommendations are intended to sustain and reinforce MFA/Norad's smart investments into global health product development in the future:

1. **MFA/Norad should maintain its current levels of global health product development funding; and, if possible, increase its funding in the longer term.**

As our analysis demonstrates, investments in global health product development can contribute to improving health in LMICs, including health economic benefits as well as strategic benefits by linking Norwegian R&D institutions with international initiatives. In this sense, sustained MFA/Norad investments in the field would be fully in line with the organization's priorities in global health and Norad research strategy objectives for the period 2015-2017.

Importantly, Norway currently contributes at least 0.01% of Norway's GDP to biomedical R&D funding for LMICs. Maintaining current investment levels would send a signal of sustained commitment to the field; and would imply that current MFA/Norad investments into prioritized diseases, products and fund recipients would continue to be made in order to bring global health products forward to meet the health needs of poor populations in LMICs.

In order to meet the narrower CEWG target of contributing 0.01% of Norway's GDP to product development funding to meet the needs of developing countries, MFA/Norad would require a four-fold increase of its annual investments to meet the target, i.e. over NOK 294 million per year. R&D for diarrheal diseases, TB and RMNCH conditions could benefit in case of an increase, provided that these diseases have received less MFA/Norad funding historically in proportion to their global disease burden. New investments in helminth infections, as well as increased investments in malaria and HIV/AIDS should also be considered, since these are all key drivers of maternal morbidity and mortality.

Although such an increase would only potentially be feasible in the long term, a more modest increase of funding in the short term by 35-50% (i.e. to NOK 114 million annually) would send a positive signal of increased commitment, also aligning MFA/Norad's position in the field with its overall position in ODA. The organization consistently ranks in the top 10 ODA providers in the world, but only in the 17th position in PRIND R&D.

2. **MFA/Norad should continue to support the currently funded PDPs, while maintaining its flexible funding approach based on core funding and increasing the predictability of its funding through expanded grant cycles.**

Although MFA/Norad investments into the five PDPs have not always translated R&D into new products, several of them are now on the brink of achieving tangible outputs, and others have recently achieved critical milestones that are promising significant R&D advancements in the next few years. Sustained MFA/Norad investments into the five PDPs can contribute to the continuation of their important R&D efforts, and can maintain momentum for greater strategic synergies between PDP funding and Norwegian research capacities in the future.

Core funding, which MFA/Norad has always provided to PDPs, is crucial to dealing with risks and complexities that are inherent in product development processes. Core funding should continue to be the preferred way of PDP funding. Moreover, MFA/Norad should consider increasing its PDP grant cycles from three years to at least six years, matching PDP business cycles more closely, and signalizing more clearly its long term commitments to individual PDP strategies. Besides the benefit of more predictable funding for PDPs, such an increase would also benefit MFA/Norad, which would be better placed to thoroughly evaluate PDP progress in conducting R&D over a six year period – provided that R&D is a lengthy and highly complex process. Longer grant cycles would also imply reduced transaction costs and administration for MFA/Norad since technical appraisals, contracting and M&E processes would take place less frequently.

3. **MFA/Norad should continue to invest in pooled financing mechanisms for RMNCH related product innovations and should consider channeling any future funds for Ebola R&D into the newly established Pooled R&D Fund hosted by the WHO TDR.**

On one hand, SLAB provides a good platform for the transfer of low cost research into product innovations for RMNCH in LMICs, by brokering deals between early innovation ideas and commercialization platforms between small sized innovators and larger scale private sector actors. The mechanism also offers certain advantages to MFA/Norad investments, such as the opportunity for ICT, eHealth and other app-based technologies developed by Norwegian researchers for the domestic market which may also be applicable abroad (and vice versa). Continued support of SLAB's product innovation elements would not only contribute to MFA/Norad's sustained commitment in RMNCH R&D as per its first priority in global health; it would also potentially foster greater synergies in the sense that investments in new products for national use by the Norwegian government could turn out to have global applicability.

On the other hand, despite its flexible and responsive funding of Ebola vaccine R&D, MFA/Norad remains a very small funder in comparison to total funding requirements for the continuation of these costly and risky R&D efforts in the future. In light of an emerging consensus between governments to support future Ebola R&D efforts through a pooled R&D fund hosted by WHO TDR, MFA/Norad should consider the opportunity to leverage its limited resources in the field through such a fund. This would be in line with MFA/Norad's global health priority on improving human security through health; and would also be in line with the CEWG recommendation that funders dedicate at least 20% of their funding obligations in the field into a single pooled financing mechanism. Potential trade-offs to alternative financing options (e.g. GLOBVAC) should be considered prior to any final decision, such as: differences in overhead and administration costs; ability to channel funds quickly and flexibly; restrictions on participation or other operational principles.

4. **MFA/Norad should improve coordination of global health product development funding with other funders.**

First, MFA/Norad should continue to engage in PFG-led coordination activities, including standardizing reporting requirements to PDPs, exploring opportunities for joint PDP evaluations, and sharing information on PDP assessments through meetings and other communication tools proposed by the PFG.

Second, MFA/Norad should more proactively explore information sharing options on a bilateral basis with other funders supporting common R&D projects and/or PDPs, who may

have a deeper understanding of technical aspects of projects and/or organizations that are commonly supported.

Third, MFA/Norad should explore options for joint financing schemes in the future with other funders in special areas of common interest (e.g. late stage TB vaccine R&D supported by MFA/Norad, where MFA/Norad funded PDPs can no longer support due to scope restrictions). The benefits of joint financing schemes should be weighed against 1) any political compromises required to align objectives with the other funders, and 2) managerial and transaction costs incurred by coordinating with the other funders.

Annex 1: Results from investments in DNDi, 2013-2015

DNDi is a virtual non-profit drug R&D organization set up in 2003 to develop new treatments against the most neglected communicable diseases and with a particular focus on kinetoplastid diseases. It has headquarters in Geneva, four regional offices in endemic countries (Kenya, Brazil, India, Malaysia), one affiliate in USA, one office in Japan and one project support office in DRC; with total staff of 108.

DNDi has historically focused its R&D efforts on six diseases: HAT, leishmaniasis, Chagas disease, specific filarial diseases, malaria and pediatric HIV. In its mission against these diseases the PDP has delivered 6 new improved treatments, including 1 HAT combination therapy (NECT); 2 ACTs for malaria (ASAQ, ASMQ); 1 Visceral Leishmaniasis combination therapy for East Africa (SSG & PM); 3 Visceral Leishmaniasis combination therapies for East Asia; 1 Chagas pediatric dosage formulation (Benznidazole 12.5mg).[65]

Its current R&D portfolio from early discovery to projects under regulatory review comprises of 27 projects, with the majority of these concerning drug development efforts against kinetoplastid diseases, such as leishmaniasis (39%), American Trypanosomiasis (26%) and Human African Trypanosomiasis (17%). In recent years the PDP has initiated new drug R&D efforts in pediatric HIV and lymphatic filariasis (3 projects in clinical testing ; and projects in discovery/late preclinical respectively); and it is in the process of phasing out entirely its malaria drug R&D portfolio which is being transferred to another Geneva-based PDP, the Medicines for Malaria Venture (MMV).

In 2013, DNDi signed a grant agreement of NOK 15 million with MFA/Norad for the support of its new drug development program against Human African Trypanosomiasis (HAT) during the period 2013 – 2015. This was a core restricted funding grant, and the first that the PDP would receive from MFA/Norad.

The program aimed to contribute towards the elimination of HAT by allowing a simplified HAT management and control strategy through the development of two efficacious, safe, oral, short-course and affordable treatments. Key results indicators included:

1. Registration dossier for fexinidazole, a drug candidate for T.b. gambiense in a phase II/III trial for stage 2 HAT, to be completed in 2017 (EMA);
2. Progression of SCYX-7158, a new chemical entity, to phase II/III trial with recruitment beginning in Q3 2014;
3. Two additional clinical studies for specific patient groups (children and patients not included in clinical trials; patients with T.b. rhodesiense).
4. Three new clinical trial centers (Mushie, Katanda, Isangi), strengthening the clinical research capacity of HAT endemic countries.

Relevance

DNDi's HAT program has been highly relevant to global strategies, Norwegian policies and priorities, and product development needs in the field. Nationally, the program has been in line with priorities of strategic papers of the MFA, such as the report to the Storting (White Paper) Long-term perspectives – knowledge provides opportunity;[51] and the Report to Parliament (white paper) Global health in foreign and development policy.[51] Internationally, the goals of the program have been consistent with the WHO MDG to combat HIV/AIDS, malaria and other neglected tropical diseases;[44] the WHO objective of eliminating HAT by 2020;[123] and the London Declaration on Neglected Tropical Diseases launched in 2012.[124]

Effectiveness & Risk

Efforts for a registration dossier for fexinidazole to be submitted to EMA in 2017 are on track. Recruitment for the fexinidazole phase II/III trial has been completed since April 2015, ongoing 18 months follow-up period. EMA has been flexible enough to allow for only one pivotal study with a small number of participants to be considered for approval to use in target populations. This partly reflects the stage of the elimination efforts of the disease, and partly DNDi's own experience in liaising with regulatory authorities and in designing clinical trials efficiently and adequately in order to mitigate against potential drug registration risks. In effect, EMA will review a dossier for fewer than 500 patients, and phase IV studies will be expected for follow-up safety measurement.

Advancement of SCYX-7158 to a phase II/III trial with recruitment beginning in 2014 has been delayed. The advancement of SCYX-7158 to a phase II/III trial has been delayed due to toxicity challenges arising during a phase I dose study, and DNDi expects that the Phase II/III trial will now be initiated in 2016. SCYX-7158 is DNDi's first new chemical entity out of the PDP's own lead optimization efforts. Together with the testing of other compounds belonging to the same family of oxaboroles but at earlier stages of R&D, this project is crucial both for providing backup to DNDi's clinical development of fexinidazole, and for simplifying HAT treatment administration to an extent that makes DNDi's contribution to the 'test and treat' strategy towards HAT elimination feasible in the next few years.

Two additional clinical studies of fexinidazole have been initiated as planned for specific patient groups (children and patients not included in ongoing clinical trials; patients with T.b. rhodesiense). Two new complementary fexinidazole cohort studies were launched in 2014, one for early stage 2 and stage 1 adults, and another for children between 6 and 14 years of age. These additional studies were intended to respond to the unmet needs of patients groups excluded from the fexinidazole phase II/III trial and to facilitate wider use and implementation of fexinidazole to treat HAT. DNDi intended to make data available to include in the registration dossier to support treatment recommendations for children, patients with stage 1 HAT and patients with both Gambiense and Rhodesiense HAT. Enrolment in the first arm of these studies is on track; however enrolment in the pediatric study is slower than anticipated. These challenges do not impact dossier submission procedures to the EMA, which has allowed for only one pivotal study to be considered for product registration.

New clinical trial centers (Mushie, Katanda, Isangi) have been set up, further strengthening the clinical research capacity of HAT endemic countries. DNDi has taken sufficient actions to strengthen the clinical research capacity of HAT endemic countries. Specifically, to conduct its study on fexinidazole for HAT, DNDi renovated and/or equipped 5 new clinical trial centers in 2013 – 4 sites in DRC (Dingila, Katanda, Mushie and Isangi) and 1 in Central African Republic (Batangafo).[125] Clinical research capacity strengthening included infrastructure improvements such as installing power supply and telecommunications, equipment rehabilitation for laboratory diagnostic and hospitalization services, setting up of waste treatment facilities and provision of new equipment and consumables such as for biological testing, digital microscopy and ECG. The set up was supported by initiation visits to the clinical trial sites, Good Clinical Practice (GCP) training, annual HAT Platform scientific and steering meetings and related activities.

A number of operational, political and financial risks have emerged during the period 2013-2015 against which DNDi has taken adequate mitigation measures. Speed of recruitment in clinical trials of fexinidazole has been slower than anticipated, pushing timelines back a few weeks to some months as well as increasing costs. This has been due to a reduction of cases in the areas of the clinical trials, partly thanks to intensive screening efforts around the sites. The pace of recruitment has also been affected by insecurity and conflict in Central African Republic during 2013, as well as the DRC authorities' decision not to allow financial compensation incentives to clinical trial participants, which would induce trial participation but could skew the trial results. In effect, new sites have had to open periodically, each of which has taken 2 to 3 months to set up, including staff training. Despite the challenges, with the help of Sanofi, fexinidazole has become much easier to manipulate and to package in relation to NECT. And with the help of MSF, DNDi can deliver the drug under severe constraints, in remote areas where the disease is most prevalent.

Clinical advancement of SCYX-7158 was delayed because of the long half-life of the drug discovered with Human volunteers during the phase I study, the pharmaco-kinetic profile of SCYX-7158 has taken some time for DNDi to define appropriate dose levels which would have allowed for a phase II/III study to be initiated in 2014 as the PDP had originally planned. The drug has been documented as very safe in the Phase 1.

Efficiency

Organizationally DNDi is a highly efficient PDP that has achieved tremendous cost reductions in R&D over time. By having a high proportion of its income in core funds, it allows for quicker and more efficient re-allocation of funds between projects, depending on progress of each project against the pre-set Go/No Go criteria.[126] Regional disease-specific platforms reduce risks and costs including human resources of implementing clinical trials, liaising with national stakeholders and preparing the ground for product rollout. An efficient R&D chain structure keeping development costs down for its candidates. According to DNDi estimates that include the usual attrition rate in the field of infectious diseases, the PDP's costs of developing an improved treatment of marginal innovation are EUR 10 - 40 million; and the costs of developing a new chemical entity of breakthrough innovation are EUR 100 – 150 million.[5] These figures are substantially lower to the industry average for commercial diseases. Finally, overheads are kept at reasonably low levels (12.5%) and the PDP's salary policy (see section below) maintains salary costs at competitive levels.

The HAT specific activities have faced some delays and budget increases. There have been some time delays and additional costs with the fexinidazole study due to the difficulty of enrolling participants to the trial fast enough, and due to the need to set up new clinical research centers in order to achieve enrolment targets. There have also been some challenges with SCYX-7158, to define the dose due to the pharmaco-kinetic profile (very long half-life) and it is most likely that phase II/III trials will not have been initiated before 2016. This has also led to additional costs as new preclinical dosing studies had to be implemented prior to advancing the candidate to late stage clinical testing.

Added value

There is a clear value add from DNDi's HAT drug R&D activities. There has been no new chemical entity to treat HAT since eflornithine in 1990,[127] and before that since 50 years further back[128]. The experience from the marketing and distribution of NECT in all 8 HAT Platform countries demonstrates that 99% of Stage 2 patients are now treated in line with these guidelines in 12 countries that over 13,000 lives have been saved since 2009.[126] Building on the NECT success, a good outcome from DNDi's ongoing clinical development efforts will not only signalize a breakthrough in R&D, but will also ensure a step closer to disease elimination. If successful, DNDi efforts will also have significant implications for strategy development and policy formulation. First, it will bring us one step closer to meeting the WHO 2020 elimination objective. Second, it will influence strategies of global procurement funds and efforts and initiatives to accelerate access of commodities in the global effort to save lives. Finally, if successful, these efforts are expected to stimulate additional investments in R&D, as further studies will be required, including potential re-formulations for different demographic groups e.g. children etc.

Sustainability

Sustainability of R&D efforts appears to be at the heart of DNDi's product development efforts. First, DNDi has backup candidates for all lead candidates in its R&D pipeline, which ensures a smooth continuation of its R&D program over time. Second, DNDi actively pursues a policy of continuation of treatment services for patients in clinical trial sites participating in the PDP's clinical studies in LMIC settings, following completion of these studies. Third, as per the PDP's access policy, national Ministries of Health, the WHO and NGOs like MSF are integral implementers of new treatments and collaborations are being established to support implementation through the HAT Platform, which allows DNDi to remain involved as a facilitator and to ensure that partners can work effectively together to deliver the interventions to patients.[126] Therefore fexinidazole will be provided by Sanofi to the WHO for distribution, in collaboration with MSF Logistique, through national disease control networks; PNLTHA will collect safety data and the WHO will monitor treatment safety.

There are additional, longer term positive environmental externalities from DNDI's current clinical development efforts. For instance, melarsoprol and eflornithine have high risks of production due to toxicity. Moreover, all medicines and materials for four NECT treatments are packaged in a 36kg box, and a 14 infusion-based treatment is required over a period of 10 days in a hospital environment. A new, one-dose oral treatment that does not require clinical monitoring would reduce manufacturing risks associated with melarsoprol and eflornithine, whereas a positive impact on the environment should be expected as treatment would not require hospitalization and involves less packaging and disposal.

Other capacities & dynamic capabilities

DNDi has a robust governance and operational model, driving low cost and open access innovations for affordable and suitable drugs to LMIC- specific needs.

The PDP has a 50:50 funding ratio policy by public and private sectors and places a 25% cap in the share of total funding by any single funder, ensuring independence to develop its own strategy. It also has a salary policy, whereby all wages are earmarked to standard market equivalents in the pharma sector of Switzerland, helping maintain salary and overall institutional operating costs at reasonable, yet attractive enough levels for competent staff to be engaged with the organization. Scientific oversight is conducted by an independent Scientific Advisory Committee (SAC) of 17 members with a balanced (50:50) participation ratio between "North" and "South", reviewing project portfolio on biannual basis and issuing recommendations to the Board of Directors based on Go/No Go decision criteria.

Clinical trial management & capacity building is conducted through region- and disease-specific Platforms, reducing risks and costs including human resources (e.g. by avoiding duplication of training), and preparing the ground for product roll-out (e.g. by early inclusion of the national control programs and of national regulatory authorities to regulatory discussions with EMA and the WHO). For instance, the HAT platform has been instrumental in facilitating the timely implementation of clinical trials and adoption of new treatment recommendations. The platform has also advocated for the development of simpler diagnostic tools and treatments that are needed for a simplified HAT management and control strategy, ultimately contributing towards the elimination of the disease.

The PDP has a well-defined access strategy according to which: TPPs for all products must reflect target population needs and be publicly available; terms of reference are agreed early on with industrial partners for lowest cost-of-goods, affordable pricing and IP for global access; tailored approaches are pursued depending on disease and geographical area of operations; local operations in target regions are essential to ensure access.

DNDi has a policy of not being a marketing authorization holder combined with an IP and licensing policy that focuses on the PDP's public health mission, and which revolves around principles of non-exclusivity, non-rivalry, and royalty-free transferability. Increasingly the PDP has also been advocating for open innovation policies in neglected disease R&D according to the principles laid out by the WHO CEWG process.

In recent years DNDi has designed improved regulatory models for its products and has established new collaborations to ensure better alignment with disease- specific elimination strategies. For instance, DNDi's regulatory model for fexinidazole has allowed DNDi to work closely with the WHO and the EMA to conduct dossier review while providing simultaneously scientific opinion to LMICs affected by the disease. Although a bit time consuming, as stakeholders argue, this model has helped DNDi and its partners to prepare a robust strategy for product rollout. DNDi has been providing guidelines throughout the entire process. Its industrial partner, Sanofi, has been responsible for submitting the dossier. And partners within the HAT platform have facilitated timely interactions with LMIC regulators resolving queries and preparing the ground for product introduction. Moreover, new collaborations with FIND and some academic institutions such as Antwerp University and the Swiss Tropical Institute have solidified new approaches to assessing better treatments against HAT which require improved diagnostics.

Annex 2: Results from MFA/Norad investments in IAVI, 2013-2015

IAVI is a Product Development Partnership established in 1996 to develop safe, effective, accessible, preventive AIDS vaccines for use throughout the world, with a particular focus on vulnerable populations of developing countries. In addition to R&D, the PDP conducts policy research, social research and observational epidemiology studies, and advocates for the AIDS vaccine R&D field. Although IAVI started off as an advocacy organization trying to make AIDS vaccine R&D a priority on the global public health agenda, it simultaneously became a central force of translational research, vaccine design and clinical research capacity building, in an effort to fill critical gaps in the field.[58] IAVI currently employs 162 FTEs located in the US, Europe, Africa and India.[129]

Since inception, IAVI has evaluated 15 AIDS vaccine candidates in 27 early-stage human trials in 11 countries on four continents. In recent years the PDP has contributed to the discovery of dozens of bNAbs (now around 80), revealing new vulnerable sites on the virus which researchers can target for vaccine design.[59] Its current R&D portfolio comprises of 10 projects in preclinical and early clinical development; and six different approaches to the design of novel immunogens with the potential of inducing neutralizing antibodies requiring further development.

A number of challenges inherent in the AIDS vaccine science (as demonstrated by clinical trial failures but also breakthrough achievements in basic research and discovery), political de-prioritization of HIV prevention in recent years with significant budgetary implications for the PDP (a drop of 34% in total funding to the PDP since 2008), have led to a substantial reshaping of IAVI's organizational structure, R&D pipeline focus and human resource pool.

In 2013, IAVI signed a grant agreement of NOK 18 million with MFA/Norad for the support of the PDP's strategic plan towards the development of safe, effective, accessible, preventive AIDS vaccines for use throughout the world. This was a core unrestricted funding grant covering the period 2013-2015, and it was in continuation of the NOK 169.5 million that MFA/Norad had provided to IAVI previously, since 2001.

As part of the 2013-2015 MFA/Norad grant and the PDP's ongoing research strategy, IAVI aimed to address the key scientific issue of HIV hyper-variability, which is currently impeding vaccine development efforts in the field. Specifically, IAVI would:

1. Design vaccines that result in broadly neutralizing antibodies to protect against HIV infection
2. Develop replicating viral vector-based vaccines that confer durable protection against HIV
3. Leverage IAVI resources to accelerate AIDS vaccine development for the field

Relevance

IAVI's AIDS vaccine R&D mission is highly relevant to global strategies, Norwegian policies and priorities. IAVI's mission to ensure the development of safe, effective, accessible, preventive AIDS vaccines for use throughout the world is also highly appropriate and consistent with the WHO Global Health Sector Strategy on HIV/AIDS 2011-2015, the UNAIDS strategy 2011-2015, the HIV and AIDS policy of the Norwegian government, UN MDGs 3 - 6, the Norwegian Government's White Paper towards Global Health 2020, and the strategic plan of the Global HIV/AIDS Vaccine Enterprise.[130] IAVI has already contributed to securing support for AIDS vaccine R&D in the UN Political Declaration on HIV/AIDS and initiated work to securing similar support in the Sustainable Development Goals agenda – guiding the international response over the next 10-15 years. This reflects the relevance of developing an AIDS vaccine, especially for vulnerable populations to international efforts to tackle the epidemic.

There is further coherence and complementarity with many other national and foreign policies and interventions such as: MFA development strategies and humanitarian policies, such as the Norwegian Development Cooperation Strategy – and its key priority to reach vulnerable population groups, through a rights based approach;[131] the PDP Funders Group strategic framework;[121] other donor policies and funding interventions, including the Gates Foundation strategy on HIV/AIDS R&D financing, and the European Commission's Horizon 2020.

Although remarkable progress has been made in the control of the HIV/AIDS pandemic in the last 15 years, the battle cannot be won easily without a preventive AIDS vaccine. According to UNAIDS figures,[132] the world has made significant progress over the last 10 – 15 years towards the goal of ending the AIDS epidemic by reducing HIV transmission and halting AIDS related deaths, as well as improving access to antiretroviral therapy (ART). Yet significant challenges remain. The cost of ART is still forbiddingly high at US$ 140 per person per year. HIV treatment coverage in LMICs is low at 32-37% of the total number of eligible people for treatment. There are ongoing challenges, including unsafe sexual behavior, gender-based violence, and low political commitment and punitive laws, in many countries. A preventive AIDS vaccine can offer a highly cost-effective way to halt the AIDS pandemic,[133] even if it is moderately effective.[134]

Effectiveness & Risk

IAVI has made considerable progress in the design of vaccine candidates that elicit broadly neutralizing antibodies (bNAbs) against HIV. Under IAVI's strategic objective (SO) 1, the PDP has been playing a leading role in the design and development of vaccine candidates that elicit bNAbs to block HIV. Since 2009, dozens of highly potent bNAbs have been isolated and their molecular structures have been characterized. During the last two years, IAVI has studied multiple different approaches to design vaccine candidates for their potential to induce neutralizing antibodies, and two candidates, BG505-SOSIP trimer and eOD-GT8, have been selected to advance to the clinic. An additional immunogen, inactivated VSV (iVSV), was selected for development, but resource constraints have placed this candidate on hold. Two novel candidates have advanced to phase 1 clinical trials: AAV-PG9 (A003 trial) which delivers a bNAb via gene therapy; and HIV Env trimeric gp140 (X001 trial). Slow enrolment has created some delays to the initiation of the phase 1 clinical trials.

Moreover, a validated model to screen the best candidates at the discovery and early development level is still lacking, and IAVI has been testing multiple pre-clinical model approaches to help establish a validated system to screen HIV envelope proteins. This is crucial for candidate comparisons and optimal stage-gating decisions.

Efforts to design replicating viral vector-based AIDS vaccine candidates have produced mixed results. Under SO 2, IAVI has been designing replicating viral vector vaccine candidates against HIV/AIDS that mimic the efficacy of live-attenuated vaccines. Applying live-attenuated vaccines to HIV is impractical due to safety risks and replicating viral vectors present a potentially effective alternative for delivering HIV immunogens in the context of a viral infection.[135] Out of the seven candidates in IAVI's portfolio of replicating viral vectors originally established in 2005, three vectors have advanced to further development in recent years. Out of these three, IAVI's leading candidate, Sendai Virus (S001 trial), failed to meet phase 1 clinical trial immunogenicity targets in 2014[xxx]. Its second candidate, a prototype Canine Distemper Virus vector (CDV), is being evaluated in Non-Human Primate (NHP) challenge studies; and its third candidate, a Vesicular Stomatitis Virus vector (VSV-G6), has been prioritized for clinical development based on satisfactory cell line development and NHP data.

According to stakeholder impressions it is unlikely that replicating vectors inducing T-cell responses alone will be sufficient to protect against HIV infection.[136] For this reason, IAVI aims to consolidate its replicating vector and bNAb program once promising approaches in each have been identified with the aim to deliver immunogens, including those inducing bNAbs, through replicating vectors.

IAVI has provided substantial technical support to advance additional AIDS vaccine candidates by other vaccine developers. Through its Vaccine Product Development Centre (VxPDC), IAVI has provided expertise and support to 13 projects, helping advance AIDS vaccine candidates by other developers through the development process. The PDP has partnered with others to support the clinical development of three additional candidates: Ad35GRIN + MVA.HIVconsv +/- DNA HIV.consv (+/-EP) (Prot HIVCORE004); DNA + AIDSVAX B/E (EUROVAC-UVRI "IDEA" trial); Ad26 Mosaic Vectors + Soluble trimer gp140 Env protein (HIV-V-A004). Positive clinical data on the latter may support a decision to advance to phase IIb clinical efficacy testing by 2017, which is a key target for IAVI's current strategy.

IAVI has continued to strengthen clinical research capacity in Africa and has created new linkages for South-South R&D collaborations. Under SO 4, IAVI has long played a leading role in building clinical research capacity in Africa, having established a network of 8 clinical research centers (CRCs) in five African countries[xxxi] for the implementation of clinical vaccine research since the PDP's inception; and having recently (2012) launched a joint venture with India's Translational Health Science and Technology Institute - the HIV Vaccine Translational Research Laboratory (HVTR lab) - to generate novel concepts in HIV/AIDS vaccine design.[137]

[xxx] Despite the decision to not advance the candidate, the work done will help accelerate replicating vectors in the future. The Sendai clinical trial marked the first trial of an HIV replicating vaccine vector in Africa, paving a regulatory pathway for future clinical trials of replicating vectors. And the Sendai project also provided opportunities for capacity building around mucosal sampling since it represented the first time vaccine trial participants in Africa have undergone gut biopsy for the purpose of examining mucosal tissue. CRC-KAVI is passing on this mucosal sampling expertise to the other CRCs.
[xxxi] in total 11 CRC with India included

Recent developments include the launch of the Vaccine, Immunology, Science and Technology for Africa (VISTA) program; an international training program; increased funding to investigator-driven research projects; and collaboration strengthening between East African and Indian researchers and developers.

Indicative achievements of IAVI's efforts in the last couple of years include the build-up of expertise by IAVI- supported CRCs and their implementation of national and regional, South-South training sessions in HIV research ethics, mucosal sampling and facilitating access to VCT services for study volunteers; the scale up of immunogen design and screening activities by the HVTR lab; the implementation of six investigator-driven epidemiology and/or socio-behavioral studies on acute HIV infection cases as well as vulnerable (or most-at-risk) populations including fishing communities, sex workers (female and male) and men who have sex with men (MSM); and the establishment of an Indo-East African collaboration framework for linking African and Indian scientists working on AIDS vaccine R&D.

IAVI has maintained its global leadership in advocacy, policy and communications activities for global investments in AIDS vaccine R&D. Despite a downward trend in HIV/AIDS R&D financing globally, IAVI and others' efforts in Europe have contributed to the creation of a new funding line for AIDS vaccine R&D under the European Commission's Horizon 2020 program. In Africa the PDP's advocacy work has resulted in the inclusion of AIDS vaccines and other new prevention technologies in six national and regional strategies for research in Africa. In India IAVI received support by the government to establish a Program Proposal Management Unit for setting up an early development initiative for vaccines. And internationally, the PDP updated its impact modelling work to strengthen the case for AIDS vaccines in the context of a refined UNAIDS-initiated model for the overall discourse of the pandemic; showing that AIDS vaccines are essential in any scenario to bring new HIV infections down towards zero.

Efficiency

IAVI has substantially increased its organizational efficiency in managing its operations in recent years. Under SO 6, IAVI has restructured its organizational and operational structure significantly over the last few years, reducing its general operating costs by 20% only in the last two years (and by 40% since 2011) through a more focused portfolio management approach (e.g. re-focusing on early stage development and smaller experimental trials); removing some of its organizational support costs by sharing resources with other organizations / PDPs for instance by subletting the capacity of CRCs to other research activities; improving its grant management strategy; and generating some funding from license fees, which together with private sector funding covers 4% of IAVI's received funding currently.

Safety concerns, slow enrolment and lack of validated models are causing time delays and are increasing costs of clinical and preclinical development activities. For instance, a safety finding in the AAV-PG9 phase 1 clinical trial led to a half year delay and additional testing in all participants of the study. Another phase 1 clinical trial (X001 trial) testing HIV Env trimeric gp140 was delayed by a year due to slow enrolment.

Added value

IAVI's R&D efforts and accumulated expertise are filling in critical gaps for the understanding of the AIDS vaccine science. Although IAVI is several years away from delivering an effective preventive AIDS vaccine for global use, the PDP has historically added value in the field by advancing the basic science around neutralizing antibodies and designing novel vaccine candidates using multiple approaches for clinical testing. IAVI believes that understanding how bNAbs bind to the HIV virus and block its entry into its target cells can establish the foundation for the development of broadly and highly effective HIV/AIDS vaccines.[138] The PDP's focus on bNAbs has created a unique space for IAVI in the vaccine development field.

LMIC partners are increasingly engaged in AIDS vaccine R&D through the IAVI platform. Partners from India and several African countries are increasingly involved in and taking leadership of clinical development projects and South-South knowledge sharing initiatives.

The PDP is becoming increasingly a hub for technical support of a broader community of AIDS vaccine developers. IAVI's accumulated expertise in vaccine design and development has generated 13 new project collaborations funded under the VxPDC; the launch of the Human Vaccines Project; three new R&D partnerships with academic, industry and other research consortia, and ongoing collaborations on vaccine related research issues with other PDPs (e.g. Aeras and PATH).

Sustainability

A steady decline in AIDS vaccine R&D funding by aid agencies in recent years, and a decline in unrestricted funding levels have challenged IAVI to effectively match available funding with its R&D portfolio priorities.[139] Although IAVI follows a more focused R&D portfolio management approach today, it is worth noting that its 2015 R&D candidate portfolio has been significantly re-structured in comparison to 2009[139, 140]. Restricted funding also creates time lags between failed R&D candidates and backup candidates that can sustain a healthy pipeline. As several vaccine candidates are moving towards clinical development, large investments for manufacturing and scaling-up will be needed in addition to funds that can support next generation candidates.

Overall, IAVI projects a funding gap of US$ 6 – 36 million over the next three to five years, pending Go/No Go decisions on different vaccine candidates in IAVI's portfolio, and new strategic goals to be defined during the development of the new Strategic Plan 2016-2020 for IAVI.

Other capacities & dynamic capabilities

IAVI has a unique operational model, ensuring high levels of in-house scientific capabilities, and competitive vaccine design and development competencies. The PDP has a large number of staff conducting R&D and supporting work, spanning across four continents (Africa, America, Asia, Europe) with a diverse range of skills and expertise covering biomedical and translational research, social research, global health policy and advocacy. Its in-house technical expertise, together with its extensive global network of

laboratories, research facilities and clinical research centers, has allowed the PDP to advice on translational development of HIV vaccine concepts on behalf of others (e.g. US NIH or BMGF) who lack the capacity to manage complex relationships with contract manufacturing organizations (CMOs). Over the last couple of years the PDP has been exploring additional approaches to vaccine manufacturing in collaboration with new industry partners.

IAVI is maintaining clear access commitments in IP arrangements with partners and is promoting prioritized access to a potentially licensed AIDS vaccine for the most vulnerable populations. IAVI has long developed an exit strategy to ensure that a successful preventive AIDS vaccine will be promptly registered, manufactured in adequate quantities and distributed at reasonable prices in LMICs. This, the PDP argues, is achieved through maintaining legally binding IP agreements with industrial partners that stipulate a clear set of access commitments for all vaccines that are being sponsored by IAVI. A recent example of such an arrangement was the 2014 collaboration agreement between IAVI and Johnson & Johnson.[139] Further, IAVI seeks to work with GAVI, the Vaccine Alliance to prioritize access to a licensed AIDS vaccine for those individuals and communities who are most vulnerable and at greatest risk of HIV infection.

Annex 3: Results from MFA/Norad investments in IPM, 2013-2015

The International Partnership for Microbicides (IPM) is a Product Development Partnership (PDP) focusing on the development and availability of safe and effective microbicides and other HIV prevention, sexual and reproductive health technologies for women in LMICs. Established in 2002 as a non-profit organization, the PDP has headquarters in Silver Spring, Maryland, USA, and an office in Paarl, Western Cape, South Africa; with a total staff of 74.

Since inception, IPM has led R&D efforts globally in developing the first long-acting ARV-based microbicide for HIV prevention in women. It has worked in over 10 countries in Africa, Europe and North America to conduct 25 clinical trials on microbicide candidates, and 13 epidemiological studies. It has helped strengthen capacity at 15 research centres (RCs) in Africa (10 of these newly established by IPM), and has trained 850 clinical staff and community advisors on microbicide trial implementation. The PDP has developed competencies in: developing and evaluating microbicides and multi-purpose technologies (MPTs) to address women's health needs; negotiating royalty-free licenses for ARVs as microbicides; and streamlining manufacturing processes.

Its current R&D portfolio comprises of 14 projects at clinical and preclinical development stages. Most projects concern ARV-microbicide development efforts for HIV prevention in women. In recent years IPM has initiated a new project for the development of a multi-purpose, ARV-contraceptive technology for HIV prevention and contraception in women.

In 2013, IPM signed a grant agreement of NOK 20 million with MFA/Norad for the advancement of the PDP's microbicide research, development and access program. This was a core restricted funding grant covering the period 2013-2015, and it was in continuation of the NOK 182 million that MFA/Norad had provided to IPM previously, since 2002.

As part of the 2013-2015 MFA/Norad grant and the PDP's ongoing strategy, the purpose was to develop and help ensure access to safe and effective microbicides that prevent HIV infection in women in developing countries. Specifically, IPM would:

- Continue to implement the dapivirine ring study (IPM 027)
- Conduct additional clinical trials required for licensure of the dapivirine ring
- Continue preparations for regulatory dossier filings

Relevance

IPM's dapivirine ring clinical development and licensure program is highly appropriate and consistent with the strategic context and priorities given by the WHO Global Health Sector Strategy on HIV/AIDS 2011-2015, the UNAIDS strategy 2011-2015 and the UN Political Declaration on HIV and AIDS, the Microbicides Development Strategy of the Alliance for Microbicide Development, the HIV and AIDS policy of the Norwegian government, UN MDGs 3 - 6, and the Norwegian Government's White Paper on Global Health in Foreign and Development Policy, towards Global Health 2020. The program is also coherent and complementary with many other national and foreign policies and interventions, such as: the MFA development strategies and humanitarian policies;[131] the PDP Funders Group strategic framework;[121] and other donor policies and funding interventions, including the Gates Foundation's strategy on HIV/AIDS microbicide R&D financing and the European Commission's Horizon 2020.

Effectiveness & Risk

IPM has successfully completed enrolment in the dapivirine ring study. The study was initially planned to enroll 1650 women IPM increased the sample size to 1950 participants i.e. enrolled up to 300 additional participants, to compensate for non-adherence detected at one RC and to ensure 1100 women on drug product for two years.

By the end of 2014, 1,959 women had enrolled in IPM 027 at seven RCs in South Africa and Uganda, and 2,629 women had enrolled in the dapivirine ring sister study implemented by NIH, MTN-020, at 15 RCs in Malawi, South Africa, Uganda and Zimbabwe.[141] Both studies are needed for ensuring scientific excellence in the dapivirine ring's clinical development, robust statistical analysis of clinical trial data, and market approval by stringent regulatory authorities. Although the NIH study is funded independently, IPM maintains regulatory sponsorship of the product. The two organizations have been working well together to align the phase III study protocols ensuring adequate clinical data and sufficient provision of technical expertise across all stages of the program.

IPM has successfully completed a number of complementary studies and has recently initiated additional studies in response to regulatory authority requirements. Six additional clinical and preclinical studies have been completed successfully and with good outcomes in the last couple of years[xxxii]. Five studies are ongoing[xxxiii], and following clinical pharmacology meetings with the FDA and EMA, as well as interactions with the MCC in South Africa, four new studies have been initiated in 2014, or are being planned for in 2015[xxxiv]. Although residual drug level testing is ongoing for IPM 027 and MTN-020, data from another study had to be regarded as exploratory due to a lack of vendor compliance with GMP and Good Clinical Laboratory Practice (GCLP).[141]

[xxxii] These include: a drug-drug interaction study (IPM 028); an open-label extended-use pharmacokinetic study (IPM 034); a male condom functionality study (IPM 029); a female condom functionality study (IPM 033); and a carcinogenicity study.
[xxxiii] Other ongoing studies include a follow-up clinical care study for women discontinued from the ring study while enrolled at a RC no longer included in the study (IPM 037A); a socio-behavioral study on ring non-adherence observed at the RC no longer part of the clinical development program (IPM 037B); a seroconverter study; an adolescent safety study (MTN-023/IPM 030); a post-menopausal women safety study (MTN-024/IPM 031); and CMC gap filling studies.
[xxxiv] These include: a dapivirine uterine contractibility study; a second drug-drug interaction study (IPM 036); a menses and tampon impact study (IPM 035); a study to evaluate protein binding of dapivirine in vaginal fluids; and a phase IIIb open-label follow-on study (IPM 032), assessing long-term safety of and adherence to the monthly dapivirine ring in healthy, HIV-negative, sexually active women who have participated in IPM 027.

Significant progress has been made with the manufacture of the dapivirine ring. Since the closure of IPM's clinical trials manufacturing facility several years ago, the drug delivery device manufacturing function has been outsourced to commercial partners. Specifically in relation to the dapivirine ring, QPharma, a Swedish contract manufacturing company, has been contracted by IPM as its launch partner, due to its high level of internal expertise and global leadership in silicon ring making, ease of technology transfer from IPM's own facilities in Pennsylvania (now shut down), and unique position globally to manufacture rings on a contract basis, allowing for more efficient, low cost manufacturing.

Despite some challenges around single sourcing of silicon supplies and packaging requirements by regulatory authorities, contractual arrangements for the long-term supply of silicone have been made[xxxv], manufacturing activities for GMP drug supply have been completed as planned and CMC gap filling studies are continuing; the results of which will be integrated in the regulatory dossier in 2015. The build up to a commercial partner manufacturing partnership is ongoing.

There have been some challenges with reaching and engaging regulatory authorities, which IPM has successfully managed to overcome. The regulatory risk is high, since no microbicides have been approved by a regulatory authority before. This is reflected by FDA's recent reclassification of the dapivirine ring as a drug-device product, its expansion of regulatory requirements for IPM's New Drug Application to the agency and its proviso for IPM to justify applicability of foreign data to US population / medical practice.[141] Successful submission of data packages to the Data Safety Monitoring Board (DSMB) during 2014, resulted in a positive signal for the continuation of the clinical trial as planned, and the US Investigational New Drug (IND) application for the dapivirine ring continues to be maintained.

There have been some difficulties with reaching out and engaging with the South African regulatory authority, which IPM has now resolved. Routine safety filings have been completed with the MCC as well as with the national regulatory authorities in Uganda. As per MCC's request, a protocol for a phase IIIb study has also been submitted for review to the MCC.

IPM's systematic approach to product adherence has significantly reduced risk of non-adherence in recent years, and RC partners have been important contributors to this effort. Adherence remains a complex and significant challenge for microbicides. IPM has correctly prioritized this as the greatest risk to the successful completion of the dapivirine ring clinical development program. Adherence remains a risk for effective product roll-out in the future. IPM and its RC partners have undertaken a systematic approach to product adherence, including monthly measurement of dapivirine residual levels in rings, and a number of coordination and community engagement measures at the local level[xxxvi]. The last set of activities is crucial, as several stakeholders agree, since participation in microbicide trials is a family driven, collaborative decision.

[xxxv] IPM recently completed an agreement with NuSil for the long-term supply of silicone, with an initial term through December 31, 2025.

[xxxvi] In summary, these activities include: regular discussions with RCs on recruitment, retention, protocol compliance and blinded objective adherence data trends and concerns; adherence enhancement initiatives implemented by RCs at the community level in coordination with IPM; routine health examinations, contraceptive supplies and HIV / STI risk reduction counselling; provision of small stipends for participation in the trials (travel compensation and free health check-ups); follow up of HIV infected individuals in a seroconverter study and a socio-behavioral study as well as optional clinical care for those who have been discontinued due to the closure of one of the RCs in 2013.

Efficiency

Planned activities have been conducted on-time and within budget. IPM has managed to meet all its milestones on-time for 2013 and 2014. Moreover, due to a multiplicity of factors such as exchange rate fluctuations, timing of new staff hires, and other improved institutional operating efficiencies,[141] the PDP has met its targets for the two year period without exceeding its previously projected budget.

As IPM notes, it is likely that expenditures on clinical development and global access initiatives will increase in 2015 as the PDP is moving towards the analysis and utilization of the dapivirine ring trial results. These are anticipated changes that should not have any significant effect on the IPM's overall budgeting and planning. Moreover, as stakeholders have noted in consultations, additional donor documentation requests can lead to loss of time and sometimes budgetary implications due to accumulated administrative costs and multi-week or multi-month delays.

Added value

If clinically effective and successfully licensed, the dapivirine ring will be the first long-acting, female-initiated HIV prevention technology brought to market worldwide, with great life-saving potential. Given that a big bulk of the clinical testing is being conducted in rural settings, an efficacious outcome would be even more important, as stakeholders suggest, reflecting the relevance of the product to real, rural areas with HIV infections. The final product, if approved by regulators, will also potentially avert thousands of HIV infections in women in Sub-Saharan Africa.

If successful, the product will also have large implications for future strategy and policy formulation in maternal health and family planning. The ring formulation appears to be superior to vaginal gels, which have proven to be suboptimal delivery systems. As evidence and consultation based impressions suggest, the vaginal ring is an inert system that women apply themselves and which does not require as much maintenance. Other delivery systems, such as vaginal gels, require more frequent use and are likely to lead to non-adherence. Moreover, the ring allows for combinations of ARVs with contraceptives, STI products and HPV prevention technologies. Therefore the ring strategy, several stakeholders argue, is the right one. If this program proves successful, next generation combination products will be able to deal simultaneously with HIV infections and conditions such as unintended pregnancies, women's and maternal health issues.

The engagement of IPM in the development of HIV microbicides has been catalytic for the involvement of industry and its sustained R&D commitment in the field, as well as for ensuring lower manufacturing cost and better access arrangements. As multiple stakeholders argue, to date, big pharma remains largely un-interested in microbicide R&D due to insufficient market incentives and shareholder accountability lines. The legal responsibility has therefore historically lied with IPM, and IPM has in turn been a catalytic force for any industry involvement to date. In the absence of PDPs like IPM, several stakeholders argue, there would be zero industry investments in the field.

Moreover, by identifying the right partners, e.g. biotechs that are privately owned and embrace a long run philanthropy perspective in their missions, and by maintaining an open

IP strategy while ensuring regulatory sponsorship of its product, IPM has: allowed for IP to be generated without company partners demanding more role than contract based development and manufacturing activities; secured crucial access agreements by big pharma for the drug in LMIC settings; remained in control and distribution of the product, putting downward pressure on the anticipated product price upon approval. The goal is to gradually drop manufacturing costs to less than US$3per unit.

IPM has contributed to research capacity and public health strengthening in LMICs where the dapivirine ring study has been implemented. As our consultations with IPM partners suggest, the PDP has brought a good structure and sense of pride to collaborating RCs, improving skills for clinical research purposes and facilitating a greater understanding of the role of research in clinical practice and the value of good clinical data, even if this is particularly difficult in rural environments. As some stakeholders argued, in rural areas having good staff and obtaining good data is an art. IPM has contributed to smooth RC operations due to its great problem-solving capacity. Through systematic audits, organizational reviews and certifications of sound R&D practices, regular knowledge sharing initiatives among RCs and data monitoring, as well as through training of dozens of employees in clinical trial support and good management practices, IPM has created a network of responsive RCs that are becoming increasingly engaged and interested in the PDP's product development efforts, while retaining increasingly competent employees that can better serve their local communities. In a way, as stakeholders argue, IPM has generated a form of positive competition among RCs which is contributing to greater efforts to tackle adherence and increase compliance to the product collectively. Equally important, IPM has gained the trust and recognition by RCs over time, who feel that the PDP understands the issues of poverty, public health needs and skills gaps for locally owned health research efforts.

The dapivirine ring program is supporting the expansion of manufacturing capacities and is stimulating investments into the field of HIV microbicide R&D. For instance, IPM has knowledgeable staff on manufacturing but without externalizing its manufacturing function it would struggle both financially and technically. Therefore partnering with industry is instrumental, which enables smooth transition from prototype to scale up production, facilitates better product design and reduces the overall cost-of-goods in manufacturing.

Moreover, stakeholders have stated that IPM's extension of the ring study to adolescent populations has been supported by European partners, so that IPM can access additional EU funds through EDCTP, creating a 'triangle of synergy'.

Sustainability

Resource constraints are the greatest barrier to the sustainability of IPM's dapivirine ring development efforts. As IPM argues, the dapivirine ring study could not have been launched without public funding, which has made it economically and politically feasible. However, several stakeholders argue, investments have not been enough in terms of sheer size. As the study is coming to completion, and new follow up studies need to be implemented, large resources need to be accumulated in order to ensure licensure and access. This implies a major structural shift in getting the dapivirine ring to market. The PDP is looking into models for doing this. However, being the market authorization holder increases costs substantially. A pipeline gap at earlier R&D stages is emerging and some RCs

are at risk of staff loss or closure if new investments are not made in clinical development of IPM products.

Overall, IPM has a funding gap of approximately US$ 50 million over the next three to five years.

Other capacities & dynamic capabilities

IPM plays a crucial role in HIV microbicide and multi-purpose prevention technology development, as organizations from the academic or industrial sectors would not be able to, or willing to, work independently and without the scientific direction by the PDP. This also applies to access, where the PDP has built know-how in recent years and, arguably, is in a position to lead even if others are better positioned to implement access related activities.

The PDP has successfully phased out and outsourced its clinical trials manufacturing function, increasing efficiencies and transitioning successfully into a leading virtual R&D organization in the microbicides field. IPM carries a unique feature in that it acts as the sole regulatory sponsor for its products, including worldwide IP ownership.

Over the years IPM has accumulated technical expertise that allows it to act as an honest broker in a strong network of partners internationally, at multiple fronts of the R&D and access pipeline. The PDP has negotiated royalty free licenses for eight ARVs as microbicides in developing countries. It has strengthened its strategic partnership with NIH during the dapivirine ring licensure program implementation and with contract manufacturing and contract research organizations for effective production and data monitoring activities. Despite the challenges with some RCs, the PDP has established new partnerships with aspirational LMIC partners (RCs and others) who have leveraged the PDP's ability to advance its clinical development efforts and to facilitate marketing authorizations in their countries once clinical trials will have achieved successful outcomes.

Over the past two years IPM has extended three partnerships for manufacturing (two to scale up ring manufacturing; one for multi-purpose technologies); has set up a new partnership with a vendor to compile the dapivirine ring dossier and setup of Electronic Common Technical Document (eCTD) team; has appointed a new Director in place for Global Product Access; has initiated collaborations with three new RCs (two in South Africa; one in Uganda). The PDP has also improved its model for pharmacodynamic testing in early clinical trials; and has increased its knowhow on vaginal ring formulation and polymer chemistry.

Annex 4: Results from MFA/Norad investments in MMV, 2013-2015

Medicines for Malaria Venture (MMV) is Product Development Partnership (PDP) established in 1999 as a non-profit foundation to discover, develop and deliver new, effective, and affordable antimalarial drugs to disease-endemic country settings. Its focus is on building a strong R&D pipeline leading to a new generation of medicines that will form a critical part of malaria eradication efforts. It has headquarters in Geneva, with 65 members.

Since its inception, MMV has built the largest and most diverse portfolio of antimalarial drug projects in history. With its partners it has brought forward five antimalarial product, most of which have received WHO prequalification: Coartem® dispersible; artesunate injection for severe malaria; Pyramax®; Eurartesim®; and SP+AQ. Its current R&D portfolio includes 35 projects in discovery, 7 projects in preclinical, 8 projects in clinical development, and 2 projects under regulatory review, targeting a range of mechanisms of action and chemotypes. Its extensive malaria screening campaign of 6 million compounds has been continuously supplying MMV's R&D pipeline as well as assisting the broader malaria R&D community through open access innovations and data sharing.

In 2013, MMV signed a grant agreement of NOK 15 million with MFA/Norad for the support of the development of new drugs for malaria eradication. This was a core unrestricted funding grant, and the first that the PDP would receive from MFA/Norad.

The program aimed to contribute to the elimination and eradication of malaria by discovering, developing and facilitating delivery of new, effective and affordable antimalarial medicines. Key expected results included:

1. Access / Product Management	○ WHO prequalification of an affordable drug for Seasonal Malarial Chemoprevention (SMC) ○ WHO prequalification of an affordable rectal artesunate for pre-referral treatment granted
2. Development	○ At least one new paediatric Artemisinin-based Combination Therapy formulation registered with the European Medicines Agency (EMA)
3. Single Dose Cure	○ Pivotal Phase III of Tafenoquine for single dose cure for Plasmodium vivax relapse prevention on-going ○ Dose-ranging study in patients with single dose cure of OZ439-piperaquine for the treatment of uncomplicated malaria initiated and moved towards completion
4. Translational	○ Two new compounds brought to Proof of Concept declaration
5. Discovery	○ Six new compounds with at least 3 new modes of actions and at least one targeting transmission blocking (TCP3b) declared as preclinical candidates

Relevance

MMV implemented activities during 2013-2015 have been appropriate and consistent with a series of international strategies and priorities, including: the UN MDGs (specifically 6c, 4 and 5); the WHO Global Malaria Program; Roll Back Malaria's (RBM) Global Malaria Action Plan (GMAP); the malaria research eradication agenda (malERA); and the key functions and objectives of Malaria Eradication Scientific Alliance (MESA).

All activities have been grounded on a sound evidence based gap analysis and profiling exercise of the new generation antimalarials needed to cure the disease, tackle resistance, and contribute to the elimination and eventual eradication of the disease (labelled as SERCaP).[142] Activities have also been coherent and complementary with many other national and foreign policies and interventions:

- Coherent with Norwegian Government's White Paper towards Global Health 2020
- Complementary with MFA development strategies and humanitarian policies[131]
- Complementary with PDP Funders Group strategic framework[121]
- Complementary with other donor policies and funding interventions, such as: Gates Foundation strategy on malaria R&D financing, and the European Commission's Horizon 2020
- Coherent with the WHO / CEWG recommendations on open knowledge innovation

Effectiveness & Risk

MMV has been on track with most of its R&D and access portfolio activities, and significant milestones have been achieved which can be linked to Norad funding.

In autumn 2014 the WHO announced the prequalification of Guilin Pharmaceutical's co-blistered sulfaxine-pyrimethamine + amodiaquine (SP+AQ) tablets for children aged 1 to 5, which is expected to benefit Sahel and sub-Sahel regions of Africa that have adopted WHO recommended seasonal malaria chemoprevention (SMC) policies to protect children from malaria during the rainy season.[143] According to WHO estimates SMC using SPAQ can protect 25 million children of ages 1-5, averting 75% of malaria episodes[144] and 20,000 deaths a year.[145] WHO prequalification of an affordable rectal artesunate of pre-referral treatment of severe malaria is expected end-2015 to early-2016. Two manufacturers have committed to pursuing WHO prequalification and bioequivalence studies are currently underway, with a plan to submitting dossiers later in 2015.

A dossier for registration of a Pyronaridine-Artesunate (Pyramax®) Paediatric formulation was submitted to EMA in 2014 by MMV / Shin-Poong, with results expected by end-2015.

Progress, yet with challenges, has been made towards developing a single-encounter radical cure and prophylaxis (SERCaP) for elimination and eradication. A pivotal phase III trial (DETECTIVE II) of tafenoquine for single dose cure for relapse prevention in patients with P. vivax malaria started in 2014, with recruitment completion expected by February 2016. Another planned phase III trial (GATHER) was delayed due to lack of approval in Columbia. Tafenoquine is the first novel compound of MMV's portfolio to have received Breakthrough Therapy Designation from the FDA.

A phase IIb dose-ranging study in patients with single-dose cure of another antimalarial (OZ439-piperaquine) was initiated ahead of schedule in 2014 for the treatment of

uncomplicated malaria. OZ439 is the first effective single cure candidate that has shown much better results than artemisinin, providing the first strong alternative to the artemisinin-based gold standard therapies to date. Some challenges with the formulation of OZ439 have been encountered and MMV is working with formulation development experts - industry partners such as Sanofi and Takeda, and PDPs such as the TB Alliance, to rapidly test new formulation approaches that can ensure the compound remains affordable according to MMV's Target Product Profile (TPP).

Two new compounds reached Proof of Concept. First, DSM265 – a novel plasmodium dihydroorotate dehydrogenase inhibitor – successfully complete a phase I study, and phase II studies started in January 2015. DSM265 is one of very few inhibitors of the malaria parasites with long term efficacy results, which can also act as a chemoprevention candidate (the first since malarone in prophylaxis). Second, MMV048 – a plasmodium-specific phosphoinositol 4-kinase inhibitor – completed a phase I study establishing proof of pharmacokinetics and pharmacodynamics in humans. This is the first African-discovered molecule to enter clinical trials in malaria (see chapter 3).

Seven new compounds have moved from discovery to preclinical development, 50% of which are focused on novel mechanisms of action and 85% on novel chemotypes, with four new modes of action and one targeting all lifecycle stages. In addition, two new chemical entities have been recently recommended as preclinical candidates by MMV's Scientific Advisory Committee.

One candidate (ELQ300) has been terminated due to formulation issues. Another candidate (21A092) is currently on hold, whereas the AstraZeneca mini-portfolio project has been terminated due to the closure of the AstraZeneca facility in India.

MMV's R&D efforts towards its short term goal for pregnant women have not fully materialized, as the AZ-CQ candidate for intermittent preventive treatment in pregnancy (IPTp) showed poor efficacy results. MMV has been conducting further evaluation of data on antimalarial regimens and their fit to regulatory requirements for IPTp, but generating conclusive results has been challenging due to study setups and the further work had to stop for futility reasons.

Efficiency

Activities have been conducted on-time and within budget. MMV has managed to meet all its MFA/Norad related milestones for 2013 and 2014. Lower than expected costs were recorded in a number of projects due to factors listed below, including MMV048 and DSM265. Some cost savings were recorded due to failed candidates (ELQ-300), terminated discovery collaborations and studies (IPTp), or slow negotiations with suppliers as well as Ebola-outbreak related delays pushing the UNTAID-sponsored APM project timeline further into the future.

MMV efficiencies are supported by robust organizational and other innovations. A number of new technologies and platforms have contributed to improved development timelines over the past years:

- Controlled human malaria infection (CHMI) model, assessing the transmission-blocking potential of new compounds, saving 1.5 – 2 years and US$2m between phase I studies and approval of dossiers for clinical trials

- High-throughput P.*vivax* liver-stage assay, accelerating the identification of appropriate prophylactic therapies capable of treating and preventing relapsing malaria
- Standard membrane feeding assay, increasing capacity to screen 30 compounds per year and achieving standardization allowing for its use by multiple screening centres
- Drug-resistance assay, improving data for optimal formulation selection and optimal dosing decisions
- Improved pharmacokinetic modelling in SCID mice

Due to these models and other innovations, MMV has achieved significant cost-savings across all stages of R&D:

- Cost savings of US$ 8 – 20.5 million per candidate at the discovery stage in relation to standard industry average, due to reductions in costs with suppliers, the co-investment by MMV partners, the lower overheads due to the virtual organization setup.
- Cost savings of US$ 0.7 – 2.2 million per candidate at preclinical development in relation to standard industry average, due to cost sharing by pharmaceutical partners, price negotiations, and in-kind contributions by contract research organizations in spirit of corporate social responsibility
- Reductions in average drug clinical development costs down to US$ 54 million (almost a quarter of the standard industry equivalent) due to the systematic support of small biotech firms with capacities to deliver effective and high quality drugs (e.g. in the case of Guilin Pharmaceutical and Shin Poong Pharmaceuticals).
- Cost savings of one hundred-fold magnitude in screening and testing molecule leads due to process alignment across assay platforms and creation of centers of excellence
- Additional efficiencies due to portfolio management and competitive procurement processes

Added value

MMV's activities have had a clear health impact on the ground. To date, MMV and partners have distributed 286,5 million treatments: 250 million of Coartem© Dispersible and 36,5 million of Artesun©. Over 650,000 lives have been saved due to the rollout of Coartem® *Dispersible* and Injectable Artesunate. SP+AQ, an antimalarial for children that recently obtained WHO prequalification, is expected to save an additional 20,000 lives per year. Eurartesim® and Pyramax® have obtained approvals by several countries and are expected to contribute further to treating malaria and saving the lives of women, children, and other adult populations in disease-endemic countries worldwide.

MMV's activities have had a clear impact in terms of filling in critical R&D gaps. In the past two years the PDP has brought five new candidates to discovery (with an approximately 50:50 ratio of new:withdrawn candidates); seven new candidates to preclinical stage; two new candidates to clinical stage; and one new ACT formulation to registration by end of 2015. New chemical entities comprise 73% of MMV's R&D portfolio from preclinical stage to registration. The PDP has also continued to contribute to the scientific knowledge supporting malaria elimination by publishing dozens of open access papers on various topics.

Activities have stimulated additional positive implications. First, MMV has taken ownership of DNDi's antimalarials ASAQ and ASMQ to include in its access and delivery portfolio. Second, over the past two years, its networks in drug manufacturing and

development have expanded with seven industry and one regional access partners. Third, numerous partners including other PDPs have benefited from MMV's clinical trial networks. Fourth, MMV has been critical in building discovery to clinical research capacity in LMICs and in building regional centers of excellence such as the team leading the development of MMV048 at the University of Cape Town, South Africa. Beyond empowering African-based R&D institutions to take greater ownership of malaria drug R&D activities, the PDP has been instrumental in engaging the South African government to co-fund malaria drug R&D activities that are conducted by domestic institutions. This is a novelty that is not commonly seen outside the space of government-to-government or donor-to-recipient interactions.

Sustainability

MMV makes strong links between its R&D activities and long term interventions to achieve malaria elimination and eradication. Its robust access post-approval portfolio and its balanced R&D pipeline with a strong share of novel compounds from discovery to late stage clinical development provide a strong guarantee for improving access to improved antimalarials to tackle the disease and all its related challenges such as resistance over time. There are several candidates in the PDP pipeline that serve as potential backups in case of failure of lead candidates to demonstrate proof of concept or safety and efficacy in clinical testing.

As several stakeholders suggest, the MMV model is sustainable because it demonstrates clearly a high level of technical expertise; it has become the focal point for discovery and development of malaria drugs worldwide; it has a reputation that is built off its extended network of partners; it is highly focused on delivering affordable and LMIC-specific appropriate drugs; it has a powerful mindset in the way its staff operate and interact with partners on an equal-partnership, open access and collaborative basis; it has a robust mobilization strategy; and it has clear sets of principles of respect, integrity, transparency, accountability, and excellence in its operations, reflected by its various policies and standard operating procedures on ethics, anti-corruption, and conflict-of-interest.

Other capacities & dynamic capabilities

MMV has an excellent partnership-building capacity with institutions and building networks to discover, develop and deliver new malaria drugs.

Since inception it has built an extensive network of over 375 partners in at least 50 countries across the globe, to support R&D from early discovery to late stage clinical development and access. In the last two years MMV has partnered with 4 new industry partners in development; three industry partners in manufacturing; and one regional network in access.

Importantly, MMV works with partners in malaria-endemic countries through board membership, scientific advisory participation, partnerships for clinical trials, partnerships to launch access projects, and to address manufacturing issues. Prime example is the novel malaria molecule discovered by African researchers in collaboration with the PDP (see MMV390048) and the ongoing collaboration for its clinical testing at the University of Cape Town, South Africa. In total, MMV has maintained a network of 96 clinical trial sites in 30 malaria-endemic countries since 2005.

Its partnership-building track record is supported by two key drivers. First, the PDP has highly skilled teams of malaria specialists and drug development experts, technical consultants, policy and advocacy professionals. This is very attractive feature to industry, as several stakeholders suggest. Second, MMV applies stringent procurement processes to select and retain providers for required activities based on experience, added value, and quality of services. MMV ensures that agreements are non-exclusive, royalty-free, and transferable, with the aim to always maximize the PDP's public health mission.[146] MMV engages in price negotiations early in the R&D process and usually applies a cost plus pricing strategy with a US$1 per pill target. The appropriate management of intellectual property and marketing rights has encouraged many industry partners to work with MMV, including most recently Sanofi.

MMV has developed new organizational and scientific models in recent years, which have improved the innovativeness and average probability of success of R&D candidates. Scientific innovations include: (1) Controlled human malaria infection (CHMI) model; (2) High-throughput Plasmodium *vivax* liver-stage assay; (3) Standard membrane feeding assay; (4) Drug-resistance assay; (4) Pharmacokinetic modelling in SCID mice.

Portfolio management innovations include: (1) improved TPPs fully aligned with WHO, consistent with eradication strategies and relevant to MDGs 4, 5 and 6; (2) SOPs for subcontractor selection; (3) calls for proposals at early discovery; (4) ongoing go/no decision processes utilizing an Expert Scientific Advisory Committee (ESAC).

As the PDP's R&D pipeline has grown in quantity and quality over the years, MMV has had greater capacity to process critical information to develop more novel classes of compounds and to explore new combinations of drugs or drug classes; increase the potential of drug discovery platforms to identify potent compounds with antimalarial activity and to accelerate their development, enriching its preclinical and clinical portfolio ahead of emerging threats such as drug resistance; process information to improve the stage-gating process and make more effective, data-driven funding allocation decisions; reduce attrition risks (4/13 compounds (30%) have advanced from discovery to translational research to date, significantly better than 95% standard attrition in the commercial sector).

The PDP's in-house financial management capacity is strong, ensuring for instance that 25% of its investments are always allocated to discovery and 25% in translational research; maintaining at least 80% of its resources as non-earmarked, allowing for flexibility of project financing based on need; having managed to keep low administrative overheads; securing in-kind support from partners that more than doubles MMV's own contributions to some projects; and periodically driving down costs through mini innovations in some of its R&D projects. For instance, the PDP has already established new translational medicine tools that have facilitated earlier 'confident' decision making in the R&D process that have expedited development by around 2 years and have reduced costs to proof-of-concept by around 40% (see efficiency section). In the last couple of years the PDP has secured five new funders while maintaining the support by 14 existing funders.

Annex 5: Results from MFA/Norad investments in TBVI, 2013-2015

The TuBerculosis Vaccine Initiative (TBVI) is a Product Development Partnership supporting, integrating, translating and prioritizing mostly European R&D efforts to discover and develop new accessible and affordable TB vaccines for global use. Established in 2008 as a European non-profit organization, the PDP has headquarters in the Netherlands, with a total staff of seven employees, 10 consultants, and a network of 50 universities, institutes and industry partners from about 20 countries in Europe, North America, Africa, Asia and Australia.

Since inception, TBVI has acted as a support structure to vaccine developers, without taking ownership of vaccines or claiming intellectual property.. The history of TBVI however dates back to the early 2000s, when it was originally established as Tuberculosis Vaccine Cluster funded by the European Commission's Research Framework Programme FP5. In the past 14 years TBVI has supported activities on vaccines and correlates of protection, which have resulted in 8 vaccine candidates in being evaluated in clinical trials and 17 characterized and initially validated and 18 new biomarkers.

Its current R&D portfolio – which spans from discovery to phase I/II clinical development by organizational design – comprises of 29 candidates, 69% of which are strategies at discovery, 17% are projects in preclinical development, and 13% are projects in clinical development. Another four candidates are currently in late stage efficacy testing which had previously been supported by TBVI. Overall, TBVI actively supports almost half of the global TB vaccine pipeline from discovery to early clinical development.

In 2013 TBVI signed a grant agreement of NOK 15 million with MFA/Norad for the support of TB vaccine R&D activities. This was a core restricted funding grant covering the period 2013-2015, and the first that the PDP would receive from MFA/Norad.

As part of the 2013-2015 MFA/Norad grant the purpose was to contribute to a diverse global vaccine and biomarker portfolio by translating (novel) TB vaccine and biomarker approaches into product and clinical development and by prioritizing (novel) candidates of the TBVI portfolio. Specifically, TBVI would:

- Support the preclinical and early clinical development of new promising priming and boosting vaccines
- Establish a robust and centralized preclinical prime-boost model and evaluate prime-boost approaches in preclinical animal models (two proof of concept experiments)
- Continue and sustain the TBVI core biomarker work to test and validate candidate markers and develop these into assays and continue with discovery of new biomarkers
- Support the TB vaccine candidate selection and portfolio management efforts led by TBVI's independent technical advisory groups (PDT and CDT)
- Support advocacy, communication, resource mobilization and project management activities, including meetings and investment case reports for TB vaccines

Relevance

Activities have been consistent with global strategies and priorities, including the strategic context stipulated in the Stop TB Strategy,[147] the 2012 Strategic Blueprint for TB vaccines towards 2020,[148] and UN MDG 6c. The implemented activities were also coherent and complementary with many other national and foreign policies and interventions:

- Coherent with Norwegian Government's White Paper towards Global Health 2020
- Complementary with MFA development strategies and humanitarian policies[131]
- Complementary with Meld. St. 18 (2012-2013)[149] as it claims that it will support domestic research in Europe and aims to engage with Norwegian partners to develop specific components of the project
- Complementary with PDP Funders Group strategic framework[121]
- Complementary with other donor policies and funding interventions, such as: Gates Foundation strategy on TB vaccine financing and the European Commission's Horizon 2020

Effectiveness & Risk

TBVI is on track with its MFA/Norad funded vaccine R&D activities, with minor deviations due to clinical trial preparation challenges in one of its clinical development projects. Preparations for a phase Ib clinical trial of MTBVAC in South Africa have been underway, including the submission of documentation for conducting a randomized, double blind, dose escalation clinical trial in newborns with a safety arm in adults to the South African Health Authorities in late 2014; documentation for GMO approval for using MTBVAC in early 2015; and the provision of additional clarifications upon the Authorities' request in spring 2015. If the trial is approved by the South African authorities, the trial will start in summer 2015, expected to be completed by summer 2016.

Another candidate, ChadOxPPE15, moved to preclinical and clinical testing in 2015. At the preclinical level, TBVI partners are comparing protective efficacy of PPE15 when administered alone, in a prime boost combination with MVA and when used with a prior BCG prime. At the clinical level TBVI partners are testing a combination candidate of ChadOxPPE15-MVA, after an antigen tested in preclinical models in the US and in Uganda had demonstrated satisfactory results.

Formulation studies of MTBVAC+, an inactivated MTBVAC strain in preclinical development, have also been completed, pending results in summer 2015 to guide further GMP development and dose definition studies prior to preclinical efficacy testing.

Delays occurred with MTBVAC due to unexpected regulatory and ethical approval bottlenecks in South Africa, where TBVI's partner Biofabri is currently planning to conduct the phase I clinical trial. These challenges have pushed back timelines for clinical trial implementation. TBVI does not currently have strong networks in LMICs to smoothen communications with national regulatory and ethical approval authorities. It relies on partners to collaborate with other experienced organizations on aspects concerning clinical trials in LMIC settings. Efforts to build clinical trial networks have been attempted previously through EDCTP. Having clinical project managers in place to deal with LMIC regulatory authorities, and improving collaboration arrangements with clinical trial centers

in LMICs, would allow TBVI to have its own clinical trial strategy and partnership structure in place that is now lacking.

TBVI and partners have established novel models for preclinical testing of vaccine candidates, requiring further standardization and funding. Preclinical models and especially the TBVI standardized models for head-to-head comparisons of candidates are key tools for TB vaccine R&D prioritization and portfolio management processes. As prime-boost vaccine regimes have become more and more popular in the field, TBVI had set to establish a novel preclinical prime-boost model to evaluate innovative prime-boost regimes. Studies completed in 2014 demonstrated that the efficacy of BCG can be significantly improved when boosted with a subunit viral vector in a long prime-boost interval; and that a short prime-boost interval improves efficacy when BCG is boosted with a live vaccine.[150] The model requires further standardization and coordination with preclinical models developed by other organizations such as Aeras and BMGF.

Several biomarkers have been identified through different approaches and a preliminary database has been developed to guide R&D prioritization and population stratification for clinical trials. The TB Biomarker Core Group (TBCC) is one of the long-term TBVI projects supported by the European Commission and by MFA/Norad as a bridging grant between FP7 and Horizon 2020. Effective biomarkers can help predict potential protective efficacy of TB vaccine candidates and as such can be instrumental in stage gating and prioritizing R&D candidates through the pipeline. Over time TBVI's work on biomarkers has allowed to make 40 discoveries out of which 20 candidates were further developed, six of which advanced towards assay development. Understanding the mechanisms of protection against TB in humans remains a challenge, which constrains the identification of suitable biomarkers or correlates of protection.

Portfolio management and candidate prioritization / stage gating procedures have been improved by adding evidence-based decision making criteria and ensuring greater alignment of candidates and resources with other TB vaccine developers. TBVI improved its portfolio management approach in 2014 as a follow up to the stage gating procedures that it had been using in previous years.[148] The portfolio management process is applied at entry, stage gating and priority setting of candidates. This has been developed together with Aeras, a peer TB vaccine PDP, revolving around four pillars to ensure alignment of candidates and resource:

- New entry criteria for including new candidates into the pipeline, ensuring diversity and complementarity
- New framework on stage gating, a decision aiding process for advancing and investing further in candidates through the R&D pipeline
- A new matrix process for priority setting of candidates competing for available resources
- Shared principles on resource mobilization and fund management

Considerable advocacy, resource mobilization and coordination activities have been made, including investment case reports, milestone meetings and new grants secured. Two major reports on TB vaccine investments[151] and strategies have been published since 2013.[152] And according to TBVI records over 30 additional papers have been published in scientific peer-reviewed journals. New grants of over € 25 million in total have been received by Horizon 2020, UK, Switzerland, South Korea and Australia. The UK grant was

jointly allocated to TBVI and Aeras. And a new Global TB Partnership in being developed in collaboration with Aeras, the European Commission, the European Investment Bank (EIC) and BMGF for a more integrated portfolio management and resource coordination effort in the field of TB vaccines. Several stakeholders have suggested that TBVI has the structures and people in place to offer portfolio management and pipeline selection services, increasing donor efficiencies globally. However, EIB has recently expressed reservations about supporting this structure, though it still wants to move into the broader scope of PRINDs through a multi-year risk-sharing loan scheme. As some stakeholders have argued, it is important to have a major funder in the field, to reduce uncertainty of access to funding for PDPs, especially for TB vaccines that is a slow topic of R&D.

Efficiency

Efficiency-wise, TBVI has been both on track and within budget for all its MFA/Norad activities. There has only been a small deviation from the original planning of the MTBVAC phase I clinical trial in Africa but this has now been resolved. Minor budget discrepancies against the total funds provided by MFA/Norad have occurred due to exchange rate fluctuations between the NOK and the euro in the past couple of years. This however does not affect MFA/Norad's investments nor debilitates TBVI's capacity in any way to deliver the work using the available resources as planned.

Added value

TBVI R&D activities are filling in critical gaps in the TB vaccine R&D pipeline up to and including early clinical efficacy testing. Out of 20 TB vaccine candidates in preclinical and clinical development worldwide in 2015, TBVI has been involved, or is currently engaged, in the development of over 50% of these candidates. Specifically TBVI is actively supporting nine candidates, and it has supported four additional candidates that are now in late stage efficacy testing. TBVI does not execute late stage clinical efficacy testing such as phase IIb and phase III trials and it does not provide in-house large scale manufacturing services. As some stakeholders suggest, for downstream R&D one needs more powerful consortia that are structured differently and in which different organizations undertake different tasks. This requires additional portfolio management approaches at the global level, which TBVI and Aeras are currently looking into, by harmonizing TPPs for TB vaccines, and by further coordinating stage gating and priority setting processes for more effective studies.

Additional investments have been generated and new researchers have joined the TBVI network. New grants have been provided by five public funders and 38 new researchers have been recruited for the NEWTBVAC and TBTEA projects, six of whom are post-doc students from African countries. Some linkages with Norwegian researchers have also been made, for instance through invitations to meetings, invitations to pre-selection proposals for EU funded consortia on TB vaccine R&D, and technical support to a proposal submission by NMBU to the GLOBVAC program of the Research Council of Norway.

TBVI has increasingly recognized the need to explicitly address affordability and access concerns in its interactions with TB vaccine development partners. By design TBVI does not take ownership or IP, arguably to allow partner organizations to manage IP issues according to their strategic interests while the PDP maintaining a neutral broker position. However, access and affordability of TB vaccines for the developing world is a

statutory objective of TBVI and a commitment that is part of each project grant agreement supported by TBVI. Without a more detailed IP strategy it might become difficult both to manage potential conflicts of interest between partnering organizations as well as enforce conditions for affordability and global access of vaccines when these are successfully developed. TBVI's new business plan for 2015-2017 tries to address this by suggesting roadblocks or guarantees in its portfolio management and prioritization processes against access and affordability criteria. IP management is a crucial part of product development and without explicit strategies access and affordability issues are likely not be addressed. TBVI would benefit by looking at how other PDPs have operationalized their IP strategies and learn from their successes.

Sustainability

Restricted funding and limited industry engagement are potential barriers to the sustainability of TBVI's activities over time. Although funding sources have been diversified in recent years to include six new government funders, TBVI is still heavily reliant on public funding and particularly one single source of funding, the EU, in order to conduct its operations. As this funding is competitive and restricted on a project-by-project basis, it creates uncertainties and gaps in the R&D funding continuum that places TBVI's R&D pipeline sustainability at risk over time. Several stakeholders have argued that it is difficult to maintain stability in networks of scientists working collaboratively over time if funding is not there.

Relying on industry partners is difficult as these are simply not enough in the TB vaccine development space. Industry's absence is in part due to technical risks across preclinical and early clinical development stages across the TB vaccine field.

Overall, TBVI has a funding gap of € 18 million for the next three years (2015-2017).

Other capacities & dynamic capabilities

TBVI has a robust portfolio management approach with well- defined stage gating and priority setting criteria for advancing TB vaccine candidates through the R&D pipeline. Its Portfolio Management Committee and its advisory groups (PDT & CDT) are responsible for the systematic quality check of suitable vaccine candidates advancing through different R&D stages, against multiple decision criteria such as suitability to TPP targets, innovativeness, feasibility, and others; the identification and evaluation of potential R&D partners, including guidance on how to translate their research into vaccine development; and the evaluation of funding needs for the prioritized candidates. For instance, this mechanism has facilitated the accelerated advancement of candidates from preclinical to clinical development (e.g. shortening the timelines of candidate advancement to later R&D stages in the case of MTBVAC). And where needed, it has halted the advancement of poorer candidates from discovery to preclinical development, reducing overall attrition rates at later stages of development.

Several stakeholders have suggested that TBVI's TPPs need to be specified further to better match the WHO's three TPPs for priming, boosting, immunotherapeutic vaccines. TBVI mainly focuses on priming and boosting TPPs that target adolescents and adults. However it is currently evaluating the role of priming vaccines for neonates and of an

immunotherapeutic TPP within the context of its portfolio management mechanism. This would bring it closer to the WHO's targets on vaccines for fighting the TB epidemic.

TBVI is a lean organization with a small management team that offers an open platform of collaboration for a large network of scientists, particularly within Europe. The PDP offers technical advice, mobilizes resources and shares knowledge among is partners to facilitate and coordinate their work, without claiming any IP ownership and with administrative overheads not exceeding 5% of operations. This model, some stakeholders argue, ensures efficiency in coordination and communication, and avoids duplication of efforts. By deliberately not directing the science and working with the consortium scientists via a 'bottom up approach', TBVI allows for a broad portfolio of R&D activities to be developed in an environment of mutual trust, especially among academic institutions at the European level, as several stakeholders have stated. In effect, TBVI supports almost half of the global TB vaccine R&D pipeline globally today.

The TBVI model allows for blue-sky thinking, focusing on stages from discovery to early clinical development (up to and including phase IIa clinical safety and immunogenicity testing). To date, most TB vaccine candidates in TBVI's portfolio have come out of European R&D institutions that have joined TBVI to be part of this collaborative community and to share reagents and protocols, to develop joint proposals, to identify suitable partners in order to advance their projects through the R&D pipeline and to achieve greater efficiencies, while maintaining ownership of their work.

Partner selection is dome mainly through competitive calls for proposals, at least for the largest projects funded by the EC. This is a novel way for picking out high quality and innovative collaborators. TBVI pre-selects its partners through calls for proposals, especially for the buildup of R&D consortia funded by the EC. This has allowed for a transparent selection and modest expansion of the PDP network by European R&D institutions mainly. For instance 13 new partners joined the PDP in 2014 and 38 new researchers are now working on two of TBVI's leading R&D projects funded by the EC.

Annex 6: List of stakeholders consulted

ID	Name	Organization
1	Tore Godal, Helga Fogstad, Kårstein Måseide, Lene Lothe, Bjørg Sandkjær, Haitham El-Noosh	Norwegian Ministry of Foreign Affairs (MFA) / Norwegian Agency for Development Cooperation (Norad)
2	Bernard Pecoul, Julia Fahrmann	Drugs for Neglected Diseases Initiative (DNDi)
3	Margaret McGlynn, Fiona Barr, Ardi Voets	International AIDS Vaccine Initiative (IAVI)
4	Zeda Rosenberg, Lynn Bodarky, Lauren Dolak, Michael Goldrich	International Partnership for Microbicides (IPM)
5	David Reddy, Andrea Lucard, Neil McCarthy, Christina Do Paco	Medicines for Malaria Venture (MMV)
6	Nick Drager, Danielle Roordink, Rene Coppens, Anne Meinema	TuBerculosis Vaccine Initiative (TBVI)
7	Helen Mcshane	Oxford University (TBVI partner)
8	Oswaldo Alvarez	Biofabri (TBVI partner)
9	Tom Ottenhof	University of Leiden (TBVI partner)
10	Valerie-Faillat-Proux	Sanofi (DNDi partner)
11	Lynsey Haskayne; Paul Bilson	Aptuit (DNDi partner)
12	Crispin Lumbala	National Program for the Fight Against Human African Trypanosomiasis (DNDi partner)
13	Kelly Chibale	University of Cape Town (MMV partner)
14	Nick Cammack	GlaxoSmithKline (MMV partner)
15	Kenneth Stokholm	Qpharma (IPM partner)
16	Carl Dieffenbach	National Institute of Allergy and Infectious Diseases (IPM partner)
17	Hugo Tempelman	Ndlovu RC, Elandsdoorn (IPM partner)
18	Philip Kotze	Qhakaza Mbokodo Research Clinic, Ladysmith (IPM partner)
19	Pontiano Kaleebu	Uganda Virus Research Institute (IAVI partner)
20	Sanne Frost Helt	Ministry of Foreign Affairs, Denmark (DANIDA)
21	Lorraine Gallagher	Irish Aid
22	Wieneke Vullings	Ministry of Foreign Affairs, Netherlands (DGIS)
23	Hannah Akuffo	Swedish International Development Cooperation Agency, Sweden (SIDA)
24	Susanna Hausmann Muela	Swiss Agency for Development and Cooperation (SDC)
25	Åse Marit Kristiansen, Wenche Dageid	Research Council of Norway (GLOBVAC / RMNCH)
26	Ole Olesen	European & Developing Countries Clinical Trials Partnership (EDCTP)
27	Rob Terry; Garry Aslanyan; John Reeder	Special Programme for Research and Training in Tropical Diseases (WHO TDR)
28	Christopher Egerton-Warburton	Global Health Investment Fund (GHIF)
29	BT Slingsby	Global Health Innovative Technology Fund (GHIT Fund)
30	Anne Hrardsky	Deutsche Stiftung Weltbevoelkerung (DSW)
31	Alex Fullem; Sue Kinn; Sue Perl	PDP Funders Group (PFG)
32	Stefan Jungbluth, Odile Leroy, Nathalie Imbault	European Vaccines Initiative (EVI)
33	David Kaslow	PATH
34	Mel Spigelman, Benjamin Alsdurf	TB Alliance
35	Toni Hoover, Samia Saad	Bill & Melinda Gates Foundation (BMGF)
36	John-Arne Røttingen, Kathrine-Stene Johansen	Norwegian Institute of Public Health (NIPH)

Annex 7: Licensed products the development or re-purposing of which PDPs have contributed to, 2000-2015

Disease / Condition	Product type	Product description	PDP involved in developing or re-purposing products
American Trypanosomiasis (Chagas Disease)	Diagnostics	Chagas diagnostic	IDRI
American Trypanosomiasis (Chagas Disease)	Drugs	Benznidazole Paediatric	DNDi
Cholera	Vaccines (preventive)	Killed whole-cell oral cholera vaccine (Shanchol)	IVI
HIV/AIDS	Other devices	Packaging Solutions for Nevirapine (HIV mother-to-child transmission)	PATH
Human African Trypanosomiasis (sleeping sickness)	Diagnostics	Loopamp Trypanosoma brucei Detection Kit	FIND
Human African Trypanosomiasis (sleeping sickness)	Diagnostics	Mini Anion Exchange Centrifugation Technique (mAECT)	FIND
Human African Trypanosomiasis (sleeping sickness)	Diagnostics	Primo Star iLED fluorescence microscope	FIND
Human African Trypanosomiasis (sleeping sickness)	Diagnostics	SD Bioline HAT RDT	FIND
Human African Trypanosomiasis (sleeping sickness)	Diagnostics	Serodiagnosis RDT	FIND
Human African Trypanosomiasis (sleeping sickness)	Drugs	NECT	DNDi
Leishmaniasis	Diagnostics	Leishmaniasis RDTs e.g. Kalazar Detect - rK39-based immunochromatographic test (ICT), Kala-azar Latex Agglutination Test (KAtex), Direct agglutination test (DAT)	IDRI
Leishmaniasis	Drugs	New VL treatments for India	DNDi
Leishmaniasis	Drugs	SSG&PM (Sodium Stibogluconate and Paromomycin Combination therapy for VL in Africa)	DNDi
Leishmaniasis	Drugs	Paromomycin I/M	OWH
Leishmaniasis	Drugs	Miltefosine (Impavido)	WHO TDR
Leprosy	Diagnostics	NDO-LID	IDRI
Malaria	Drugs	ASAQ FDC	DNDi
Malaria	Drugs	ASMQ FDC	DNDi
Malaria	Drugs	Artemether-Lumefantrine	MMV
Malaria	Drugs	Artemether-Lumefantrine Dispersible	MMV
Malaria	Drugs	Artesunate for Injection	MMV

Disease / Condition	Product type	Product description	PDP involved in developing or re-purposing products
Malaria	Drugs	DHA-Piperaquine	MMV
Malaria	Drugs	Pyronaridine-Artesunate	MMV
Malaria	Drugs	Sulfadoxine Pyrimethamine + Amodiaquine	MMV
Malaria	Drugs	SP+AQ	MMV
Malaria	Drugs	Artemotil (B- Arteether)	WHO TDR
Malaria	Drugs	Chlorproguanil/dapsone	WHO TDR
Meningococcal disease	Vaccines (preventive)	MenAfriVac	PATH
Multiple kinetoplastid diseases	Vector Control Products	Actellic CS	IVCC
Multiple kinetoplastid diseases	Vector Control Products	IQK (Insecticide Quantification Kits)	IVCC
Multiple kinetoplastid diseases	Vector Control Products	K-Othrine Polyzone	IVCC
Onchocerciasis	Diagnostics	SD BIOLINE Onchocerciasis IgG4 rapid test	PATH
RMNCH	Diagnostics	careHPV™ DNA Test (cervical cancer prevention)	PATH
RMNCH	Other devices	Neonatal Resuscitator (Birth asphyxia)	PATH
RMNCH	Other devices	Safety Management System for Human Milk Banks (Breast milk)	PATH
RMNCH	Other devices	NIFTY Infant Feeding Cup (breastfeeding difficulties)	PATH
RMNCH	Other devices	SILCS Diaphragm (contraception)	PATH
RMNCH	Other devices	BIRTHweight III Scale (Low birth weight)	PATH
RMNCH	Other devices	Delivery Kit (maternal and perinatal mortality)	PATH
RMNCH	Other devices	Affordable Sanitary Pad (Menstruation management)	PATH
RMNCH	Other devices	Woman's Condom (multi-purpose prevention)	PATH
RMNCH	Other devices	Gentamicin in Uniject (neonatal sepsis)	PATH
RMNCH	Other devices	Oxytocin in Uniject (Obstetric hemorrhage)	PATH
RMNCH	Other devices	Antishock Garment (Postpartum hemorrhage)	PATH
RMNCH	Other devices	Balloon Tamponade (Postpartum hemorrhage)	PATH
RMNCH	Other devices	Chlorhexidine for Umbilical Cord Care (Severe infection)	PATH
RMNCH	Other devices	Continuous Positive Airway Pressure (CPAP) and Oxygen Blender	PATH
Rotavirus	Vaccines (preventive)	ROTAVAC	PATH
Tuberculosis	Diagnostics	LED microscopy	FIND
Tuberculosis	Diagnostics	Line Probe Assay (1st line)	FIND
Tuberculosis	Diagnostics	Liquid Culture and DST	FIND
Tuberculosis	Diagnostics	Rapid Speciation	FIND
Tuberculosis	Diagnostics	Xpert MTB/RIF	FIND

Annex 8: Detailed Methodology

The scope, objectives and methodological approach were finalized during an inception phase comprising a draft report that presented: the background and rationale to this study, including illustrative issues to be addressed; an interim progress update of the five PDPs currently funded by MFA/Norad. Data collection methods, templates and lists of potential interviewees were discussed in a meeting with MFA/Norad officials in January 2015 and were finalized in February / March 2015. The report was developed by two NIPH researchers between March and June 2015.

Scope & definitions

This report is focused on MFA/Norad global health product development funding for:

- Infectious and neglected diseases of poverty that disproportionately affect LMIC populations, and for which there are insufficient commercial markets to attract R&D by industry;
- Maternal, child and reproductive health conditions that persist in LMIC settings;

Since the concept of global health product development can range from very narrow to extremely broad interpretations, we hereby define product development in terms of:

- **Geography**: Investments that are specifically targeted at LMIC R&D needs
- **Product types**: Health products types include drugs, vaccines (preventive and therapeutic), diagnostics, microbicides, vector control products (pesticides, biological control agents and vaccines targeting animal reservoirs), as well as platform technologies (adjuvants, diagnostic platforms and delivery devices). The latter category concerns technologies that can potentially be applied to a range of neglected diseases and products, but which have not yet been attached to a specific product for a specific disease.
- **Parts of the R&D process that is being addressed:** Basic science is excluded, and so is applied research that is not directly linked to development of a specific product. For instance prevalence and disease burden studies are not included in this definition. All activities in the product development process up to and including market approval are included. Post-marketing approval activities such as pharmacovigilance, manufacturing scale-up, commercialization, market shaping, etc., are not included.

[This definition is adapted from http://www.policycures.org/downloads/Y7%20GFINDER%20full%20report%20web%20.pdf]

Methods

To perform this review we gathered and analyzed three different types of data:

Literature and document review:

Literature search in PubMed for all articles published between 2009 and February 2015 containing the following terms:

- ("global health" OR "neglected diseases" OR "infectious diseases of poverty") AND ("product development" OR "product development partnerships" OR "R&D" OR financing) AND (challenges OR opportunities)
- (tuberculosis OR HIV) AND vaccine AND R&D
- (malaria OR sleeping sickness) AND drug AND R&D
- ("sleeping sickness" OR "human African trypanosomiasis") AND drug AND R&D
- (HIV OR HIV/AIDS) AND microbicide AND R&D
- IAVI OR "International AIDS Vaccine Initiative"
- TBVI OR "Tuberculosis Vaccine Initiative"
- MMV OR "Medicines for Malaria Venture"
- DNDi OR "Drugs for Neglected Diseases Initiative"
- International Partnership for Microbicides

The terms were chosen in order to identify recent literature on: global health product development achievements, challenges and funding opportunities; the role and performance of PDPs in general, as well as of the five PDPs currently funded by MFA/Norad. We reviewed the abstracts, and included all relevant papers in our detailed review.

Moreover, we reviewed grey literature, past evaluations and recent progress reports by PDPs, all related to assessing PDP performance, identified through: google searches; communications with PDPs, MFA/Norad and other PDP funders and NIPH experts with knowledge of the field.

Consultations:

We conducted expert consultations with representatives of 35 institutions, including: (1) MFA/Norad officials; (2) PDPs currently funded by MFA/Norad; (3) select partners of PDPs currently funded by MFA/Norad; (4) other relevant funders or funding mechanisms of global health product development; (5) other experts and stakeholders. Two rounds of consultations were conducted with PDP officials – the first round had the objective of obtaining an overall overview of PDP performance and satisfaction with the MFA/Norad funding scheme; the second round had the objective of a more detailed assessment of PDP capacities and capabilities based on a framework presented below (see table 3). Moreover, we conducted a series of informal consultations and data validation discussions with a number of in-house disease and R&D experts at the Norwegian Institute of Public Health.

Data collection:

We explored and analyzed R&D pipeline and financial data gathered, from PDPs and other consultation stakeholders, PDP annual progress reports, PDP annual Funders reports, published reports, and specific databases and sources.

Data sources for R&D pipelines included:

- BioVentures for Global Health (**BVGH)** (http://www.bvgh.org/Current-Programs/Neglected-Disease-Product-Pipelines.aspx)
- Treatment Action Group (**TAG)** (http://www.treatmentactiongroup.org/sites/g/files/g450272/f/201407/2014%20Pipeline%20Report%20Full.pdf)
- International Federation of Pharmaceutical Manufacturers & Associations (**IFPMA)** (http://www.ifpma.org/fileadmin/content/Publication/2015/IFPMA_2014_Status_Report_NTDs_FINAL.pdf)

- **WHO**: **malaria vaccines** (http://www.who.int/immunization/research/development/Rainbow_tables/en/)
- **MMV/RollBack Malaria: Malaria drugs** (http://www.rollbackmalaria.org/files/files/partnership/wg/wg_procurementsupply/docs/24_GJAGOEMMVNewAntimalarialsPipeline.pdf)
- **UNITAID: HIV diagnostics** (http://www.unitaid.eu/images/marketdynamics/publications/UNITAID_2015_Semi-annual_Update_HIV_Diagnostics_Technology_Landscape.pdf)
- **UNITAID: malaria diagnostics** (http://www.unitaid.eu/images/themarketshare/Malaria_Diagnostics_Landscape_Update_Fe_2015.pdf)
- **UNITAID: malaria vector control products** (http://www.unitaid.eu/images/projects/malaria/UNITAID_Malaria_Vector_Control_Landscape_2nd_Ed_December_2014.pdf)
- **PhRMA: infectious disease vaccines** (http://www.phrma.org/sites/default/files/pdf/Vaccines_2013.pdf)
- **WHO: dengue vaccines** (http://www.who.int/immunization/research/development/en/)
- **WHO ebola** (http://www.who.int/medicines/ebola-treatment/ebola_r_d_effort/en/)
- **PDP websites**

Data sources for financial data included:

- **G-FINDER** Public Search Tool (https://gfinder.policycures.org/PublicSearchTool/)
- **MFA/Norad** data on investments into DNDi, IAVI, IPM, MMV, DNDi, SLAB
- **WHO TDR** data on MFA/Norad investments into WHO TDR (http://www.who.int/tdr/about/funding/en/)
- **Projects Bank of the Research Council of Norway** on MFA/Norad investments into GLOBVAC (https://www.forskningsradet.no/prosjektbanken/)

Data extrapolations:

- MFA/Norad investment data for GLOBVAC have been extrapolated from G-FINDER and the Research Council of Norway's Projects Bank assuming that MFA/Norad project-by-project contributions proportionate to MFA/Norad's share of total annual contributions to GLOBVAC. For 2013-2015 specifically, the Projects Bank of the Research Council of Norway was mined to identify eligible R&D projects and corresponding investment data was included in the analysis if within scope of the product development definition applied in this report.

Data analysis:

- We analyzed PDP performance based on a framework that builds on: (1) the OECD DAC evaluation criteria; (2) and the MFA/Norad PDP funding appraisal framework that was developed for the selection of PDPs in 2013. Questions on R&D capacities and dynamic capabilities were formulated according to current literature evidence on R&D performance measurement methods.[153]

Table 3: PDP performance-assessment framework

Dimension / Criterion	Questions / indicators
Relevance	❖ To what extent were the activities implemented consistent with: global priorities; Norwegian policies and priorities; specific MFA/Norad grant scheme objectives; and product development challenges these activities were meant to address?
Effectiveness & Risk	❖ Were all activities completed / or are they on track towards timely completion by the end of the current grant cycle? ❖ Were the outputs of the activities of satisfactory quality? ❖ Did any of the foreseen risks in the MFA/Norad grant scheme occur, and if so, were the proposed mitigation measures to handle these risks (e.g. technical / operational, organizational, financial) sufficient? (Discuss with examples) ❖ What other risks, or constraints, emerged, and how were they dealt with?
Efficiency	❖ Were the activities completed within the budget requirements of the grant scheme? ❖ Were the activities completed within the timeline requirements of the grant scheme?
Added value	❖ Have the activities contributed to saving lives and/or filling in R&D gaps upon successful completion? ❖ Have the activities stimulated any additional investments in innovation and/or more innovation outputs that would not have occurred in their absence? ❖ Have the activities generated any positive or negative implications for future R&D, manufacturing, R&D capacity building in LMICs, and/or access strategy formulation?
Sustainability	❖ Have the activities generated any links with other R&D efforts, existing interventions, or exit strategies for R&D continuation? ❖ Have the activities generated any positive or negative implications for the environment and climate change, fight against corruption, local ownership of results etc.? If so, what actions were taken to address these implications?
Other capacities & dynamic capabilities	❖ Were all partners involved in this program capable or experienced enough to complete the planned activities? Were there any challenges with the partnership model, and if so, how were they addressed? ❖ Has the institutional capacity of the PDP to conduct, or to manage R&D, changed in any way since 2013? ○ New employees (especially for R&D and particularly in LMIC settings) or withdrawals? ○ New partners or partner withdrawals or ongoing lack of partners (especially industry per R&D stage; LMIC partners for all stages)? ○ New or extended clinical trial partnership networks and/or capabilities in LMIC settings? ○ New or improved capabilities or networks for discovery, manufacturing, regulatory prep and access efforts? ○ New funders or funder withdrawals? ○ New publications or evidence on increased cross-citations of PDP related publications? ○ New candidates per R&D stage or candidate withdrawals from the PDP pipeline? ○ How many new chemical entities are in your R&D pipeline currently, and what is their % share of your overall candidate portfolio (total and by R&D stage)? How has this changed from 2013? ○ New or improved technologies / platforms, or other innovations, improving the innovativeness, time-to-stage gates and/or the average probability of success of R&D candidates? ○ New or improved R&D portfolio management approaches? ○ New or improved candidate prioritization / stage gating procedures? ○ New or improved Target Product Profiles / Target Product Candidate Profiles? How representative are these of the global needs / how aligned or acceptable are they considered by international agencies, for instance by the WHO? ○ New or improved IP strategies / open source initiatives or pricing models / agreements with partners? ○ New or improved governance structures (Board, advisory groups, other)? ○ New or improved business plans and/or R&D, manufacturing, or access strategies?

Reported currencies:

- All MFA/Norad investment figures are reported in current NOK, and are not inflation-adjusted. Regarding MFA/Norad investment data on GLOBVAC between 2007 and 2013, G-FINDER data was converted from US$ 2013 to current US$, then to current NOK values. Moreover, MFA/Norad investment data for WHO TDR between 1974 and 2013 was converted from current US$ to current NOK after distributing total investments for this period equally across all respective years.
- All PDP investment figures for the period 2007-2014 in chapter 3 are reported in US$2013, and are inflation-adjusted. For 2007-2013 specifically, G-FINDER data was gathered, which is reported in US$2013. For 2014, PDP reported data was converted into US$2013, applying the same methodology as G-FINDER for currency conversion and inflation adjustment.

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